

Typical reflux disease

Recognition and management of resistance to therapy

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Diagnosis of gastro-oesophageal reflux disease depends on recognising the cardinal symptoms of heartburn and regurgitation, with faulty diagnosis contributing to apparent failures of medical management. Management of persistent reflux symptoms, including heartburn, regurgitation and chest pain, that are not well controlled by medical therapy may require insightful physiological management. Laparoscopic surgery can offer excellent and durable outcomes in this patient group.

Gastro-oesophageal reflux disease (GORD) is a chronic disease caused by effortless reflux of gastric fluid into the oesophagus or extraoesophageal space, causing troublesome symptoms.¹ The prevalence of GP-diagnosed GORD in Australia has been estimated at 11.3%.² Prevalence has been reported in the USA as 18.1 to 27.8%, and in Europe as 8.8 to 25.9%.³ Medically refractory GORD refers to reflux symptoms that continue despite lifestyle changes and the use of proton pump inhibitors (PPIs). This resistance to therapy can lead to

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KEY POINTS

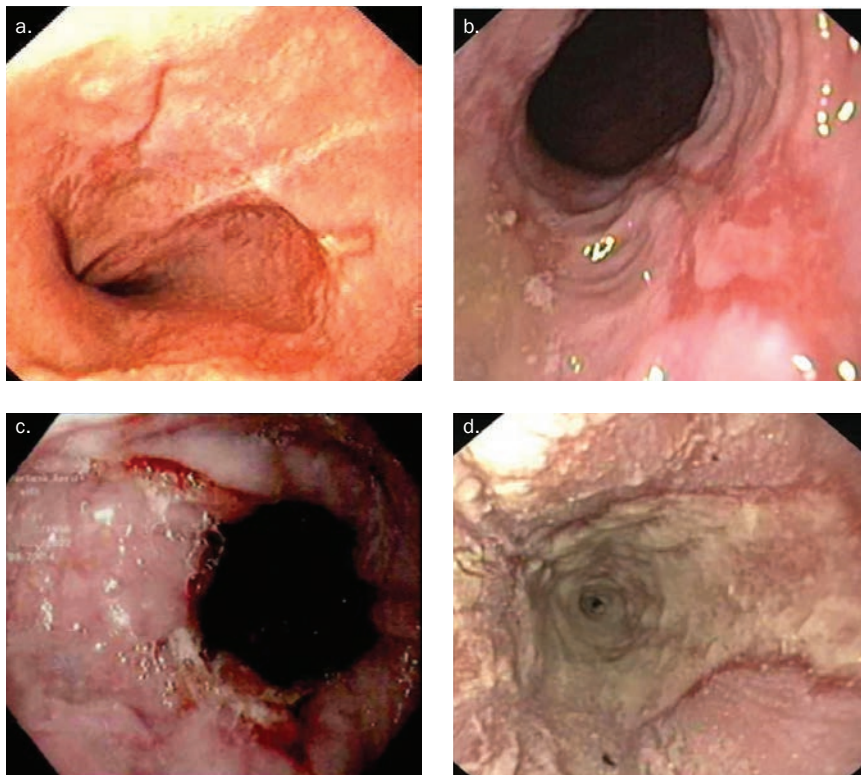
- Proton pump inhibitors (PPIs) are the mainstay of treatment for most patients with gastro-oesophageal reflux disease, but 20 to 30% of patients remain symptomatic despite therapy.
- If medical treatment does not adequately control symptoms, diagnosis requires an oesophageal physiology study (manometry and 24-hour pH impedance testing) while the patient is not taking PPIs.
- Endoscopy is only 30% sensitive for the diagnosis of gastro-oesophageal reflux disease.
- Double-dose PPIs are only marginally effective for symptom control in the medium term.
- Systematic reviews have found that minimally invasive laparoscopic antireflux surgery is superior to medical management in treating refractory reflux disease.

significantly reduced health-related quality of life for patients.⁴

This article aims to guide the selection of patients with typical reflux who have poorly controlled disease and may be suitable for minimally invasive surgery to further reduce symptoms and improve their quality of life. The relative merits of managing severe reflux disease with continued medication, increased medication and ancillary therapies are discussed, along with the efficacy of surgery.

Mechanisms of abnormal reflux

Multiple physiological abnormalities may lead to abnormal frequency or duration of reflux or distribution of reflux events, causing symptoms. Disease may be confined within the oesophagus or become extraoesophageal, causing different symptoms depending on the sites affected. Symptoms and oesophagitis (Figure 1) are caused by an imbalance between the duration of acid exposure of the oesophagus and mucosal defences; this can also lead to 'flooding' of extraoesophageal sites.



Figures 1a to d. Grades of oesophagitis at endoscopy. Grade A (a, top left). Grade B (b, top right). Grade C (c, bottom left). Grade D (d, bottom right).
Images courtesy of the authors.

Reflux events may be initiated by failure of the antireflux barrier, due to an abnormal crural diaphragm (CD), diminished lower oesophageal sphincter (LOS) function or delayed oesophago-gastric clearance. Symptoms and mucosal damage are influenced by the gastric acid pocket located just below the LOS, the aggressiveness of constituents of reflux fluid, oesophageal clearance and the balance of mucosal resistance.^{5,6} The antireflux barrier between the stomach and the oesophagus comprises the LOS, the CD and the gastric sling filaments. The anatomically normal region may allow abnormal reflux through increased transient LOS relaxation, low LOS basal pressure, swallow-induced relaxations and straining. The severity of acid exposure corresponds to the level of physiological abnormality and is more extreme once anatomical changes, namely hiatal herniation, occur. A hiatal herniation dislocates the otherwise coinciding LOS and

CD, rendering the antireflux mechanism less effective and allowing more frequent reflux events.⁷

Refluxate may consist of acid, especially from the acid pocket below the LOS, and is not well titrated by feeding. Acid reflux is associated with heartburn, regurgitation and chest pain when disease is located within the oesophagus. Extraoesophageal proximal manifestations include throat symptoms, reflux cough, choking and inhalation. These do not reflect atypical reflux disease but are symptoms of volume reflux occurring in a patient with index symptoms of heartburn or regurgitation. Volume reflux is common in patients with treatment-resistant disease. Reflux events may occur during treatment with PPIs and may be associated with the sensation of regurgitation – a breakthrough symptom that patients find disturbing.^{8,9}

Biliary pancreatic fluid may be present in refluxate in a third of patients and is

especially prominent in patients with Barrett's oesophagus.¹⁰ The noxious effect of bile is not influenced by acid suppression and is a possible cause of refractory symptoms.

The duration of exposure to refluxate may be extended by ineffective oesophageal and gastric clearance. Diminished efficacy of peristalsis contributes to delayed reflux bolus clearance. Chemical neutralisation by saliva reduces acid exposure time and is important for symptom control. Hiatal herniation may act as a reservoir for re-reflux and prolonged lower oesophageal exposure to refluxate.¹¹

Diagnosis

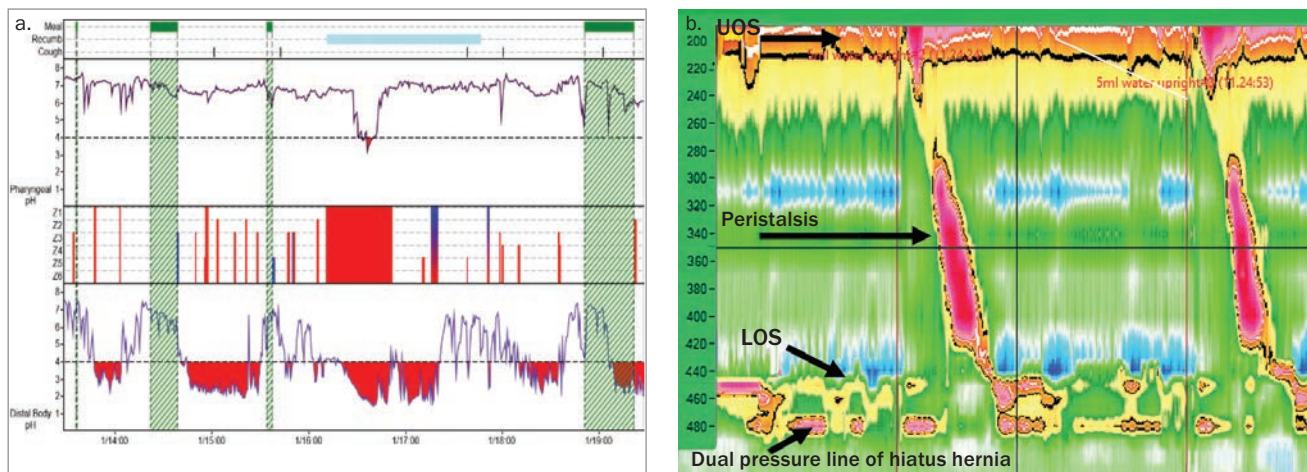
Symptomatic evaluation

Typical reflux is largely diagnosed by identifying an abnormal frequency of heartburn and regurgitation symptoms before a patient has started taking medication. Other symptoms (e.g. belching, bloating, epigastric burn, gastric dyspepsia or throat burn) have a very low probability of being associated with reflux disease. Both the sensitivity and specificity of symptoms for diagnosing GORD are only about 65%.¹² Diagnosis may be difficult because as many as two-thirds of patients with 'refractory reflux' do not have GORD.¹³

Differential diagnosis of reflux symptoms includes:

- abnormal oesophageal motility
- gastric emptying abnormality
- other oesophageal inflammatory conditions
- gallbladder disease
- peptic ulceration
- cardiorespiratory disease
- rumination syndrome
- bulimia
- irritable bowel syndrome
- neoplasia
- dyspepsia.

Reflux disease is the most common cause of noncardiac atypical chest pain.¹⁴ It is important to identify alarm symptoms that require urgent exclusion of other diseases, particularly malignancy. These symptoms include progressive new-onset



Figures 2a and b. Oesophageal diagnostic studies. 24-hour impedance study, red areas indicate acid reflux exposure (a, left). High-resolution manometry (b, right).

Abbreviations: LOS = lower oesophageal sphincter; UOS = upper oesophageal sphincter. Images courtesy of the authors.

symptoms, dysphagia, weight loss, vomiting, upper gastrointestinal bleeding, iron deficiency and new-onset dyspepsia.

Proton pump inhibitor test

Although it seems logical that symptoms that respond to a four-week trial of PPI therapy would be likely to confirm the diagnosis of GORD, this is poorly validated scientifically and has been considered neither sensitive nor specific. Making the diagnosis on the basis of symptomatic response to medical therapy is therefore not recommended. Nonetheless, if good symptom control is established, PPIs become effective treatment and further diagnostic assessment is generally not required.

In assessing the efficacy of PPI therapy, it is not enough to only ask the patient if the heartburn has resolved. The physiological cause of regurgitation events remains and reflux events will continue, although the patient will be less symptomatic when acid concentration is reduced. Regurgitation causing coughing, choking, disturbed sleep and postprandial chest pain may persist. The patient may have dysphagia secondary to continued oesophagitis or dysmotility. Heartburn must be retrosternal to have diagnostic efficacy for GORD, whereas gastric and throat burning are considered atypical symptoms that are not diagnostic

of reflux disease and are not likely to respond to PPI therapy.

Endoscopy evaluation

Endoscopy has a sensitivity of only 30% for the diagnosis of GORD, diminishing its diagnostic value.¹⁵ It is largely used to determine complications of reflux disease and to exclude other conditions that may mimic it. Only about 10% of patients with reflux will show the presence of reflux oesophagitis on endoscopy. The only endoscopic criteria considered positive for diagnosis of reflux are grades C and D oesophagitis under the Los Angeles (LA) classification (Figure 1). LA grade A oesophagitis is poorly diagnostic of reflux disease. LA grade B oesophagitis, Barrett's oesophagus and peptic stricture are highly suggestive of reflux disease.¹⁵ Presence of stricture may indicate a need for further treatment and exclusion of neoplasia. Identification of Barrett's oesophagus is a likely indication for premalignant surveillance.

Oesophageal physiology

A 24-hour pH impedance study combined with oesophageal manometry (Figure 2) is generally the most accurate method of identifying typical reflux disease and the relationship between the reflux event and symptoms – known as symptom association

probability (SAP). The SAP is vital in categorising patients by the various phenotypes of reflux disease, to enable appropriate treatment.¹⁶ Phenotypes include:

- GORD or erosive reflux disease, where oesophagitis occurs secondary to reflux disease
- nonerosive reflux disease, where reflux of acid or nonacid material is abnormally elevated but there is no oesophagitis
- reflux hypersensitivity, where there is normal acid or nonacid exposure and positive SAP
- functional heartburn, where there is no evidence of reflux disease and negative SAP, with normal reflux event frequency.¹⁷

Acid-related disease can be treated with acid suppression or surgery, whereas reflux hypersensitivity and functional heartburn require different therapy (Table).¹⁶

Oesophageal function testing can be used to aid diagnosis in patients with poor or incomplete symptomatic response to medication and with no or minimal oesophagitis seen on endoscopy. Multiple international guidelines recommend performing this test without acid suppression. There are no normative data supporting the use of reflux testing in patients when taking PPIs.

TABLE. PHENOTYPES OF TYPICAL REFLUX DISEASE¹⁶

	Erosive reflux disease	Nonerosive reflux disease	Reflux hypersensitivity	Functional heartburn
Endoscopy	• Oesophagitis	• No oesophagitis	• No oesophagitis	• No oesophagitis
Acid studies	• Increased AET	• Increased AET	• Normal AET	• Normal AET
Symptoms	• Heartburn • Regurgitation • Other extraoesophageal reflux symptoms secondary to flooding	• Heartburn • Regurgitation • Other extraoesophageal reflux symptoms secondary to flooding	• Heartburn • Regurgitation • Heightened sensitivity	• Chest pain • Heartburn
SAP	• Positive	• Positive	• Positive	• Negative
Management	• Lifestyle changes • Acid suppression • LARS	• Lifestyle changes • Acid suppression • LARS	• Lifestyle changes • Neuroleptics • LARS*	• Lifestyle changes • Psychological intervention

Abbreviations: AET = acid exposure time; LARS = laparoscopic antireflux surgery; SAP = symptom association probability (assessed by 24-hour pH impedance study).
* LARS may be effective in symptom management.

Therapy

Antisecretory therapy

The mainstay of treatment of persistent reflux symptoms is continuous PPI therapy. Although dose minimisation is preferable, involving use of antacids and intermittent PPIs or regular H₂ antagonists, patients with severe symptoms require continuous treatment.¹⁸ When adequate symptom control is not achieved, a recent meta-analysis showed that doubling the dose of PPIs does not improve efficacy in the medium term.¹⁹

Conservative management with PPIs is beneficial in 70 to 75% of patients with typical reflux disease when adequately diagnosed. However, large PPI dosage evaluation studies have shown a lack of symptom control in the remaining 25 to 30% of patients, who may be candidates for surgical therapy to improve their quality of life.²⁰⁻²²

Lifestyle management

Although effective in patients with mild to moderate reflux disease, lifestyle management is less effective for those with more severe disease and often affects quality of life.²³ Elevating the head of the bed may disturb sleep, and there is little evidence that this is effective. Equally, weight loss, cessation of smoking and avoiding late-evening gastric load, although practically useful and worth trialling for patients with mild disease, have very little supporting

evidence and are less likely to be of benefit for patients with more severe disease.²⁴

Minimally invasive laparoscopic antireflux surgery

Meta-analysis of randomised controlled trials (RCTs) of medical therapy with PPIs compared with laparoscopic antireflux surgery (LARS; Figure 3) has shown surgery to be more symptomatically effective than PPIs in the treatment of medically refractory GORD.^{25,26} There was a significant long-term reduction in heartburn in the LARS groups compared with the medical groups. Objective control of reflux disease, measured by 24-hour pH study, was substantially improved in the surgical groups.²⁵ However, studies showed a relatively high level of bias and poor long-term evaluation, so further RCTs are suggested.²⁶ No significant difference in adverse events was seen between surgery and PPI therapy. Importantly, there was no difference between the two groups in the symptom of dysphagia after recovery (a symptom frequently attributed to surgery).

It is important to note that most RCTs were conducted in an environment of full-time and experienced antireflux surgical practice, usually in a university hospital. Excellent results were obtained in 87 to 94% of patients, depending on responses to PPIs.²⁷⁻²⁹ High-volume surgeons have been

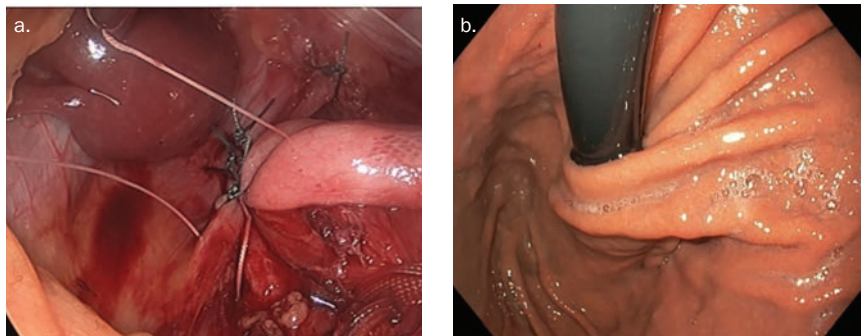
reported to achieve superior early outcomes.³⁰ The results, therefore, reflect expert management in a high-volume antireflux surgical service and may not be generalisable to broader surgical practice.

Morbidity and mortality from LARS are low. In a national study of 8947 patients, there was one surgery-related death, and the three-month reoperation rate was 0.4%.³¹ Morbidity is generally considered to be about 3 to 4%.³² Assessment of quality of life 20 years after total fundoplication in 131 patients found that 82% reported satisfaction.³³

Selection of patients for antireflux surgery

Patients who have an inadequate response to continuous acid suppression for control of symptoms, or who have continued complications of reflux disease despite properly administered medication, are potential candidates for LARS, following adequate investigation (Box). Patients with reflux hypersensitivity and functional heartburn are generally not considered for surgery.

Patients requiring a double dose of PPIs are likely to benefit, provided a substantive initial response to PPI therapy has been observed.¹⁹ The ICARUS guidelines (international consensus regarding preoperative examinations and clinical characteristics assessment to select adult patients for



Figures 3a and b. Laparoscopic view of fundoplication (a, left). Completed fundoplication snug around the endoscope (b, right).
Images courtesy of the authors.

antireflux surgery) note that patients with a partial response to PPIs, hiatus hernia or oesophagitis of LA grade B or higher and Barrett's oesophagus can expect a favourable symptomatic outcome from LARS.³⁴

Minimally invasive antireflux surgery is underused, potentially reducing quality of life for a large group of patients.³⁵ There are multiple consensus recommendations for performing endoscopy and manometry before antireflux surgery, and a 24-hour pH impedance reflux study is necessary in all patients without high-grade oesophagitis.³⁴ Such patients can be evaluated by an experienced antireflux service and tested accordingly. Adequate patient selection is paramount, and specialised antireflux surgical groups are generally

expert in reflux physiological testing. Various physiological anomalies exist, and personalised management is valuable in achieving optimal outcomes.³⁶

Conclusion

There is a large group of patients with initial symptoms of heartburn and regurgitation (typical reflux) who have continued reflux symptoms that are incompletely managed by medication. These patients are potential candidates for minimally invasive antireflux surgery after adequate physiological investigation. RCTs of medical treatment compared with surgical management support this approach in reducing symptoms and improving quality of life for appropriately selected patients. **MT**

INDICATIONS FOR LAPAROSCOPIC ANTIREFLUX SURGERY IN PATIENTS WITH MEDICALLY REFRACTORY REFLUX DISEASE

- Inadequate control of heartburn, regurgitation or pulmonary inhalation (aspiration, recurrent chest infections, aspiration pneumonia)
- Nocturnal symptoms (nocturnal cough, choking, laryngospasm, sleep disturbances)
- Unacceptable lifestyle restrictions (restrictive diet, inability to socialise, abnormal sleeping position, disturbed sleep)
- Breakthrough extraoesophageal symptoms (postprandial chest pain, dyspnoea, coughing)
- Patient aged <60 years taking continuous PPI therapy
- Medication intolerance in a younger patient (aged <60 years) taking continuous PPI therapy and with osteoporosis
- Free reflux and volume reflux symptoms, despite medical therapy

Abbreviation: PPI = proton pump inhibitor.

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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