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Baishideng Publishing Group Inc
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REVIEW

Role of gastroesophageal reflux disease in lung transplantation

Kelly E Hathorn, Walter W Chan, Wai-Kit Lo

Kelly E Hathorn, Division of Internal Medicine, Brigham and Women's Hospital, Boston, MA 02115, United States

Walter W Chan, Wai-Kit Lo, Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Boston, MA 02115, United States

Walter W Chan, Wai-Kit Lo, Harvard Medical School, Boston, MA 02115, United States

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Correspondence to: Walter W Chan, MD, MPH, Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, United States. wwchan@partners.org
Telephone: +1-617-7326389
Fax: +1-617-5250338

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Abstract

Lung transplantation is one of the highest risk solid organ transplant modalities. Recent studies have demonstrated a relationship between gastroesophageal reflux disease (GERD) and lung transplant outcomes, including acute and chronic rejection. The aim of this review is to discuss the pathophysiology, evaluation, and management of GERD in lung transplantation, as informed by the most recent publications in the field. The pathophysiology of reflux-induced lung injury includes the effects of aspiration and local immunomodulation in the development of pulmonary decline and histologic rejection, as reflective of allograft injury. Modalities of reflux and esophageal assessment, including ambulatory pH testing, impedance, and esophageal manometry, are discussed, as well as timing of these evaluations relative to transplantation. Finally, antireflux treatments are reviewed, including medical acid suppression and surgical fundoplication, as well as the safety, efficacy, and timing of such treatments relative to transplantation. Our review of the data supports an association between GERD and allograft injury, encouraging a strategy of early diagnosis and aggressive reflux management in lung transplant recipients to improve transplant outcomes. Further studies are needed to explore additional objective measures of reflux and aspiration, better compare medical and surgical antireflux treatment options, extend follow-up times to capture longer-term clinical outcomes, and investigate newer interventions including minimally invasive surgery and advanced endoscopic techniques.

Key words: Lung transplant; Reflux; Aspiration; Rejection; Bronchiolitis obliterans syndrome; Fundoplication

Core tip: Gastroesophageal reflux disease (GERD) has been associated with increased morbidity in lung transplant patients through a proposed pathway of reflux, aspiration, immunomodulation, and allograft injury, culminating in functional decline and rejection. This paper reviews the mechanisms of GERD-induced

injury, describes outcome measures important in post-transplant assessment, and discusses the timing and modalities of diagnostic evaluation and management, including medical and surgical antireflux treatment, in optimizing post-transplant outcomes. A greater awareness of the harmful effects of GERD in the lung transplant population is important in the early diagnosis and management of such patients to minimize allograft injury and improve outcomes.

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INTRODUCTION

Lung transplantation has proven to be an effective therapeutic option for the treatment of different end-stage pulmonary disorders, improving the quality of life and extending survival[1] for the recipients. Since the first human lung transplant in 1963[2], we have seen improvements in surgical technique, lung preservation, immunosuppression, and the treatment of ischemic reperfusion injury and infection. However, it remains one of the highest risk solid-organ transplant modalities, with 5-year survival rates of 53%[3], compared to 75% for heart transplantation[4], and 71% for liver transplantation[5].

Over time, transplanted lungs may become susceptible to injury manifesting as acute or chronic rejection, diagnosed clinically and histologically using established guidelines of the International Society of Heart and Lung Transplantation (ISHLT)[6]. Acute rejection is an early manifestation of allograft injury occurring usually within the first year after transplantation, impacting up to 55% of patients[7,8], and includes acute cellular rejection (grade A rejection), and lymphocytic bronchiolitis (grade B rejection). Both are independently associated with later development of chronic rejection[7-9].

Chronic rejection traditionally encompassed the spectrum of bronchiolitis obliterans (BO) and bronchiolitis obliterans syndrome (BOS). Bronchiolitis obliterans is a type of progressive airway obstruction occurring as a result of macrophage and myofibroblast infiltration, which induces fibrous obliteration and scar formation[10-12]. The diagnosis is made histologically, requiring surgical biopsy which can be invasive, and may present additional challenges given the patchy involvement of disease[10,13]. Therefore, the clinical correlate of BOS is often applied. BOS was originally defined as a persistent drop in forced expiratory volume in 1 s (FEV1) by 20% in the absence of other identifiable causes[14]. However, given the significance of BOS in predicting poor long-term outcomes, the criteria were adjusted to include an early BOS stage (BOS 0-p) in which an FEV1 of 81%-90% and/or a drop in mid-expiratory flow rate (FEF 25-75) may alert physicians to a need for closer functional monitoring and in-depth assessment[15]. BOS has a variable course, with some patients experiencing rapid decline in lung function, while others develop a slower and more gradual loss of function[16]. Regardless of the speed of progression, BOS remains one of the greatest impediments to long-term survival after lung transplantation, as it ultimately affects up to 80% of transplant recipients by five years[17-19], and most transplant deaths beyond the first year occur directly or indirectly as a result of BOS[7,14].

Recently, a new restrictive form of chronic rejection has been described, termed restrictive allograft syndrome (RAS). RAS manifests as progressive, restrictive physiology with an appearance of increasing fibrosis on imaging studies[20,21], and is defined as a persistent decline in total lung capacity alongside a decline in FEV1[22]. RAS is histologically characterized by diffuse alveolar damage and extensive fibrosis in the alveolar interstitium, visceral pleura, and interlobular septa, and may also contain scattered obliterative bronchiolitis lesions[21-24]. Recent research using immunofluorescence labeling for α-smooth muscle actin has demonstrated massive infiltration of myofibroblasts in the peripheral lung tissue of RAS patients; whereas in BOS, myofibroblasts were observed predominantly in the small airway obliterative bronchiolitis lesions and not in the peripheral lung[21], affording a potential method to differentiate the two types of chronic allograft rejection.

As a consequence of these findings, a new descriptor of the effects of chronic rejection, termed chronic lung allograft dysfunction (CLAD), has been created to cover obstructive, restrictive, and all other manifestations of chronic rejection, including those as yet undetermined, with resulting clinical decline[25]. This review will focus on the chronic rejection syndromes of BO and BOS, which have been studied more extensively in the setting of gastroesophageal reflux disease (GERD).

Immune-mediated lung injury, including cellular and humoral rejection, has been recognized as the leading cause of BOS[7,26-28] and chronic rejection; however, non-immune mechanisms, such as infection, ischemic reperfusion injury, brain death, chronic aspiration, and GERD may also contribute[14,15,19,26,29-32]. GERD, in particular, has been identified as a potential risk factor for both early allograft injury[27], including acute rejection and lymphocytic bronchiolitis, and chronic airway rejection associated with BOS[28,29]. Although no clear causal link has yet been demonstrated, many studies have proposed that GERD is a risk factor in the development of BOS through silent aspiration of stomach contents, leading to direct airway injury and/or upregulation of the inflammatory response in the lung[29,33-38]. Given the significant commonality between GERD and chronic respiratory diseases, the high prevalence of GERD in the lung transplant population[33,39-41], and the more rapid progression to BOS in transplant recipients with objective evidence

of aspiration[34,40,42,43], many groups have begun investigating the impact of diagnosis and treatment of reflux on pulmonary outcomes in this population.

GERD AND LUNG DISEASE: SIGNIFICANCE OF THE PROBLEM

Population-based studies have demonstrated that as many as 11% of Americans experience typical symptoms of reflux daily, and 33% experience symptoms during a 72-h period[44]. It is well known that there may be a higher prevalence of GERD in patients with end-stage lung disease[33,34,45-48]. For example, D' Ovidio *et al*[47] described a 63% (49 of 78 patients) prevalence of gastroesophageal reflux-related symptoms in end-stage lung disease, 38% with documented significant acid reflux on objective testing, which was often asymptomatic[47,49]. Additionally, in patients with idiopathic pulmonary fibrosis (IPF), GERD has been shown to have increased prevalence in comparison to other chronic lung diseases[46,50,51]. Gavini *et al*[52] demonstrated that patients with IPF undergoing pre-lung transplant evaluation have a significantly higher prevalence of abnormal reflux compared to those with COPD, after controlling for potential confounders such as underlying disease severity. Savarino *et al*[53] demonstrated that IPF patients had a higher total reflux episodes and total proximal reflux episodes compared to both non-IPF chronic lung disease patients and healthy volunteers. These findings support the theory that GERD may increase microaspiration episodes, resulting in activation of an inflammatory cascade in lung tissue, which over time, induces fibrotic changes that characterize IPF[42,54,55].

In addition to its higher prevalence in patients with underlying lung disease prior to transplantation, numerous studies have also documented that GERD is increased following transplantation. Young *et al*[56] have shown that the incidence of GERD rose from 35% pre-transplant to 65% post-transplant in their cohort of patients. Similarly, other groups have demonstrated a prevalence of reflux as high as 51-69% in patients after transplant[33,48]. D'Ovidio *et al*[57] have investigated the prevalence of reflux at 3- and 12-mo post-transplant, and found that it increased from 32% to 53%, suggesting that transplantation may itself induce worsened reflux[56,57]. Fisichella *et al*[58] have demonstrated that distal and proximal reflux were more prevalent in patients with bilateral lung transplant or re-transplant, and less prevalent in patients after unilateral transplant, regardless of the cause of their lung disease, suggesting not only the importance of screening for reflux in the post-transplant population, but also the necessity for higher vigilance in patients following double lung transplantation. Various factors have been implicated, including intraoperative vagal nerve damage, loss of cough reflex, impaired mucociliary clearance, and development of gastroparesis as a side effect of calcineurin inhibitors, steroids, mycophenolate mofetil, and other post-transplant immunosuppression treatments[16,39,56,57,59-70].

BACKGROUND AND PATHOPHYSIOLOGY

The association between reflux and rejection post-lung transplant has been investigated in both animal and human studies (Table 1). Stovold *et al*[35] demonstrated that in rats, exposure of the lung allograft to gastric juice leads to high grade acute rejection, which is characterized by monocyte infiltration, fibrosis, and lung destruction. Aspiration has also been shown to increase allograft CD8+ T cells, which are involved in acute rejection[71], and chronic aspiration has been associated with bronchiolitis obliterans[72]. Meltzer *et al*[73] demonstrated similar results in a miniature swine study where chronic aspiration was associated with increased shedding of allograft alloantigens and increased activity of the indirect alloimmune response, which may contribute to fibrosis, obliterative bronchiolitis, and infection.

The central belief is that BOS is a chronic inflammatory and fibrotic process of the small airways, marked by recurrent injury, remodeling, and repair, ultimately resulting in allograft failure typified by obliterative fibrosis[74,75]. Multiple studies supporting this claim have shown that aspiration of gastroduodenal contents is linked to immunomodulation, including increased local levels of IL-1α, IL-1B, IL-6, IL-10, TNF-α, TNF-β[72], increased alveolar neutrophils[37,76,77], increased IL-8[37,76], increased IL-15, IL-17, basic-FGF, TNF-α, and MPO and reduced alpha-1-antitrypsin[42], augmented indirect allorecognition[73], and reduced levels of surfactant proteins SP-A and SP-D[57].

Additionally, numerous studies have investigated the specific role of bile acids and pepsin in the association between reflux and BOS. Bile acids and pepsin, used as markers of aspiration and reflux, have been demonstrated in bronchoalveolar (BAL) fluid of post-lung transplant patients[35,37,57,78,79]. Bile aspiration is cytotoxic, disrupts cellular membranes, and damages type II pneumocytes[80], which are responsible for surfactant protein and phospholipid production and homeostasis[37,57,81,82]. D'Ovidio *et al*[37] investigated 120 post-transplant patients, and found that 20 (17%) had high concentrations of bile acids in BAL. They also noted an association between the presence of bile acids and decreased surfactant proteins and phospholipids, suggesting that aspiration of bile acids may have impaired the innate immunity of the allograft[37]. Importantly, they demonstrated that the highest concentrations of bile acids were found in 70% of patients with early onset (< 1 year post-transplant) and most severe manifestation of BOS, suggesting a temporal and dose-related relationship[37,57]. Blondeau *et al*[78] found that 50% of the lung transplant patients in their study demonstrated elevated levels of bile acids, and 70% of

Table 1 Papers summarizing effects of gastroesophageal reflux disease on transplant outcomes

Ref.	Population	Definition GERD and/or aspiration	Outcomes evaluated	Adjunctive therapy
King *et al*[29], 2009	59 pts. Post-LTx	Abnormal acid and non-acid reflux on esophageal impedance monitoring	Effect of reflux on time to development of BOS *via* hazard ratio	
Hadjiliadis *et al*[33], 2003	43 pts. Post-LTx, survived > 6 mo, and underwent pH and manometry testing	Abnormal acid exposure time on 24-h pH testing	Effect of reflux on FEV1 (*via* Pearson correlation coefficient for time of study, *via* multivariable linear regression to assess overall effect)	PPI d/c'ed > 5 d prior to testing, H2 blockers and pro-motility agents > 1 d prior to testing
Stovold *et al*[35], 2007	36 asymptomatic pts. Post-LTx *vs* 4 healthy volunteers *vs* 17 patients with chronic cough	Increased levels of pepsin in BALF	Presence of pepsin, association between level of pepsin and acute rejection	30 LTx patients on antireflux therapy
Blondeau *et al*[36], 2009	24 pts. Post-LTx	Abnormal reflux on 24-h impedance-pH testing, bile acids in BALF	Relationship between acid exposure, volume exposure, or reflux events and bile acids in BALF	PPI d/c'ed 1 wk prior to testing
D'Ovidio *et al*[37], 2005	120 pts. Post-LTx	Increased levels of bile acids in BALF	Relationship between increased levels of bile acids, IL-8, neutrophils on development of BOS	
Benden *et al*[41], 2005	10 pts. Post-LTx	Abnormal reflux on 24-h pH testing	Prevalence of GERD in population	
Fisichella *et al*[42], 2013	105 pts. Post-LTx with 257 BALF samples	24-h pH testing and DeMeester score calculation, Increased levels of pepsin in BALF	Association between aspiration and patterns of dysregulation of immune mediator concentrations and BOS	PPI d/c'ed 2 wk prior to testing, H2 blocker d/c'ed 3 d prior to testing
Young *et al*[56], 2003	23 pts. evaluated pre- and post-LTx	Total, upright, and supine acid exposure time on 24-h pH testing, esophageal manometry, gastric-emptying study	Paired comparison between pre-transplant and post-transplant results (paired *t* test)	Acid suppression and gastric motility meds discontinued before testing
D'Ovidio *et al*[57], 2006	70 pts. Post-LTx	Esophageal manometry, 24-h pH-testing (DeMeester score calculation, Castell's method) and gastric emptying study; BALF analysis	Actuarial freedom from BOS, impact of aspiration on pulmonary surfactant collectin proteins	PPI d/c'ed 7 d prior, H2-blockers d/c'ed 2 d prior
Fisichella *et al*[58], 2012	61 pts. Post-LTx	Esophageal impedance-manometry, 24-h pH testing (DeMeester score calculation), EGD, barium swallow, gastric emptying study	Relationship between prevalence and extent of GERD and type of transplant (unilateral *vs* bilateral *vs* retransplant)	PPI d/c'ed 14 d prior to pH testing, H2 blockers stopped 3 d prior to pH testing
Fisichella *et al*[74], 2012	8 pts. Post-LARS and LTx in whom BALF had been collected	Esophageal 24-h impedance-pH testing (DeMeester score calculation), gastric emptying study	Comparison of BALF concentrations of leukocytes, immune mediators, and pepsin pre- and post-LARS and post-LTx	PPI d/c'ed 14 d prior to pH testing, H2 blockers stopped 3 d prior to pH testing
Blondeau *et al*[78], 2008	45 pts. Post-LTx off PPI, 18 pts. Post-LTx on PPI	Esophageal 24-h impedance-pH catheter, BALF analysis for pepsin and bile acids	Association between the prevalence and type of reflux and gastric aspiration in pts. with and without BOS	Antacids and promotility agents d/c'ed > 14 d prior to testing *vs* remained on for testing
Griffin *et al*[45], 2013	18 pts. Post-LTx	RSI, esophageal manometry and 24-h impedance-pH monitoring, BALF analysis	Quantification of reflux, aspiration, and allograft injury immediately post-operatively	Testing performed on PPI
Davis *et al*[84], 2013	100 pts Post-LTx with 252 BALF samples	BALF pepsin concentration, esophageal manometry, esophageal 24-h pH catheter (DeMeester score calculation), gastric emptying study	Association between concentration of pepsin in BALF and results of esophageal function testing, barium swallow and gastric emptying to identify risk factors for GERD	PPI d/c'ed 14 d prior to pH testing, H2 blockers d/c'ed 3 d prior to pH testing
Hartwig *et al*[71], 2006	7 models of rat lung transplantation	Weekly injection of gastric contents for 4-8 wk	Degree of pulmonary allograft dysfunction reflective of chronic aspiration	N/A
Li *et al*[72], 2008	9 models of rat lung transplantation	Weekly injection of gastric contents for 8 wk	Association between chronic aspiration and development of OB	N/A
Meltzer *et al*[73], 2008	3 models of swine lung transplantation	Daily injection of gastric contents for 50 d	Effect on chronic aspiration on the direct and indirect pathways of allorecognition	N/A

BALF: Bronchoalveolar lavage fluid; BOS: Bronchiolitis obliterans syndrome; OB: Obliterative bronchiolitis; RSI: Reflux severity index; GERD: Gastroesophageal reflux disease; N/A: Not available.

those with BOS had elevated bile acids, compared to 31% without BOS, indicating that bile acid may be a specific marker for allograft injury.

Pepsin is a proteolytic enzyme, active at acidic pH, which is increasingly reported as a marker of inflammation in asthma, COPD, bronchiectasis, CF, and following cardiothoracic surgery[83]. Numerous studies have documented increased levels of pepsin in BAL of patients following lung-transplantation[35,78,79,84]. In a small study by Ward *et al*[79], pepsin was present in the BAL of all lung allografts, while not detected in the control group. In a later follow-up study of 36 post-transplant patients, 4 normal volunteers, and 1 patient with unexplained chronic cough, it was shown that pepsin levels were significantly higher in the transplant cohort; among these patients, pepsin levels were highest in those with acute rejection, a risk factor for the progression to BOS[85,86]. Stovold *et al*[35] also demonstrated consistently elevated levels of pepsin in the BAL fluid of lung transplant patients, again with the highest levels in association with acute rejection. Davis *et al*[84] have even specifically compared patients with IPF to those with alpha-1-antitrypsin deficiency, cystic fibrosis, or COPD, and have found that patients with IPF had higher pepsin concentrations and greater frequency of acute rejection than those with other diseases. Interestingly, despite higher pepsin concentrations and rates of acute rejection, IPF patients did not have a significantly greater incidence of BOS compared with other indications for lung transplantation[84], though the short follow-up time was a significant limitation that likely reduced development of the BOS outcome.

Furthermore, as previously mentioned, both acute cellular rejection[7-9] and lymphocytic bronchiolitis[9] are independently associated with bronchiolitis obliterans. Acute cellular rejection may represent an earlier endpoint in the model of chronic lung injury, supporting the relationship between early allograft injury and eventual development of BOS. Lymphocytic bronchiolitis not only represents an independent risk factor for bronchiolitis obliterans[9], but also has been associated with the occurrence and severity of acute cellular rejection[10]. While no causal relationship between lymphocytic bronchiolitis and BOS has been identified, a prior study has documented the presence of lymphocytic infiltration and esophageal inflammation in association with GERD in the upper gastrointestinal tract, which improves with acid suppression therapy[87]. Therefore, GERD and aspiration may play a role in early development of both lymphocytic bronchiolitis and acute cellular rejection, which in turn, independently predict onset of BOS[7-9].

EVALUATION AND DIAGNOSIS

There is mounting evidence that patients with reflux have a higher risk of poor outcomes post-transplant. For example, King *et al*[29] have demonstrated that increased reflux is associated with BOS, even after controlling for the graft ischemic time, type of surgery, recipient age, underlying pathology, CMV mismatch, or HLA mismatches, concluding that reflux is a prevalent and modifiable risk factor[29]. Hadjiliadis *et al*[33] have even demonstrated a negative correlation between measurements of FEV1 and pH test results in a post-transplant population. These and other studies highlight the importance of identifying patients at risk for allograft injury relating to GERD. Typical GI symptoms, such as heartburn and regurgitation symptoms, have not been predictive of respiratory symptoms attributed to GERD, and are an unreliable correlate between reflux and airway disease[16,29,47,49-51,88-92]. Sweet *et al*[49] have demonstrated that in patients with IPF, 67% had pathologic reflux, which frequently extended into the proximal esophagus, and that heartburn symptoms were unreliable means of patient detection, demonstrating sensitivity of 65% and specificity of 71%. This again emphasizes the importance of screening transplant candidates for GERD to identifying those at increased risk of poor outcomes.

In the past, gastric transit studies[62], esophagoscopy[93], and radiologic swallow studies[93] were used as tenuous proxies for reflux. Recently, a variety of more sophisticated techniques have been utilized to characterize reflux in the lung transplant population, including 24-h ambulatory pH monitoring, multichannel intraluminal impedance and pH (MII-pH) testing, and bronchoscopy with BAL evaluation. Collection of exhaled breath condensate for pH and other chemical assays has been used with limited accuracy and poor availability, and is primarily a research tool[87-89]. While ambulatory pH testing is the most universally advocated, the optimal testing modality remains undefined.

Ambulatory pH testing has the longest history of use in the assessment of transplant patients. Hadjiliadis *et al*[33] used 24-h pH monitoring to demonstrate that 69.8% of patients in their post-transplant group had abnormal total acid exposure times, and that there was an inverse correlation between total or upright acid reflux and FEV1 at the time of the ambulatory pH study. Similarly, Young *et al*[56] have also used pH monitoring to demonstrate that 65% of their patients had abnormal acid exposure times post-transplant. However, ambulatory pH monitoring has had variable sensitivity for reflux detection in this population, ranging from 50%-80%[41,84,90]. One possible reason for this limitation may be that the test underestimates the amount and frequency of reflux, as it is not capable of detecting nonacidic or bolus reflux. Other modalities for evaluation of acid reflux, such as BRAVO capsule-based pH monitoring (Given Imaging, Yoqneam, Israel)[94] have not been assessed in the transplant population, but may offer few benefits over catheter-based testing as it requires endoscopic evaluation prior to placement.

To better assess potential contributions from nonacid and bolus reflux, impedance testing was developed to sensitively detect the presence of liquid bolus, its direction of movement, and the proximal extent of reflux, independent of pH[29,95,96]. Through this minimally

invasive outpatient procedure, patients at risk of reflux and aspiration can be identified[29]. In one study, impedance detected 96% of reflux events compared with 28% detected by ambulatory pH study alone[97], highlighting that a significant portion of reflux events may be nonacidic or weakly acidic events not detectable by pH testing, but still potentially contributing to the pathophysiology of post-transplant reflux-induced allograft injury. Similarly, our group has demonstrated that impedance data, specifically the additional information regarding nonacid reflux, offers statistically significant advantages over their corresponding pH-only parameters in predicting lung transplant outcomes[98]. It is our general belief that impedance is being under-utilized, and our data suggests a role for more routine use of impedance as a standard part of pre-transplant evaluation[98].

Although not specifically for reflux assessment, use of high resolution esophageal manometry (HREM) is also growing in the transplant population. Practically, HREM may help identify the lower esophageal sphincter to guide proper placement of the pH catheter. Additionally, esophageal motility disorders may present primarily with GERD symptoms and can impact GERD severity, including connective tissue diseases, so HREM may be helpful in the diagnosis of secondary reflux. Esophageal dysmotility may also impact candidacy for surgical antireflux treatment. Further studies are required to assess the relationship between HREM measures of esophageal function and pulmonary outcomes.

Oelschlager *et al*[89] have demonstrated that in 518 patients, the combination of symptoms, esophageal manometry, and ambulatory pH monitoring was insufficient to accurately identify reflux as the cause of aspiration. While this included only standard ambulatory pH monitoring rather than MII-pH, it raises the possibility that additional tests may be required to more directly assess reflux severity. Some groups have proposed that BAL fluid analysis may contribute additional information in the evaluation of these patients. For example, BAL may be used to quantify pepsin and bile acids as markers of aspiration, which have been associated with progression to BOS[75,79,99-101]. However, bronchoscopy sampling is relatively expensive, more invasive than other techniques, and time consuming[29]. Additionally, because only a single sample is taken at a moment in time[29,39], without standardization of results or a full understanding of temporal changes in bile acid or pepsin concentrations, this test may be exquisitely sensitive to provider technique[39]. In short, clinical feasibility remains a challenge.

In addition to poor consensus on the optimal mode of reflux testing among lung transplant candidates[98], there is no standard for timing of testing. Our group favors routine pre-transplant impedance testing, as we have previously shown that prolonged bolus clearance, increased total distal reflux episodes, and increased total proximal reflux episodes on pre-transplant MII-pH were associated with decreased time to early allograft injury after lung transplantation[102]. Researchers from Duke University have suggested the following approach based on available data, and previous experience at their center: Prior to transplant, all patients undergo esophageal manometry, 24-h ambulatory pH or MII-pH study (off anti-secretory therapy), and upper GI series[13]. However, not all groups have adopted this pre-transplant assessment approach, especially given the tenuous pulmonary status of some transplant candidates. It does seem, however, that if evaluation were to be performed post-transplant, the importance of early assessment should not be ignored. As mentioned previously in this review, there are several processes during and after transplant surgery that may result in worsening of reflux, and thus, it is imperative to screen for reflux in the early post-transplant period if not before. Griffin *et al*[45] recommended that all patients should be routinely assessed within 1 mo post-transplant given the high prevalence of reflux and aspiration in the immediate post-transplant period, despite use of proton-pump inhibitor (PPI). Additionally, as our group has demonstrated the benefits of timely antireflux surgery in improving transplant outcomes[103], earlier reflux assessment may be essential to guide management.

TREATMENT

Medical treatment of reflux consists of the conventional pharmacologic methods of histamine-2 receptor blockers and PPIs, and prokinetic agents to enhance esophageal and gastric clearance. These agents may ameliorate symptoms, diminish the acid component of gastric refluxate, and promote bolus clearance. Additionally, recent publications have suggested that antireflux therapies may prolong survival and decrease the incidence of acute disease exacerbation in patients with IPF (Table 2)[53,104-109]. Blondeau *et al*[78] demonstrated that PPI use did reduce acid exposure in lung transplant patients, but had minimal effect on pepsin as a surrogate marker of aspiration. Unfortunately, additional literature on the effects of medical acid suppression in the lung transplant population is sparse. Azithromycin has been used as a therapy for BOS with some success, possibly relating to its mild pro-kinetic effects, although the full mechanism of action is not clearly defined[32,110,111]. Mertens *et al*[112] used impedance and BAL testing to evaluate the effect of azithromycin on reflux and gastric aspiration parameters, and found that patients on azithromycin had significantly less reflux, including decreased number of reflux events, fewer proximal reflux episodes, and decreased esophageal acid exposure. In addition, bile acid levels in the BAL were significantly reduced after azithromycin treatment[112]. However, given the unclear mode of action and concern for antibiotic overuse, routine application of azithromycin has not been recommended.

While the aforementioned pharmacologic therapies may ameliorate symptoms, diminish the acid

Table 2 Papers on the effect of pharmacologic reflux treatment on transplant outcome

Ref.	*n*	Population	Treatment type	Adjunctive treatments	Outcomes assessed
Yates *et al*[32], 2005	20	Post-LTx with diagnosis of BOS (*n* = 18) or potential BOS (*n* = 2)	AZI 250 mg QOD from time of BOS diagnosis to time of manuscript writing (mean 6.25 mo)	Immunosuppressive regimen, no additional antireflux agents specified	Effect on FEV1
Verleden *et al*[110], 2004	8	Post-LTx with significant decrease in their FEV1 attributed to BOS	AZI 250 mg qd × 5 d then 250 mg po QOD	Immunosuppressive regimen, no additional antireflux agents specified	Effect on FEV1
Verleden *et al*[111], 2006	14	Post-LTx with BOS	AZI 250 mg po qd × 5 d then AZI 250 mg po 3 × /wk × 3 mo	Immunosuppressive regimen, no additional antireflux agents specified	Reduction in airway neutrophilia and IL-8 mRNA, effect on FEV1
Mertens *et al*[112], 2009	12	Post-LTx on AZI with pH monitoring	AZI 250 mg PO 3 ×/wk	Immunosuppressive regimen, held antireflux treatments × 1 wk prior to testing	Effect on impedance-pH monitoring, gastric aspiration *via* BAL analysis
Blondeau *et al*[78], 2008	18	Post-LTx on PPI *vs* off PPI at time of testing (secondary cohort)	Omeprazole 20 mg PO BID	Immunosuppressive regimen	Prevalence of reflux on objective testing, effect on aspiration in BAL

n: Patients in the study in the treatment arm; BOS: Bronchiolitis obliterans syndrome; LTx: Lung transplant; AZI: Azithromycin; QOD: Every other day; FEV1: Forced expiratory volume in 1 s; BID: Twice a day.

component of gastric refluxate, and improve clearance, the underlying mechanism provoking reflux often persists[29,39,78,113-116]. For example, Patti *et al*[114] demonstrated that while acid-reducing medications alter the pH of the refluxate, clinical symptoms may recur, suggesting persistence of pathology in spite of medical antireflux therapy, and that surgery may provide more definitive treatment of reflux and aspiration regardless of pH. Blondeau *et al*[78] demonstrated that 71% of lung transplant recipients taking PPIs had increased non-acid reflux, and that PPI use did not reduce the number of reflux events, non-acid reflux exposure, proximal reflux extent, or markers of aspiration on BAL.

Consequently, many groups are now turning to antireflux surgery as a more definitive approach to reflux management and for prevention of further complications. Previous studies have shown that antireflux surgery is a safe procedure in this patient population[34,40,75,117-122], and is associated with improved survival and stabilization of lung function (Table 3)[29,33,34,40,43,75,117,118,123-125]. For example, Robertson *et al*[75] demonstrated that post-lung transplant antireflux surgery resulted in no deaths or serious post-operative complications in all 16 patients undergoing surgery, although one patient required minor surgical revision for dysphagia. Fisichella *et al*[119] similarly demonstrated that post-lung transplant patients had perioperative morbidity and mortality rates similar to those of transplant-free controls undergoing laparoscopic antireflux surgery. However, these and other studies have been limited by single-center experiences and small patient numbers. Subsequently, Kilic *et al*[17] performed a study using the all-payer database in the United States to evaluate nationwide outcomes of antireflux surgery in transplant recipients *vs* transplant-free controls, confirming similar outcomes in both groups. The post-lung transplant group did not demonstrate an increased risk of respiratory complications, although they did have a longer median hospital stay, higher resource utilization, and higher median cost of inpatient care[17]. In congruence with these results, O'Halloran *et al*[121] demonstrated that while lung transplant patients in their study also required longer hospital stay and had higher rates of readmission compared to controls, no differences were detected with regard to operative time, estimated blood loss, or peri-operative complications. Furthermore, no intra- or peri-operative deaths were seen, and both transplant and control groups reported symptom resolution following surgery.

Additional studies have focused on the efficacy of antireflux surgical management with regard to transplant outcomes such as pulmonary function and allograft rejection. Halsey *et al*[124] published a case report on a post-transplant patient with progressive allograft dysfunction, associated with a significant decline in FEV1 and FVC, despite twice-daily use of PPI. Their patient underwent impedance testing, which demonstrated ongoing non-acid reflux, and proceeded to laparoscopic Nissen fundoplication. Post-operatively, the patient improved symptomatically and spirometry results returned to baseline[124]. Hoppo *et al*[16] demonstrated that antireflux surgery either improved or prolonged native lung or allograft function during the pre- or post-lung transplant period, respectively. One year after antireflux surgery, significant improvement in FEV1 was detected in 91% of the post-lung transplant patients ($P < 0.01$) and 85% of the pre-lung transplant patients ($P = 0.02$)[16]. Additionally, all patients in this study were using anti-secretory medications, which lends further credence to the observation that acid suppression alone may not be sufficient to prevent reflux in every case[16]. Hartwig *et al*[126] have similarly demonstrated that early fundoplication was associated with preservation of lung function, and Lau *et al*[118] reported that 67% of lung transplant recipients actually had improvement in

Table 3 Papers of surgical antireflux procedures and lung transplant outcomes

Ref.	*n*	Population undergoing surgery	Type of surgical intervention (Type Nissen: *n*)	Outcomes assessed
Davis *et al*[32], 2003	43	Post-LTx with abnormal pH study (*n* = 39), severe reflux with normal manometry (*n* = 2), repetitive aspiration events leading to retransplant (*n* = 1) or pneumonia (*n* = 1)	Laparoscopic: 36 Open: 3 Partial Toupet: 4	In-hospital or 30-d mortality, FEV1 pre- and post-procedure
Cantu *et al*[40], 2004	74	Post-LTx with abnormal pH studies	Laparoscopic: 71 Open: 5 Partial Toupet: 4 Other: 5[1]	In-hospital or 30 d mortality, freedom from BOS in early *vs* late fundoplication groups
Robertson *et al*[75], 2012	16	Post-LTx undergoing antireflux surgery	Laparoscopic: 16	Effect on quality of life, peri-operative mortality and complications, reduction in deterioration of lung function
Linden *et al*[117], 2006	19	Pre-LTx IPF with h/o reflux, symptoms, and severe reflux on pH and manometry testing	Laparoscopic: 19	Peri-operative complications, post-operative lung function
Lau *et al*[118], 2002	18	Post-LTx with documented GERD	Laparoscopic: 13 Open: 1 Partial Toupet: 4	Length of hospital stay, post-operative lung function, morbidity and mortality
Fisichella *et al*[119], 2011	29	Post-LTx with GERD dx on symptoms, BAL, or decreased lung function; with abnormal pH monitoring	Laparoscopic: 27	30-d morbidity and mortality, hospital readmissions
Fisichella *et al*[43], 2011	19	Post-LTx with GERD symptoms, aspiration on BAL, or unexplained decrease in lung function	Partial Toupet: 2 Laparoscopic: 19	decreased aspiration as defined by the presence of pepsin in the BALF
Fisichella *et al*[74], 2012	8	Post-LTx patients with GERD and evidence of reflux on ambulatory pH monitoring	Laparoscopic: 8	Quantification and comparison of pulm leukocyte differential and concentration of inflammatory mediators in BAL, freedom from BOS, effect on FEV1, and survival
Burton *et al*[120], 2009	21	Post-LTx with reflux confirmed on EGD, pH testing, or BALF	Laparoscopic: 5 Partial Toupet: 16	Patient satisfaction, symptom changes and side effects, effect on lung function, BMI, rate progression to BOS
O'Halloran *et al*[121], 2004	28	Post-LTx with reflux on pH testing and manometry	Laparoscopic: 28	Perioperative complications, length of stay, readmission rate, effect on lung function
Gasper *et al*[122], 2008	35	Pre-LTx in 15 patients, Post-LTx in 20 patients with GERD or delayed gastric emptying study	Laparoscopic: 27 Partial Toupet: 5 Other: 3[2]	Length of stay, perioperative complications pre- or post-LTx
Kilic *et al*[17], 2013	401	Post-LTx who pursued elective antireflux procedure	Laparoscopic: 338[3] Open: 23	Inpatient mortality, length of stay, perioperative complications, hospital costs
Hoppo *et al*[16], 2011	43	Pre-LTx in 19 patients, Post-LTx in 24 patients with documented symptoms or signs of GERD on EGD, barium, manometry, pH or impedance testing; or declining lung function	Laparoscopic: 24 Other: 17[4]	Effect on lung function, number cases of pneumonia and acute rejection episodes
Hartwig *et al*[126], 2011	157	Post-LTx with abnormal acid contact times before or early after transplantation	Laparoscopic: 157[3]	Effect on lung function
Lo *et al*[103], 2016	48	Pre-LTx or Post-LTx patients with persistent symptoms on maximal PPI and with objective evidence of reflux on pH testing	Laparoscopic = 48	Time to early allograft injury in pre-LTx *vs* early *vs* late post-LTx groups
Patti *et al*[114], 2000	39	Pt with GERD and respiratory symptoms on H2 agents *vs* PPI *vs* pro-kinetic agents, ± bronchodilators (*n* = 3) and bronchodilators/prednisone (*n* = 4)	Laparoscopic = 39	Outcome of surgery on GERD-induced respiratory symptoms

[1]Three cases Belsey-Mark IVs, 1 Toupet and 1 Nissen at OSH (without further information); [2]Two cases had pyloroplasty without fundoplication, 1 case had hypotension at induction and was discharged without operation; [3]Does not specify full Nissen *vs* partial toupet, only laparoscopic *vs* open approach; [4]Seventeen cases underwent laparoscopic Dor procedure. *n*: Study patients in the fundoplication group specifically; LTx: Lung transplant; BALF: Bronchoalveolar lavage fluid; BOS: Bronchiolitis obliterans syndrome; GERD: Gastroesophageal reflux disease; BMI: Body mass index; EGD: esophagogastroduodenoscopy.

their pulmonary function following antireflux surgery. Interestingly, Fisichella *et al*[119] investigated changes in BAL fluid analysis four weeks after antireflux surgery, and showed that in 8 lung transplant recipients, the percentages of neutrophils and lymphocytes in the BAL fluid were reduced, the concentration of myeloperoxide

and IL-1b tended to decrease, and the percentage of macrophages was increased. While this was a limited study given its small sample size, the findings suggest that antireflux surgery may restore the physiologic balance of pulmonary leukocyte populations with ensuing reduction in pro-inflammatory mediators[119]. Additionally, this same group detected decreased pepsin levels in transplant recipients with reflux that underwent antireflux surgery, compared to those that did not receive surgery. Both groups had higher pepsin levels compared against controls, whose levels were undetectable[43]. Notably, subjects with increased pepsin levels were noted to have more acute rejection episodes and faster progression to BOS[43], further underscoring the relevance and necessity of reflux and aspiration management in this patient population.

One important consideration surrounding antireflux surgery in this population is the appropriate timing of the procedure, not just before or after transplant, but also how soon after transplant would be of greatest benefit. Several groups argue that antireflux surgery should be considered in the pre-transplant period[50,117,122]. Linden *et al*[117] focused specifically on IPF patients, and demonstrated no perioperative complications or decrease in lung function over the 15-mo average follow-up. Importantly, patients treated with antireflux surgery had stable oxygen requirements, while control patients with IPF on the waiting list had a statistically significant deterioration[117]. Thus, in spite of theoretical risks in the setting of pre-transplant pulmonary compromise, the absence of serious complications in clinical practice led to the conclusions that pre-transplant antireflux surgery is safe, may ameliorate the progression of underlying disease while awaiting transplant, and provide early protection from reflux and aspiration upon transplantation[117]. Other groups similarly note that pre-transplant surgery may be performed safely, but acknowledge the high-risk nature of these patients given their limited pulmonary reserve. To accommodate these risks, the decision to operate should be made individually, based on objective measures of pulmonary function[16], and under the guidance of an experienced surgical team[122].

In patients that are unable to tolerate pre-transplant antireflux surgery, the timing of surgery post-transplant may be of great importance. Cantu *et al*[40] demonstrated that early fundoplication within 90 d of transplantation resulted in greater freedom from BOS and improved survival compared to later fundoplication, with post-transplant reflux incidence of 76%. Importantly, both BOS and survival were improved in the early post-transplant antireflux surgery group, compared to those with later surgery as well as those with reflux but without surgical intervention. Our group has similarly demonstrated the importance of early intervention. In a retrospective cohort study of 48 patients, we detected a significant increase in early allograft injury in late post-transplant antireflux surgery patients (mean time from transplant 1.8 years) compared to pre-transplant (mean time 3.5 years prior to transplant) and early post-transplant (mean time from transplant 118 d) antireflux surgical groups[103]. The surgeries were well tolerated in the pre- and early post-transplant groups. One death was reported in the late post-transplant group in a patient that had already developed BOS. The trend in this study supports the pathophysiologic model in which antireflux surgery reduces microaspiration events, as suggested by prior studies[16,34,74], and it is our speculation that the earlier antireflux surgery is performed, the greater the protection against reflux and aspiration events, which lowers the risk of pulmonary decline[103]. Interestingly, our study also highlights the lack of additional benefit to providing antireflux surgery pre-transplant compared to within 6 mo post-transplantation. Given the potentially elevated risks of pre-transplant surgery in this population, it may be reasonable to wait for the early post-transplant period to reduce peri-operative risks. Finally, although antireflux surgery performed concurrently with lung transplantation has been reported anecdotally, it has not been extensively studied and is not available at our institution. Over time, with the development of new and less invasive antireflux technologies such as the LYNX magnetic reflux management system (Torax, Shoreview, MN, USA), concurrent surgical antireflux management alongside transplantation may come under greater consideration.

CONCLUSION

This review has highlighted an abundance of research regarding the role of reflux in the pathophysiology of allograft injury following lung transplantation, along with options for diagnosis and management. Nevertheless, unanswered questions remain, and additional studies are needed to clarify the optimal modality and timing for reflux evaluation and management in these patients. As King *et al*[29] have previously discussed, there remains frustratingly no clear causal relationship between reflux and the development of BOS. Additionally, the absence of a gold standard to diagnose GERD, and the difficulties of defining and describing reflux severity continue to limit accuracy in patient stratification, given potential contributions from acid reflux, non-acid or bolus reflux, and aspiration[29]. Future studies should explore different objective measurements of reflux and aspiration parameters, better compare medical and surgical antireflux treatment options, extend follow-up times to capture longer-term clinical outcomes such as RAS or CLAD, and investigate newer antireflux interventions including minimally invasive surgery and advanced endoscopic techniques. However, it is clear that a definite association exists between reflux and lung disease, which represents a tangible and significant target to improve outcomes in the lung transplant population.

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