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Gastroesophageal Reflux and Altered Motility in Lung Transplant Rejection

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Abstract

Background—Lung transplantation has become an effective therapeutic option for selected patients with end stage lung disease. Long-term survival is limited by chronic rejection manifest as bronchiolitis obliterans syndrome (BOS). The aspiration of gastric contents has been implicated as a causative or additive factor leading to BOS. Gastroesophageal reflux (GER) and altered foregut motility are common both before and after lung transplantation. Further, the normal defense mechanisms against reflux are impaired in the allograft. Recent studies using biomarkers of aspiration have added to previous association studies to provide a growing body of evidence supporting the link between rejection and GER. Further, the addition of high-resolution manometry (HRM) and impedance technology to characterize bolus transit and the presence and extent of reflux regardless of pH might better identify at-risk patients. Although additional prospective studies are needed, fundoplication appears useful in the prevention or treatment of post-transplant BOS.

Purpose—This review will highlight the existing literature on the relationship of gastroesophageal reflux and altered motility to lung transplant rejection, particularly BOS. The article will conclude with a discussion of the evaluation and management of patients undergoing lung transplantation at our center.

Background/Introduction

Both single and double lung transplantation have become effective treatments for end stage lung disease resulting from a variety of etiologies [1]. Currently in the United States, there are nearly 30,000 solid organ transplants performed each year of which nearly 1,200 are lung [2]. Since the first human lung transplantation in 1963 [3], improvements in surgical technique, lung preservation, immunosuppression and the treatment of ischemic reperfusion injury and infection have increased the 1-year survival of lung transplant recipients to over 80% [4,5]. Despite these improvements, the survival of lung allograft recipients is significantly lower than with other solid organ transplants [2]. The primary limiting factor in long-term survival is the development of chronic rejection characterized by bronchiolitis obliterans (OB) [6].

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Obliterative Bronchiolitis and Bronchiolitis Obliterans Syndrome

OB is distinguished pathologically by the compromise of small airways via lymphocytic infiltration and collagen deposition leading to luminal obliteration and progressive airway obstruction [7]. Because of patchy involvement, OB is challenging to diagnose by transbronchial biopsy [8]. As such, a clinical correlate for OB was introduced in 1993 known as bronchiolitis obliterans syndrome (BOS), which characterizes the progressive decline in forced expiratory volume in one second FEV1 [9]. The prevalence of BOS at five years post transplant is 50% [10]. Five-year survival after the onset of BOS is only 30% to 40%, and survival at 5 years after transplantation is 20% to 40% lower in patients with BOS [11].

Several risk factors for the development of BOS have been identified including alloimmune-dependent mechanisms such as the number and severity of acute rejection episodes and HLA mismatching [12]. Infection, particularly from CMV, and ischemia have been identified as alloimmune independent factors [12] [13].

More recently, aspiration secondary to gastroesophageal reflux (GER) and altered foregut motility has been identified as potential contributors to lung allograft dysfunction [14,15]. Although establishing a causal relationship between GER and BOS has been difficult, there is accumulating evidence supporting the role of GER, whether primary or additive to other factors in the development of chronic allograft dysfunction. Establishing the role of GER in allograft dysfunction along with elucidating mechanisms and causative agents is important, as GER is amenable to treatment.

Gastroesophageal reflux and lung disease

Gastroesophageal reflux has long been associated with lung disease. Common in advanced lung disease, changes in diaphragmatic position, decreased lower esophageal sphincter pressure, and changes in intrathoracic pressure are proposed mechanisms favoring reflux [16]. Several studies have shown GER to be highly prevalent in numerous lung diseases including pulmonary fibrosis, systemic sclerosis, cystic fibrosis, COPD, and asthma [16–21]. To this point, the relationship between GER and lung disease has been based on association studies. The largest of these studies was a retrospective case-control study using esophagitis or peptic stricture as a surrogate for GER involving more than 200,000 US veterans. This study showed increased odds ratios associated with underlying GER of 1.36 for pulmonary fibrosis, 1.51 for asthma, 1.28 for chronic bronchitis, and 1.22 for chronic obstructive pulmonary disease (COPD), which all met statistical significance [17].

Altered motility in lung disease

Ineffective esophageal motility (IEM) is the most common motility disorder in patients with GER-associated respiratory symptoms [22]. Fouad *et al.* retrospectively investigated the frequency of esophageal motility abnormalities in patients with extra-esophageal symptoms of GERD and abnormal esophageal acid exposure on pH-metry [22]. They found IEM in 41% of patients with chronic cough ($p < 0.003$) and 53% with asthma ($p < 0.01$). The presence of IEM was associated with delayed esophageal acid clearance. While the criteria and terminology have evolved [23–25], the principle behind IEM is to identify manometric abnormalities that lead to ineffective esophageal bolus transit. The characterization of effective bolus clearance was initially based on normal esophageal contraction parameters in 95 healthy adults [26], and the evaluation of bolus clearance using video-manometry during barium swallows [27–29]. Manometric findings of failed or hypotensive peristalsis were shown to correlate with impaired forward transit and retrograde escape of barium [27]. Prior to this, in 1979 Pellegrini *et al.* evaluated 100 patients with abnormal pH studies. Using

symptoms along with pH and manometry studies, they found that patients aspirating (drop in pH, followed by acid taste and onset of cough or wheezing spell) had a 75% incidence of esophageal motor abnormality characterized by non-peristaltic contractions, and that acid clearance was significantly delayed in the supine position. Thus, without adequate esophageal motility and effective acid clearance, reflux events were more likely to cause respiratory symptoms. They also noted that subjective GER symptoms were insensitive for objective findings on pH studies [30].

DeMeester *et al.* evaluated 77 patients with respiratory symptoms for occult GER [31]. They found that the presence of nonspecific esophageal motility abnormality, subsequently re-classified as IEM, was directly related to increased esophageal acid exposure and the number of respiratory symptoms during pH testing ($p < 0.05$). Similarly, Patti *et al.* identified a higher prevalence of ineffective esophageal peristalsis and decreased lower esophageal sphincter (LES) pressure in patients with unexplained respiratory symptoms [32]. They diagnosed aspiration by respiratory symptoms during or within 3 minutes of a reflux episode on pH-metry. In patients aspirating, abnormal peristalsis caused delayed clearance in the proximal esophagus and higher acid exposure. Further, Sweet *et al.* evaluated 109 patients with end stage lung disease awaiting transplantation. They also found that reflux symptoms were not predictive of finding GER on pH-metry. Among patients with reflux, there was high prevalence of a hypotensive LES (55%) and impaired esophageal peristalsis (47%) [33].

Newer technology, as shown by Fox *et al.* with HRM [34], and Bulsiewicz et al. [35] with HRM combined with multichannel intraluminal impedance, has the ability to more accurately evaluate bolus clearance. Using this technology in patients with lung disease may strengthen the evidence for abnormal bolus transit as a contributor to GER-related aspiration. Further, as symptoms have been shown to be a poor correlation for objective findings, advancements in technology may allow more accurate identification of patients at risk. As discussed later, this is particularly relevant after lung transplantation.

Gastroesophageal reflux and altered motility in lung transplantation

Impaired Defense Mechanisms

Lung transplant recipients appear to be at increased risk of GER and aspiration through a number of mechanisms. The cough reflexes and mucociliary clearance which are the normal defense mechanisms against aspiration are dramatically impaired [36]. Further, mucociliary clearance has been measured to be less than 15% of normal in transplanted lungs [37,38]. Therefore, it can be hypothesized that even small amounts of aspiration could lead to significant injury, particularly with multiple repeated episodes over time.

Esophageal Dysmotility

To date, there are limited data on the impact of lung transplantation on esophageal motility. An increase in esophageal dysmotility and delayed gastric emptying after pneumonectomy has been described, which may be attributed to vagal nerve injury, ischemia, and local scarring related to surgery [39,40]. A small prospective study showed that a decrease in coordinated esophageal peristalsis was common after pneumonectomy for carcinoma [41]. Our center is currently investigating this potential association further in lung transplant recipients. Given the impaired defense mechanisms against reflux in this population, it can be hypothesized that impaired bolus transit may be of particular importance.

Gastroparesis

Gastroparesis is frequently present after heart and lung transplantation [42–45]. D'Ovidio *et al.* found delayed gastric emptying in 39 of 43 (91%) at 3 months and 17 of 21 (81%) at 12 months after lung transplant [44]. A recent AGA technical review indentified lung transplantation as a cause of gastroparesis, and concluded that gastroparesis in lung transplant recipients predisposes to GER with microaspiration [46]. Proposed mechanisms for gastroparesis in this population include vagal nerve injury related to surgery, infection, and effects of immunosuppressive drugs [42]. Gastroparesis in these patients can make medical management difficult. It may lead to complications such as electrolyte abnormalities, malnutrition, and weight loss. Further, variable absorption of immunosuppressive medications may increase the risk of allograft rejection. The nausea, vomiting, and gastroesophageal reflux related to gastroparesis may also increase the risk of aspiration pneumonitis.

Gastroesophageal Reflux After Transplantation

The potential relevance of GER and chronic aspiration as a cause for OB after lung transplantation was first proposed in a case series of eleven heart-lung transplant recipients in 1990 [14]. In this study, 5 patients had slow gastric emptying and aspiration with OB in 3 of these patients. More recently, a retrospective study involving lung transplant patients who survived at least six months and had pH-metry showed that 30 of 43 (69.8%) patients had abnormal total acid contact times. Further, a negative correlation was found between total or upright acid reflux and the FEV1 ratio at the time of pH-metry. This correlation persisted after multivariable analysis [47].

GER to the proximal sensor of a pH probe has been shown to be a reasonable surrogate for predicting the risk of aspiration [32,48,49]. In 1993, Patti *et al.* used dual sensor pH studies to strengthen the correlation between GER and respiratory symptoms in a group of 340 patients who underwent fundoplication for GER. They performed pH studies with a sensor at 5 and 20 cm above the manometrically-determined LES. They found a more predictable response to surgery in patients whose cough was correlated with both abnormal proximal and distal acid exposure [50]. They concluded that GER-related respiratory symptoms are multifactorial. They proposed that with only distal reflux, symptoms might be related to activation of a vagal reflex with consequent bronchoconstriction. However, with reflux into the proximal esophagus, symptoms are likely related to microaspiration [50]. Interestingly, they also commented that acid-reducing medications alter the pH of the refluxate, but the underlying mechanisms causing reflux persist and anti-reflux surgery more definitively treats reflux regardless of pH [50].

Multichannel Intraluminal Impedance

The introduction of esophageal multichannel intraluminal impedance testing by Silny in 1991 has provided a more accurate method of describing intraesophageal bolus movement [51]. Impedance testing is able to discriminate between gas and fluid reflux regardless of pH [52]. As expected, the use of esophageal impedance has confirmed that PPIs alter the pH of gastric refluxate, but do not significantly change the number of reflux events [53].

Impedance testing has recently started to be applied to the lung transplant population. Halsey *et al* published a single case report of a lung transplant patient with progressive allograft dysfunction on twice-daily PPI. Evaluation with impedance revealed significant non-acid reflux, which led to a laparoscopic Nissen fundoplication. The patient improved symptomatically, and spirometry values returned to the post-transplant baseline [54]. King *et al* evaluated 59 lung transplant patients with impedance. They found a significant prevalence of GER, both acid (65%) and non-acid (27%). They also found symptoms to be unreliable as

a predictor of objective findings. Further, they were able to demonstrate BOS-free survival in patients without abnormal liquid reflux exposure when both acid and non-acid events were included. The authors concluded that the method of identifying reflux is important and strengthens the association between GERD and BOS. This study provides further evidence that acid suppression may be inadequate to prevent GER-related BOS [55]. Although further studies are needed, the added information from impedance testing should continue to strengthen the association between GER and BOS.

Evaluation of Biomarkers

The agent in gastric refluxate that leads to allograft dysfunction is currently unknown and is an area of active investigation. There has been accumulating evidence related to the investigation of biomarkers in brochoalveolar lavage fluid (BALF). Ward *et al* measured pepsin in the serum and BALF of stable lung transplant patients and controls. Although there is currently no validated method to standardize measured levels, pepsin was found in all allograft recipients suggesting gastric aspiration. Further, in the non-transplant control group, pepsin levels were below the limit of detection. Treatment with a PPI was not correlated with pepsin levels [56]. This group then performed a larger prospective study to further investigate pepsin in BALF [57]. They looked at a group of 36 transplant patients, 4 normal volunteers, and 17 patients with unexplained chronic cough. They again found that pepsin levels in BALF were significantly higher in the transplant group. Interestingly, among transplant patients, pepsin levels were highest in the patients with acute rejection, a risk factor for progression to BOS [12,58]. Thus, the highest risk of significant aspiration leading to acute rejection may be early after transplantation. Continued efforts to better identify patients at risk of aspiration early after transplantation, and subsequent treatment may prevent or delay the development of BOS. Additionally, this study highlights that cough does not necessarily equal aspiration. In normal subjects, if refluxate reaches the upper airway it is likely to be cleared by intact defense mechanisms. However, as discussed previously, these defense mechanisms are dramatically impaired in the allograft.

As described previously, decreased foregut motility is common after lung transplantation, which may place transplant recipients at risk for duodenogastroesophageal reflux (DGER). D'Ovidio *et al.* investigated this further by evaluating for bile acids in BALF, and their potential role in BOS [59]. Elevated BALF bile acids were found in 20 (17%) of 120 transplant patients. Further, freedom from BOS was significantly reduced in patients with elevated BALF bile acids. Blondeau *et al.* used impedance and BALF testing for both pepsin and bile acids to further characterize GER in lung transplant recipients with and without BOS and non-transplant controls [60]. Similar to previous studies [56,57], all lung transplant recipients had increased levels of pepsin in the BALF compared to controls. Patients with BOS did not have increased GER or elevated pepsin in BALF. However, 70% of the patients with BOS had bile in BALF, compared with 31% of stable patients. Overall, bile acids were detected in BALF of 49% of the transplant patients and none of the non-transplant patients. Again, PPI treatment reduced acid reflux but did not affect nonacid reflux. Importantly, pepsin and bile levels in BALF were not reduced by PPI. The authors concluded that pepsin might be a more general marker of gastric aspiration. Further, bile acids may be a more specific marker for BOS and act as an important pathophysiologic factor. D'Ovidio *et al.* added to their previous work by further investigating whether GER and aspiration in lung transplant patients predicted the development of BOS. Proximal and distal esophageal pH testing and BALF assays for bile acids were performed prospectively at 3-months post-transplant in 50 patients. Freedom from BOS was reduced in patients with abnormal (proximal and/or distal) pH findings or BALF bile acids. They also found impaired pulmonary surfactant phospholipids and surfactant-associated proteins which function in the innate immune defense mechanisms of the lung. [44]. They concluded that bile acids could

promote BOS through direct epithelial injury or indirect dysregulation of lung surfactant proteins. Blondeau *et al* sought to determine reflux characteristics that may promote aspiration of bile acids using impedance. They studied 24 stable patients 1 year after transplantation. Acid exposure and the number of reflux events were unrelated to the presence of bile acids in the BALF. However, both nocturnal esophageal volume exposure and the number of nocturnal weakly acidic reflux events were significantly higher in patients who had bile acids in BALF. The authors hypothesized that the diminished defense mechanisms in transplant patients may be further impaired by physiologic changes that occur at night. These changes include delayed esophageal clearance and delayed gastric emptying. Further gastric bile acids have been found to be highest at night [61–63].

Animal Model

Hartwig *et al* have recently published a study using a model of rat lung transplantation to study the affects of filtered gastric aspirate on allograft dysfunction [64]. In these studies in which bile acids were directly aspirated into the transplanted lung, aspiration led to an exacerbation of lymphocytic lung inflammation and allograft rejection. This model may allow further elucidation of mechanisms leading to rejection, and provide additional candidate biomarkers involved in allograft injury.

Treatment

Macrolides

With the increased prevalence of disordered motility after transplant, and evidence suggesting that DGER may be important in BOS, it can be hypothesized that medications that modify motility may have a beneficial effect. Azithromycin (AZI) is a macrolide antibiotic that has frequently been used as a therapy for BOS with some success, although the mechanism of benefit is currently unknown [65–67]. Macrolide antibiotics produce a prokinetic effect on esophageal and gastric motility via activation of the motilin receptor [68]. Edelbroek *et al* has shown that erythromycin increases the rate of total and proximal stomach emptying of both solids and liquids [69]. To investigate this further, Mertens *et al* used impedance and BALF testing to evaluate the effect of azithromycin on GER and gastric aspiration parameters. They studied 3 groups; 35 patients off AZI, 12 patients on AZI (250mg, three times per week), and a separate group of 30 patients studied both before and after AZI treatment. They observed several notable findings. Patients on AZI treatment had significantly less GER, including decreased total number of reflux events, fewer reflux episodes reaching the proximal sensor, and decreased esophageal acid exposure. Additionally, bile acid levels in the BALF were significantly reduced after AZI treatment [70]. They speculated that AZI reduces gastric volume and modifies fundic acid distribution. AZI might also reduce duodenopancreatic contents in the stomach. Sifrim *et al.* have shown that AZI increases postprandial motility, and that gastric contractions originate more proximally in the stomach with AZI use [71]. Further, Koek *et al.* found that erythromycin induces faster clearance of DGER from the stomach [72]. Several recent studies have described a postprandial acid pocket that typically resides just below the GE junction. In patients with reflux, this acid pocket shows greater proximal extension. In normal subjects, this pocket can persist up to 2 h postprandially and remains highly acidic compared with the body of the stomach [73–75]. It is currently unknown what effect altered foregut motility has on this acid pocket. This may be particularly relevant in the lung transplant population.

Fundoplication

In 2000, Palmer *et al.* were the first group to demonstrate improvement in pulmonary function after fundoplication in a lung transplant recipient [76]. The patient initially received a double lung transplant for cystic fibrosis. However, the development of OB ultimately led

to retransplantation. There was an initial improvement in pulmonary function, but after 3 months, the FEV1 began to decline. Bronchoscopy with biopsy revealed inflammation without infection or rejection. Upper endoscopy revealed severe esophagitis, and a gastric-emptying study revealed marked gastroparesis with no appreciable emptying at 120 minutes. An upper GI series confirmed severe gastroparesis without mechanical obstruction. Despite aggressive medical treatment with TID PPI and QID cisapride, the patient had persistent decline in the FEV1 consistent with BOS. The patient therefore underwent fundoplication and experienced a dramatic and sustained improvement in the FEV1. In addition, the bronchial inflammation present in previous biopsy specimens completely resolved after surgery.

Davis *et al.* later published a retrospective review of 128 patients who underwent pH studies after transplantation [77]. The pH study was abnormal in 93 (73%) of patients, and 43 underwent fundoplication. At the time of fundoplication, 26 patients met criteria for BOS. After fundoplication, 16 patients had improved BOS scores such that 13 no longer met criteria for BOS. Further, in patients at least 6 months after lung transplantation and 6 months after fundoplication, the FEV1 improved by an average of 24%. Overall actuarial survival was significantly better in patients who had either normal pH studies or underwent fundoplication. The authors further hypothesized that it might be important to perform fundoplication before the late stages of BOS when irreversible scarring may be present.

Based on the hypothesis that treatment of reflux with early fundoplication might prevent BOS and improve survival, Cantu *et al.* performed a retrospective review in which patients were stratified into four groups: no history of reflux, history of reflux, history of reflux and early (< 90 days) fundoplication, and history of reflux and late fundoplication [78]. Post-transplant reflux was found in 76% of patients. In the 14 patients who underwent early fundoplication, actuarial survival was 100% at 1 and 3 years, compared to those with reflux and no intervention where survival was 92% and 76% at 1 and 3 years ($p < 0.02$). Further, freedom from BOS was 100% at 1 and 3 years in the early fundoplication patients, compared to 96% and 60% in patients with reflux and no fundoplication ($p < 0.01$). Although these results are intriguing, additional prospective randomized clinical trials (RCT) are needed to determine if surgical fundoplication provides a lasting benefit in terms of BOS prevention. At present, our center is in the process of initiating a multi-center RCT to prospectively evaluate the effect of fundoplication versus acid suppression alone on the development of BOS.

Peri-Transplant Evaluation and Management

Based on available data, experience at our center, and existing diagnostic modalities, we are currently using the following approach for the evaluation and management of patients undergoing lung transplantation. Prior to transplant, all patients undergo the following diagnostic studies:

1. High-resolution esophageal manometry
2. 24-hour pH or pH-impedance study (off anti-secretory therapy)
3. Upper GI series

Presently, we perform both 24-hour pH and pH-impedance studies off anti-secretory medications to increase the diagnostic yield. However, as stated previously, the proximal extent of GER may be an important parameter and our approach may change, as data emerge specific to this population.

When abnormal GER is identified pre-transplantation, the patient is treated medically with twice-daily PPI, and a fundoplication is performed as soon as clinically practical after allowing appropriate time for recovery from transplant surgery. Typically, this is within the first few weeks after transplantation. In an attempt to limit aspiration, these patients are made NPO until after fundoplication, and receive nutrition beyond the pylorus by a jejunal feeding tube placed at the time of transplantation. A gastric emptying study is obtained prior to fundoplication.

In patients who do not have a contraindication, it is currently our practice to perform a laparoscopic Nissen fundoplication in all patients with an abnormal pre-transplant pH study. There is debate in the literature regarding altering the type of fundoplication performed in patients with esophageal dysmotility. In non-transplant patients, it has been shown in two RCTs that the type of fundoplication need not be altered in patients with IEM [86–88]. At our institution, patients with more severe dysmotility generally undergo a Toupet (270 degree) fundoplication. In patients with aperistalsis, the management is more complicated. In some cases, these patients may not qualify for lung transplantation on the basis of the severity of esophageal dysmotility. If these patients do undergo lung transplantation, they typically receive a Nissen fundoplication with both a gastrostomy and jejunostomy tube for nutrition and medication delivery. This approach has been shown to be both safe and effective [89–91].

It can be debated whether a pre-operative EGD should be standard, or performed based on findings from an upper GI series and clinical symptoms. Given the often-tenuous pulmonary status of patients with end stage lung disease, we have favored the latter approach.

Post-Transplant Evaluation and Management

Approximately one month after transplantation patients without pre-operative reflux findings receive a follow-up 24-hour pH-impedance study off of anti-secretory medications. This is based on the insensitivity of symptoms to predict GER, and the suggestion that early rejection may lead to BOS. Further post-operative studies including manometry, gastric emptying, and pH testing is based on clinical course. Patients with an abnormal pH-impedance study post transplant who did not undergo fundoplication immediately after transplantation on the basis of an abnormal pre-transplant study will receive fundoplication at this time.

The management of gastroparesis after transplantation is similar to that in non-transplant patients, with anti-emetics, pro-kinetics, acid suppression, and dietary modification being the mainstay of initial therapy. Unfortunately, in refractory cases, there are limited suitable options. The injection of botulinum toxin into the pylorus may provide transient relief of symptoms [92,93]. However, a recent systematic review of available high-quality trials concluded that overall, there is insufficient evidence to recommend botulinum toxin therapy in patients with gastroparesis [94].

Although not ideal, in severe gastroparesis, surgical options including pyloroplasty or gastric bypass with esophagojejunostomy have been effective in case series [43,95]. When significant gastroparesis is identified prior to transplantation, pyloroplasty can be performed at the time of fundoplication.

Interestingly, the use of gastric electrical stimulation (GES) for severe gastroparesis has recently shown promise in this population. Yiannopoulos et al. first described the successful use of GES for the management of severe gastroparesis associated with malnutrition and recurrent aspiration in a heart-lung allograft recipient [96]. Filichia et al. reported similar success in a post-lung transplant patient treated with GES who had significant improvement

in symptoms and decreased variability in serum levels of immunosuppressive medications [97]. They further reported a series of three lung transplant patients who had improvement in nausea, vomiting, early satiety, appetite, and abdominal pain after GES [98]. Given the limited options in refractory gastroparesis, this data is intriguing. However, GES will need to be evaluated in a larger population to confirm its effectiveness.

Conclusions

Lung transplantation is an effective treatment for end stage lung disease. However, long-term survival is limited by the development of chronic allograft dysfunction manifest as BOS. GER and altered motility are common among patients with lung disease and the post lung transplant population. The evidence collected to date strongly supports a role for the aspiration of gastric contents as a causative or additive etiology to developing BOS. This is of great clinical importance as GER and aspiration are modifiable. Ongoing efforts to determine the ideal method for detecting GER-related aspiration should clarify which patients will benefit from treatment. Ideally, multicenter prospective studies will be performed to further address these issues.

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References

1. Theodore J, Lewiston N. Lung transplantation comes of age. N Engl J Med. 1990; 322(11):772–774. [PubMed: 2308605]
2. Mulligan MS, et al. Heart and lung transplantation in the United States, 1997–2006. Am J Transplant. 2008; 8(4 Pt 2):977–987. [PubMed: 18336700]
3. Blumenstock DA, Lewis C. The first transplantation of the lung in a human revisited. Ann Thorac Surg. 1993; 56(6):1423–1424. discussion 1424–5. [PubMed: 8267457]
4. Belperio JA, et al. Chronic lung allograft rejection: mechanisms and therapy. Proc Am Thorac Soc. 2009; 6(1):108–121. [PubMed: 19131536]
5. Hosenpud JD, et al. The Registry of the International Society for Heart and Lung Transplantation: eighteenth Official Report-2001. J Heart Lung Transplant. 2001; 20(8):805–815. [PubMed: 11502402]
6. Taylor DO, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-first official adult heart transplant report--2004. J Heart Lung Transplant. 2004; 23(7):796–803. [PubMed: 15285065]
7. Stewart S. Pathology of lung transplantation. Semin Diagn Pathol. 1992; 9(3):210–219. [PubMed: 1523359]
8. Yousem SA, et al. Revision of the 1990 working formulation for the classification of pulmonary allograft rejection: Lung Rejection Study Group. J Heart Lung Transplant. 1996; 15(1 Pt 1):1–15. [PubMed: 8820078]
9. Cooper JD, et al. A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allografts. International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 1993; 12(5):713–716. [PubMed: 8241207]
10. Trulock EP, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-first official adult lung and heart-lung transplant report--2004. J Heart Lung Transplant. 2004; 23(7):804–815. [PubMed: 15285066]
11. Valentine VG, et al. Actuarial survival of heart-lung and bilateral sequential lung transplant recipients with obliterative bronchiolitis. J Heart Lung Transplant. 1996; 15(4):371–383. [PubMed: 8732596]

12. Kroshus TJ, et al. Risk factors for the development of bronchiolitis obliterans syndrome after lung transplantation. J Thorac Cardiovasc Surg. 1997; 114(2):195–202. [PubMed: 9270635]
13. Novick RJ, et al. Influence of graft ischemic time and donor age on survival after lung transplantation. J Heart Lung Transplant. 1999; 18(5):425–431. [PubMed: 10363686]
14. Reid KR, et al. Importance of chronic aspiration in recipients of heart-lung transplants. Lancet. 1990; 336(8709):206–208. [PubMed: 1973771]
15. Lubetkin EI, et al. GI complications after orthotopic lung transplantation. Am J Gastroenterol. 1996; 91(11):2382–2390. [PubMed: 8931422]
16. Tobin RW, et al. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1998; 158(6):1804–1808. [PubMed: 9847271]
17. el-Serag HB, Sonnenberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. Gastroenterology. 1997; 113(3):755–760. [PubMed: 9287965]
18. Raghu G, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. Eur Respir J. 2006; 27(1):136–142. [PubMed: 16387946]
19. Bassotti G, et al. Esophageal dysfunction in scleroderma: relationship with disease subsets. Arthritis Rheum. 1997; 40(12):2252–2259. [PubMed: 9416865]
20. Casanova C, et al. Increased gastro-oesophageal reflux disease in patients with severe COPD. Eur Respir J. 2004; 23(6):841–845. [PubMed: 15218995]
21. Blondeau K, et al. Gastro-oesophageal reflux and aspiration of gastric contents in adult patients with cystic fibrosis. Gut. 2008; 57(8):1049–1055. [PubMed: 18372497]
22. Fouad YM, et al. Ineffective esophageal motility: the most common motility abnormality in patients with GERD-associated respiratory symptoms. Am J Gastroenterol. 1999; 94(6):1464–1467. [PubMed: 10364008]
23. Leite LP, et al. Ineffective esophageal motility (IEM): the primary finding in patients with nonspecific esophageal motility disorder. Dig Dis Sci. 1997; 42(9):1859–1865. [PubMed: 9331148]
24. Tutuian R, Castell DO. Clarification of the esophageal function defect in patients with manometric ineffective esophageal motility: studies using combined impedance-manometry. Clin Gastroenterol Hepatol. 2004; 2(3):230–236. [PubMed: 15017607]
25. Blonski W, et al. Revised criterion for diagnosis of ineffective esophageal motility is associated with more frequent dysphagia and greater bolus transit abnormalities. Am J Gastroenterol. 2008; 103(3):699–704. [PubMed: 18341490]
26. Richter JE, et al. Esophageal manometry in 95 healthy adult volunteers. Variability of pressures with age and frequency of "abnormal" contractions. Dig Dis Sci. 1987; 32(6):583–592. [PubMed: 3568945]
27. Kahrilas PJ, Dodds WJ, Hogan WJ. Effect of peristaltic dysfunction on esophageal volume clearance. Gastroenterology. 1988; 94(1):73–80. [PubMed: 3335301]
28. Spechler SJ, Castell DO. Classification of oesophageal motility abnormalities. Gut. 2001; 49(1): 145–151. [PubMed: 11413123]
29. Richter JE, et al. Relationship of radionuclide liquid bolus transport and esophageal manometry. J Lab Clin Med. 1987; 109(2):217–224. [PubMed: 3805872]
30. Pellegrini CA, et al. Gastroesophageal reflux and pulmonary aspiration: incidence, functional abnormality, and results of surgical therapy. Surgery. 1979; 86(1):110–119. [PubMed: 36677]
31. DeMeester TR, et al. Chronic respiratory symptoms and occult gastroesophageal reflux. A prospective clinical study and results of surgical therapy. Ann Surg. 1990; 211(3):337–345. [PubMed: 2310240]
32. Patti MG, Debas HT, Pellegrini CA. Esophageal manometry and 24-hour pH monitoring in the diagnosis of pulmonary aspiration secondary to gastroesophageal reflux. Am J Surg. 1992; 163(4): 401–406. [PubMed: 1558280]
33. Sweet MP, et al. The prevalence of distal and proximal gastroesophageal reflux in patients awaiting lung transplantation. Ann Surg. 2006; 244(4):491–497. [PubMed: 16998357]

34. Fox M, et al. High-resolution manometry predicts the success of oesophageal bolus transport and identifies clinically important abnormalities not detected by conventional manometry. Neurogastroenterol Motil. 2004; 16(5):533–542. [PubMed: 15500509]
35. Bulsiewicz WJ, et al. Esophageal pressure topography criteria indicative of incomplete bolus clearance: a study using high-resolution impedance manometry. Am J Gastroenterol. 2009; 104(11):2721–2728. [PubMed: 19690527]
36. Veale D, et al. Ciliary beat frequency in transplanted lungs. Thorax. 1993; 48(6):629–631. [PubMed: 8346493]
37. Kirk AJ, et al. Impaired gastrointestinal motility in pulmonary transplantation. Lancet. 1990; 336(8717):752. [PubMed: 1975923]
38. Herve P, et al. Impairment of bronchial mucociliary clearance in long-term survivors of heart/lung and double-lung transplantation. The Paris-Sud Lung Transplant Group. Chest. 1993; 103(1):59–63. [PubMed: 8380268]
39. Suen HC, Hendrix H, Patterson GA. Special article: physiologic consequences of pneumonectomy. Consequences on the esophageal function. 1999. Chest Surg Clin N Am. 2002; 12(3):587–595. [PubMed: 12469489]
40. Suen HC, Hendrix H, Patterson GA. Physiologic consequences of pneumonectomy. Consequences on the esophageal function. Chest Surg Clin N Am. 1999; 9(2):475–483. xiii. [PubMed: 10365277]
41. Dougenis D, et al. Motility disorders of the esophagus before and after pneumonectomy for lung carcinoma. Eur Surg Res. 1996; 28(6):461–465. [PubMed: 8954323]
42. Berkowitz N, et al. Gastroparesis after lung transplantation. Potential role in postoperative respiratory complications. Chest. 1995; 108(6):1602–1607. [PubMed: 7497768]
43. Sodhi SS, et al. Gastroparesis after combined heart and lung transplantation. J Clin Gastroenterol. 2002; 34(1):34–39. [PubMed: 11743243]
44. D'Ovidio F, et al. The effect of reflux and bile acid aspiration on the lung allograft and its surfactant and innate immunity molecules SP-A and SP-D. Am J Transplant. 2006; 6(8):1930–1938. [PubMed: 16889547]
45. Au J, et al. Upper gastrointestinal dysmotility in heart-lung transplant recipients. Ann Thorac Surg. 1993; 55(1):94–97. [PubMed: 8417718]
46. Parkman HP, Hasler WL, Fisher RS. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. Gastroenterology. 2004; 127(5):1592–1622. [PubMed: 15521026]
47. Hadjiliadis D, et al. Gastroesophageal reflux disease in lung transplant recipients. Clin Transplant. 2003; 17(4):363–368. [PubMed: 12868994]
48. Johnson DA, et al. Pulmonary disease in progressive systemic sclerosis. A complication of gastroesophageal reflux and occult aspiration? Arch Intern Med. 1989; 149(3):589–593. [PubMed: 2919934]
49. Patti MG, Debas HT, Pellegrini CA. Clinical and functional characterization of high gastroesophageal reflux. Am J Surg. 1993; 165(1):163–166. discussion 166–8. [PubMed: 8418693]
50. Patti MG, et al. Effect of laparoscopic fundoplication on gastroesophageal reflux disease-induced respiratory symptoms. J Gastrointest Surg. 2000; 4(2):143–149. [PubMed: 10675237]
51. J S. Intraluminal multiple electric impedance procedure for measurement of gastrointestinal motility. J Gastrointest Motil. 1991; 3:151–162.
52. Bredenoord AJ, Smout AJ. Esophageal motility testing: impedance-based transit measurement and high-resolution manometry. Gastroenterol Clin North Am. 2008; 37(4):775–791. vii. [PubMed: 19028317]
53. Vela MF, et al. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. Gastroenterology. 2001; 120(7):1599–1606. [PubMed: 11375942]
54. Halsey KD, et al. Non-acidic supraesophageal reflux associated with diffuse alveolar damage and allograft dysfunction after lung transplantation: a case report. J Heart Lung Transplant. 2008; 27(5):564–567. [PubMed: 18442725]

55. King BJ, et al. Gastroesophageal reflux in bronchiolitis obliterans syndrome: a new perspective. J Heart Lung Transplant. 2009; 28(9):870–875. [PubMed: 19716037]
56. Ward C, et al. Pepsin like activity in bronchoalveolar lavage fluid is suggestive of gastric aspiration in lung allografts. Thorax. 2005; 60(10):872–874. [PubMed: 16055614]
57. Stovold R, et al. Pepsin, a biomarker of gastric aspiration in lung allografts: a putative association with rejection. Am J Respir Crit Care Med. 2007; 175(12):1298–1303. [PubMed: 17413126]
58. Egan JJ, et al. Obliterative bronchiolitis after lung transplantation: a repetitive multiple injury airway disease. Am J Respir Crit Care Med. 2004; 170(9):931–932. [PubMed: 15504816]
59. D'Ovidio F, et al. Bile acid aspiration and the development of bronchiolitis obliterans after lung transplantation. J Thorac Cardiovasc Surg. 2005; 129(5):1144–1152. [PubMed: 15867792]
60. Blondeau K, et al. Gastro-oesophageal reflux and gastric aspiration in lung transplant patients with or without chronic rejection. Eur Respir J. 2008; 31(4):707–713. [PubMed: 18057058]
61. Blondeau K, et al. Nocturnal weakly acidic reflux promotes aspiration of bile acids in lung transplant recipients. J Heart Lung Transplant. 2009; 28(2):141–148. [PubMed: 19201339]
62. Gotley DC, et al. Composition of gastro-oesophageal refluxate. Gut. 1991; 32(10):1093–1099. [PubMed: 1955160]
63. Pasricha PJ. Effect of sleep on gastroesophageal physiology and airway protective mechanisms. Am J Med. 2003; 115 Suppl 3A:114S–118S. [PubMed: 12928086]
64. Hartwig MG, et al. Chronic aspiration of gastric fluid accelerates pulmonary allograft dysfunction in a rat model of lung transplantation. J Thorac Cardiovasc Surg. 2006; 131(1):209–217. [PubMed: 16399314]
65. Yates B, et al. Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. Am J Respir Crit Care Med. 2005; 172(6):772–775. [PubMed: 15976371]
66. Verleden GM, et al. Azithromycin reduces airway neutrophilia and interleukin-8 in patients with bronchiolitis obliterans syndrome. Am J Respir Crit Care Med. 2006; 174(5):566–570. [PubMed: 16741151]
67. Verleden GM, Dupont LJ. Azithromycin therapy for patients with bronchiolitis obliterans syndrome after lung transplantation. Transplantation. 2004; 77(9):1465–1467. [PubMed: 15167610]
68. Peeters TL. Erythromycin and other macrolides as prokinetic agents. Gastroenterology. 1993; 105(6):1886–1899. [PubMed: 8253365]
69. Edelbroek MA, et al. Effects of erythromycin on gastric emptying, alcohol absorption and small intestinal transit in normal subjects. J Nucl Med. 1993; 34(4):582–588. [PubMed: 8455074]
70. Mertens V, et al. Azithromycin reduces gastroesophageal reflux and aspiration in lung transplant recipients. Dig Dis Sci. 2009; 54(5):972–979. [PubMed: 19241165]
71. Sifrim D, et al. Comparison of the effects of midecamycin acetate and azithromycin on gastrointestinal motility in man. Drugs Exp Clin Res. 1994; 20(3):121–126. [PubMed: 7956719]
72. Koek GH, et al. Mechanisms underlying duodeno-gastric reflux in man. Neurogastroenterol Motil. 2005; 17(2):191–199. [PubMed: 15787939]
73. Beaumont H, et al. The position of the acid pocket as a major risk factor for acidic reflux in healthy subjects and GERD patients. Gut. 2009
74. Fletcher J, et al. Unbuffered highly acidic gastric juice exists at the gastroesophageal junction after a meal. Gastroenterology. 2001; 121(4):775–783. [PubMed: 11606490]
75. Tytgat GN, et al. New algorithm for the treatment of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2008; 27(3):249–256. [PubMed: 17973975]
76. Palmer SM, et al. Gastroesophageal reflux as a reversible cause of allograft dysfunction after lung transplantation. Chest. 2000; 118(4):1214–1217. [PubMed: 11035701]
77. Davis RD Jr, et al. Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation. J Thorac Cardiovasc Surg. 2003; 125(3):533–542. [PubMed: 12658195]
78. Cantu E 3rd. J. Maxwell Chamberlain Memorial Paper. Early fundoplication prevents chronic allograft dysfunction in patients with gastroesophageal reflux disease. Ann Thorac Surg. 2004; 78(4):1142–1151. discussion 1142–51. [PubMed: 15464462]

79. Lund RJ, et al. Laparoscopic Toupet fundoplication for gastroesophageal reflux disease with poor esophageal body motility. J Gastrointest Surg. 1997; 1(4):301–308. discussion 308. [PubMed: 9834362]
80. Freys SM, et al. Tailored augmentation of the lower esophageal sphincter in experimental antireflux operations. Surg Endosc. 1997; 11(12):1183–1188. [PubMed: 9373290]
81. Chrysos E, et al. Laparoscopic surgery for gastroesophageal reflux disease patients with impaired esophageal peristalsis: total or partial fundoplication? J Am Coll Surg. 2003; 197(1):8–15. [PubMed: 12831918]
82. Biertho L, Sebajang H, Anvari M. Effects of laparoscopic Nissen fundoplication on esophageal motility: long-term results. Surg Endosc. 2006; 20(4):619–623. [PubMed: 16508818]
83. Pizza F, et al. Influence of esophageal motility on the outcome of laparoscopic total fundoplication. Dis Esophagus. 2008; 21(1):78–85. [PubMed: 18197944]
84. Ravi N, et al. Acid normalization and improved esophageal motility after Nissen fundoplication: equivalent outcomes in patients with normal and ineffective esophageal motility. Am J Surg. 2005; 190(3):445–450. [PubMed: 16105534]
85. Herbella FA, et al. Effect of partial and total laparoscopic fundoplication on esophageal body motility. Surg Endosc. 2007; 21(2):285–288. [PubMed: 17122978]
86. Booth MI, et al. Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. Br J Surg. 2008; 95(1):57–63. [PubMed: 18076018]
87. Robertson AG, et al. Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry (Br J Surg 2008; 95: 57–63). Br J Surg. 2008; 95(6):799. author reply 799–800. [PubMed: 18446759]
88. Strate U, et al. Laparoscopic fundoplication: Nissen versus Toupet two-year outcome of a prospective randomized study of 200 patients regarding preoperative esophageal motility. Surg Endosc. 2008; 22(1):21–30. [PubMed: 18027055]
89. Hartwig MG, Appel JZ, Davis RD. Antireflux surgery in the setting of lung transplantation: strategies for treating gastroesophageal reflux disease in a high-risk population. Thorac Surg Clin. 2005; 15(3):417–427. [PubMed: 16104132]
90. O'Halloran EK, et al. Laparoscopic Nissen fundoplication for treating reflux in lung transplant recipients. J Gastrointest Surg. 2004; 8(1):132–137. [PubMed: 14746846]
91. Lau CL, et al. Laparoscopic antireflux surgery in the lung transplant population. Surg Endosc. 2002; 16(12):1674–1678. [PubMed: 12140642]
92. Bromer MQ, et al. Endoscopic pyloric injection of botulinum toxin A for the treatment of refractory gastroparesis. Gastrointest Endosc. 2005; 61(7):833–839. [PubMed: 15933684]
93. Reddymasu SC, et al. Endoscopic pyloric injection of botulinum toxin-A for the treatment of postvagotomy gastroparesis. Am J Med Sci. 2009; 337(3):161–164. [PubMed: 19174691]
94. Bai Y, et al. A Systematic Review on Intrapyloric Botulinum Toxin Injection for Gastroparesis. Digestion. 2010; 81(1):27–34. [PubMed: 20029206]
95. Akindipe OA, et al. The surgical management of severe gastroparesis in heart/lung transplant recipients. Chest. 2000; 117(3):907–910. [PubMed: 10713028]
96. Yiannopoulos A, et al. Gastric pacing for severe gastroparesis in a heart-lung transplant recipient. J Heart Lung Transplant. 2004; 23(3):371–374. [PubMed: 15019648]
97. Filichia LA, Baz MA, Cendan JC. Simultaneous fundoplication and gastric stimulation in a lung transplant recipient with gastroparesis and reflux. JSLS. 2008; 12(3):303–305. [PubMed: 18765058]
98. Filichia LA, Cendan JC. Small case series of gastric stimulation for the management of transplant-induced gastroparesis. J Surg Res. 2008; 148(1):90–93. [PubMed: 18570936]