GERD and End Stage Lung Disease

Disclosures

• No disclosures relevant to this presentation
GERD and End Stage Lung Disease

Objectives

- Discuss relationship between GERD and end-stage lung disease
  - Review pathophysiology
  - Discuss medical and surgical treatment
- Discuss role of GERD in the evaluation and treatment of patients with end-stage lung disease before and after transplant
Pulmonary Disease in Progressive Systemic Sclerosis
A Complication of Gastroesophageal Reflux and Occult Aspiration?

- Prospective evaluation of consecutive series of 13 patients with SSc at Bethesda Naval Hospital
- At enrollment all completed reflux questionnaire to determine presence of heartburn, regurgitation, dysphagia
- Evaluation included
  - EGD with biopsy (3-5 and 15-17 cm above LES)
    - Esophagitis based in Ismail-Beigi criteria
  - Conventional manometry
  - Dual probe pH monitoring (score > 22 defined as abnormal)
  - Tc99 sulfur colloid aspiration scan
Pulmonary Disease in Progressive Systemic Sclerosis
A Complication of Gastroesophageal Reflux and Occult Aspiration?

- Documented reflux on endoscopy
  - Visible esophagitis in 8/13 (62%), 4 had Barrett’s
  - Esophagitis on histology in 13/13 distally, proximally in 9/13 (69%)
- Abnormal pH testing in 7/13 (54%)
- Motility findings
  - Defective LES in 10/13 (77%), absent peristalsis in 10/13 (77%) and weak peristalsis in 3/13 (33%)
- Strong inverse correlation ($r^2=0.84$) between both the proximal and distal pH scores and the DLCO
**GERD and End Stage Lung Disease**

Reflux and GERD Commonly Coexist

<table>
<thead>
<tr>
<th>Disease</th>
<th>Author</th>
<th># of Subjects</th>
<th>+ Reflux</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>Casanova C 2004</td>
<td>42</td>
<td>62% abnormal pH</td>
</tr>
<tr>
<td></td>
<td>Kamble N 2013</td>
<td>50</td>
<td>78% abnormal pH</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>Feigelson J 1987</td>
<td>46</td>
<td>63% esophagitis</td>
</tr>
<tr>
<td></td>
<td>Button BM 2005</td>
<td>11</td>
<td>91% abnormal pH</td>
</tr>
<tr>
<td></td>
<td>D’Ovidio F 2005</td>
<td>5</td>
<td>100% symptoms</td>
</tr>
<tr>
<td>Idiopathic Pulm Fibrosis</td>
<td>Mays EE 1976</td>
<td>48</td>
<td>73% hiatal hernia 44% spont. reflux</td>
</tr>
<tr>
<td></td>
<td>Tobin RW 1998</td>
<td>17</td>
<td>94% abnormal pH</td>
</tr>
<tr>
<td></td>
<td>Raghu G 2006</td>
<td>46</td>
<td>87% abnormal pH</td>
</tr>
<tr>
<td></td>
<td>D’Ovidio F 2005</td>
<td>26</td>
<td>65% symptoms</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Stentoft P 1987</td>
<td>55</td>
<td>70% symptoms 54% abnormal pH</td>
</tr>
<tr>
<td></td>
<td>D’Ovidio F 2005</td>
<td>10</td>
<td>50% symptoms</td>
</tr>
<tr>
<td></td>
<td>Marie I 2001</td>
<td>42</td>
<td>40% esophagitis</td>
</tr>
<tr>
<td></td>
<td>Savarino E 2009</td>
<td>40</td>
<td>70% abnormal pH</td>
</tr>
</tbody>
</table>
GERD and End Stage Lung Disease
Possible Relationships

• Association by chance alone
• GERD and end stage lung disease share an underlying cause
• End stage lung disease causes (or worsens) reflux
• Reflux causes (or worsens) end stage lung disease
Comorbid Occurrence of Laryngeal or Pulmonary Disease With Esophagitis in United States Military Veterans

- Case population included all veterans discharged from 172 VA Hospitals with diagnosis of esophagitis/stricture from 1981-1994
  - 92,860 with esophagitis, 14,201 stricture, 5,695 both
- Control population consisted of unmatched subjects randomly selected from files each year of the study
  - Significantly younger, more females and fewer whites
- Logistic regression performed to assess the association between esophagitis/stricture and pulmonary disorders
Comorbid Occurrence of Laryngeal or Pulmonary Disease With Esophagitis in United States Military Veterans

Table 2. Pulmonary Disorders Associated With Esophagitis or Stricture

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>OR</th>
<th>95% CI</th>
<th>Wald’s $\chi^2$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic bronchitis</td>
<td>1.28</td>
<td>1.22–1.34</td>
<td>107.049</td>
<td>0.00001</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>1.51</td>
<td>1.43–1.59</td>
<td>242.097</td>
<td>0.00001</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1.22</td>
<td>1.16–1.27</td>
<td>68.698</td>
<td>0.00001</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>1.36</td>
<td>1.25–1.48</td>
<td>53.675</td>
<td>0.00001</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>1.26</td>
<td>1.09–1.47</td>
<td>9.350</td>
<td>0.0022</td>
</tr>
<tr>
<td>Pulmonary collapse</td>
<td>1.31</td>
<td>1.23–1.40</td>
<td>67.177</td>
<td>0.00001</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.15</td>
<td>1.12–1.18</td>
<td>103.067</td>
<td>0.00001</td>
</tr>
</tbody>
</table>
Exacerbations of COPD and symptoms of gastroesophageal reflux: a systematic review and meta-analysis

- Systematic review and meta-analysis of seven studies (n=341) reporting association between GERD and COPD and risk of exacerbation
- Frequency of GERD higher in patients with COPD than controls (RR 13.06, CI 3.64-46.87, p<0.001)
Hypothesis #1

**GERD is a Result of ESLD**

- Drugs used to treat lung disease can promote reflux
  - Theophylline, beta-agonists, anticholinergics, steroids
- Changes in diaphragm position
  - Hiatal hernia, altered geometry of the LES
- Exaggerated respiratory effort can overcome the LES barrier
- No data exist that reversal of lung disease (i.e. transplantation) eliminates reflux
  - Young LR, CHEST 2003;124:1689-93
    - Abnormal pH testing in 8/23 (35%) pre-txp, 15/23 (65%) post-txp
    - All patients with abnormal reflux preop had it postop
Hypothesis #2 – GERD Causes ESLD

Conditions Necessary to Establish a Causal Link

- Human/animal studies showing inducing GERD creates lung disease X
- Epidemiologic evidence that the two conditions co-exist more commonly than expected by chance ✓
- There is a plausible pathophysiologic mechanism
- Demonstration of a “dose-response” relationship between amount of acid exposure and severity of disease
- Evidence that elimination of reflux leads to healing or halts progression
Hypothesis #2

**GERD Causes/Exacerbates ESLD**

**Figure 1**

The artist’s representation illustrates the proposed mechanisms by which aspiration of GERD is thought to induce lung deterioration and BOS. Risk factors of GERD that may play a role in the pathophysiology of GERD-induced aspiration are depicted: decreased esophageal peristalsis, hypotensive LES, TLESR episodes, DGE, the presence of duodenogastric reflux, and a transdiaphragmatic gastroesophageal pressure gradient.
GERD and End Stage Lung Disease
Clinical Evidence of Aspiration

- Case control study demonstrates higher pepsin levels in BAL fluid during exacerbation of IPF\(^1\)
- Salivary pepsin levels are frequently elevated in IPF (81% vs. 36% controls)\(^2\)
- Salivary pepsin is elevated in 61% of patients with COPD\(^3\)
- Pepsin in exhaled breath condensate correlates with GERD symptoms in COPD\(^4\)
- Meta-analysis demonstrated GERD as a risk factor for exacerbations of COPD\(^5\)

\(^1\) Lee JS, Eur Respir J 2012;39:352-8
\(^2\) Dudziak JM, Thorax 2013;68:A18-19
\(^3\) Strugala V, researchgate.net/publication/271513713
\(^4\) Timms C, J Breath Res 2012;6:016003
\(^5\) Sakae TM, J Bras Pneumol 2013;39:259-71
### Table 2—Incidence of Radiographically Demonstrable Hiatal Hernias and Reflux in Control Group as Compared to Patients with Pulmonary Fibrosis at Given Ages

<table>
<thead>
<tr>
<th>Age Groups of Subjects in Years</th>
<th>Control Group</th>
<th>Pulmonary Fibrosis Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>No.</td>
</tr>
<tr>
<td>20-29</td>
<td>49</td>
<td>1</td>
</tr>
<tr>
<td>30-39</td>
<td>47</td>
<td>1</td>
</tr>
<tr>
<td>40-49</td>
<td>102</td>
<td>4</td>
</tr>
<tr>
<td>50-59</td>
<td>146</td>
<td>15</td>
</tr>
<tr>
<td>60-69</td>
<td>89</td>
<td>15</td>
</tr>
<tr>
<td>&gt;69</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>Totals</td>
<td>468</td>
<td>63</td>
</tr>
</tbody>
</table>

*P < 0.001, Chi-square.

- **Control Group**
  - Upper gastrointestinal series: 49, 47, 102, 146, 89, 35
  - Patients with hiatal hernia: 2, 4, 10, 43, 28, 5
  - Patients with reflux: Not tabulated

- **Pulmonary Fibrosis Group**
  - Upper gastrointestinal series: 1, 1, 7, 20, 22, 12
  - Patients with hiatal hernia: 1, 1, 4, 15, 15, 10
  - Patients with reflux: 0, 1, 2, 12, 8, 5

- **Totals**: 46, 73
Prevalence of Gastroesophageal Reflux in End-Stage Lung Disease Candidates for Lung Transplant

Abnormal body manometry in 26/78 (33%) of patients

Table 4. Manometric Findings for All Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>LES tone (normal range 16–30 mm Hg)</td>
<td>13 (5–32)</td>
<td>13 (5–25)</td>
<td>12 (5–32)</td>
</tr>
<tr>
<td>Wave amplitude (normal range 40–180 mm Hg)</td>
<td>74 (0–195)</td>
<td>75 (0–195)</td>
<td>68 (15–177)</td>
</tr>
<tr>
<td>% Peristalsis (normal &gt;80%)</td>
<td>100% (0–100)</td>
<td>100% (0–100)</td>
<td>100% (10–100)</td>
</tr>
<tr>
<td>% of Patients With Abnormal Test</td>
<td>All Patients (78)</td>
<td>Symptomatic (49)</td>
<td>Asymptomatic (29)</td>
</tr>
<tr>
<td>↓ LES tone</td>
<td>72% (56)</td>
<td>78% (38)</td>
<td>62% (18)</td>
</tr>
<tr>
<td>↓ Wave amplitude</td>
<td>21% (16)</td>
<td>18% (9)</td>
<td>24% (7)</td>
</tr>
<tr>
<td>↓ Peristalsis</td>
<td>24% (19)</td>
<td>29% (14)</td>
<td>17% (5)</td>
</tr>
</tbody>
</table>

*Values are given as median (range).

LES = lower esophageal sphincter; ↓ = reduced.
Prevalence of Gastroesophageal Reflux in End-Stage Lung Disease Candidates for Lung Transplant

Delayed gastric emptying present for solids [16/36 (44%)] and liquids [7/29 (24%)] of patients

Table 6. Gastric Emptying Findings

<table>
<thead>
<tr>
<th>Variable</th>
<th>Liquids Gastric Emptying</th>
<th>Solids Gastric Emptying</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COPD (5)</td>
<td>CF (3)</td>
</tr>
<tr>
<td>Half-time (min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>median (range)</td>
<td></td>
</tr>
<tr>
<td>% Prolonged</td>
<td>20% (1)</td>
<td>33% (1)</td>
</tr>
</tbody>
</table>

CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; IPF = idiopathic pulmonary fibrosis.
GERD and End Stage Lung Disease
Pathophysiology

Risk factors for GERD, such as impaired esophageal and gastric motility, may indirectly affect the aspiration process. In fact, although impaired esophageal and gastric motility is not independently a cause of lung deterioration or allograft failure, they may cause or exacerbate GERD (Fig. 1).

The introduction of sophisticated diagnostic technologies, such as high-resolution manometry (HRM) and multichannel pH-impedance testing, has allowed clinicians to document subtle motility pattern disturbances along with nonacidic reflux events previously undetectable or indistinguishable from GERD. With increasing availability and incorporation of such diagnostic testing, abnormalities in patients with ESLD and lung transplantation have been better recognized (Figs. 2-4). For example, although the high prevalence of abnormal gastroesophageal reflux in patients with IPF has been clearly and extensively documented in the literature, recent studies have incorporated new diagnostic testing for esophageal motility and GERD in this patient population.

A recent prospective study conducted by Raghuram et al. in 2006 reported that 87% of 65 IPF patients had abnormal reflux determined by the use of 24-h pH monitoring, which was thought to be an underestimate because 65% of the patients were on antireflux medication. However, despite the increased prevalence of GERD in patients with IPF, the contribution of abnormalities of esophageal peristalsis and the lower esophageal sphincter (LES) on the development of GERD in these patients is less clear and may reflect patient selection in different lung transplant centers or study methodology. For instance, colleagues at the University of California, San Francisco, evaluated 109 patients with ESLD awaiting lung transplantation and found a high prevalence of a hypotensive LES (55%) and impaired esophageal peristalsis (47%) among patients with GERD. Patients with IPF, however, comprised only 25% of the patient population.

Another follow-up study on 35 patients with GERD (15 patients before and 20 patients after transplantation) showed that impaired esophageal peristalsis was frequent (it was present in 10 of 15 patients before transplantation and in 15 of 20 patients after transplantation), although only five and four patients had IPF before and after transplantation, respectively. To further clarify the role of abnormal esophageal motility in patients with IPF, a study jointly conducted at our institution and University of Chicago attempted to bring to light this point by using HRM, barium swallow, 24-h pH monitoring, and upper endoscopy to characterize patterns of esophageal...
We hypothesized that an increase in the pressure some patients with pulmonary disease may induce GERD exaggerated negative intrathoracic pressure that occurs in Dig Dis Sci (2011) 56:1718–1722 1719

Patients with a manometrically defective LES were referred to our esophageal function laboratory for assessment of reflux symptoms. The evaluation included esophageal manometry and 24-h ambulatory pH monitor-video-esophagram, upper gastrointestinal endoscopy, and documented chronic pulmonary disease were excluded. This 

Materials and Methods

cause of increased esophageal acid exposure in some patients with a manometrically normal LES. Patients with IEM or esophageal stricture were also excluded. The LES pressure fluctuation was calculated and a score 14.72 was considered abnormal.

Calculations of the Intra-Abdominal and Intra-Thoracic Pressure Gradient Across the Gastroesophageal Junction

Fig. 1

Thoraco-abdominal pressure gradients during the phases of respiration contribute to gastroesophageal reflux disease.

Line A: intra-abdominal inspiratory pressure
Line B: intra-abdominal expiratory pressure
Line C: intra-thoracic expiratory pressure
Line D: intra-thoracic inspiratory pressure

Abdominal pressure fluctuation: A-B
Thoracic pressure fluctuation: C-D
Inspiratory pressure gradient: A-D
Expiratory pressure gradient: B-C

Keck Medical Center of USC

Thoraco-Abdominal Pressure Gradients During the Phases of Respiration Contribute to Gastroesophageal Reflux Disease

Table 3 Multi-variable analysis of the predictors for an abnormal composite pH score in patients with a manometrically normal barrier*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspiratory thoraco-abdominal pressure gradient</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Residual pressure on relaxation</td>
<td>0.002</td>
</tr>
<tr>
<td>Intra-thoracic pressure fluctuation</td>
<td>0.023</td>
</tr>
<tr>
<td>Resting pressure of the LES</td>
<td>0.049</td>
</tr>
<tr>
<td>Overall length of the LES</td>
<td>0.205</td>
</tr>
<tr>
<td>Gender</td>
<td>0.356</td>
</tr>
<tr>
<td>Intra-abdominal pressure fluctuation</td>
<td>0.519</td>
</tr>
<tr>
<td>Abdominal length of the LES</td>
<td>0.598</td>
</tr>
<tr>
<td>Age</td>
<td>0.971</td>
</tr>
<tr>
<td>BMI</td>
<td>0.982</td>
</tr>
<tr>
<td>Expiratory thoraco-abdominal pressure gradient</td>
<td>0.999</td>
</tr>
</tbody>
</table>

LES lower esophageal sphincter, BMI body mass index
*All the parameters except gender were entered as continuous variables into this multi-variable analysis
Thoraco-Abdominal Pressure Gradients During the Phases of Respiration Contribute to Gastroesophageal Reflux Disease

An abnormal composite pH score was present in 60 (39.7%) of the 151 patients. Demographic information (Table 1) and manometric data (Table 2) are compared between patients with a normal and an abnormal composite pH score. Patients with an abnormal pH score had significantly higher intra-thoracic pressure fluctuations and a higher thoraco-abdominal pressure gradient during both inspiration and expiration. The thoraco-abdominal pressure gradient during inspiration was higher than the resting barrier pressure in 27 patients, and an abnormal composite pH score was significantly more common in these patients (23/27 vs. 37/124, \( \chi^2 = 28.4, P < 0.001 \)) (Fig. 2). The odds ratio for an abnormal composite pH score in a patient where the inspiratory thoraco-abdominal pressure gradient exceeded the resting LES pressure was 13.5 (95% confidence interval, 4.4–41.8).

Multivariable analysis identified four independent predictors of an abnormal composite pH score in patients with a manometrically normal LES and no hiatal hernia (Table 3). These were: (1) an elevated inspiratory thoraco-abdominal pressure gradient, (2) a reduced LES residual pressure during a swallow-induced relaxation, (3) a larger intra-thoracic pressure fluctuation, and (4) a lower resting LES pressure.

If inspiratory gradient exceeds LES resting pressure by 5mmHg or more, 85% have abnormal reflux vs. 30% when the inspiratory gradient is less than the LES resting pressure.
Pathophysiology of Gastroesophageal Reflux in Patients with Chronic Pulmonary Obstructive Disease Is Linked to an Increased Transdiaphragmatic Pressure Gradient and not to a Defective Esophagogastric Barrier

• Consecutive series of 48 patients evaluated at pulmonary rehab program in San Paolo
• All underwent high resolution manometry
  • Assessment of LES mechanics
  • Body peristaltic function
  • Calculation of transdiaphragmatic pressure gradient
    • Subtracting average pressure over a 30 second interval 2 cm above LES from pressure 2 cm below LES
  • Calculation of LES retention pressure
    • Subtracting transdiaphragmatic pressure gradient from mid-respiratory LES resting pressure
Pathophysiology of Gastroesophageal Reflux in Patients with Chronic Pulmonary Obstructive Disease Is Linked to an Increased Transdiaphragmatic Pressure Gradient and not to a Defective Esophagogastric Barrier

- GERD symptoms were present in 24/48 (50%)
- Abnormal pH testing in 21/48 (44%)
- Low LES resting pressure in 9/48 (19%)
- Patients with GERD had higher transdiaphragmatic gradients (10 vs 5 mmHg, p=0.001)
- LES retention pressure was lower in patients with GERD (10 vs. 18 mmHg, p=0.01)
- No difference in LES resting characteristics between GERD + and GERD - patients
Hypothesis #2 – GERD Causes ESLD
Conditions Necessary to Establish a Causal Link

• Epidemiologic evidence that the two conditions co-exist more commonly than expected by chance ✔

• There is a plausible pathophysiologic mechanism ✔

• Demonstration of a “dose-response” relationship between amount of acid exposure and severity of disease

• Evidence that elimination of reflux leads to healing or halts progression
Exacerbations of COPD and symptoms of gastroesophageal reflux: a systematic review and meta-analysis

• Systematic review and meta-analysis of seven studies (n=341) reporting association between GERD and COPD and risk of exacerbation

• Frequency of GERD higher in patients with COPD than controls (RR 13.06, CI 3.64-46.87, p<0.001)
Esophageal Involvement and Pulmonary Manifestations in Systemic Sclerosis

- Prospective study from Roen France of 43 patients with Scleroderma
- 3 groups based on degree of esophageal involvement
  - Normal motility in 11 patients (Stage I)
  - Hypoperistalsis in 11 patients (Stage II/III)
  - Aperistalsis in 21 patients (Stage IV)

<table>
<thead>
<tr>
<th></th>
<th>Stage I (n=11)</th>
<th>Stage II/III (n=11)</th>
<th>Stage IV (n=21)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLCO %</td>
<td>103.7</td>
<td>93.6</td>
<td>68</td>
<td>0.048</td>
</tr>
<tr>
<td>ILD by HRCT</td>
<td>18%</td>
<td>27%</td>
<td>57%</td>
<td>0.037</td>
</tr>
</tbody>
</table>
Esophageal Involvement and Pulmonary Manifestations in Systemic Sclerosis

Table 4. Pulmonary function test data at 2-year followup as a function of manometric esophageal findings in patients with systemic sclerosis*

<table>
<thead>
<tr>
<th>Esophageal manometric involvement</th>
<th>Stage I/II/III (n = 8)</th>
<th>Stage IV (n = 10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>+0.09%</td>
<td>-3.65%</td>
<td>0.386</td>
</tr>
<tr>
<td>VC</td>
<td>+0.76%</td>
<td>+0.17%</td>
<td>0.656</td>
</tr>
<tr>
<td>TLC</td>
<td>+0.31%</td>
<td>-2.50%</td>
<td>0.656</td>
</tr>
<tr>
<td>RV</td>
<td>+25.21%</td>
<td>-25.25%</td>
<td>0.093</td>
</tr>
<tr>
<td>FRC</td>
<td>-8.26%</td>
<td>-8.29%</td>
<td>0.657</td>
</tr>
<tr>
<td>FEV₁</td>
<td>-2.98%</td>
<td>+0.98%</td>
<td>0.858</td>
</tr>
<tr>
<td>FEV₁/VC</td>
<td>-2.66%</td>
<td>-0.51%</td>
<td>0.374</td>
</tr>
<tr>
<td>DLCO</td>
<td>+1.47%</td>
<td>-16.04%</td>
<td>0.022</td>
</tr>
<tr>
<td>C dyn</td>
<td>+29.33%</td>
<td>-5.88%</td>
<td>0.179</td>
</tr>
</tbody>
</table>

* Value at 2-year followup (%) – value at initial evaluation (%).
FVC = forced vital capacity; VC = vital capacity; TLC = total lung capacity; RV = residual volume; FRC = functional respiratory capacity; FEV₁ = forced expiratory volume in 1 second; FEV₁/VC = forced expiratory volume in 1 second as % of vital capacity; DLCO = carbon monoxide diffusing capacity with single-breath method; C dyn = dynamic compliance. P values were determined by Mann–Whitney tests.

Presence of severe esophageal involvement and reflux associated with it correlated with the presence of ILD on HRCT (70% vs. 25%, p=<0.05)
Gastroesophageal Reflux and Pulmonary Fibrosis
A Study Using pH-Impedance Monitoring

- Prospective study of 40 consecutive newly diagnosed patients with systemic sclerosis in immunology clinic in Genoa Italy
  - GERD symptoms present in 50%

- Study protocol
  - Conventional manometry
  - Impedance-pH monitoring
    - Abnormal defined as percent time pH < 4 greater than 4.2%
  - PFTs – Abnormal defined as FEV1, FVC < 80%, DLCO < 75%
  - HRCT scan – Abnormal defined as Warrick score > 7
Gastroesophageal Reflux and Pulmonary Fibrosis
A Study Using pH-Impedance Monitoring

Abnormal distal acid exposure more common in ILD group 83% vs. 59%, p<0.001
Gastroesophageal Reflux and Pulmonary Fibrosis
A Study Using pH-Impedance Monitoring

Correlation between the degree of pulmonary fibrosis (HRCT score) and gastroesophageal reflux episodes. 

Graphs showing the correlation between HRCT score and gastroesophageal reflux episodes:
- Left graph: Total number of reflux episodes vs. HRCT score
  - $r^2 = 0.637, p = 0.001$
- Right graph: Number of reflux episodes at 15 cm above the LES vs. HRCT score
  - $r^2 = 0.644, p < 0.001$

References

19. Sontag SJ, O'Connell S, Khandelwal S, Miller T, Nemchausky B, Schnell TG, Serlovsky R. Most asthmatics have gastroesophageal reflux with or without bronchodilator therapy.
22. Littner MR, Leung FW, Ballard ED Jr, Huang B, Samra NK. Effects of lansoprazole therapy on asthma symptoms, exacerbations, quality of life, and pulmonary function in adult asthmatic patients with acid reflux symptoms.
GERD and End Stage Lung Disease
Which Is It?

I was here first!
Hypothesis #2 – GERD Causes ESLD

Conditions Necessary to Establish a Causal Link

- Epidemiologic evidence that the two conditions co-exist more commonly than expected by chance ✔
- There is a plausible pathophysiologic mechanism ✔
- Demonstration of a “dose-response” relationship between amount of acid exposure and severity of disease ✔
- Evidence that elimination of reflux leads to healing or halts progression
Laparoscopic fundoplication in patients with end-stage lung disease awaiting transplantation

• Retrospective review of 149 patients on lung transplant list at Brigham
  • Fourteen had IPF and symptoms of GERD who underwent Lap Nissen
  • All had failed to respond to medical therapy
  • GERD defined as total % time pH<4 of >4.0 or composite score > 14.72
• Lung function compared to 31 patients with IPF on transplant list who did not have Nissen
Laparoscopic fundoplication in patients with end-stage lung disease awaiting transplantation

TABLE 3. Comparison of sequential oxygen requirement, walk distance, and pulmonary function of patients with IPF undergoing Nissen fundoplication with values in those not undergoing Nissen fundoplication (control group)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group: n = 23</th>
<th>Nissen group: n = 11</th>
<th>Median (range)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen requirement (L/min)</td>
<td>Pre, median (range)</td>
<td>Post, median (range)</td>
<td>13 (1-57)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.0 (0-10)</td>
<td>3.0 (0-15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control group: n = 12</td>
<td>Nissen group: n = 8</td>
<td>1324.5 (618-1355)</td>
<td>383 (180-1308)</td>
</tr>
<tr>
<td>6-Min walk (ft)</td>
<td>Pre, median (range)</td>
<td>Post, median (range)</td>
<td>8 (1-15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1283 (691-2005)</td>
<td>1241.5 (790-1479)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>Control group: n = 14</td>
<td>Nissen group: n = 8</td>
<td>56.5 (42-79)</td>
<td>63 (33-76)</td>
</tr>
<tr>
<td></td>
<td>57.5 (45-81)</td>
<td>54 (40-84)</td>
<td></td>
<td>.881</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>Control group: n = 14</td>
<td>Nissen group: n = 8</td>
<td>59.5 (42-84)</td>
<td>62 (32-81)</td>
</tr>
<tr>
<td></td>
<td>62 (49-80)</td>
<td>56 (44-103)</td>
<td></td>
<td>.973</td>
</tr>
<tr>
<td>DLCO (% predicted, adjusted)</td>
<td>Control group: n = 8</td>
<td>Nissen group: n = 6</td>
<td>30.5 (25-50)</td>
<td>26.5 (11-56)</td>
</tr>
<tr>
<td></td>
<td>36 (27-45)</td>
<td>35 (11-50)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P < .05 indicates a statistically significant difference between the change in parameters between the Nissen and control groups. Pre, prefundoplication; Post, postfundoplication; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; DLCO, diffusing capacity of lung for carbon monoxide.
Antireflux Surgery Preserves Lung Function in Patients With Gastroesophageal Reflux Disease and End-stage Lung Disease Before and After Lung Transplantation

- Retrospective study of patients who underwent fundoplication before (n=19) or after (n=24) bilateral lung transplant at Pittsburgh
- Testing performed for symptoms of GERD or decline in FeV1
  - EGD, esophagogram, manometry, pH testing, impedance
- All were on PPI therapy at time of referral
- Typical symptoms in 8/43 (19%)
Antireflux Surgery Preserves Lung Function in Patients With Gastroesophageal Reflux Disease and End-stage Lung Disease Before and After Lung Transplantation

Table 3. Pulmonary Function Test Results Before and After ARS in Patients With ESLD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before ARS</th>
<th>After ARS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-LTx patients (n=22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, % predictedᵃ</td>
<td>81.5 (61.3-92.8)</td>
<td>92.5 (65.8-102.5)</td>
<td>&lt;.01ᵇ</td>
</tr>
<tr>
<td>FVC, % predictedᵃ</td>
<td>77.5 (63.5-87.3)</td>
<td>81.5 (70.5-94.5)</td>
<td>.04ᵇ</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅, % predictedᵃ</td>
<td>53.5 (31.3-100.3)</td>
<td>58 (44.5-118)</td>
<td>.03ᵇ</td>
</tr>
<tr>
<td>Pneumonia, No./total No. (%)</td>
<td>7/24 (29)</td>
<td>1/24 (4)</td>
<td>.03ᵇ</td>
</tr>
<tr>
<td>Rejection, No./total No. (%)</td>
<td>8/24 (33)</td>
<td>1/24 (4)</td>
<td>.03ᵇ</td>
</tr>
<tr>
<td>Pre-LTx patients (n=13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, % predictedᵃ</td>
<td>55 (44.3-76.3)</td>
<td>68 (49-82)</td>
<td>.02ᵇ</td>
</tr>
<tr>
<td>FVC, % predictedᵃ</td>
<td>61 (50-71)</td>
<td>71 (52-75)</td>
<td>&lt;.01ᵇ</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅, % predictedᵃ</td>
<td>49.5 (19.3-78.8)</td>
<td>70 (23-81)</td>
<td>.26</td>
</tr>
<tr>
<td>Pneumonia, No./total No. (%)</td>
<td>6/16 (38)</td>
<td>3/16 (19)</td>
<td>.09</td>
</tr>
</tbody>
</table>

Abbreviations: ARS, antireflux surgery; ESLD, end-stage lung disease; FEF₂₅₋₇₅, midexpiratory flow rate; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LTx, lung transplantation.

ᵃMeasurements immediately before ARS and the most recent post-ARS measurements are expressed as median (interquartile range).
ᵇP < .05.
Antireflux Surgery Preserves Lung Function in Patients With Gastroesophageal Reflux Disease and End-stage Lung Disease Before and After Lung Transplantation

Figure 2. Impact of antireflux surgery (ARS) on forced expiratory volume in 1 second (FEV₁) (% predicted) for individual patients after lung transplantation (post-LTx) (A) and before LTx (pre-LTx) (B) 1 year before ARS, pre-ARS, and post-ARS. Overall, FEV₁ improved in 20 of 22 post-LTx patients (91%) and in 11 of 13 pre-LTx patients (85%). Of patients with a declining FEV₁ before ARS, 92% of post-LTx patients (11 of 12) and 88% of pre-LTx patients (7 of 8) had a reversal of this trend. In contrast, FEV₁ declined after ARS in 2 of 22 post-LTx patients (9%) and in 2 of 13 pre-LTx patients (15%).
GERD and End Stage Lung Disease
Medical Treatment

- Most patients in studies of ARS were already on a PPI which they failed
  - FeV1 declined while on medical therapy (Hoppo T, 2011)
- Abnormal reflux persists on omeprazole 20-80mg/d in 12/23 (56%) of patients with scleroderma¹
- Significantly less reflux by all parameters on PPI but mean values still above normal range in patients with scleroderma on standard dose omeprazole²
- Addition of ranitidine at hs does not decrease acid exposure or NAB³

¹ Hendel L, Aliment Pharmacol Ther 1992;6:565-77
² Shoenut JP, Aliment Pharmacol Ther 1993;7:509-13
High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis

**FIGURE 1.** Prevalence of acid gastro-oesophageal reflux (87%) in patients with idiopathic pulmonary fibrosis (IPF) with and without proton pump inhibitor therapy at the time of the pH probe study. This is a conservative estimate based on 46 subjects not receiving anti-reflux therapy at the time of pH probe study. +: positive; -: negative.
GERD and Lung Transplant
Case Presentation

- 61 yo female with IPF referred in August 2011 for GERD evaluation prior to transplant
  - 10 year history of heartburn on omeprazole
  - Recent onset of solid food dysphagia
  - Nocturnal regurgitation and cough 3x/week

- Results of foregut evaluation
  - UGI – good clearance, no hernia
  - EGD – carditis with focal IM
  - LES characteristics – OL 3.8, AL 0.4, RP 12.3, normal relaxation
  - Body manometry – 100% peristaltic, normal amplitude
  - Dual probe pH monitoring – distal score 1.1, proximal 2.7
GERD and Lung Transplant
Case Presentation

• Right single lung transplant in Nov 2014
• Bronchoscopy for decline in FeV1 in Nov 2015
  • No rejection, no OB, vegetable matter on TBBx
GERD and Lung Transplant

Case Presentation

- Now complaining of worsening heartburn 4x/week, complete relief on protonix
- Results of foregut evaluation
  - UGI – good clearance, no hernia
  - EGD – carditis with no IM
  - LES characteristics – OL 2.1, AL 0.8, RP 33, IRP normal
  - Body manometry – 100% peristaltic, increase in MWA (181.2)
  - Dual probe pH monitoring – distal score 20.7, proximal 4.4
  - Gastric emptying scan – t ½ 143 minutes
  - Transdiaphragmatic gradient elevated at 15mmHg
# Lung Transplant Exacerbates GERD

- Retrospective review of 23 patients who had reflux studies before (66d) and after (100d) lung transplant
  - pH monitoring, manometry, GE scan
  - Abnormal reflux in 8/23 (35%) pre-txp vs. 15/23 (65%) post-txp

## Table: pH Reflux Before and After Transplant

<table>
<thead>
<tr>
<th>Position</th>
<th>Pretransplant, %</th>
<th>Posttransplant, %</th>
<th>Mean Change, Interquartile Range</th>
<th>p Value</th>
<th>Normal Values, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5.6 ± 7.2</td>
<td>9.3 ± 9.2</td>
<td>3.7 ± 8.0</td>
<td>0.035</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Supine</td>
<td>5.1 ± 8.9</td>
<td>11.4 ± 15.5</td>
<td>6.3 ± 12.0</td>
<td>0.019</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Upright</td>
<td>6.2 ± 6.6</td>
<td>7.8 ± 7.4</td>
<td>1.6 ± 8.8</td>
<td>&gt; 0.200</td>
<td>&lt;8</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.*
Table 2: Abnormal pH findings at 3 and 12 months after TX

<table>
<thead>
<tr>
<th>Abnormal tests (%)</th>
<th>All patients</th>
<th>COPD</th>
<th>CF</th>
<th>IPF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 months</td>
<td>12 months</td>
<td>3 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Total time%</td>
<td>24% (12)</td>
<td>53% (16)</td>
<td>11% (2)</td>
<td>40% (4)</td>
</tr>
<tr>
<td>Upright T%</td>
<td>12% (6)</td>
<td>37% (11)</td>
<td>5% (1)</td>
<td>30% (3)</td>
</tr>
<tr>
<td>Supine T%</td>
<td>36% (18)</td>
<td>43% (13)</td>
<td>28% (5)</td>
<td>40% (4)</td>
</tr>
<tr>
<td>No. episodes</td>
<td>26% (13)</td>
<td>47% (14)</td>
<td>17% (3)</td>
<td>50% (5)</td>
</tr>
<tr>
<td>No. episodes &gt;5 min</td>
<td>10% (5)</td>
<td>40% (12)</td>
<td>11% (2)</td>
<td>40% (4)</td>
</tr>
<tr>
<td>Longest episode</td>
<td>28% (14)</td>
<td>43% (13)</td>
<td>11% (2)</td>
<td>40% (4)</td>
</tr>
<tr>
<td>DeMeester score</td>
<td>26% (13)</td>
<td>50% (15)</td>
<td>17% (3)</td>
<td>40% (4)</td>
</tr>
<tr>
<td>Proximal upright T%</td>
<td>0</td>
<td>10% (3)</td>
<td>0</td>
<td>10% (1)</td>
</tr>
<tr>
<td>Proximal supine T%</td>
<td>14% (7)</td>
<td>17% (5)</td>
<td>17% (3)</td>
<td>10% (1)</td>
</tr>
</tbody>
</table>

Abnormal proximal and/or distal exposure in 16/50 (32%) at 3 months and 16/30 (53%) at 12 months
Delayed Gastric Emptying Scintigraphy in Cystic Fibrosis Patients Before and After Lung Transplantation

- Gastric emptying studies performed before and after heart-lung (n=17) or bilateral lung (n=17) transplant at mean 1.6 years
  - Preop delayed GE for solids in 20/30 (67%), liquids in 4/30 (13%)
  - Postop delayed GE for solids in 29/30 (97%), liquids in 20/30 (67%)

### Table 1. Results (Mean ± 1.96 SD) of GE Scintigraphy for Controls

<table>
<thead>
<tr>
<th>Controls</th>
<th>n</th>
<th>T50 of solids (min)</th>
<th>RR2 of solids (%)</th>
<th>RR3 of solids (%)</th>
<th>T50 of liquids (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>11</td>
<td>81.95 ± 36.91</td>
<td>23 ± 25</td>
<td>5 ± 15</td>
<td>39.88 ± 22.07</td>
</tr>
<tr>
<td>Male</td>
<td>42</td>
<td>73.72 ± 26.95</td>
<td>17 ± 18</td>
<td>3 ± 6</td>
<td>41.59 ± 33.71</td>
</tr>
<tr>
<td>Whole group</td>
<td>53</td>
<td>75.43 ± 29.65</td>
<td>18 ± 20</td>
<td>3 ± 9</td>
<td>41.24 ± 31.48</td>
</tr>
</tbody>
</table>

Gastric emptying (GE) results in 53 asymptomatic healthy volunteers (11 women, mean age 31.80 years ± 7.34 (SD) and 42 men, mean age 29.28 years ± 5.69). These control volunteers had no history of gastrointestinal disease or gastrointestinal symptoms of dyspepsia and were not taking any medications, which affect the gastrointestinal tract (previously published data).
Delayed Gastric Emptying Scintigraphy in Cystic Fibrosis Patients Before and After Lung Transplantation

Etiology of DGE
Impact of vagotomy
Calcineurin inhibitors slow emptying
GERD and Lung Transplant

Background

- Lung transplantation is a viable option for select patients with ESLD – improved function, enhanced survival
- Long-term survival is limited by obliterative bronchiolitis
  - Recognized clinically by bronchiolitis obliterans syndrome (BOS)
  - Long associated with frequency and severity of acute rejection episodes
  - No effective treatment other than re-transplantation
  - With improved immunosuppression, non-alloimmune mechanisms appear to play an increasing role
    - Recognized association with reperfusion injury, HLA mismatching, CMV pneumonitis, viral infection
    - GERD recently recognized as a non-immune risk factor
The diagnosis and severity of BOS based on the ratio of current FEV$_1$ to baseline FEV$_1$ (FEV$_1$ ratio). These findings are supported by research in trying to individualize the patient's treatment.

Treatment modalities for GERD in patients with ESLD and after lung transplantation are limited. In terms of medical management, azithromycin has gained a lot of attention in recent research.

Aspiration has been confirmed by our data showing that the morbidity and mortality of LARS in lung transplant patients, compared it with the control group, and found that the LARS is safe even in high-risk lung transplant patients. In 2011, we analyzed our transplant population, compared it with the control group, and the additional comparison of the pathophysiological characteristics is more likely because of its anti-inflammatory actions rather than its prokinetic qualities.

The detection of pepsin identifies those who aspirate and that aspiration has been confirmed by our data showing that the clinical benefit of azithromycin in BOS progression is more likely because of its anti-inflammatory actions rather than its prokinetic qualities.

To date, the most successful management of GERD in patients has been the use of anti-reflux medications. The acceptance of GERD as a potential cause of allograft rejection in the absence of histologic confirmation of OB requires a lung biopsy for definitive histopathologic confirmation of OB, which is a chronic form of rejection that is not all risk factors for GERD play the same role in all patients. The most successful management of GERD in patients has been the use of anti-reflux medications.
Gastroesophageal Reflux as a Reversible Cause of Allograft Dysfunction After Lung Transplantation

- 23 yo male had bilateral transplant in 1995 for CF
- Underwent re-transplant in 1997 for BOS
  - No GERD symptoms before initial or re-transplant
- Four month post re-transplant he c/o heartburn and regurgitation
- Endoscopy showed grade 4 erosive esophagitis
- Markedly delayed GE (no emptying at 120 min)
- UGI showed marked gastroparesis
- Medical therapy with lansoprazole 30mg tid and cisapride bid
- Six weeks later UGI improved, symptoms of GERD persisted, offered fundoplication
Gastroesophageal Reflux as a Reversible Cause of Allograft Dysfunction After Lung Transplantation

The patient's FEV1 again began to decline approximately 3 months after the initial improvement. After retransplantation, the patient's FEV1 gradually improved over the first few months. The explanted lungs were negative. After retransplantation, treatment with aggressive medical therapy, which included pantoprazole (30 mg three times daily) and cisapride (20 mg twice daily), was undertaken. Despite these measures, the patient had no improvement in pulmonary function after 6 weeks of medical management. A repeat upper GI series, however, revealed improved gastric emptying with medical treatment. A radionucleotide gastric-emptying study was not repeated. Be-cause improved upper GI studies revealed marked gastroparesis with no appreciable emptying of the tracer at 120 min (for healthy subjects, the mean gastric emptying is 85% at 120 min). In addition, an upper GI series was performed that confirmed severe gastroparesis without mechanical obstruction and also revealed reflux of swallowed contrast up to the level of the clavicles. Based on these results, the patient was treated with aggressive medical therapy, which included motility agents and additional antireflux surgery.

The patient continued to experience frequent heartburn and frequent waterbrash. Additional testing, therefore, was undertaken. First, an upper GI endoscopy procedure was performed, which revealed severe, grade 4 erosive esophagitis. The testing of esophageal biopsy specimens was negative for infection (including stains for viral and fungal pathogens), which is consistent with acid reflux as the etiology of the esophagitis. A gastric-emptying radionucleotide study was performed that confirmed severe, grade 4 erosive esophagitis. The testing of esophageal biopsy specimens was negative for infection (including stains for viral and fungal pathogens), which is consistent with acid reflux as the etiology of the esophagitis. A repeat upper GI series, however, revealed improved gastric emptying with medical treatment. A radionucleotide gastric-emptying study was not repeated. Because the patient developed a decline in FEV1 several months later. Based on the current nomenclature, this patient met BOS criteria after retransplantation for OB. The patient initially experienced an appropriate improvement in pulmonary function after undergoing repeat transplantation but de-scended a dramatic and sustained improvement in the FEV1 after undergoing antireflux surgery (Fig 1). The patient also experienced a significant improvement in the midexpiratory phase of forced expiratory flow after fundoplication (prior to surgery, 24% predicted; 6 months after surgery, 52% predicted). In addition, 2 years after fundoplication, pH monitoring revealed only mild chronic sinus disease, which would not explain the lower lobes. A sinus CT scan also was performed that revealed bronchiectasis, predominantly in the lower lobes. A repeat transplantation to evaluate the etiology of the patient's pulmonary function after undergoing repeat transplantation was related to pulmonary function after undergoing repeat transplantation. The transbronchial biopsy at that time revealed bronchiolar inflammation, as shown in Figure 1. Lung function before and after fundoplication.

Figure 1. Lung function before and after fundoplication.
Gastroesophageal Reflux as a Reversible Cause of Allograft Dysfunction After Lung Transplantation

Pre-ARS TBBx

Post-ARS TBBx

Palmer SM, CHEST 2000;118:1214-17
Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation

- Retrospective review of 396 consecutive lung transplants, 128 of whom had pH monitoring
  - Abnormal reflux defined as total % time pH<4 of > 5%, upright time > 8%, supine time > 3%
  - Reflux present in 93/128 (73%) of patients
- PFT results compared pre and post transplant
- Freedom from BOS calculated

Davis RD, JTCVS 2003;125:533-42
Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation

Survival

Days

Survival, as determined by means of Kaplan-Meier analysis, in the patients with normal pH study results was significantly improved compared with that of patients with abnormal pH study results ($P < 0.047$, Figure 2). Overall survival was similar at 1 year (94% in the normal pH group and 96% in the reflux group); however, survival was substantially better at 3 and 5 years after transplantation in patients with normal pH study results (91% and 82%, respectively) compared with in those with reflux (77% and 48%, respectively).

Fundoplication group.

Survival, as determined by means of Kaplan-Meier analysis, in the fundoplication group was significantly improved compared with that in the routine transplant population ($P < 0.013$). Overall 1-year survival in the fundoplication group was 95% versus 78% in the overall series. Three- and 5-year survival was 86% and 71% in the fundoplication group compared with 69% and 48% in the overall series (Figure 3).

Kidney, heart, and lung allograft survival.

Kaplan-Meier actuarial survival was performed on 6-month survivors of kidney, heart, and lung allografts performed after 1990 at Duke to correct for early differences in outcomes between heart, kidney, and lung transplants as a result of technical reasons. A significantly worse outcome for patients undergoing lung transplantation occurred (Figure 4, A). In contradistinction, patients undergoing lung transplantation documented to be without reflux or whose reflux was treated with fundoplication have allograft survival equivalent to that of patients who have undergone a kidney or heart transplantation (Figure 4, B).

Discussion

There is a high incidence and prevalence of GERD in patients with end-stage lung disease awaiting lung transplantation. This is particularly true for those patients with pulmonary fibrosis, in whom the incidence is greater than 50%. However, after lung transplantation, the incidence increases to three fourths of the patients. The increase in reflux presumably is multifactorial, including vagus nerve injury or dysfunction, effects of immunosuppression medication on lower esophageal sphincter function, and relative changes in intrathoracic and intra-abdominal pressures.

The consequence of GERD in patients undergoing lung transplantation with denervated lungs, markedly impaired cough reflux, and abnormal mucociliary function is that...
Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation.
Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation

![Bar chart showing FEV1 improvement after fundoplication](chart.png)
Early Fundoplication Prevents Chronic Allograft Dysfunction in Patients With Gastroesophageal Reflux Disease

- Retrospective review of 320 patients after lung transplantation
- Stratified into 4 groups based on pH testing
  - No reflux (n=47), reflux no fundoplication (n=79), reflux early (<90d) fundoplication (n=14), reflux late fundoplication (n=180)
- Reflux defined as total % time pH<4 of > 5%, upright time > 8%, supine time > 3%
- Chronic medical therapy in 47%
Early Fundoplication Prevents Chronic Allograft Dysfunction in Patients With Gastroesophageal Reflux Disease

Fig 2. Freedom from BOS in ICD-9 segregated groups. ■ = no history of reflux; □ = reflux, no surgery; △ = reflux, early surgery; ▲ = reflux, late surgery. (BOS = bronchiolitis obliterans syndrome; ICD = international classification of diseases.)

Keck Medical Center of USC

Cantu E, Ann Thorac Surg 2004;78:1142–51
Early Fundoplication Prevents Chronic Allograft Dysfunction in Patients With Gastroesophageal Reflux Disease

- Early ARS can prevent BOS
- Delayed ARS does not
  - Delayed ARS has similar rate of BOS to patients with reflux and no ARS
- Definition of abnormal reflux after transplant may be too strict
  - Rate of BOS similar in no reflux and reflux no fundoplication group
Both Pre-Transplant and Early Post-Transplant Antireflux Surgery Prevent Development of Early Allograft Injury After Lung Transplantation

• Consecutive series of 48 patients who had ARS before or following lung transplant at Brigham
  • Three patient groups: ARS pre-txp, ARS early (<6mo) post-txp and late (>6mo post-txp)
  • Freedom from BOS compared

<table>
<thead>
<tr>
<th>Fundoplication timing and early allograft injury</th>
<th>Kaplan-Meier log-rank p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late post-transplant vs pre-transplant</td>
<td>0.007</td>
</tr>
<tr>
<td>Late post-transplant vs early post-transplant</td>
<td>0.05</td>
</tr>
<tr>
<td>Early post-transplant vs pre-transplant</td>
<td>0.27</td>
</tr>
</tbody>
</table>
Both Pre-Transplant and Early Post-Transplant Antireflux Surgery Prevent Development of Early Allograft Injury After Lung Transplantation
Study aim: to determine if pepsin is present in BAL fluid from large cohort of lung transplant recipients and to determine if high levels are associated with acute rejection and/or BOS

Study groups
- 36 allograft recipients – no GERD symptoms
- 4 normal volunteers – no GERD symptoms, no respiratory dz
- 17 patients with chronic cough (10 w/ GERD, 7 w/out)

Aliquot of BAL submitted to ELISA for pepsin
Pepsin, a Biomarker of Gastric Aspiration in Lung Allografts

All transplant groups had higher pepsin levels than control groups. No differences were seen between BOS and stable transplant groups (A0/A1). No difference in pepsin levels with and without PPI therapy was observed.

* p<0.01

* p<0.05
Bile Acid Aspiration and the Development of Bronchiolitis Obliterans after Lung Transplantation

- Study aim: to investigate the role of aspiration in development of BOS in 120 lung transplant recipients
  - Determine prevalence of bile acid in BAL fluid
  - Correlate bile acid presence with markers of BOS including alveolar neutrophilia, IL-8 and IL-15
- Routine TBBx and BAL at 2 and 6 weeks and q 3mo for 1 year and q 6mo for 1 year and as needed thereafter
- Diagnosis of BOS based PFTs per ISHLT criteria
  - Early vs. late onset based on 12 month onset
- BAL sample analyzed for bile acid and ELISA for IL-8 and IL-15
  - Bile acid levels classified as low vs. high based on upper limit for serum (<8μmol/L)
Bile Acid Aspiration and the Development of Bronchiolitis Obliterans after Lung Transplantation

BOS grade 0p–3 diagnosed in 36/107 patients (37%).

Mean bile acid concentration across all BAL samples for each patient shown.
Bile Acid Aspiration and the Development of Bronchiolitis Obliterans after Lung Transplantation
Bile Acid Aspiration and the Development of Bronchiolitis Obliterans after Lung Transplantation
**Gastro-oesophageal Reflux and Gastric Aspiration in Lung Transplant Patients with and without Chronic Rejection**

- **Study aim**: characterize the prevalence and type of GERD (acid, non-acid) and degree of gastric aspiration in a cross-sectional study of 63 lung transplant patients
  - Minimum follow-up 1 year
  - Anastomotic complications excluded
  - Two cohorts: 45 studied off PPI, 18 studied on PPI
- **Impedance pH** performed in all patients
- **Pepsin and bile acid concentration** measured in BAL fluid
  - 14 BAL samples in non-transplant patients served as controls
Gastro-oesophageal Reflux and Gastric Aspiration in Lung Transplant Patients with and without Chronic Rejection

- No PPI group
  - Only 18/45 (40%) had typical reflux symptoms
  - Abnormal reflux 22/45 (49%) – highest in CF
    - Abnormal acid reflux in 16/22 (73%)
    - Abnormal non-acid reflux in 6/22 (27%)
  - All had detectable pepsin in BAL fluid
    - Higher concentration than controls (541 ng.mL\(^{-1}\) vs. 24 ng.mL\(^{-1}\))
  - Bile acids detectable in 22/45 (49%) patients
    - Association shown between presence of bile acid and BOS > 1

- PPI Group
  - Abnormal reflux in 7/18 (39%) – decreased acid, increased non-acid events
  - All had pepsin detected, bile acid present in 9/18 (50%)
Gastro-oesophageal Reflux and Gastric Aspiration in Lung Transplant Patients with and without Chronic Rejection

- Patients on medical therapy had less acid reflux but similar number of total reflux events (ie increased non-acid events)
- Frequency and severity of BOS was similar
- Frequency of gastric aspiration, measured by presence of pepsin, was similar (100%)
- Presence of bile acid was similar (50 vs. 49%)
- Conclusion: PPI therapy may control acid reflux but does not prevent gastric aspiration and it is probable that it will not protect against GERD induced allograft dysfunction
Reflux commonly co-exists in patients with end stage lung disease and may play a role in its development/exacerbation.

The usual mechanisms underlying reflux are at play, with the addition of an increase trans-diaphragmatic gradient contributing to the reflux seen.

Reflux is more common and more severe after transplant, where it is a reversible cause of graft dysfunction.

Medical therapy is often ineffective, but antireflux surgery leads to excellent results.