

# Gastro-oesophageal reflux and aspiration in patients with advanced lung disease

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## ABSTRACT

Numerous small observational studies have shown that gastro-oesophageal reflux is prevalent among patients with advanced lung disease. The fundamental concern is that reflux is a risk factor for recurrent microaspiration, which may cause lung injury. For example, in lung transplant patients, a molecular marker of aspiration was a risk factor for the bronchiolitis obliterans syndrome in one study. To date, however, there are no large prospective studies measuring the impact of aspiration on clinical outcomes. The major obstacle limiting the study of reflux and aspiration in patients with advanced lung disease is the absence of a reliable diagnostic tool. Proximal oesophageal acid detection by pH monitoring is the only widely available measure of aspiration risk. Impedance monitoring may be a superior measure of aspiration risk as it measures both acid and non-acid reflux episodes. Molecular markers of aspiration, such as pepsin or bile salts in the bronchoalveolar lavage or exhaled breath condensate, may be the optimal diagnostic tests, but they are not currently available outside the research setting. Larger observational studies are needed to determine the following: (1) the clinical significance of aspiration in patients with advanced lung disease and in patients who have had lung transplantation and (2) the diagnostic test that best predicts adverse outcomes.

Gastro-oesophageal reflux disease (GORD) is recognised as an aetiology of cough and aspiration related acute pulmonary injury.<sup>1,2</sup> The association between reflux, microaspiration and chronic lung injury is not well characterised. The reason this subject has generated so much interest despite the relative paucity of good outcome data is because GORD and aspiration are potentially treatable.

This review describes the association between gastro-oesophageal reflux and aspiration among adults with advanced lung disease (ALD) and among those who have had lung transplantation. The associations between reflux and asthma, laryngopharyngeal reflux and cough have been reviewed elsewhere.<sup>3</sup> This review will also address the issue of diagnostic testing and suggest directions for future studies.

## GASTRO-OESOPHAGEAL REFLUX AND LUNG DISEASE

### Historical perspective

In 1949, Belcher summarised a number of case series published in the first half of the 20th century.<sup>4</sup> He credited Vinson with the first report of a lung abscess caused by aspiration in a patient with achalasia in 1927. Several studies performed in the 1960s and 70s reported that pulmonary

fibrosis was common among patients with a radiographic or clinical diagnosis of reflux.<sup>5-7</sup>

Pellegrini *et al* published a landmark paper in 1979 that helped establish several key principles of extraoesophageal complications of GORD.<sup>8</sup> Among 100 patients with pathological reflux on pH monitoring, those with weak oesophageal peristalsis and slow oesophageal clearance were more likely to have respiratory symptoms immediately following reflux events. Therefore, without adequate oesophageal motility, reflux events were more likely to cause respiratory symptoms. Furthermore, oesophageal pH testing clarified the temporal association between reflux and cough. Some patients had reflux events following cough, presumably because of increased intra-abdominal pressures caused by coughing. Other patients had cough immediately following a reflux event, suggesting that reflux induced the cough. The authors also found that typical reflux symptoms (heartburn, regurgitation and dysphagia) had limited correlation with objectively measured reflux.

The first published report of an association between oesophageal dysfunction and parenchymal lung disease is attributed to Denis and colleagues.<sup>9</sup> In 1981, they reported that 16 of 24 patients (67%) with systemic sclerosis had impaired oesophageal motility that was associated with decreased lung compliance.<sup>9</sup> In 1989, Johnson *et al* studied oesophageal function and aspiration in a cohort of 13 patients with systemic sclerosis.<sup>10</sup> Abnormal reflux and laryngoscopic examination findings suggestive of laryngopharyngeal reflux were common. A multivariate regression model found an association between reflux and impaired diffusing capacity.

In addition to showing that reflux was associated with lung fibrosis, Johnson and colleagues<sup>10</sup> made the important contribution of measuring proximal oesophageal acid exposure with a dual sensor pH monitor. In 1993, Patti *et al* used a similar dual sensor pH monitor to correlate cough with proximal oesophageal reflux.<sup>11</sup> They speculated that when cough was temporally associated with distal reflux only, then the symptoms were attributed to a vagal reflux arc from oesophageal irritation. When cough was associated with reflux that extended into the proximal oesophagus, then microaspiration was the likely aetiology of the cough.<sup>12</sup> Furthermore, proximal oesophageal reflux was more common among those patients with motility abnormalities of the lower oesophageal sphincter and oesophageal body.

Until 1996, data on the association between reflux and respiratory complications were limited

to single institutional case series. El-Serag and Sonnenberg confirmed the findings of these case series in a population setting.<sup>13</sup> Patients with erosive oesophagitis, a sign of significant GORD, had a 1.36 odds ratio (OR) of pulmonary fibrosis, a 1.28 OR of chronic bronchitis and a 1.22 OR of chronic obstructive pulmonary disease (COPD) in a case control study of more than 200 000 US veterans. Although these data are not proof of causation, they confirm the presence of an association between GORD and ALD in a large population based setting.

As described below, GORD is prevalent among patients with diverse forms of ALD. The pathophysiology of this association is not well characterised. For several decades, oesophageal specialists have postulated that changes in diaphragmatic position (with compromise of the diaphragmatic pinch-cock action) and increases in positive intra-abdominal pressure and negative intrathoracic pressure (with a corresponding increase in the pressure gradient) have facilitated reflux. These hypotheses have never been proved.

## GASTRO-OESOPHAGEAL REFLUX AND SPECIFIC LUNG DISEASES

### Idiopathic pulmonary fibrosis/usual interstitial pneumonia

While the pathophysiology of idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF) appears to involve aberrant fibroblast proliferation as a result of recurrent epithelial injury, the aetiology is unknown.<sup>14</sup> Speculation has arisen that reflux may play a role in the pathogenesis and/or progression of IPF (specifically in acute exacerbation of IPF) as a recurrent inflammatory stimulus.<sup>15</sup> Furthermore, reflux plays a role in symptoms often attributed to interstitial lung disease, of which IPF is the most prevalent form.<sup>16</sup>

Four studies have found a high prevalence of reflux among patients with IPF (table 1).<sup>15 17–19</sup> The largest of these, by Raghu and colleagues,<sup>17</sup> used heterogeneous oesophageal testing and tested some patients while they were taking proton pump inhibitors (PPIs). These limitations prevent wide generalisation of their data. That a consistently high prevalence has been seen across all studies, however, suggests that the association is valid.

The clinical impact of reflux on IPF disease progression has not been thoroughly examined. A case series by Linden and colleagues demonstrated that 11 pre-transplant patients with IPF undergoing antireflux surgery had reduced supplementary oxygen dependence compared with other pre-transplant patients with IPF after a median of 11 months of follow-up.<sup>20</sup> Other more objective measures of pulmonary function, (eg, walk test and pulmonary function tests) however, were not improved after surgery. Raghu *et al* reported a case series of four patients with IPF and a clinical diagnosis (ie, symptoms) of reflux.<sup>21</sup> Two patients had deterioration in their pulmonary function tests that resolved with control of oesophageal acid exposure. This small study was the first to temporally correlate IPF clinical stability with control of acid reflux. Furthermore, there are anecdotal cases of IPF disease stability following treatment for reflux.<sup>20</sup> While it cannot be proven that disease stability was caused by control of reflux, they do offer hope that a subset of patients with IPF may benefit from antireflux therapy.

### Cystic fibrosis

While there are few data regarding GORD in adults with cystic fibrosis (CF), small cohort studies have consistently found a high prevalence of abnormal reflux (table 1).<sup>22–25</sup> In one study of 50 adults with CF, 47 (94%) reported symptoms of reflux and

eight of 10 studied by pH monitoring had pathological reflux.<sup>22</sup> The same authors then found that tracheal acidification followed oesophageal acidification in four of the eight patients with pathological reflux, all of whom had DeMeester scores  $\geq 60$ .<sup>26</sup> Gastroparesis, seen in 20 of 30 pre-transplant patients in another study, may be a significant contributing factor for reflux in patients with CF.<sup>27</sup> Most adults with CF, therefore, have GORD, and perhaps a broader disorder of foregut motility.

### Connective tissue disease

Systemic sclerosis often involves the oesophagus, causing profound impairment of oesophageal motility and severe reflux. A cohort study of 47 patients with polymyositis or dermatomyositis and lung disease found that 18 (47%) had dysphagia, six (14%) had aspiration pneumonia, and oesophageal motility abnormalities were found by oesophagram or oesophageal motility studies in eight of 27 patients (30%).<sup>28</sup> Among a cohort of 125 patients with scleroderma (51 (41%) of whom had pulmonary involvement), 45 (36%) had oesophagitis and 61 of the 78 (78%) who had oesophageal pH measured had pathological GORD.<sup>29</sup> These data were confirmed by an ongoing study at our institution that has found that 18 of 23 patients (83%) referred for lung transplantation with connective tissue diseases (ie, scleroderma, mixed connective tissue disease or dermatomyositis) had pathological GORD, and 18 (78%) with manometry data had aperistalsis or abnormal peristalsis (unpublished data). Again, in this subgroup with ALD, GORD and foregut dysmotility were common.

### Obstructive lung disease

GORD is also prevalent among patients with COPD, although less so than in patients with fibrotic lung disease. A cross sectional study of 512 people with bronchial asthma or chronic bronchitis found an overall prevalence of benign oesophageal disease of 44.5% compared with 34.5% of patients without known lung disease.<sup>30</sup> Oesophageal pH testing again confirmed that reflux was prevalent (table 1).<sup>25 30 31</sup>

Reflux has also been associated with COPD using population based data. In a large VA study, El-Serag and Sonnenberg found that reflux oesophagitis was associated with COPD, with an OR of 1.22 (95% confidence interval (CI) 1.16 to 1.27).<sup>13</sup> Another population based case control study found that COPD was a risk factor for a diagnosis of GORD, with an OR of 1.3 (95% CI 1.0 to 1.8).<sup>32</sup>

Little is known about the link between GORD and outcomes in patients with COPD. Using a cross sectional sample, Rascon-Aguilar found an association between the presence of GORD symptoms and increased frequency of COPD exacerbations.<sup>33</sup> Another cross sectional study found that decreases in oesophageal pH corresponded with drops in oxygen saturation among six of 15 patients with GORD and COPD.<sup>31</sup>

### Lung transplantation

The most active area of the study of microaspiration is taking place in lung transplant patients. Survival following lung transplantation is inferior to that of other solid organ transplantation, with median survival less than 5 years. Obliterative bronchiolitis, characterised by its clinical correlate the bronchiolitis obliterans syndrome (BOS), is the main complication limiting allograft survival.<sup>34</sup> Reflux and microaspiration have been shown to be risk factors for BOS following transplant.

**Table 1** Prevalences of abnormal gastro-oesophageal reflux (pH testing) and of delayed gastric emptying (nuclear medicine study)

Lung disease group	Study	Patient population	No of patients	Manometry	Abnormal distal reflux (%)	Abnormal proximal reflux (%)	Delayed gastric emptying	Comment
Usual interstitial pneumonia	Tobin 1998 <sup>15</sup>	IPF Clinic	17	Selected patients	88	71%		Manometry not used
	Raghu 2006 <sup>17</sup>	IPF Clinic	65	Yes	76	63		Some subjects taking PPIs and pH probe placement varied
	Salvioli 2006 <sup>18</sup>	IPF Clinic	18	Selected patients	67			Manometry not used
Cystic fibrosis	Sweet 2007 <sup>19</sup>	Pre-transplant	30	Yes	67	30		
	Ledson 1998 <sup>26</sup>	CF Clinic	10	Yes	80			Patients with symptoms selected
	Button 2005 <sup>23</sup>	Pre-transplant	11	No	91	Undefined		Some subjects taking PPIs, 1 patient s/p fundoplication
	Button 2005 <sup>23</sup>	Post-transplant	13	No	85	Undefined		Some subjects taking PPIs, 1 patient s/p fundoplication
	Bodet-Milin 2006 <sup>27</sup>	Pre-transplant	30				67%	
Connective tissue disease	Johnson 1989 <sup>10</sup>	Rheumatology Clinic	13	Yes	54	Undefined		
	Bassotti 1997 <sup>29</sup>	Dermatology Clinic	78	Yes	78			Acid suppression not withheld prior to study
	Gasper 2007*	Transplant Clinic	23	Yes	83	30	6 of 8 (75%)	
COPD	Andersen 1989 <sup>30</sup>	COPD Clinic	55	Yes	49			
	Casanova 2004 <sup>31</sup>	COPD Clinic	42	Yes	62			
Pre-lung transplant	Cantu 2005 <sup>40</sup>	Transplant Clinic	36	Yes	63			PPI withheld for 5 days
	D'Ovidio 2005 <sup>24</sup>	Transplant Clinic	78	Yes	32	20	13 of 27 (44%)	PPI withheld for 5 days
	Sweet 2006 <sup>25</sup>	Transplant Clinic	109	Yes	68	37		
Post-lung transplant	Cantu 2005 <sup>40</sup>	Transplant Clinic	167	Yes	76			PPI withheld for 5 days
	Berkowitz 1995 <sup>46</sup>	Transplant Clinic	38				24%	Studied both lung and heart-lung transplant patients
	D'Ovidio 2006 <sup>45</sup>	Transplant Clinic	50, 30	Yes	26, 50	0–14 and 10–17	39 of 43 (91%)	Patients studied at 2 time points: 3 and 12 months after transplant

\*Unpublished data.

COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; PPIs, proton pump inhibitors; s/p, status post.

In the 1990s, several small case series were published describing foregut dysfunction among lung and heart-lung transplant patients.<sup>35–39</sup> Subsequently, the lung transplantation team at Duke University initiated the first systematic and objective assessment of reflux in lung transplant patients. They measured distal oesophageal acid exposure in over 200 patients and found prevalences of 63% and 76% in the pre and post-transplant subgroups, respectively (table 1).<sup>40</sup>

The group began performing antireflux surgery after observing that reflux was associated with declines in lung function.<sup>41–42</sup> They reported that the BOS resolved in a few patients following fundoplication. An outcome analysis of 14 patients who had antireflux surgery within 1 month of their transplant reported 100% freedom from BOS at 1 and 3 years after transplant.<sup>40</sup> Only five patients, however, were followed-up to the 3 year time point. In this retrospective study, there was no difference in the incidence of BOS among those patients with medically managed reflux and those without reflux. If the hypothesis that aspiration is a risk factor for BOS is true, then we would expect to have seen a difference between these groups. Medical therapy normalises the pH of the refluxate, but does not stop the mechanical reflux process.<sup>43</sup> The pathogenesis of BOS is likely multifactorial, and this study did not adjust for clinical covariates. Furthermore, proximal reflux is a better predictor of aspiration risk and this study relied on distal reflux measurements only. Again, despite their limitations, these encouraging initial results support further study of this association.

Two other cross sectional cohort studies of pre-transplant patients have found high prevalences of GORD (table 1).<sup>24–25</sup> D'Ovidio *et al* found a lower prevalence than the other groups,

and this may be due to the fact that PPIs were withheld for only 5 days prior to the pH studies. Abnormal oesophageal motility was seen in 33% and 55% of the two cohorts, and delayed gastric emptying was seen in 13 of 27 (44%) of patients in one study.

#### Effect of transplant on gastro-oesophageal reflux

Lung transplant appears to worsen oesophageal reflux. Among 23 patients studied, both before and after transplant, the prevalence of abnormal distal reflux rose from 35% to 65%.<sup>44</sup> Another study found that the prevalence of pathological reflux increased from 32% at 3 months after transplant to 53% at 12 months.<sup>45</sup> This is likely because of complications of the transplantation. Vagal nerve injury is a common complication of heart or lung transplantation. Gastroparesis as a result of vagal nerve injury and/or immunosuppression may play a role in the development of reflux after transplantation. Gastric motility is frequently abnormal in heart or lung transplant patients.<sup>35</sup> Berkowitz *et al* studied 38 post-thoracic transplant patients, 24% of whom had delayed gastric emptying (table 1).<sup>46</sup> Furthermore, chronic allograft dysfunction was more frequent among patients with delayed gastric emptying. Subsequent studies of patients with lung disease have found that delayed gastric emptying was prevalent.<sup>25–44</sup> D'Ovidio *et al* reported that 91% of gastric emptying studies were abnormal among a cohort of 43 post-transplant patients.<sup>45</sup> The prevalence may be higher among some high risk populations. For instance, 29 of 30 patients (97%) with CF had abnormal gastric emptying following lung or heart-lung transplantation in one study.<sup>27</sup>

## ASPIRATION

Although abnormal reflux is prevalent among patients with ALD, we do not know who among those with reflux are aspirating. Several studies have attempted to determine the prevalence of aspiration after lung transplantation. D'Ovidio *et al* examined bile salts in the bronchoalveolar lavage (BAL) of 120 post-transplant patients in a cross sectional study.<sup>47</sup> The authors found a 17% prevalence of elevated concentrations of bile salts. Furthermore, the highest concentrations were found in patients with early onset BOS (<1 year post-transplant). The study reported mean concentrations of bile salts among those with early BOS, late BOS and no BOS. There was a trend for decreasing concentrations across the groups, suggesting a dose effect association between elevated BAL bile salt concentration and the time to development of BOS. Furthermore, the authors found that elevated BAL bile acids were associated with alveolar neutrophilia, interleukin 8 and cultures positive for bacteria and fungus.

The same group subsequently showed that the presence of bile salts in the BAL fluid at 3 months after transplant was associated with the development of BOS in a time and dose dependent manner.<sup>45</sup> This important study was the first to prospectively evaluate post-transplant patients and show that markers of aspiration are a risk factor for BOS. The prevalence of aspiration, as measured by bile salts, was 43% at 3 months after transplant. The presence of bile salts in the BAL was also associated with decreased surfactant collectin proteins and surfactant phospholipids. Bile salts may, therefore, cause lung injury by impairing the innate immunity of the allograft.<sup>48</sup> The limitations of this study are the lack of adjustment for covariates and the small cohort size of 37. The study demonstrates a dose effect and temporal association, two important indicators of causality.

Measurement of bile salts may underestimate the prevalence of aspiration, as only 58% of patients without GORD and 75–86% of those with GORD will have duodeno-gastro-oesophageal reflux with bile in the refluxate.<sup>49–51</sup> Specific markers of gastric fluid in BAL may prove more sensitive than bile salts as a screening test of aspiration. A small cross sectional study by Ward *et al* found pepsin, a gastric protease, in the BAL fluid of 13 post-transplant subjects.<sup>52</sup> No pepsin was detected in the BAL specimens from four control subjects. Another small cohort study by Farrell *et al* correlated proximal oesophageal reflux with BAL pepsin levels in 33 children with reflux.<sup>53</sup> Again, no pepsin was identified in the BAL fluid of 13 negative control patients. Stovold *et al* recently reported on a cross sectional study comparing BAL pepsin with findings of acute rejection in 36 post-transplant patients. BAL pepsin concentrations were elevated in seven of 12 post-transplant patients with acute perivascular (A2) rejection.<sup>54</sup>

The main limitation of using molecular markers of aspiration in BAL samples is the inability to standardise the concentration. It is not known how BAL pepsin or bile salt concentrations change over time following an aspiration event. Elevated levels may reflect less dilution at the time of sampling, high volume and/or high frequency aspiration events, or impaired clearance by the lung itself.

Hartwig *et al* recently published a study describing a rat lung transplant model of aspiration. They found that exposure of the lung to filtered gastric aspirate induced fibrotic changes and severe acute rejection.<sup>55</sup> This model may be useful in elucidating the immunological covariates that affect the lung's response to aspiration.

The specific elements of the aspirate that are most injurious remain unknown. Refluxate pH varies, as virtually all post-transplant patients and many patients with ALD are treated with acid suppressing drugs in conjunction with steroids. Duodenal reflux of bile salts and reflux of other gastric contents (eg, the protease pepsin as well as infectious pathogens) may be important contributing factors to lung injury caused by aspiration. Which element is most injurious has important therapeutic implications. Acid suppression can be achieved pharmacologically, but the mechanical reflux events themselves may require additional treatment in the form of prokinetic medications or surgical fundoplication. Acid suppression therapy also changes the flora of the gastric refluxate.<sup>56 57</sup>

Patients with lung disease are particularly vulnerable to aspiration events. Aspiration of nasopharyngeal contents may occur in half of otherwise healthy adults, as measured by pulmonary scintigraphy.<sup>58</sup> Such events are controlled by normal cough reflex, mucociliary clearance and a functional immune system.<sup>2</sup> Lung transplant patients have impairment of all three defences.<sup>59 60</sup> Patients with IPF and other forms of ALD are also less likely to tolerate aspiration events than are healthy people, although there are no specific data addressing this subject.

## OUTCOME

Thus far, outcome data demonstrating a causal association between reflux mediated microaspiration and chronic lung injury are limited to the single observational study of 37 post-transplant patients discussed above. The dose effect and temporal association between BAL bile salt concentration and time to onset of BOS is strong evidence of a link between these two processes.<sup>45</sup> Among the five patients with high levels of bile salts in the BAL fluid, the incidence of BOS at 30 months was 80%, four times the incidence among patients without detectable bile salts. These results must be confirmed in larger cohorts to better understand the magnitude of the effect and what covariates influence the process. At this time, there are no prospective outcome data demonstrating that reflux or aspiration are harmful in patients with ALD.

## DIAGNOSTIC TESTING: THE CURRENT LIMITING FACTOR

A fundamental issue limiting the further study of GORD related microaspiration is the lack of a gold standard diagnostic test. Clinicians use multiple different tools to screen for and diagnose reflux. The general diagnostic approach to GORD and the approach for extraoesophageal symptoms of GORD have been reviewed elsewhere.<sup>3</sup> There are, however, some specific data regarding diagnosis in patients with ALD.

Typical reflux symptoms of heartburn, regurgitation and dysphagia are of no use when screening for reflux in patients with ALD. A cross sectional study using a constellation of "gold standards" (ie, abnormality of oesophageal manometry, oesophageal pH or endoscopy) for diagnosis of GORD found that symptoms had a sensitivity and specificity of 89.5% and 47.1% among 512 people with asthma or chronic bronchitis.<sup>30</sup> When the presence of any typical reflux symptom (heartburn, regurgitation and/or dysphagia) was compared with objective findings at pH study in 109 patients with various types of ALD, the sensitivity, specificity and likelihood ratio positive were 67%, 26% and 0.91, respectively.<sup>25</sup> Similar findings of low sensitivity and specificity of reflux symptoms have been found in cohort studies of patients with COPD, CF and IPF.<sup>17 23 31</sup> In a cohort of 518 patients, Oelschlager *et al* showed that typical reflux symptoms did not discriminate among patients with and

without pharyngeal acid exposure.<sup>61</sup> Reflux is often silent in patients with ALD, and symptoms of heartburn and regurgitation are common among patients with normal objective measures of reflux.

Oesophageal pH monitoring is the most widely available test, although important limitations exist. Dual sensor pH monitoring is essential as it identifies the subgroup of patients with abnormal proximal reflux. Among a cohort of 518 patients with symptoms referred for oesophageal studies, 43 of 181 (24%) patients with abnormal acid reflux extending into the pharynx had normal distal oesophageal acid exposure.<sup>61</sup> In these patients, the frequency and duration of reflux events was within physiological norms for the distal oesophagus, but so many of these events extended upward into the proximal oesophagus that they exceeded the normal standards for proximal reflux. Temporal correlation between proximal reflux events and respiratory symptoms of cough is a strong predictor of who is most likely to benefit from antireflux therapy.<sup>12</sup> It may not be possible to measure this correlation in patients with ALD given the frequency and multiple aetiologies of cough in these patients. Potluri *et al* found that proximal reflux correlated with salivary pepsin concentration, indicating that proximal oesophageal reflux events frequently extend into the hypopharynx.<sup>62</sup> Most recently, two studies have shown that proximal reflux correlates with elevated concentrations of BAL pepsin and bile salts, two markers of aspiration.<sup>45–53</sup> The other advantage of oesophageal testing is the assessment of oesophageal motor function. As discussed above, oesophageal peristalsis is one of the key protective measures against aspiration and it is frequently abnormal in patients with ALD. The limitation of pH testing relates to the use of gastric acid as a surrogate marker of reflux events. This requires cessation of PPIs. Furthermore, pH testing will not detect neutral or mildly acidic reflux events, which are common.<sup>63–64</sup>

The ability of pH studies to predict aspiration risk is not well characterised, as only two studies have compared oesophageal pH measurement with other diagnostic tools. D'Ovidio *et al* found that 75% of patients with high levels of bile salt in the BAL had abnormal proximal oesophageal pH studies, meaning that 25% of patients with the highest quantity of aspiration had normal proximal oesophageal pH measurements. In contrast, 15% of patients without measurable bile salts had abnormal proximal oesophageal pH measurements.<sup>45</sup> Therefore, proximal oesophageal pH testing had a sensitivity of 75%, specificity of 81% and a likelihood ratio of 4 for detecting aspiration of high levels of bile salts. For any bile salt aspiration, values are 45%, 85% and 3, respectively. A study in a heterogenous cohort of 51 children with unexplained respiratory symptoms (cough, pneumonia, apnoea, asthma and laryngitis) found that aspiration, as measured by pulmonary scintigraphy, was found in 49%. Oesophageal pH studies were not helpful in the diagnosis of aspiration in this study, with a sensitivity of 24%, specificity of 65% and positive predictive value of 46%.<sup>65</sup> These studies highlight the challenges facing clinicians and investigators. The test characteristics of BAL bile salts and of pulmonary scintigraphy are not well known, and without that information, they cannot be used as the gold standard against which to compare pH studies. Furthermore, all of these tests measure a brief time period, and as such may not reflect the longer term steady state. To resolve these discrepancies between diagnostic methodologies, studies should compare which test is most strongly predictive of adverse outcomes. In the D'Ovidio study, both pH testing and BAL bile salts were predictive of BOS, but

both results were dichotomised into normal and abnormal, reducing the precision of the measurements.<sup>45</sup>

Oesophageal impedance testing is a new technology that discriminates gas and fluid reflux regardless of pH.<sup>64</sup> One study elegantly demonstrated this when the investigators measured the number and magnitude of reflux events in the same patients on and off PPI therapy. There was no change in the number or magnitude of events; the only change was the pH of the refluxate.<sup>45</sup> Impedance can be used to diagnose GORD regardless of the use of acid blocking medications.<sup>66</sup> Impedance is particularly valuable when assessing aspiration risk, as aspiration is a mechanical process, and the pH of the refluxate is not the specific concern. Tutuian *et al* demonstrated that impedance testing discriminated the subgroup of 13 patients (26% of the cohort) who had persistent cough following reflux events despite PPI therapy.<sup>67</sup> Another study found that patients with reflux symptoms and normal pH tests were more likely to have non-acid reflux episodes extending into the proximal oesophagus than were control patients.<sup>68</sup> There are no studies describing impedance measures in patients with ALD. Furthermore, as is true of pH testing, impedance can only measure aspiration risk.

Another new diagnostic test currently being studied is exhaled breath condensate (EBC). EBC may provide a rapid, reproducible, inexpensive and non-invasive way to sample the airway for markers of aspiration. EBC pH decreases following acid aspiration.<sup>68</sup> Low EBC pH has also been associated with BOS and acute rejection after lung transplantation.<sup>69</sup> Recently, pepsin has been identified in EBC fluid from post-transplant patients.<sup>70</sup> EBC pH or pepsin may be useful as an initial screening test to select those patients at highest risk for further invasive testing.

Biochemical markers of aspiration, as discussed above, will likely prove to be the best diagnostic test. Currently, few patients have been studied, and it may be difficult to establish normal standards for these tests given an inability to standardise concentration.

Although pH studies have their limitations (eg, operator dependence, patient discomfort, and imperfect sensitivity and specificity for aspiration), proximal oesophageal reflux is the only clinically available surrogate marker of aspiration risk. Until impedance testing and markers of aspiration have been more carefully studied, oesophageal pH testing remains the only widely available diagnostic tool.

## FUTURE DIRECTIONS

Future studies should be directed to answer the following two questions: (1) are reflux and microaspiration associated with adverse clinical outcomes in patients with ALD and, if so, (2) which diagnostic test best predicts those outcomes. As the majority of data currently available come from cross sectional studies, it remains unknown whether the association between reflux and ALD is causal. Furthermore, thoracic mechanical changes caused by ALD may in fact cause or worsen reflux. Therefore, the first task is to confirm that reflux and aspiration are causally associated with worse clinical outcomes. Such data are needed to develop evidence based screening protocols and to support further studies addressing pathophysiology and therapy.

Patients with ALD and those referred for transplantation are complex. Immunological risk, environmental exposure and other medical comorbidities can differ substantially among these patients. It will require systematic evaluation to identify and isolate the risk factors that play a role in this association. It is unlikely that any single institution will be able to recruit a

sufficient cohort to resolve these issues, and therefore multi-centre studies are needed.

## CONCLUSIONS

GORD and aspiration are common and often severe among patients with ALD. Following lung transplantation, both GORD and aspiration appear to be risk factors for the development of BOS. Larger prospective studies are needed to clarify the clinical impact of reflux and aspiration on clinical outcomes. These issues are of tremendous clinical importance because GORD and aspiration are modifiable. A better understanding of aspiration in ALD may provide new means of treating these otherwise challenging diseases.

**Competing interests:** None.

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## Pulmonary puzzle

### Answer

From the question on page 100

Immunoassay for *Treponema pallidum* antibodies (TPAb ELISA) and the rapid plasma reagin test (RPR) performed at presentation were positive at high titres (1:16 and 1:128, respectively). TPAb were also detected in the cerebrospinal fluid (titre 1:128). *T pallidum* DNA-PCR of lung biopsy was not performed because of the poor specimen available.

Following the clinical and serological diagnosis of secondary syphilis with involvement of the central nervous system, intravenous ceftriaxone (2 g/day) was administered for 2 weeks because the patient reported allergy to penicillin. An unexpected and significant reduction in the major lung lesion was observed at the end of the antibiotic therapy and complete radiological disappearance of all pulmonary lesions had occurred at 3-month follow-up. TPAb and RPR titres both decreased to 1:8 after 3 months and RPR was negative at 6 months.

HIV/syphilis co-infection is associated with high rates of asymptomatic primary syphilis and with atypical features of secondary disease at presentation.<sup>1</sup> Lung involvement is extremely rare during secondary syphilis and it has been described mainly in patients with tertiary stage of the disease.

David and colleagues<sup>2</sup> recently reviewed nine cases published since 1967 which met the Coleman criteria for the diagnosis of secondary pulmonary syphilis (ie, physical findings of secondary syphilis, serological diagnosis, radiological lung abnormalities, exclusion of other forms of pulmonary disease and resolution of radiological abnormalities following anti-syphilis treatment).<sup>3</sup> Interestingly, eight of the nine patients had single or multiple lesions at lower lung regions.<sup>2</sup> Our patient with diagnosed secondary syphilis also had bibasilar lesions and alternative

possible aetiologies for pulmonary lesions were excluded, both microbiologically and histologically. Even in the past when tertiary syphilis was not uncommon, one criterion to discriminate pulmonary syphilis from tuberculosis was the tendency of the former to attack the middle and lower lobes.<sup>4</sup> One explanation for the prevalent involvement of the lower lobes during pulmonary syphilis may be ascribed to the high oxygen sensitivity of the microorganism due to the absence of microbial enzymes that detoxify reactive oxygen species.<sup>5</sup> Despite its ability to spread in any tissue, *T pallidum* thus encounters an unfavourable environment in the lung. When pulmonary involvement occurs, it will conceivably take place in the less oxygenated area of the organ. The differential diagnosis for pulmonary nodules associated with cutaneous lesions includes a broad range of diseases (lymphoma, Kaposi sarcoma, metastatic malignancies, Wegener granulomatosis, sarcoidosis, mycobacteriosis, disseminated fungal infections and septic emboli); syphilis should also be added to the list.

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