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A Call for Standardisation of antireflux surgery in the Lung Transplantation population.

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**Abbreviations**
BOS= Bronchiolitis Obliterans Syndrome
GORD= Gastro-Oesophageal Reflux Disease
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Abstract:
Long-term survival post lung transplant, is reduced significantly by Bronchiolitis Obliterans Syndrome. It is suggested that extra-oesophageal reflux disease is a risk factor for Bronchiolitis Obliterans Syndrome and that anti-reflux surgery may be beneficial. Practice between centres varies greatly, however. We suggest a need for improved evidence and standardisation.
This mini-review aims to highlight the discrepancies in anti-reflux surgery in the lung transplantation population and make a call for standardisation of approaches to therapy and improved evidence of their effects. Lung transplantation is an accepted treatment strategy for end-stage lung disease but survival of lung allograft recipients is significantly lower than other organ transplant recipients. This may be due to the unique environment to which the lungs are exposed and as a result five year survival post-transplantation is 60%(1). The pathophysiological process of chronic rejection is Obliterans Bronchiolitis, characterised by progressive fibrosis of the small airways, leading to airway obstruction. This manifests clinically as Bronchiolitis Obliterans Syndrome(BOS)(1).

Traditionally, BOS was thought to be caused by cumulative alloimmune injuries but there has been no significant impact on BOS over the last twenty years, despite the use of novel immunosuppressive strategies(1, 2). One current hypothesis is a link with gastro-oesophageal reflux disease (GORD)(1). There is no doubt that GORD post-lung transplantation is common with up to 75% of patients having demonstrable reflux based on pH studies. Causative factors may include intra-operative vagal damage, an impaired cough and airway mucociliary clearance, an immunosuppression drug effect or the pre-existing presence of GORD(1, 2). However the link with BOS is yet to be validated even in animal models. A recent paper has suggested that macroaspiration of gastric fluid to be injurious in a rat model of lung-transplantation, but the pattern of injury described is a pan-lung injury, perhaps not truly OB, and more akin to Acute Lung Injury, which is believed to be caused by a large volume gastric aspiration. No animals studies have been performed looking at the effects of chronic microaspiration which is thought to occur in the clinical setting, nor the effects of gastro-duodenal aspiration versus gastric aspiration.

However clinical research does suggest an association between reflux and BOS. In a study of 43 patients undergoing pH measurements at a median of 558 days post-transplant, 76% of patients with abnormal lung function had abnormal oesophageal pH compared to 59% of patients without allograft dysfunction having an abnormal pH study. A negative correlation existed between the severity of total/upright acid reflux and FEV$_1$ ratio (r= -0.341; p=0.025)(3).

If GORD and BOS are linked, then prophylactic treatment using proton pump inhibitors to reduce gastric acid production should have an impact on outcome. These have not been shown to be effective in preventing weakly acidic reflux or aspiration in clinical studies. This suggests PPI therapy will not prevent reflux/aspiration but this is not widely understood and it is a common misunderstanding that PPIs may stop reflux(4, 5). Although intra-operative vagal damage is associated with a poor cough reflex, recent evidence suggests that the cough response improves in the first year post-transplant(6). This should protect against aspiration and the development of BOS. In contrast, azithromycin (a macrolide antibiotic) with promotility properties improves airflow limitation post-transplant even in patients with longstanding BOS could this effect be linked to an amelioration of GORD?
Nevertheless, recent studies have demonstrated a survival benefit and delayed onset of BOS when anti-reflux surgery is performed, particularly with early intervention(2, 7). The laparoscopic approach is now the procedure of choice with successful long-term control of reflux. Anti-reflux surgery was first shown as being both safe to perform and beneficial in lung transplant recipients in 2003. Davis et al. demonstrated over 80% of 43 patients who underwent anti-reflux surgery post-lung transplantation had a significant increase in FEV₁ - mean improvement 24% post-fundoplication. The more advanced the BOS, the less improvement gained(2). In a follow up to this study (n=76), survival was significantly better for patients who underwent an early (<90days) versus a late fundoplication. This was most pronounced at 3 years (100% versus 69-86%; p=0.03). This early fundoplication survival effect was also noted even when compared to patients with a “normal” pH study. The “normal” patient group included those with mild acidic reflux with an mean acid exposure (7.9%) above the normal limits. This may explain the unexpected finding of a beneficial effect of early antireflux surgery over patients with a “normal” pH study. The most recent data published in abstract form (8) suggests that early fundoplication reduces BOS but does not show an improved survival at one year. However, this follow up is limited.

There are significant limitations to this evidence, the available studies involve small numbers, have limited follow up, much of the evidence is retrospective and derived from a single centre(2, 7). Methodological problems make it difficult to draw robust conclusions.

We have therefore reviewed the published literature and contacted transplant centres in Europe, North America and Australia, to identify if there was a consensus regarding investigation of reflux and indications for intervention. The essential finding of this exercise was that there is none. There are numerous ways to detect reflux, which is assumed to be a prerequisite for aspiration. Oesophageal pH monitoring is the most traditional modality, but this assumes all reflux episodes are acid related(9). In addition assessing for reflux by pH monitoring may not be the best approach as for aspiration to occur the refluxate needs to pass through the proximal oesophagus and enter the pharynx. The Bilitec monitor has been used to detect bile-containing refluxate but has limitations. As a result, pH/impedance is now the recognised standard assessment tool, as it can detect episodes of non-acid reflux, which definitely occurs in lung transplant recipients and which is associated with aspiration(4). Similarly bronchoalveolar lavage (BAL) specimens can be analysed for the presence of aspiration biomarkers such as pepsin and bile salts, the latter suggestive of duodeno-gastro-oesophageal reflux(1, 4, 5). Our unit has demonstrated that pepsin in BAL samples is increased in lung transplant recipients and is associated with acute rejection(5). Bile salts are cytotoxic and the presence of bile salts in BAL specimens has been associated with an early onset of BOS(1, 4). It has been suggested that such biomarker approaches may be used as an indication for fundoplication. However assay variability and differing detection limits are serious problems and the available literature does not take this into account(10). Further work is needed to standardise and validate these assays. As a result, the indications for fundoplication based on the biochemical detection of aspiration are contentious.
Little is known about what happens to reflux over the first year post-transplant and there is no consensus about when to assess for reflux or if reflux is demonstrated when an anti-reflux procedure would be indicated. One paper has suggested that pre-transplant fundoplication should be performed in all “fit” patients who have demonstrable reflux(11). There are potential benefits in performing fundoplication pre-transplant, not least offering immediate protection from micro-aspiration and lung injury. There have been isolated reports of a normalisation in lung function in several patients and withdrawal from transplantation lists(12). However the risks of surgery are higher in this population and there is potentially no benefit, as several patients have died pre-transplantation.

In summary, there is growing interest in the role of extra-oesophageal reflux in BOS and the potential benefits of fundoplication in well-characterised patients. Most units state an advocacy for some form of anti-reflux surgery in either patients with demonstrable reflux or more pragmatically, in symptomatic patients with reflux. However, there is no consensus between centres. Based on the premise that surgery benefits those with reflux and biomarker evidence of aspiration or patients with deteriorating lung function, the major units are recognising the case for creating more solid guidelines. We propose that this is a priority since current evidence may suggest a benefit with early surgery and little benefit for surgery in more advanced disease. This area of investigation and treatment is in its infancy and would benefit from appropriate leadership, through national and international societies. The next steps should be standardisation of biomarker assays and surgical practice. This may then allow appropriate trials.
REFERENCES