Chapter 12
Gastroesophageal Reflux and Aspiration in Chronic Lung Allograft Dysfunction and Bronchiolitis Obliterans Syndrome: Detection and Treatment

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Abstract The role of gastroesophageal reflux (GER) as a risk factor in chronic lung allograft dysfunction (CLAD) and/or bronchiolitis obliterans syndrome (BOS) is strongly supported by the cumulative evidence collected to date. Proximal gastrointestinal tract motility studies and pH/impedance testing can be used to diagnose motility abnormalities and GER and to determine whether reflux is acid or nonacid. However, a true gold standard methodology for detecting penetrance of refluxed duodeno-gastric secretions into the lung is lacking, and a definitive marker of GER combined with microaspiration that identifies patients at significant risk for associated allograft injury and dysfunction needs to be determined. Prospective, multicenter, adequately powered clinical trials should be performed to better understand the role of GER in CLAD and to identify appropriate criteria for patient selection for possible surgical correction of GER.

Keywords Lung transplantation • Gastroesophageal reflux • Nonacid reflux • Chronic lung allograft dysfunction • Bronchiolitis obliterans syndrome

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Introduction

Over the last 3 decades, lung transplantation has become an accepted therapeutic option for patients with end-stage lung disease. A major limitation to long-term survival after lung transplantation is the development of chronic lung allograft dysfunction (CLAD), which is largely due to obliterative bronchiolitis (OB), a process of fibrous obliteration of the small airways that leads to progressive airflow obstruction. The clinical correlate of OB, bronchiolitis obliterans syndrome (BOS), is defined as persistent drop in FEV_1 to <80 % of a defined FEV_1 baseline of the mean of the two best FEV_1 values taken at least 3 weeks apart following transplantation. Alloimmune-mediated injury directed against endothelial and epithelial structures has been thought to be the underlying cause of OB. However, non-alloimmune inflammation including viral infections or ischemic injury also appears to play a role in its pathogenesis [1]. Retrograde aspiration secondary to gastroesophageal reflux (GER) has been implicated as a potential contributor to lung allograft dysfunction and, in particular, to development of CLAD and BOS [2–12]. Two forms of OB have been identified in the transplanted lung: (1) a relatively acellular, concentric fibrosing process limited to the terminal bronchioles, and (2) a focal cellular process extending into the distal alveolar spaces that is associated with aspirated material and foreign body-type giant cells [13]. The latter pathological finding is supportive of a role for GER in the development of BOS.

Pathophysiology of GER and Lung Disease

The potential of GER to cause pulmonary complications is underappreciated, although it has been recognized for a long time [14–20]. William Osler first described the relationship between asthma and GER in 1892 [14]. GER can affect the lungs via an esophago-tracheo-bronchial vagal reflex that can be associated with chronic cough and asthma, and GER with micro- or macro-aspiration has been linked to laryngitis, pneumonia, lung abscess, fibrosis, acute and chronic bronchitis and bronchiectasis.

The pathophysiology of gastro-esophageal reflux disease (GERD) is determined by a combination of factors that include decreased salivation, impaired esophageal clearance of refluxed secretions, impaired tissue resistance to potentially injurious components of refluxate, decreased resting tone of the lower esophageal sphincter (LES), the presence of hiatus hernia with a deranged anatomical relationship between the diaphragmatic hiatus and the LES, transient LES relaxations, and delayed gastric emptying. The role of the resting tone of the LES in GER is promoted by (1) increased gastric volume (e.g., large meals or increased gastric secretions) or (2) increased intra-abdominal pressure, which can be tonic (e.g., obesity, ascites, tight clothing, slouching posture) or phasic (e.g., contraction of the stomach, contraction of somatic muscles, cough, sneeze, wheeze, and strain). The LES tone is reduced or augmented by a number of substances, as given in Table 12.1.

Table 12.1 Modulators of lower esophageal sphincter (LES) tone

Agent	Decrease LES tone	Increase LES tone
Hormones	Secretin	Gastrin
	Cholecystokinin	Motilin
	Glucagon	Substance P
	Gastric inhibitory polypeptide (GIP)	
	Vasoactive intestinal peptide (VIP)	
	Progesterone	
Neuroactive agents	Alpha-adrenergic antagonists	Alpha-adrenergic agonists
	Beta-adrenergic agonists	Beta-adrenergic antagonists
	Cholinergic antagonists	Cholinergic agonists
	Serotonin	
Medications	Nitrates	Metoclopramide
	Calcium channel blockers	Domperidone
	Theophylline	Prostaglandin F
	Morphine	Cisapride
	Meperidine	
	Diazepam	
	Barbiturates	
Foods	Fat	Proteins
	Chocolate	
	Ethanol	
	Peppermint	

Transient LES relaxations are prolonged in time and not induced by swallowing, but LES relaxations can be triggered by distension of the gastric fundus and are considered the primary mechanism of non-pathologic reflux in healthy individuals as well as in patients who develop GERD. Delayed gastric emptying, which consequently causes distention of the gastric fundus, has been identified as a potent stimulus for transient LES relaxations [21, 22].

The anatomical relationship between the LES and the diaphragmatic hiatus is of importance to maintain the synergistic effect of the intrinsic LES tone and the extrinsic LES component that is provided by the diaphragmatic hiatus [23]. The importance of this anatomic relationship is well documented in the context of hiatus hernia complicated by esophageal shortening [24]. In severely advanced, end-stage lung disease, whether obstructive (as in advanced emphysema and cystic fibrosis, which are characterized by flattened or concave diaphragms) or restrictive (as in pulmonary fibrosis with severe cupping of the diaphragm) the anatomical relationship between the diaphragmatic hiatus (the extrinsic LES) and the intrinsic LES is likely stressed. The synergistic relationship between the intrinsic and extrinsic mechanisms is possibly less efficient in pulmonary fibrosis, which may especially be the case when intra-abdominal pressures change during the respiratory phases, cough, sneeze, wheeze, and strain.

The upper esophageal sphincter (UES) has no baseline tone during sleep and lacks the reflex capability to augment pressure in response to reflux; therefore, retrograde micro- or macro-aspirations are facilitated in the context of proximal GER [25]. Interestingly, impedance pH testing in normal individuals showed episodes of reflux that can be either distal or proximal, and the vast majority of such episodes are acid in the distal esophagus and nonacid when they reach the proximal esophagus [26].

GER has been shown to be prevalent in patients with a variety of lung diseases that include asthma, cystic fibrosis, idiopathic pulmonary fibrosis (IPF), and chronic obstructive pulmonary disease (COPD), and it has also been associated with the development of bronchiolitis obliterans organizing pneumonia (BOOP) a term that has been superseded by organizing pneumonia (OP) [27–37]. In a prospective study of consecutive lung transplant candidates, the LES tone was reduced in over 70 % of patient with end-stage COPD or advanced CF-associated lung disease, and in 54 % of patients with end-stage interstitial lung disease (ILD). Esophageal peristalsis may also be reduced, thus impairing esophageal clearance, as seen in 20–30 % of all end-stage lung disease patients [38]. Similar findings have been reported in other retrospective studies [39], and delayed gastric emptying has been observed in over 40 % of lung transplant candidates [38].

Proximal and distal esophagus 24-h pH testing in patients with end-stage lung disease who are candidates for lung transplantation showed that distal esophageal acid reflux (DeMeester score) was abnormal in 20 % of patients with COPD, 60 % with CF, and 32 % with ILD. Additionally, and likely more importantly, abnormal proximal esophageal acid exposure during the supine portion of the 24-h pH monitoring period was noted in 30 % of patients with COPD, 40 % with CF, and 16 % with IPF [38].

Lung defense mechanisms, including cough reflexes and mucociliary clearance, are markedly impaired in lung transplant recipients, and mucociliary clearance has been measured at less than 15 % of normal clearance time in transplanted lungs [2–7]. It is also conceivable that a prolonged contact time of aspirated gastric contents with respiratory mucosae may lead to substantially greater lung parenchymal injury. While GER may cause direct lung injury, it is also possible that it may alter innate immune responses and augment alloimmune responses by creating an upregulated local inflammatory environment.

Diagnosis of GER in Lung Transplantation

Based on the assumption that acid reflux might be an important cause of CLAD and BOS, lung transplant patients commonly receive proton pump inhibitor (PPI) therapy. This pharmacologic therapy suppress gastric acid secretion and changes the pH of the refluxate from acid to nonacid, which may alleviate the classic GER-related symptoms from prolonged exposure of the esophageal mucosa to acid reflux, but it does not appear to reduce the quantity and or the frequency of reflux episodes. This has been demonstrated by studying GER using impedance pH monitoring with

patients both on and off PPI medication [40]. Indeed, it is now well recognized that gastric secretions can still gain access to the esophagus and that such refluxate may not be acidic enough to be detected by pH monitoring such that symptoms classically associated with reflux are not evoked. Combined impedance and pH monitoring allow the detection of both acid and nonacid reflux and can determine the proximal extent to which refluxed secretions penetrate into the esophagus [41].

It should be noted that classic GER symptoms are absent in 57–94 % of patients with laryngeal manifestations of GER, in 43–73 % of patients with GER-related chronic cough, and in 40–60 % of patients with GER-related asthma [42, 43]. Moreover, a substantial number of lung transplant recipients have been found to be asymptomatic when abnormal GER is objectively documented [44–46].

Several methods have been studied that can document the relationship between lung disease and GER. These include scintigraphic monitoring, 24-h esophageal pH testing, assays for pepsin in saliva and sputum, and detection of lipid-laden macrophages, pepsin, or bile acids in bronchoalveolar lavage (BAL) [47–55]. Of note Hartwig et al. documented that chronic aspiration of acid gastric fluid accelerates the development of pulmonary allograft dysfunction in a rat model of lung transplantation [56]. The injurious agent may be gastric acid or other components of the gastroduodenal juices (bile, pepsin, trypsin, and others) rather than the acid reflux per se. In fact, chronic silent aspiration of acidic secretions alone may not be as injurious [57, 58] as aspiration of other components of the duodenal and gastric juice refluxate such as pepsin, trypsin, and bile acids. It should be noted that the bronchoalveolar environment has a pH that favors the activity of the duodeno-pancreatic agents rather than just the acidic gastric juice. Additionally, what has been considered standard pH testing does not test for the presence of alkaline ($pH > 7$) or weakly acid ($4 < pH < 7$) refluxate [59]. Multichannel intraluminal pH-impedance monitoring (in contrast to pH monitoring alone) allows monitoring of reflux episodes that are nonacid in quality, and such monitoring can discriminate between fluid and gas reflux regardless of pH, estimate the size of a refluxed secretion bolus and measure the proximal extent of GER into the esophagus while differentiating acid from nonacid reflux [41, 60–62]. This methodology is likely the best tool to investigate for significant GER in the context of lung transplantation. To date, however, the only apparatus with acceptable sensitivity for detecting the presence of duodeno-gastroesophageal refluxate remains the Bilitec 2000 (Medtronic); this spectrophotometric testing probe, which is calibrated for the detection of bilirubin, has not been widely adopted clinically due to its limited specificity, and it remains predominantly a clinical research tool [63].

GER and Chronic Lung Allograft Dysfunction

Retrospective studies with standard single-channel distal esophageal pH recordings have indicated an increased esophageal acid exposure in up to 70 % of lung transplant recipients [64, 65]. The prevalence and severity of GER following lung transplantation was found to be increased [64, 66], and the detection of GER is associated

with worse pulmonary function test results. Therefore, it has been advocated that all lung transplant recipients should be screened for GER [64]. At the time of this study, 60 % of patients had BOS and 77 % of those patients who had developed BOS had abnormal esophageal pH testing as compared with 58 % of patients who had not developed BOS [64]. The frequency and severity of reflux, especially the upright contact time, was associated with the presence chronic allograft dysfunction [64]. The Toronto group reported [67] a prospective study that used 2-channel esophageal pH monitoring (proximal 5 cm below UES, and distal 5 cm above LES, implemented according to standard criteria) and showed that 30 % of lung transplant candidates (66/218 patients) had elevated distal esophageal pH findings (high DeMeester score), and proximal esophageal pH testing was abnormal in 19 % (41/218 patients) [67]. pH testing was also prospectively performed in the same patients at 3 and 12 months post-transplant, and DeMeester scores were observed in 35 % (16/46 patients) and 31 % (10/32 patients) at the two time points, respectively. Interestingly 64 % of patients with a high DeMeester score before transplant had normal testing at 3 months, but 34 % of patients with normal pre-transplant DeMeester scores had newly detected distal esophageal acid reflux at 3 months post-transplant. Similarly, 77 % of patients with abnormal proximal esophageal acid exposure before transplant had normal testing 3 months after transplantation, and similar findings were noted when comparing pre-transplant test results to those at 12 months post-transplant. Of particular interest is the observation that when results of testing at 3 months were compared to test results at 12 months post-transplant, the DeMeester score normalized in 36 %, but acid reflux was newly diagnosed in 30 %. In addition, abnormal proximal pH testing, if detected at 3 months, was found to be normal in 100 % esophageal acid reflux was noted in 15 % [67]. Therefore, simple acid ($pH < 4$) detection by esophageal pH testing only could either overestimate or underestimate the true role of GER in the development of CLAD and BOS. These findings suggest that acid pH testing is likely not the most appropriate way to investigate GER and retrograde aspiration or to guide treatment post-transplant.

GER and retrograde aspiration are promoted by gastroparesis via the stimulation of inappropriate transient LES relaxations. Gastroparesis is a common disorder in lung transplant recipients and has been linked to the induction of BOS [10, 68, 69]. Gastroparesis has been attributed to preexisting lung disease [38, 70–74], vagal nerve injury or other intra-operative damage, or medications (especially calcineurin inhibitors) [75, 76]. In addition, the presence of other conditions, including weight loss [70], acute stress, diabetes mellitus, and uremia, may worsen gastroparesis before or after transplantation [77, 78]. Of note, the American Gastroenterology Association has included lung and heart-lung transplantation as one of the causes of delayed gastric emptying [79].

Gastric dysmotility after heart-lung transplantation has been shown to be present in nearly one-third of recipients [4]. In another study, one-third of patients with post-transplant GER had delayed gastric emptying, and 13 % had incomplete relaxation of the LES [80]. Similar findings were reported in a prospective study wherein 36 % of patients had abnormal liquid emptying at 3 months and 71 % at 12 months post-transplant [10–12]. Prolonged gastric emptying for solids was observed in

91 % of patients at 3 months after transplantation, and 80 % still had prolonged gastric emptying at 12 months [10–12].

In the context of delayed gastric emptying and considering that higher levels of bile acids are found in the stomach during the night [81], the likelihood of having nocturnal nonacid reflux is high when patients are given PPI therapy. Aspiration of nonacid gastric components during the night is facilitated by reduced protective reflexes (e.g., swallowing and coughing) [82]. Such factors might explain the association between nocturnal weakly acidic reflux and bile acid aspiration [83].

Acid and nonacid reflux may affect the allograft via two different mechanisms. Aspiration of refluxed acidic gastric juice may provoke lung inflammation, but patients treated with acid-suppression therapy (PPI) may aspirate nonacid refluxate that contains active pancreatic enzymes and bacterial substances such as lipopolysaccharides, which can also trigger significant bronchial inflammatory reaction [84].

Recently it has been demonstrated that 48 % of lung transplant patients have reflux at 1 year post-transplant, and nearly one-third of these patients exclusively had nonacid reflux as detected by pH/impedance testing [83]. Moreover, the presence of nonacid reflux as measured by pH/impedance testing increased the risk for developing BOS nearly threefold, while risk was not significantly associated with the presence of acid reflux [85]. Although abnormal acid GER can be detected via esophageal pH probe monitoring and nonacid reflux can be detected via pH/impedance monitoring, the detection of abnormal GER does not objectively identify microaspiration of refluxed gastroduodenal secretions, and a mild degree of GER can be observed in normal subjects and considered normal.

Single-center studies have used the detection of constituents of gastric juice (pepsin and bile acids) in BAL fluid of transplant recipients as a biomarker for retrograde aspiration associated with GER that is independent from the pH quality of the refluxate [10, 46, 86–88].

Pepsin in BAL fluid has been identified as a marker of GER and aspiration [87, 89, 90], and BAL pepsin levels were shown to be higher in the transplanted population when compared with normals, suggesting aspiration of gastric juice [46, 87]. Another study showed that pepsin levels in BAL were increased in lung transplant recipients without evidence of the presence of BOS, showing that pepsin can be present without airflow limitation. Interestingly, higher pepsin levels were associated with acute allograft rejection [88], which suggests that interactions between alloimmune and non-allo-immune-mediated allograft damage may occur [88]. However, others [87] have found that pepsin levels in BAL fluid did not correlate with FEV_1, while the presence of bile acids correlated with risk for developing BOS. This finding agrees with the correlation of high bile acid levels with the development of BOS that was initially reported by the Toronto group [10, 12]. They explored and described a link between GER and aspiration of bile acids in patients with BOS. Their findings suggested a role for duodeno-gastroesophageal refluxate, irrespective of the pH, retrograde aspiration of with investigations performed at a time when impedance testing was not yet widely available. Bile acids were detected in BAL fluid from 71 of 107 recipients who underwent surveillance bronchoscopies at 6 months after lung transplantation, and total bile acids were significantly

increased in patients with BOS (stages 0–p and 1–3), but this increase was essentially limited to patients who developed BOS early (within 12 months after lung transplantation) vs. those with late BOS. Additionally, high levels of bile acids in BAL fluid correlated positively with BAL IL-8 and neutrophil levels, and the presence of bile acids was associated with significantly depressed levels of surfactant protein-A, surfactant protein-D, and dipalmitoylphosphatidylcholine, which led to the suggestion that one effect of aspirated bile acids may be depression of innate immune function in the lung allograft [12].

The lung transplant group in Leuven [46] also evaluated a cohort of lung transplant recipients and detected abnormal acid and nonacid GER in 22 of 45 patients and measured bile acids and pepsin in BAL fluid. All lung transplant recipients had detectable levels of pepsin in BAL, but levels of pepsin were 23-fold increased over that of control subjects. Twenty-two lung transplant recipients had bile acids detected in BAL fluid, and although pepsin levels showed no correlation with FEV_1 values, bile acids were significantly increased in patients with BOS stages 1–3. An additional, interesting aspect of this study was the persistence of abnormal GER, especially weakly acidic GER, in patients on PPI therapy (7 of 18 patients, five with weakly acid reflux), although esophageal acid exposure and acid reflux events were significantly reduced for patients on PPI when compared to a cohort of patients studied off PPI therapy. Vos et al. [91] found a significant association of allograft colonization by *Pseudomonas aeruginosa* with the presence of bile acid aspiration in a matched lung transplant recipient cohort of 24 subjects. Indeed, taken together, these investigations suggest that bile acids aspirated into the lower respiratory tract in the transplanted lung may be particularly injurious to respiratory mucosa and induce airway injury and dysfunction that can lead to chronic infection and/or BOS.

Various biomarkers of GER have been investigated in exhaled breath condensate in order to noninvasively detect reflux and microaspiration of gastroduodenal secretions [92–97]. However, this attractive methodology does not appear to be useful as a diagnostic technique using currently available technology. To date, no correlation of biomarker levels in BAL fluid with levels measured in exhaled breath condensate has been observed.

The presence of bile acids in BAL is considered to reflect duodenogastroesophageal reflux and aspiration [10, 83, 98], and bile acid aspiration into the lung has been associated with severe pulmonary injury [66, 83] and BOS. Bile acids are cytotoxic, disrupt cellular membranes, damage type II pneumocytes [99], which are responsible for surfactant protein and phospholipid production and homeostasis [10, 12, 68], and down-regulate innate immunity by affecting receptors on monocytes and macrophages [12, 68]. Althouph, todste the role of bile acids in reflux-related lung damage remains somewhat unclear, which is partly due to the fact that bile acid concentrations are difficult to accurately measure in the lung. Additionally, there is discordance between the presence of bile acids in BAL fluid and abnormal pH findings in lung transplant patients.

The uncertain cause and effect relationship between gastric aspiration, the detection of gastric juice constituents in BAL fluid, and the ultimate development of graft failure have been investigated in animal and in vitro models. A single lung transplant

model has been developed in rats that demonstrates the harmful effects of gastric aspiration on airways. Recipients of major histocompatibility complex-mismatched grafts were exposed to repetitive airway stimulation with gastric contents via tracheal instillation. A significant increase in pulmonary infiltrates rich in CD8+ and CD68+ cells was observed in animals exposed to gastric contents, indicating a role for cytotoxic T cells and monocytes, which were associated with areas of acute airway fibrosis. Additionally, an increase in circulating levels of transforming growth factor-beta (TGF-β) was observed [100, 101]. Bile acids may alter innate immune responses by dampening the release of the lung collectins, surfactant protein-A, and surfactant protein-D, which play a key role in orchestrating the ability of lung macrophages to clear microbes [12]. Additionally, a receptor for bile acids, TGR5, that is expressed abundantly on human monocytes and macrophages has been identified, and this discovery has led to experiments that have confirmed the direct inhibitory effect of these bile acids on macrophages. The effect of bile acids on innate immune responses appears to be largely immunosuppressive, whereas other constituents of gastric juice appear to have the opposite effect and stimulate innate immune responses.

Additional studies correlating BAL markers of microaspiration with the presence of abnormal gastroesophageal GER with CLAD and/or BOS are needed to validate the predictive capability of such measurements. The combination of BAL biomarkers of aspiration with pH/impedance and proximal foregut motility studies may facilitate the accurate selection of recipients at risk for allograft dysfunction due to retrograde microaspiration from GER and facilitate the identification of lung transplant recipients who begin to display manifestations that are consistent with the onset of CLAD for more effective interventions to prevent reflux such as antireflux surgery.

Treatment Options for GER After Lung Transplantation

It is clear that GER that leads to aspiration of refluxed secretions is a significant risk factor for graft loss after lung transplantation. Therefore, one must ask what treatments or interventions can mitigate this risk, and when should such interventions be instituted. Because airway epithelia lack the defenses that protect gastric mucosae from foregut secretions, airways can be expected to be more vulnerable to aspiration injury. Therefore, treatments of gastroesophageal GER may prevent or attenuate BOS by reducing retrograde nocturnal reflux and microaspiration, which would prevent or lessen the epithelial injury and epithelial-mesenchymal transition that can lead to OB and BOS.

Acid suppression (e.g., PPI administration) is usually first-line therapy for GER and can improve classic GER symptoms, but lung transplant recipients may remain at risk to develop BOS because such therapy may only convert acid reflux into asymptomatic nonacid reflux, and gastroesophageal aspiration of bile acids may not reduced in patients on PPI therapy [46]. Lifestyle changes (avoiding late evening meals, not lying in bed for the first 2–3 h after dinner, avoiding snacks or drinks

after the evening meal, elevating the head of the bed during sleep) may reduce the amount of nocturnal reflux and, thus, may help to prevent nocturnal GER and aspiration.

Prokinetic drugs, which may improve esophageal motility and accelerate gastric emptying, have been used either alone or in combination with PPIs for the treatment of GER [102–104]. Macrolide antibiotics (e.g., erythromycin) have a significant prokinetic effect on the gastrointestinal tract and have also been proposed for the treatment of GER [105], and the neomacrolide/azalide, azithromycin, has been shown to reduce GER and gastroesophageal bile acid aspiration in lung transplant recipients [106]. On the basis of these observations, it could be hypothesized that the beneficial effect of azithromycin, which is frequently used in lung transplant recipients, is not only due to its anti-inflammatory properties but might be further potentiated by an anti-reflux effect due to its prokinetic properties on esophageal and gastric motility. Baclofen, a GABA receptor agonist, has been shown to reduce episodes of transient LES relaxation and thereby might reduce both acid and non-acid GER, but most patients experience intolerable side effects [107, 108].

Surgical fundoplication for treatment of GER in lung transplant recipients has been shown to prevent BOS and improve patient survival. Laparoscopic Nissen fundoplication can be performed with reasonable safety on lung transplant candidates with advanced lung disease prior to lung transplant [45, 109, 110], and prophylactic fundoplication may decrease the incidence of post-transplant allograft dysfunction and BOS [8, 9, 111]. Potential benefits of anti-GER surgery prior to transplant include decreased risk of perioperative aspiration and immediate protection from microaspiration of gastroduodenal secretions that increase the risk of post-transplant allograft dysfunction [109]. However, as suggested by the Toronto group, transplantation itself may resolve pre-transplant acid GER by restoring the anatomic relationship between the diaphragmatic and LES [67].

In lung transplant recipients, lung function might be improved by anti-reflux surgery and freedom from developing BOS may be enhanced [46, 86–92]. A number of investigations, both retrospective and prospective, undertaken by the lung transplant group at Duke University have repeatedly supported benefit of laparoscopic Nissen fundoplication in preventing BOS [8, 9, 111–113], particularly if adopted early after lung transplantation [8]. Similarly, other investigators have shown that anti-reflux surgery is both safe and effective [45, 114], and that it can reduce pepsin levels in BAL fluid [115].

Laparoscopic Nissen fundoplication is the favored technique in the lung transplant candidate or recipient, and it is the anti-reflux surgical procedure of choice, unless esophageal dysmotility is present [8, 113]. Caution should prevail if esophageal dysmotility is present, because a complete wrap may obstruct passage of ingested food from esophagus to stomach and lead to dysphagia [113, 116]. Partial fundoplication can be performed for such patients as an alternative to the Nissen 360-degree wrap using the techniques described by Dor and Toupet [117–119].

In lung transplant recipients with severely delayed gastric emptying, the implantation of a gastric stimulator has been suggested, although the true role of this device

in this patient population has not been explored [120–124]. Gastric emptying may improve following Nissen fundoplication and obviate the need for such a device.

Conclusion

The evidence collected to date strongly supports the role of GER as a risk factor for CLAD and/or BOS. Proximal gastrointestinal tract motility studies and pH/impedance testing can be used to diagnose motility abnormalities and GER (and determine whether refluxate is acid and/or nonacid), respectively. Unfortunately, a true gold standard for detecting aspiration of refluxed secretions into the lung is lacking, and a definitive marker of GER combined with microaspiration that identifies patients at significant risk for GER-associated allograft injury and dysfunction needs to be determined. Indications for anti-reflux surgery will most likely need to be based on reasonably stringent criteria, given that not all the patients with GER are likely to experience silent, retrograde aspiration of gastroduodenal contents into the lungs. Furthermore, GER that is identified pre-transplant may not persist following transplantation if the anatomical relationship of the gastroesophageal junction high-pressure zone is restored.

Prospective studies to determine the most effective approach to prevent reflux-related lung injury in lung transplant patients are needed, as only retrospective studies have linked prophylactic fundoplication for recipients with GER to improved post-transplant outcomes and decreased incidence and/or severity of CLAD and/or BOS. Future research should seek to identify the most effective protocols that can detect susceptibility to GER and microaspiration in lung transplant candidates and recipients. The optimal timing of diagnostic testing needs to be determined.

Prospective, multicenter, adequately powered clinical trials are needed to better understand the role of GER in CLAD and to establish appropriate criteria to select patients for anti-reflux surgery.

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