

A debate on the roles of antireflux surgery and long term acid suppression in the management of gastro-oesophageal reflux disease

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Introduction

According to the Montreal definition, gastro-oesophageal reflux disease (GORD) is a condition that develops when reflux of the stomach contents into the oesophagus causes troublesome symptoms and/or complications.¹ GORD is a chronic disorder which impacts health related quality of life (HR-QOL) and reduces work productivity.²⁻⁴ During the past two decades, the superiority of proton pump inhibitors (PPIs) over other drugs (antacids, prokinetics and H₂ receptor antagonists) has been established beyond doubt and PPIs are now considered as the mainstay of antireflux medical therapy.^{5,6} However, once healing of mucosal breaks and sufficient symptom relief have been achieved by initial therapy, the main goals of long term management are to maintain symptom control and prevent lesion recurrence, allowing a return to a nearly normal quality of life. Maintenance treatment with a PPI may be an option, offering high rates of symptom resolution and healing of oesophagitis.⁶ However, some patients are reluctant to take long term medication and may prefer to have antireflux surgery which has also been revolutionised by the development of the laparoscopic route. In this debate, we will discuss the advantages/inconvenience of both long term strategies—that is, drugs versus surgery. Our purpose is not to oppose treatments but rather to help the clinician and especially the primary care doctor who has the opportunity of making a major difference by the correct choice of treatment and investigations.

The medical arguments

There are several reasons to choose PPI long term strategy

PPI therapy is indeed a simple and quick way of bringing about symptom relief

for typical heartburn. When the patient presents with typical symptoms such as heartburn and/or regurgitation, the diagnosis does not require complex or invasive clinical investigation and is further confirmed by PPI efficacy.

Then, continuous PPI maintenance can be considered as an option if the patient relapses after one or several attempts to stop PPI treatment. Maintenance therapy has been shown to be very effective in reducing the relapse rate and maintaining patients in remission, with a nearly normal quality of life for very long time periods.⁷⁻¹¹ For example, in the ProGERD follow-up study, a clinically relevant decrease in HR-QOL scores was reported by only 3–5% of patients.⁷ In the recently published LOTUS study,¹¹⁻¹³ a parallel group comparison of antireflux surgery and esomeprazole maintenance in patients initially responding to a PPI course, the remission rates at the 3 and 5 year follow-up in the medical arm were above 90% and dimensions scores of HR-QOL were close to those of a normal population. Efficacy was approximately the same in patients with or without Barrett's oesophagus and there was no further aggravation of lesions or malignant degeneration.¹³

The role of maintenance PPI therapy in the prevention of complications is also suggested by epidemiological studies showing decreased stricture prevalence during recent decades.¹⁴

There are several reasons to stay on PPI long term therapy

The first and probably most important reason is that PPI therapy, when effective initially, usually remains effective throughout the duration of treatment although this may require dose escalation (eg, from

esomeprazole 20 to 40 mg once daily or 20 mg twice daily) in approximately one out of four patients.¹²

The second issue to consider is safety and tolerability. Indeed as GORD is not a life threatening disorder, the safety issue is crucial. Fortunately, PPIs are among the best tolerated and safe drugs available to date.^{6, 15} This is likely related to their pharmacological mode of action which is targeted very specifically on the gastric parietal cell responsible for gastric acid secretion. Diarrhoea is the most frequent adverse event reported during long term PPI use and one of the most frequent causes of PPI withdrawal. In some cases, diarrhoea is caused by enteric infections. Acid suppression with PPI may increase the incidence of enteric infections by *Campylobacter jejuni*, *Shigella* or *Salmonella* and/or increase the risk of infection recurrence after antibiotic therapy—for example, in patients treated for *Clostridium difficile* infection.^{16–18}

Pneumonia incidence also seems to be slightly increased in PPI users but the clinical relevance of this association is questionable. In fact, all of these risks, even if present, do not impact on decisions concerning the best PPI strategy for the individual GORD patient.

A recently noted concern is the risk of bone fractures.^{19, 20} Indeed, acid is known to play an important role in the absorption of calcium in the small bowel and a modest increase in hip fractures has recently been reported in patients with pernicious anaemia.²¹ In patients under long term PPI therapy, a few retrospective and uncontrolled studies have also suggested a modest increase in bone, especially hip and spine, fractures. However, more prolonged follow-up of large cohorts of patients is necessary before complete conclusions should be drawn.

The risk of increased incidence of neoplasms under PPI therapy has been discussed many times and this debate is certainly not completely closed. However, there is currently no evidence that long term PPI use is a risk factor for the development of gastric carcinoids or enterochromaffin-like cell neoplasms, although long term acid suppression is accompanied by significant histological changes of the gastric mucosa, this reflects the increased gastrin drive induced by a higher gastric pH. Additionally, the risk of oesophageal adenocarcinoma seems to remain the same in PPI treated patients. Note that PPIs have been on the market for almost 30 years and are the most frequently described drugs in western medicine, yet here has been no epidemic of gastrinomas or related malignancies.

Overall, there is no evidence that long term PPI therapy increases mortality compared with the general population.¹⁶ PPI exposure during pregnancy is not associated with increased risk of birth abnormalities.¹⁷

Finally, very few drug–drug interactions have been reported with PPIs, and these compounds have been used safely in different populations, including the elderly or those with cardiac, hepatic or renal insufficiency.

Recent observations have raised concerns that drug–drug interactions with PPIs may decrease the effectiveness of clopidogrel, through a mechanism leading to a reduction of clopidogrel conversion into its active form. However, a recent meta-analysis of the effects of PPIs on cardiovascular events and mortality in patients receiving clopidogrel, including 23 studies,²² concluded an “inconsistent and conflicting nature of reports and recommend considering the potential harms from ulcers and bleeding before deciding to omit PPIs in patients taking clopidogrel”. Recent data are reassuring that there is no measurable clinical effect of the co-prescription of clopidogrel and PPI in relation to cardiovascular events.²³

Last but not least, the cost of antireflux therapy should be considered. This cost should include not only the direct cost of the drug but also a measure of indirect costs related to the disease itself (ie, doctors’ visits and hospital investigations, loss of working days, etc). This cost is difficult to estimate and even more difficult to compare with antireflux surgery because it varies from one country to another depending on the healthcare system. Epstein *et al* showed that antireflux surgery was cost effective in the UK economy in a pragmatic trial comparing antireflux surgery with PPI therapy.²⁴ A previous study in the USA²⁵ did not find surgery more cost effective at 10 years than medical therapy. All of these estimates are sensitive to the cost of complications of surgery which in turn are very dependent on the expertise of centres.

The surgical arguments

Benefits of surgery for patient with previous PPI therapy

Patients who suffer severe symptoms of heartburn and regurgitation are often subject to a global major reduction in the quality of their life. Their first attempts to manage the problem usually involve dietary modifications, avoidance of wine and attempts to alter their environment, such as propping the head of the bed up at night and avoiding stooping. These measures have little real effect on the symptoms of GORD but they have a major effect of reminding the patient that they are suffering and the adjustments themselves make the patient feel worse; unable to enjoy their usual foods, or their glass of wine with a meal, their sleep troubles now affect their partner as well as themselves, they can no longer do their gardening or their house work and their global quality of life drops further.

Often the patient is further advised on conservative measures, reinforcing the mistaken notion that the disease is somehow the patient’s fault. Even though obesity does contribute to the development and maintenance of reflux symptoms, adopting a policy of conservative attempts at weight reduction have no benefits in relation to the symptoms of GORD.^{26, 27} The wider benefits of weight reduction are of course important but the lack of symptom response in reflux may be a

negative drive to maintaining the attempts at weight reduction.

So the approach to therapy requires a holistic approach that deals sufficiently with the underlying major issue—the pathological presence of gastric fluids, usually acid in the oesophagus, and whatever approach is taken the patient must understand the long term implications of GORD.

Reasons to consider an operation

The decision on the need for an operation to control reflux symptoms should come from the patient's desire for symptom control or quality of life issues. A surgical operation for reflux is rarely a necessity but develops out of a patient's dissatisfaction with their current circumstances or treatment. The availability of day case minimal invasive surgery with results that are equivalent to or better than open surgery^{28 29} make this a realistic aspiration for some patients. A common reason is the patient's desire to be off medication. There is a strong psychological benefit to be gained from not having chronic disease and being able to forget the daily requirement for medication.²⁴ For such patients the information made available through the LOTUS trial (comparing effective medical therapy with esomeprazole with laparoscopic antireflux surgery) is very helpful. The LOTUS trial has identified that, on average, the quality of life and long term success of surgery are similar to those of esomeprazole with dose escalation when required. Some patients have minor complications with surgery and very rarely need reoperation. This was balanced in the LOTUS trial by the better quality of heartburn and acid regurgitation control that the operation provided. Although dysphagia is a worry for some after surgery, in the LOTUS trial the 5 year outcomes have shown that dysphagia is rare and usually of mild severity after antireflux surgery.

Another reason for considering surgery is for those patients who have persistent symptoms while on a PPI. At least 10% of patients on once daily dose PPI still suffer persistent heartburn and/or regurgitation. This group are sometimes described as having refractory reflux.³⁰ They are not a uniform group of patients and they fall into a number of clinical patterns. The first group consist of poorly compliant patients, or those having an inappropriate PPI consumption because of poor timing and/or frequency of dosing. This is possibly the largest group and it is the simplest to treat, either by correcting the medical treatment (enforcing compliance, modifying the timing and/or frequency) or if necessary by antireflux surgery.

The second group contains patients whose refractory symptoms are different to their initial symptoms. PPIs often resolve severe heartburn but may fail to reduce volume reflux and regurgitation while stooping or straining. Cough, especially at night, episodes of wakening and choking, and poor sleep pattern are common refractory symptoms that prompt

a patient to seek a surgical opinion. This group of patients may have persistent heartburn and regurgitation because their reflux, although non-acidic, still contains noxious gastric and duodenal juices that are not controlled by acid suppression. Their detection is elusive unless impedance monitoring is performed which can identify weakly acid or non-acidic reflux.³¹ Mainie *et al* showed that for well selected patients with such symptoms, a successful outcome from Nissen fundoplication could be achieved.³²

A third group of patients comprises those whose refractory symptoms are due to an altered sensitivity of perception of a normal amount of acid exposure in the oesophagus. These are sometimes described as acid hypersensitivity, or even functional heartburn. When this can be confidently measured through 24 h pH testing with good symptom association (through Symptom Probability Index or Symptom Association Probability), these patients are considered as being part of the GORD spectrum. Although there is some controversy about the role of surgery in this group, some authors have reported good outcome after antireflux surgery in the circumstance of an acid hypersensitivity.³³

Extra-oesophageal respiratory symptoms such as cough (and occasionally asthma) may also be effectively treated by antireflux surgery when the association with reflux can be established by a careful diagnostic work-up. Mainie *et al* describe a significant number of these patients by their combined use of 24 h impedance and pH monitoring.³⁴ However, there are no controlled studies supporting the efficacy of antireflux surgery in extra-oesophageal manifestations of GORD in general. Therefore, these patients should be carefully informed preoperatively of the uncertainty of symptom resolution with surgical therapy.

Side effects of PPIs are unusual but a number of patients may have persistent diarrhoea with PPIs and for these patients the driving force for surgery is the improvement of this side effect.

Other indications for surgery include dysphagia or respiratory symptoms that are attributable to the presence of a large hiatal hernia or sometimes from a gastric volvulus where a para-oesophageal hernia has become a total herniation of the stomach into the chest. Although these entities do not belong to GORD, these patients are frequently on PPI therapy but their regurgitation (which is related to oesophageal outflow obstruction) and their dysphagia is not improved by medication. If these patients are fit enough, they do very well with antireflux surgery.

Special patients

Adults and children with cystic fibrosis where reflux aggravates the lung injury already present by the pathophysiology of cystic fibrosis gain great protection by antireflux surgery, as well as good control of the heartburn and regurgitation symptoms.³⁵ A

similar situation is in lung transplant patients, usually children, to protect the new lungs.³⁶ Also, children with a large hiatal hernia associated with recurrent aspiration pneumonia, often part of a more complex scenario of congenital or inherited disease, do very well both from the point of view of their lung function as well as their nutrition.

In morbid obesity, although antireflux surgery may improve symptoms of GORD, the holistic improvement achieved with bariatric techniques of gastrojejunal bypass, excluding the majority of the stomach from the oesophagus, provides a complete reflux control in the context of the other benefits of marked weight reduction. For patients with moderate obesity (body mass index >35 but <40), Anvari *et al* showed good outcomes for Nissen fundoplication with both symptom control and a moderate degree of weight loss.³⁷ For patients with a body mass index >40, gastrojejunal bypass is the preferable route but requires great patient cooperation.³⁸ On the other hand, some bariatric surgery, such as balloons or bands, can actually provoke or aggravate reflux and should be avoided in overweight patients where reflux symptoms are already a problem.

Benefits of being considered for surgery

More specific testing with endoscopy and manometry and pH monitoring is an advantage to patients whose persistent symptoms may be due to other disease. It is essential to confirm reflux before subjecting a patient to an operation and this should avoid the errors in management of achalasia or eosinophilic oesophagitis.³⁹ Additionally, the tests may exclude reflux as the cause of symptoms and direct treatment.

Disadvantages of antireflux surgery

Dysphagia, early after operation, is common but usually resolves within 3 months. Late dysphagia (5%) may require a dilatation or rarely revisional surgery. Early satiety, weight loss and discomfort with large meals may be a benefit or a problem. Associated weight loss after a Nissen fundoplication is often reversed after 6 months but may facilitate improved lifestyle and activity. Hiccup, difficulty burping or vomiting are transient usually but occasionally troublesome. Feelings of trapped wind, bloatedness and passing increased rectal flatus are common, but when measured, these were common in both medically and surgically treated patients, although more common after surgery.¹¹

Recurrence of heartburn and regurgitation is relatively rare but can occur in 10% of patients at 5–10 years postoperatively. Such a relatively high rate may be improved by following a standardised procedure such as that achieved by 40 surgeons across Europe who contributed to the LOTUS trial.¹³ The quality of surgery is very important when considering an operation and this should be restricted to units with experience and high volume throughput. Revisional

Table 1 Potential advantages and disadvantages of medical therapy and antireflux surgery in the management of chronic gastro-oesophageal reflux disease

Medical
Advantages
Non-invasive
Simple and easy to use
Reproducible effect
Very effective on symptoms and lesions of GORD
Excellent tolerance and safety profile of PPIs
Relatively cheap especially since the development of PPI generics
Disadvantages
Does not correct the underlying pathophysiological mechanisms
Continuous maintenance therapy frequently required to control the disease
Persistence of symptoms in at least 10% of patients
Rare side effects and potential drug–drug interferences
Surgery
Advantages
The only treatment capable of physically controlling reflux
Very effective (improved quality of heartburn control, reduction of regurgitation, better sleep pattern, increased range of physical activities and exercise, etc)
Avoids the need to take medication
Psychological effects of not having chronic disease
Particular clinical groups of cystic fibrosis, lung transplant and congenital hernia
Disadvantages
Still a (minimally) invasive method
Risk of mortality not nil especially in community practice
Rare but potentially severe postoperative complications
Risk of dysphagia and postoperative complaints
Risk of long term recurrence

GORD, gastro-oesophageal reflux disease; PPI, proton pump inhibitor.

surgery may variably be needed (2–5%) but is often effective when indicated.⁴⁰

Issues where there is simply no evidence

Cancer risk in GORD

This is often a major worry, especially when patients have been labelled as having the premalignant condition of Barrett's oesophagus. There are no clear data on the effects of treatment, either medical or surgical, on the development of cancer.⁴¹ For patients with Barrett's oesophagus, the decisions on medical or surgical treatments should follow the same guidelines as those without Barrett's. For cancer protection, we must await studies such as the Aspect trial in the UK where very high dose or low dose esomeprazole is being compared, with and without the addition of aspirin.⁴²

Conclusions

- In our view, the question is not about one treatment being better than another but offering a patient the treatment most appropriate to their needs. Information is crucial. Both treatments have

advantages and disadvantages (table 1). Some important recommendations should be kept in mind when considering the long term therapeutic strategy in GORD.

- For patients where medication is effective, ensure the patient receives the right dose of the right drug and maintain it to ensure symptoms of this chronic disease are controlled in the long term.
- For patients where surgery is an option, ensure the right surgeon performs a standardised operation for the right indications in the right patient and provides good preoperative education and testing and postoperative support.
- When a patient is refractory to medical treatment, reconsider the diagnosis of GORD before switching to surgery. Always discuss the responsibility of GORD or other causes if symptoms persist, especially if extra-digestive manifestations are concerned.

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