

Gastroesophageal reflux disease after esophagectomy—a narrative review

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Background and Objectives: Esophagectomy and subsequent gastrointestinal tract reconstruction provide treatment for both benign and malignant diseases. It can be performed by open and minimally invasive esophagectomy (MIE) techniques with either trans-thoracic (TT) or trans-hiatal (TH) approaches. Regarding the intrinsic differences of each procedure, some postoperative complications are highly common in all types of esophagectomy. Gastroesophageal reflux disease (GERD) is one of the most common postoperative complications of esophageal resection. This review aims to discuss reflux after esophagectomy and its correlation to the surgical technique adopted, the pathophysiological mechanisms involved, its clinical impact, as well as the strategies for diagnosis, preventing measures and clinical or surgical treatment options.

Methods: The authors performed a narrative review evaluating the reflux after esophagectomy.

Key Content and Findings: The causes for its occurrence are multifactorial, including loss of anti-reflux mechanisms and other hypothetical mechanisms. There is no consensus regarding the diagnostic methods and when to start the reflux investigation after esophagectomy. Nevertheless, the initial assessment should be performed with endoscopy. Further diagnostic evaluation with pH-metry or impedance monitoring is not routinely indicated, given the absence of standardization of the positioning of the pH-metry catheter. In order to avoid its occurrence, both intraoperative and postoperative measures should be adopted to mitigate the risks of postoperative gastroesophageal reflux. Understanding risk factors and aspects of surgical technique may decrease the impact of this complication. This review discusses reflux after esophagectomy and its correlation to the surgical technique adopted, the pathophysiological mechanisms involved, its clinical impact, the strategies for investigating this condition, and the measures to prevent and treat it.

Conclusions: Gastroesophageal reflux after esophagectomy is a common complication, demanding complex management. Understanding the pathophysiological mechanisms, the clinical impact, its diagnosis and prevention and treatment options may help reduce its morbidity.

Keywords: Esophagectomy; gastro-oesophageal reflux disease; postoperative complications

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Introduction

Esophagectomy with gastrointestinal tract reconstruction provides treatment for esophageal cancers (1), mainly squamous cell carcinoma and adenocarcinoma, and benign conditions, such as achalasia (2) and stenosis (3).

Esophagectomy is a complex and demanding procedure. Despite surgical technique and perioperative care improvements over the years, the morbidity and complication rates remain high (1-4). The overall morbidity rate reaches up to 59% and comprises anastomotic leak, wound infection, pneumonia, respiratory failure, heart attack or stroke, and blood clots, among others (5). Besides, more than half of the patients will present chronic gastrointestinal disorders or symptoms after esophagectomy (6). Reflux (39%), dysphagia (37%), dumping syndrome (21.4%), and anastomotic stricture (16%) are some of the most common issues (7). These complications impact the quality of life, promote weight loss, malnutrition, Barrett's metaplasia, and even cancer (8,9).

Reflux is probably the most common long-term disorder after esophagectomy. This condition may remain silent and, despite its clinical relevance, there is no consensus on its management. This review aims to discuss reflux after esophagectomy and its pathophysiological mechanisms, its clinical impact, the strategies for investigating this condition, and the measures to prevent and treat it. We present this article in accordance with the Narrative Review reporting checklist (available at <https://dmr.amegroups.com/article/view/10.21037/dmr-23-8/rc>).

Methods

This is a narrative review evaluating the reflux after esophagectomy and its pathophysiological mechanisms, its clinical impact, the strategies for investigating, and measures to prevent and treat it. A search was done by filtering the keywords "Esophagectomy", "gastroesophageal reflux disease"/"GERD", "Esophagectomy", and "postoperative complications"/"postoperative issues" on the databases PubMed, Embase, Lilacs/BVS, Cochrane Central, and Google Scholar (Table 1).

Results

The surgical technique in esophagectomy

Esophagectomy options include open and minimally invasive esophagectomy (MIE) techniques with either

trans-thoracic (TT) or trans-hiatal (TH) approaches. The TH approaches consist of a blunt dissection of the thoracic esophagus and the formation of a cervical esophagogastric anastomosis through a left cervical incision (10).

The TT or Ivor Lewis approach replaces blunt thoracic esophageal dissection with a thoracotomy with the formation of the esophagogastric anastomosis at the thoracic space (10).

The level of the anastomosis is correlated to incidence of gastroesophageal reflux disease (GERD) as demonstrated by Sakai *et al.* In their study (11), the reflux was statistically more severe in those with a lower relative level of anastomosis.

Therefore, reflux is significantly higher in patients with intrathoracic anastomosis than in those with neck anastomosis. This may be explained by the negative intrathoracic pressure that creates a pressure gradient between the abdomen and thorax (11).

Traditionally, esophagectomy includes the division of the vagal nerves and surgical alteration of the stomach. The vagal-sparing technique preserves the vagal nerves and gastric reservoir, maintaining gastric secretory, motor and reservoir function (12).

It involves stripping the esophagus out of the mediastinum and inverting it. This results in shearing the nerve fibers off the muscularis propria, leaving the esophageal plexus intact (12).

As a result, patients have normal alimentation postoperatively, as well as bowel regulation and no weight loss (12). The ability to maintain a normal meal capacity that empties properly minimizes the occurrence of reflux.

Moreover, Luyer and colleagues (13) conducted a study in rats in which vagotomy was shown to increase bacterial translocation across the intestines. This may explain the decrease in post-operative infections found when compared to the vagotomy procedure.

An important surgical step is the re-establishment of gastrointestinal continuity by replacing the esophagus with a new conduit. The stomach is the election of many surgeons, given its sufficient length, predictable vascular supply and requirement of only a single anastomosis (14).

However, there are many scenarios when the stomach is unavailable to use, such as caustic ingestions in which both the esophagus and the stomach are critically injured, prior gastrectomy and previous abdominal surgery with compromising of the right gastroepiploic artery, as well as the gastric extension of distal esophageal tumors. In these circumstances, the colonic and jejunal interpositions should be considered.

Table 1 The search strategy summary

Items	Specification
Date of search	June 24, 2023
Databases and other sources searched	PubMed, Embase, Lilacs/BVS, Cochrane Central, and Google Scholar
Search terms used	“Esophagectomy”, “gastroesophageal reflux disease”/“GERD”, “Esophagectomy”, and “postoperative complications”/“postoperative issues”
Timeframe	Studies from 1990 to 2023
Inclusion and exclusion criteria	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Human and pre-clinical studies • Studies that evaluate reflux after esophagectomy • Language restrictions: English, Portuguese, and Spanish <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Full text unavailable
Selection process	The process was conducted independently by two authors (ENL, ITDL)

In a recent literature review comparing the two alternative conduits, Bakshi *et al.* (14) made some important considerations. In regards of colonic interposition, the benefits include its similar length of the native esophagus, as well as its resistance to acid, and, for the right colon mobilization, the presence of the valve of Bauhin may further decrease reflux. Disadvantages include the development of disassortative diarrhea and redundancy of the conduit due to its lengthening over time.

Alternatively, the use of jejunum is supported because it has a reliable blood supply, which is clearly enhanced at the level of the anastomosis with Longmire’s supercharging technique. The significant amount of redundant jejunum and its intrinsic peristalsis are also favorable features.

The disadvantages of jejunum conduits include the need for microvascular anastomosis, which increases operating time and technical complexity. In some patients, jejunal conduits may not be long enough to reach the hypopharynx, and fatty mesentery may also inhibit the surgeon’s ability to pull the conduit (15).

The mechanisms for reflux after esophagectomy

The reflux after esophagectomy seems to reach its peak approximately two months after the surgery, and the degree of severity decreases after six months (16).

Gastroesophageal reflux can be explained by the compromise of physiological antireflux mechanisms (17). The resection of the lower esophageal sphincter (LES) and

angle of His, as well as the disruption of the diaphragmatic sling, annul the main antireflux mechanisms that are present in normal patients. Besides, the positioning of the stomach within the chest cavity is another driving factor for reflux (17). The natural negative intrathoracic pressure from the pleural space and the intra-abdominal positive pressure creates a gradient pressure that promotes gastroesophageal reflux (17). *Figure 1* schematizes the main factors associated with gastroesophageal reflux after esophagectomy.

Esophagectomy is a complex procedure, rousing intense serum inflammatory cytokines in patients that are already under a baseline inflammatory status due to cancer (18). Conventional postoperative management after esophagectomy often involves routine admission to intensive care units, and some patients are left intubated and ventilated for extended periods (19). All these factors enhance the surgical stress, which usually increases gastric acid production and may be relevant to the onset of reflux in the postoperative course.

Other factors have been investigated for the development of reflux after esophagectomy. Hasan *et al.* (20) recently demonstrated that the gastric conduit length, which can be influenced by patient height, may be a predictor of worse patient-reported reflux symptoms. This would explain why women, generally shorter in height than men, report more symptoms of reflux than male in several studies. This finding indicates, perhaps, that the esophageal conduit should be constructed to tailor the patient biotype, particularly aiming to create a larger conduit for female

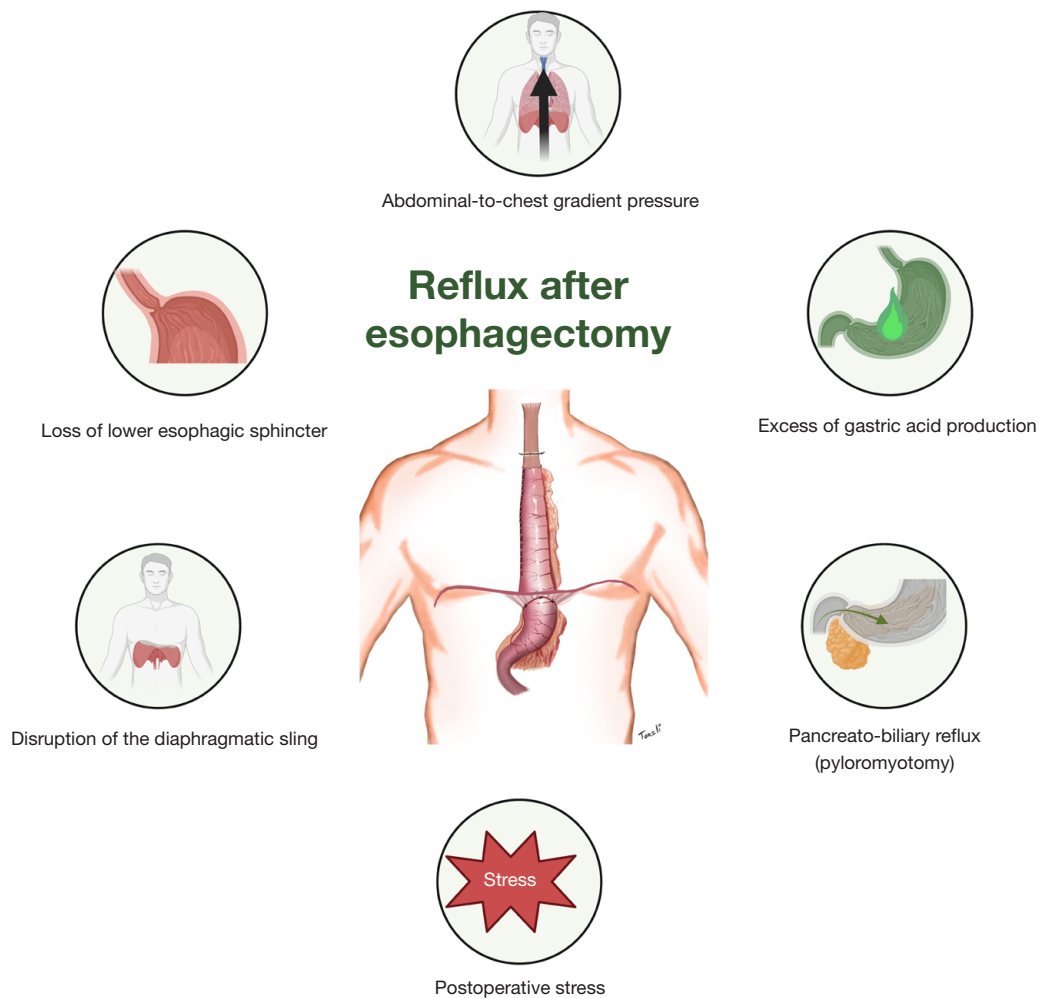


Figure 1 Main mechanisms for the development of reflux after esophagectomy. Author's personal file.

patients (20).

Both *in vitro* and *in vivo* studies suggest a synergistic influence of gastric acid and bile in the pathogenesis of Barrett's metaplasia after esophagectomy (8). Dresner *et al.* (8) found that the median time to the first detection of columnar mucosa was as short as 14 months after surgery, which is consistent with the theory that a segment of Barrett's esophagus develops rapidly with little subsequent change. Their study also reported that increased acid exposure appears to be associated with longer segments of columnar mucosa, which, in turn, exhibit a higher incidence of intestinal metaplasia. It is, therefore, possible that ongoing reflux may alter the length as well as the phenotype of Barrett's mucosa (8).

In a 10-year follow-up study of 101 patients submitted to esophagectomy and cervical gastroplasty due to achalasia, an

increasing incidence of esophagitis and Barrett's esophagus in the esophageal cervical stump was observed over time (21). Cases of squamous cell carcinoma and adenocarcinoma in the esophageal remnant were also reported.

The impact of reflux after esophagectomy

The most common long-term persistent symptoms are gastroesophageal reflux, dumping syndrome, delayed gastric emptying, and dysphagia (22). Fortunately, it is noticed that the symptoms tend to improve six months after the operation (22) and that, despite such symptoms, the quality of life judged by the patients themselves remains similar to how it was previously (6). De Boer *et al.* (6) have studied the impact on the quality of life of long-term survivors (2 years) following esophageal resection for cancer and concluded

that although some residual symptoms may persist, the general quality of life is similar to other healthy individuals of the same age.

It is noteworthy here that most esophagectomies are performed to treat some diseases that, as a basis, already cause symptoms such as heartburn, regurgitation, and, among other symptoms, cause a loss of quality of life. Therefore, postoperative gastroesophageal reflux is frequently not perceived as disabling compared to the preoperative period.

Investigating the reflux after esophagectomy

There is no consensus regarding the diagnostic methods and when to start the reflux investigation after esophagectomy. Nevertheless, the initial assessment should be performed with endoscopy. It allows both macroscopic and histologic assessment. Barrett's metaplasia, stump esophagitis, and even adenocarcinoma could be diagnosed.

Further diagnostic evaluation with pH-metry or impedance monitoring is not routinely indicated. The lack of standardization of the positioning of the pH-metry catheter limits its routine use. In normal individuals, the placement occurs right above the inferior esophageal sphincter, which is absent after esophagectomy (23).

However, a standardized assessment of symptoms is recommended. In this regard, the GERD-health-related quality of life (GERD-HRQL) score, according to Velanovich, and the HRQL questionnaires published by the European Organization for Research and Treatment of Cancer (EORTC) have proven their clinical benefit (24).

Measures to prevent reflux during esophagectomy

Recent studies aimed to determine strategies to prevent reflux symptoms following esophagectomy, analyzing technical and postoperative clinical factors that may influence the occurrence and severity of reflux.

Considering the surgical techniques modifications proposed, a high esophagogastronomy anastomosis (cranial to the azygos vein) should be preferred, as it was found that the lower the anastomosis, the worse becomes the severity of reflux esophagitis (25). The esophageal conduit should be constructed to tailor to the patient's biotype, particularly aiming to create a longer conduit for female patients.

There is no consensus regarding pyloroplasty in esophagectomy. The procedure may facilitate gastric emptying and reduce reflux. However, pyloroplasty may

facilitate duodenal and bile reflux into the esophagus (7).

The confection of antireflux anastomosis has also been proposed and may help in avoiding reflux symptoms and also help protect against anastomotic leaks (26). It is based on Nissen's modified fundoplication, adding it to the conventional anastomosis in esophagectomies. For the modified Nissen fundoplication, the anastomosis is shaped on the anterior wall of the stomach, which is a position 3 to 4 cm below the apex of the gastric tube and near the greater curvature of the gastric tube. After conventional anastomosis, the apex of the gastric tube is drawn to the left side of the remnant esophagus. This is placed so that the gastric tube extends beyond the two sides of the remnant esophagus (26).

Treatment of reflux after esophagectomy

Both Cho and Donington recommend lifestyle changes and recommend continuous use of proton pump inhibitors (PPI) (7,25). Patients should be instructed to eat six small meals daily and remain upright for as long as possible after eating.

Despite poor evidence, PPI therapy should be administered prophylactically early after esophagectomy to relieve and prevent reflux-related symptoms and complications (27). Okuyama and colleagues reported relief in 81% of their patients regularly receiving the therapy (27).

Proton-pump inhibitors are also important to help prevent Barrett's metaplasia in the esophageal remnant. Treating Barrett or even adenocarcinoma in the esophageal remnant is complex, and the management should be multidisciplinary and individualized (28).

Ultimately, there are patients with severe and persistent GERD even after optimized clinical therapy. In these cases, surgical strategies should be considered.

Simon *et al.* (29) published a recent cohort that studied the Roux-en-Y loop with total duodenal diversion for treating resistant reflux after esophagectomy with gastric pull-up. The authors evaluated nine patients with severe symptoms, with no response to medical therapy. They concluded it to be a safe technique that resulted in regression of symptoms in the majority of patients and improvement of quality of life.

Recently, the use of the magnetic sphincter augmentation (MSA) device for the laparoscopic treatment of GERD has been studied for typical reflux symptoms, reducing the use of proton-pump inhibitors and decreasing esophageal acid exposure (30). It consists of a series of titanium beads interlinked that form a dynamic implant placed around

the esophagus in order to augment the LES. This allows for expansion to accommodate a swallowed bolus or the escape of elevated gastric pressure associated with belching or vomiting (30). However, currently, there is no study for MSA after esophageal resection. Theoretically, MSA could be valid for patients that underwent partial esophagectomy with preservation of the LES (31,32).

Discussion

Postoperative reflux is a common complication with a complex therapeutic approach. It is important for specialists to closely monitor patients after an esophagectomy for the development of reflux and to take appropriate steps to manage and treat it. An early diagnosis and a healthy lifestyle may mitigate symptoms and complications related to reflux.

Regarding the procedure, an election of some surgical techniques, if feasible, may help prevent this complication. That includes the mobilization of the colon for the alternative conduit, given the presence of the valve of Bauhin, and the confection of an anti-reflux anastomosis.

Nowadays, there is still a lack of consensus about the recommendations and standardizations for gastroesophageal reflux after esophagectomy. There is still a deep gap in medical literature for developing high-quality, evidence-based guidelines. Randomized studies comparing different surgical techniques regarding reflux mechanisms, different treatment modalities, and standardized diagnosis approaches are needed for a greater level of evidence.

Conclusions

Gastroesophageal reflux after esophagectomy is a common complication, demanding complex management. Understanding the pathophysiological mechanisms, the clinical impact, the strategies for investigating this condition, and the measures to prevent and treat reflux after esophagectomy may help clinicians construct rationality for its management.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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