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Does Chronic Microaspiration Cause Idiopathic Pulmonary Fibrosis?

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Abstract

Idiopathic pulmonary fibrosis is a diffuse fibrotic lung disease of unknown etiology with no effective treatment. Emerging data support a role for chronic microaspiration (i.e. subclinical aspiration of small droplets) in the pathogenesis and natural history of idiopathic pulmonary fibrosis. However, the precise relationship between chronic microaspiration and idiopathic pulmonary fibrosis remains unknown. Gastroesophageal reflux, a presumed risk factor for microaspiration, has been strongly associated with idiopathic pulmonary fibrosis with an estimated prevalence of 90%. This review aims to describe the relationship between chronic microaspiration and idiopathic pulmonary fibrosis by laying out the clinical and biologic rationale for this relationship and exploring the scientific evidence available. The gaps in our current understanding of the diagnosis of chronic microaspiration and idiopathic pulmonary fibrosis and the ongoing uncertainties in management and treatment will be highlighted. Defining the role of chronic microaspiration in idiopathic pulmonary fibrosis is essential as it has potential clinical, pathobiological and treatment implications for this deadly disease.

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CONFLICT OF INTEREST STATEMENT

This manuscript represents original work and all authors meet the criteria for authorship. Dr. Lee has no conflicts of interest to disclose. Dr. Collard has provided consulting services to Actelion, Amira, InterMune, Gilead Science, Genzyme, CV Therapeutics, Nektar Therapeutics, and Roche, has served on an advisory committee for InterMune, and speaks regularly about idiopathic pulmonary fibrosis. Dr. Raghu has given lectures on the diagnosis and management of interstitial lung diseases, and has discussed the potential role of chronic silent microaspiration in the pathogenesis of idiopathic pulmonary fibrosis. Dr. Sweet has no conflicts of interest to disclose. Dr. Hays has no conflicts of interest to disclose. Dr. Campos has no conflicts of interest to disclose. Dr. Golden has no conflicts of interest to disclose. Dr. King has given lectures on the diagnosis and management of interstitial lung diseases, and has discussed the recent papers that have discussed the potential role of chronic silent microaspiration in the pathogenesis of idiopathic pulmonary fibrosis and as a potential cause of the acute respiratory decompensation manifested by some patients with idiopathic pulmonary fibrosis. In 2007, Dr. King provided expert testimony that a patient's diffuse parenchymal lung disease (lung fibrosis) was, more likely than not, caused by chronic aspiration.

Keywords

pulmonary fibrosis; respiratory aspiration; gastroesophageal reflux; etiology; diagnostic techniques and procedures

INTRODUCTION

Idiopathic pulmonary fibrosis, often abbreviated as IPF, is a chronic, fibrotic lung disease.1 There is no proven therapy and the median survival is between 2 and 3 years from the time of diagnosis.[2] By definition, the cause of idiopathic pulmonary fibrosis is unknown, although several associations have been described: cigarette smoking; exposure to wood and metal dusts; chronic viral infection; exposure to some drugs (e.g. antidepressants); and hereditary factors (e.g. mutations in the genes encoding telomerase components).[1, 3, 4]

Recent focus has shifted to the potential role of chronic silent microaspiration (i.e. subclinical aspiration of small droplets) in the pathogenesis of idiopathic pulmonary fibrosis.[1] Further, it has been suggested that the acute respiratory decompensation (i.e. acute exacerbation) manifested by some patients with idiopathic pulmonary fibrosis may be due to microaspiration. 5 As a result, there is a growing consensus that elucidating the impact of microaspiration on the pathogenesis and natural history of idiopathic pulmonary fibrosis is important.

This review aims to explore the relationship between microaspiration and idiopathic pulmonary fibrosis, highlighting the scientific evidence supporting a potential causative role. Our hope is to raise awareness of this topic among clinicians and scientists, establish a solid foundation for future scientific investigation in this field, and emphasize the need for further studies to determine the significance of microaspiration in idiopathic pulmonary fibrosis.

SILENT MICROASPIRATION AND LUNG DISEASE

Aspiration is defined as the inhalation of oropharyngeal or gastric contents into the larynx and lower respiratory tract.[6] The clinical syndrome due to aspiration (e.g. aspiration pneumonitis, aspiration pneumonia) depends on the nature and volume of aspirated material, the frequency of aspiration, and the host's response to the aspirated material.

The term "silent" microaspiration is used when patients have asymptomatic aspiration of small volumes of oropharyngeal secretions or gastric fluid into their lungs. Approximately half of all healthy adults aspirate small amounts of oropharyngeal secretions during sleep7 and other co-morbidities may increase the risk of aspiration (e.g. scleroderma, cerebrovascular disease, and degenerative neurologic disease).6, 8, 9 However, normal host defenses (e.g. glottis closure, cough reflex) are usually able to compensate.10 Depending on the frequency and intensity of the silent microaspiration, and, perhaps, genetic predisposition, patients may manifest with cough, wheeze, or mild gas exchange abnormalities.11

Gastroesophageal reflux and silent microaspiration is associated with several lung diseases and among those who have had lung transplantation.12, [13] Lipoid pneumonia is caused by the silent microaspiration of exogenous lipid (usually a complication of long-term ingestion of oil-based compounds) that leads to a chronic inflammatory pneumonitis that often progresses to fibrosis. [10] Silent microaspiration has also been suggested as a cause of chronic bronchiolar and interstitial lung disease.14 Lastly, data from the lung transplantation literature strongly suggests that chronic silent microaspiration is associated with post-transplantation bronchiolitis obliterans, the primary lesion in chronic organ rejection.15 In fact, several studies have suggested that early fundoplication improves survival and decreases chronic allograft rejection in this population, presumably through reducing the frequency of silent microaspiration.16, [17]

SILENT MICROASPIRATION AND PULMONARY FIBROSIS

Evidence from experimental models in animals and descriptive studies in humans support the concept of microaspiration as a potential cause of pulmonary fibrosis.

Animal data

Acute aspiration—Gastric juice is found to have rapid distribution in the lungs and is detected in the subpleural zones within 20 seconds following instillation in the main bronchus of dogs.18 Delivery of a single dose of acid solution to the lungs of rabbits and dogs leads to a wide array of histopathologic changes including alveolar hemorrhage, pulmonary edema, and neutrophilic inflammation.19, 20 A low-mortality acid aspiration lung injury model demonstrated loss of normal parenchymal architecture and wide-spread collagen deposition at 2 weeks.[21] In addition, acid treated rodent lungs have demonstrated increased transforming growth factor (TGF)-beta 1 expression in the lung lavage and increased expression of collagens III/IV and fibronectin in the lung tissue, suggesting profibrotic mechanisms may be involved in aspiration-induced lung fibrosis.[22]

Chronic aspiration—Histologic specimens from rodent models of repetitive gastric fluid aspiration exhibited prominent giant cells, lymphocytic and obliterative bronchiolitis, and parenchymal fibrosis.[23] Cytokine analysis showed increased production of TGF-beta. The effects of whole gastric fluid as well as its individual components were also studied using a similar chronic aspiration model.[24] Interestingly, their findings, characterized by granulomatous interstitial pneumonitis, were independent of gastric fluid pH.

Human data

In vitro studies—There are limited *in vitro* data on the effects of gastric fluid aspiration on human epithelial cells, alveolar macrophages, and resident fibroblasts. A component of bile acid, chenodeoxycholic acid, has been shown to induce TGF-beta production from human airway epithelial cells via a p38 MAP-kinase dependent pathway.[25] Fibroblast cell proliferation was also increased with exposure to chenodeoxycholic acid, a response which was inhibited by dexamethasone and anti-TGF-beta antibodies.

Clinical studies—There is no direct data demonstrating that microaspiration leads to pulmonary fibrosis in humans. Instead, studies have focused on investigating risk factors for microaspiration – primarily gastroesophageal reflux. Pearson and Wilson described the presence of gastroesophageal reflux and hiatal hernia, a risk factor for gastroesophageal reflux, in patients with diffuse pulmonary fibrosis,[26] and Mays et al suggested that repeated small tracheobronchial aspiration of gastric secretions over a long period of time could lead to lung fibrosis.[27]

Recently, a strong association between gastroesophageal reflux and idiopathic pulmonary fibrosis has been reported.[28-32] Esophageal 24-hour pH monitoring has estimated the prevalence of gastroesophageal reflux in idiopathic pulmonary fibrosis at 67-88% for distal esophageal reflux and 30-71% for proximal esophageal reflux. These studies also demonstrated that typical symptoms of reflux (e.g. heartburn, regurgitation) are poor predictors for the diagnosis of gastroesophageal reflux in this population.

Despite a strong association between idiopathic pulmonary fibrosis and gastroesophageal reflux, a causal relationship is unclear. A retrospective case series described 4 patients with idiopathic pulmonary fibrosis whose clinical course stabilized over several years with primarily medical therapy targeted at adequate suppression of gastroesophageal reflux.[33] A second retrospective review of 14 patients with idiopathic pulmonary fibrosis awaiting lung

transplantation showed stabilization of oxygen requirements in those patients who had undergone a laparoscopic Nissen fundoplication, but no difference in change in pulmonary function.[34]

SILENT MICROASPIRATION AND IDIOPATHIC PULMONARY FIBROSIS

The above animal and human data support the concept of silent microaspiration leading to pulmonary fibrosis, but many questions remain. Perhaps the most significant is how to reconcile the observed histopathology of aspiration-related lung injury (i.e. airways injury and granulomatous inflammation) with that of idiopathic pulmonary fibrosis (i.e. usual interstitial pneumonia pattern).

Usual interstitial pneumonia pattern is characterized by histologic heterogeneity of fibrosis, with alternating areas of normal lung and dense, mature collagen deposition with evidence of microscopic honeycomb change and characteristic aggregates of spindle-shaped cells beneath hyperplastic alveolar lining (i.e. fibroblastic foci).[35] The fibrosis of usual interstitial pneumonia is anatomically located at the periphery of the secondary pulmonary lobule and is predominantly subpleural. Inflammation and granuloma formation, as described in some aspiration models, are not prominent features of usual interstitial pneumonia and may suggest alternative diagnoses, such as hypersensitivity pneumonitis. Hypersensitivity pneumonitis is due to the inhalation of organic antigens that, like microaspiration, can lead to inflammation and fibrosis in the lung parenchyma.

In clinical practice, distinguishing some cases of usual interstitial pneumonia from hypersensitivity pneumonitis is not straightforward, as both can demonstrate diffuse fibrotic lung disease. [36, 37] A recent study describing the role of surgical lung biopsy in separating chronic hypersensitivity pneumonitis from idiopathic pulmonary fibrosis demonstrated that while most patients with chronic hypersensitivity pneumonitis had histologic evidence of bronchiolocentric inflammation and/or granuloma formation, 2 patients had a usual interstitial pneumonia pattern on surgical lung biopsy.[37] Interestingly, one of these patients had a previous surgical lung biopsy that showed features more typical of hypersensitivity pneumonitis. Histopathologic findings of interstitial fibrosis and parenchymal distortion have also been described in lipoid pneumonia, another example of microaspiration leading to peripheral lung disease.[10] These data support the hypothesis that chronic microaspiration could lead to the histopathologic pattern of usual interstitial pneumonia.

MAKING THE DIAGNOSIS OF MICROASPIRATION

Several approaches for diagnosing microaspiration have been suggested, each having its own set of advantages and disadvantages (Table 1). We describe a few of these methods below.

Symptoms

Symptoms of microaspiration or of conditions that increase the risk for microaspiration (e.g. gastroesophageal reflux) are poor diagnostic tools. Sweet et al found symptom screening for proximal esophageal reflux had a sensitivity and specificity of 60% and 39%, respectively.[31]

Radiology

Several radiologic studies have been used to diagnose microaspiration and risk for microaspiration including barium swallow, computed tomography scan, and scintigraphy. Gastroesophageal-pulmonary scintigraphy involves ingesting a radio-labeled compound, typically technetium labeled hepatate or colloid. If this compound is subsequently aspirated by the subject, the presence of the radio-labeled compound can be detected in the lung.[38]

However, limitations include its poor sensitivity (due to potential infrequency of aspiration events), inter-observer variation, availability, and cost.

Esophageal studies

Esophageal studies, including 24-hour pH monitoring and pH-impedance testing have been used in the diagnosis of gastroesophageal reflux; 24-hour pH monitoring is currently considered the gold standard for this diagnosis.[39] pH-impedance testing may provide some advantage in its ability to diagnose both acid and non-acid reflux events, as well as the height and volume of the refluxate.[40] However, both of these measures can only assess the risk for microaspiration.

Biomarkers

Measurements of pepsin and bile salt in the airways have been investigated as direct biomarkers of microaspiration given their specificity to the gastrointestinal tract, being gastric and biliary in origin, respectively. Pepsin is not normally found in the lower respiratory tract41-43 and patients with gastroesophageal reflux do not necessarily have elevated pepsin levels in their bronchoalveolar lavage (BAL) fluid, suggesting that identifying gastroesophageal reflux is not sufficient for diagnosing microaspiration.[42] Pepsin in BAL has been shown to be a highly specific (100%) and sensitive (80%) method for diagnosing gastroesophageal reflux - associated pulmonary aspiration in children.43 In another study, BAL pepsin level correlated with the number of proximal reflux events as measured by 24-hour pH monitoring.44 The limitations of this method include the lack of standardized methodology and unknown half-life and clearance mechanisms from the lower respiratory tract.

At this time, a diagnostic gold-standard for microaspiration remains unknown. However, based on the current data, the specificity of pepsin and bile salt to the gastrointestinal tract makes this diagnostic approach highly appealing.

CLINICAL MANAGEMENT

Until further evidence is available, we cannot recommend a specific screening, diagnostic, and/or management algorithm for microaspiration in idiopathic pulmonary fibrosis. Much has been written about the need to screen and treat gastroesophageal reflux in this population.[45, 46] However, there is equipoise in the idiopathic pulmonary fibrosis community as to how aggressively to pursue this diagnosis. Even within this group of authors, there are differences in practice patterns. This is primarily because there are no convincing data demonstrating a clinical benefit to treatment of gastroesophageal reflux in idiopathic pulmonary fibrosis and there are risks to medical treatment. Studies have suggested an increased risk for community-acquired pneumonia in association with current use of proton pump inhibitors (PPI).[47] PPIs have also been associated with an increased risk of hip fracture.48 Further, PPIs only change the acidity of the refluxate; they do not prevent reflux or microaspiration of gastric contents.

It is also unknown if other measures, such as lifestyle modifications (e.g. small meals, avoidance of certain foods and alcohol), other pharmaceutical interventions (e.g. prokinetics), and/or surgical barrier creation (e.g. Nissen fundoplication), have a role in the treatment of microaspiration. Collaboration with our gastroenterology and surgery colleagues will be essential in addressing all of these issues.

GAPS IN KNOWLEDGE

One possible mechanism of microaspiration leading to pulmonary fibrosis is illustrated in Figure 1. However, many questions need to be addressed in future studies to clarify the role of silent microaspiration in patients with idiopathic pulmonary fibrosis:

- What is the true prevalence of microaspiration in patients with idiopathic pulmonary fibrosis? The finding of gastroesophageal reflux does not imply microaspiration and there is no consensus on a gold standard for the diagnosis of microaspiration in the pulmonary community. Respiratory symptoms are well recognized extra-esophageal manifestations of gastroesophageal reflux,[49] and reflux extending into the proximal esophagus and cricopharyngeal region is thought to reflect a high risk for microaspiration,[50-52] however, its sensitivity and specificity are unknown. The measurement of pepsin and bile salt in BAL may help clarify this issue.
- If gastroesophageal reflux is an accurate biomarker for microaspiration in idiopathic pulmonary fibrosis, why is there such a discrepancy between the prevalence of gastroesophageal reflux (20,000 per 100,000) and the prevalence of idiopathic pulmonary fibrosis (approximately 14-43 per 100,000)?[53, 54] Possibilities include variation in the degree or duration of microaspiration, the involvement of other co-morbidities (e.g. *Helicobacter pylori* infection), or differences in genetic predisposition to fibroproliferation. Perhaps in genetically predisposed individuals, the pulmonary parenchyma responds in an aberrant "pro-fibrotic" manner to epithelial injury (e.g. recurrent acid injury), resulting in the clinical development of idiopathic pulmonary fibrosis.[55, 56]
- Which components of the gastric refluxate are most injurious to the lung? Depending on the origin of the refluxate (stomach, duodenum), contents that move retrograde past the lower esophageal sphincter could contain acid, bile salts, proteases (pepsin, trypsin) and upper gastrointestinal organisms. As noted previously, animal studies have suggested that lung injury from chronic aspiration is independent of pH, implying that non-acid reflux may also be relevant.
- Should patients with idiopathic pulmonary fibrosis be treated for presumed microaspiration? We do not know if clinical outcomes for patients with idiopathic pulmonary fibrosis are improved by treatment of microaspiration. The studies described previously suggest a possible benefit with the treatment of gastroesophageal reflux;[33, 34] however there is insufficient data at this time to recommend this strategy. The role of treatment can only be addressed once the precise relationship between microaspiration and idiopathic pulmonary fibrosis has been defined.
- Does microaspiration cause idiopathic pulmonary fibrosis or does idiopathic pulmonary fibrosis cause microaspiration? The latter theory argues that idiopathic pulmonary fibrosis leads to progressive architectural distortion of the mediastinal structures, traction on the esophagus and the diaphragm, and weakening of the lower esophageal sphincter. Weakening of the lower esophageal sphincter would predispose patients to gastroesophageal reflux and microaspiration. Evidence contrary to this theory includes two studies that demonstrated no association between lung function and acid exposure times,[29, 32] and a third showing an inverse relationship between lung function and the presence of gastroesophageal reflux.[31] Regardless, a weakened lower esophageal sphincter could allow for chronic microaspiration, causing repetitive injury to the already diseased lung and leading to the accelerated decline and/or acute respiratory decompensation seen in some patients with idiopathic pulmonary fibrosis.
- Does microaspiration cause acute exacerbations in idiopathic pulmonary fibrosis? Recent studies have reported on the clinical significance of acute exacerbations in increasing the morbidity and mortality of idiopathic pulmonary fibrosis.[5] Acute exacerbations of idiopathic pulmonary fibrosis are characterized by the development of diffuse alveolar damage superimposed on underlying usual interstitial pneumonia pattern. Clinically occult aspiration may be a cause of acute exacerbations of

idiopathic pulmonary fibrosis as aspiration of gastric contents is a known cause of diffuse alveolar damage.[10]

CONCLUSION

The data summarized in this review are provocative and implicate a potential role for microaspiration in the etiology and natural history of idiopathic pulmonary fibrosis. We firmly believe defining the precise relationship between microaspiration and idiopathic pulmonary fibrosis is critically important because of its potential pathobiological and therapeutic implications. In general, current treatment strategies in idiopathic pulmonary fibrosis have focused on modulating the fibrotic tissue response after the injury, not on preventing the injury itself. Microaspiration may represent a source of repetitive injury in idiopathic pulmonary fibrosis and may be modifiable with medical and/or surgical therapy. Perhaps combining treatment of microaspiration with biologic agents targeted at key cellular and biological aspects of inflammation and fibrosis would provide a synergistic approach to preventing further lung injury from microaspiration and controlling disease progression in these patients.

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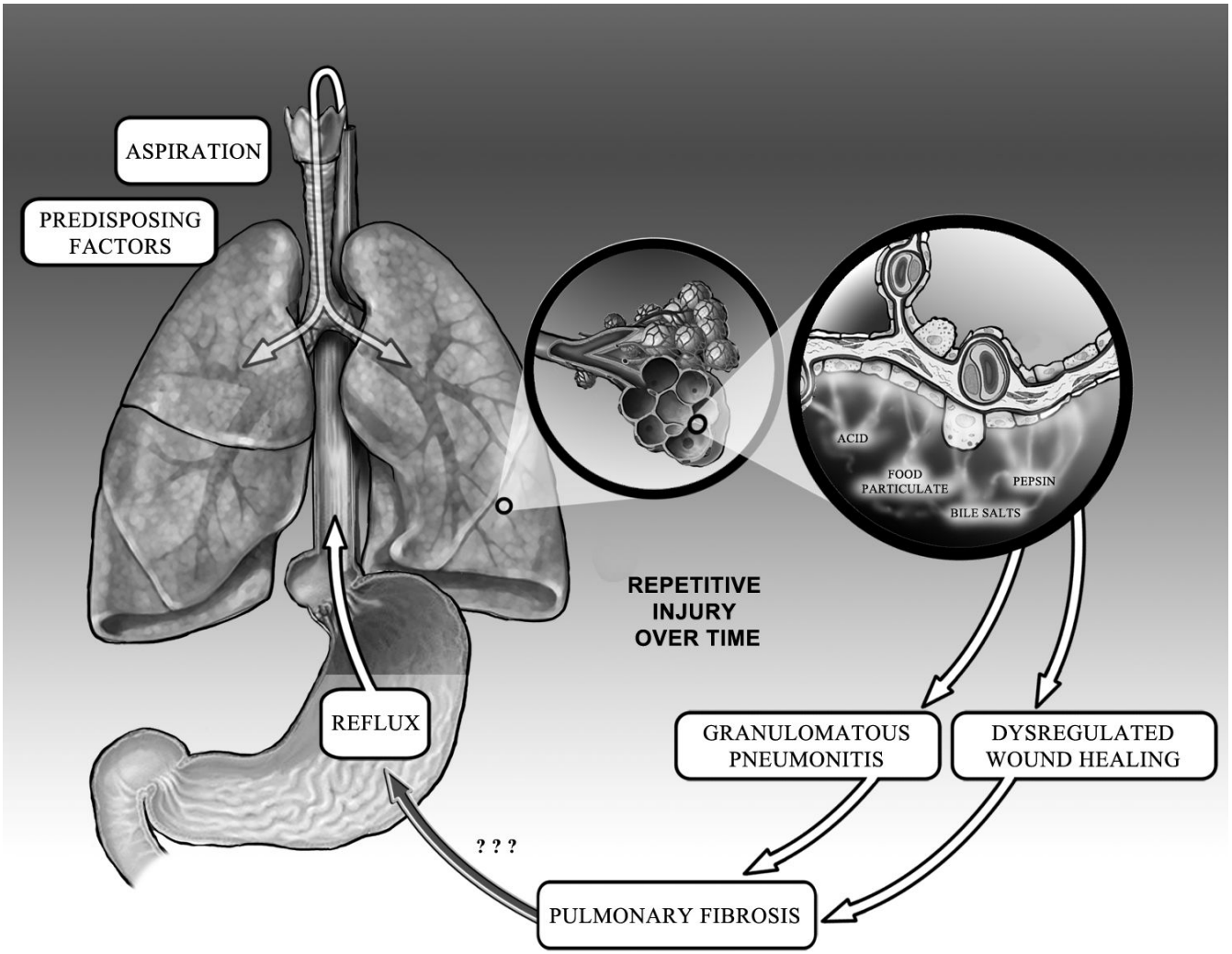

Figure 1. Possible Pathogenetic Mechanism for Chronic Microaspiration in Idiopathic Pulmonary Fibrosis

Gastric fluid can travel in a retrograde fashion through a weakened lower esophageal sphincter (e.g. secondary to a hiatal hernia, traction from the diaphragm, or medications) up into the esophagus. The gastric refluxate can travel as high up as the cricopharyngeal region and enter the airway. Normal host defenses likely clear most gastric refluxate without clinical sequelae. However, in some cases, components of the gastric refluxate (e.g. acid, bile, particulates) may directly injure the lung epithelium. In the genetically or otherwise predisposed patient, chronic microaspiration of gastric refluxate may cause repetitive injury over time leading to granulomatous pneumonitis, dysregulated wound healing, and eventual lung fibrosis. Additionally, progressive pulmonary fibrosis may lead to distortion of the mediastinal structures and traction on the esophagus. This could cause additional weakening of the lower esophageal sphincter, which could in turn lead to microaspiration, lung injury, and the accelerated decline and/or acute respiratory decompensation seen in some patients with idiopathic pulmonary fibrosis.

Table 1

Summary of Diagnostic Tools for Microaspiration

Diagnostic Test	Description	Advantages	Disadvantages
Symptoms 28-32	Heartburn, regurgitation, dysphagia	• Simple • Non-invasive	• Low sensitivity (65%) • Low specificity (71%)
Modified barium swallow 57	Use of radio-opaque agent to visualize the process of swallowing from the oral cavity +/− esophagus, performed by a speech pathologist and radiologist	• Directly evaluates for aspiration • Simple and brief • No patient preparation prior to test • Inexpensive	• X-ray exposure • Detects aspiration during the procedure only • Subjective interpretation • Poor sensitivity
Gastroesophageal-pulmonary scintigraphy 38, 58	Nuclear medicine technique using technetium labeled colloid or hepatate	• Directly evaluates for aspiration • Lower radiation exposure than barium or CT scan	• Not widely available • Expensive • Subjective interpretation • Poor sensitivity
Computed tomography (CT) scan 59, 60	CT study of the thorax can give information on mediastinal structures (hiatal hernia) and pulmonary parenchyma (centrilobular nodules, airway thickening)	• Specific for large hiatal hernias • Presence of an air-fluid level or prolonged air column in the esophagus may be associated with aspiration	• Does not actually measure aspiration • Parenchymal changes are non-specific • Not sensitive for the presence of small-medium hiatal hernia • Not well studied for this purpose
Dual sensor 24-hour pH monitor with manometry 39, 52, 61	Continuous recording of acid pH <4 in the distal and proximal esophagus with measurements of esophageal peristalsis	• Widely available • Picks up asymptomatic acid reflux and esophageal dysmotility • Considered the gold standard for diagnosis of gastroesophageal reflux disease	• Doesn't detect non-acid reflux or volume of refluxate • Does not actually measure aspiration • Operator dependence • Unclear what is the optimal location for detection of proximal esophageal reflux
Multichannel intraluminal pH-impedance monitoring 39, 40	Discriminates all gas and fluid reflux, regardless of pH, by exploiting differences in electrical conductivity of the esophageal wall and intraluminal content to identify bolus presence	• Measures non-acid reflux • Measures volume of refluxate • Measures height of reflux	• Not widely available • No studies in IPF • Only measures aspiration risk
Pepsin and bile salts 41-44, 62-64	Biomarkers that reflect the presence of gastric refluxate in the	• Direct marker of aspiration	• Not widely available

Diagnostic Test	Description	Advantages	Disadvantages
	lungs	• Studied in other populations (post-lung transplant, pediatrics, asthmatics, and mechanically ventilated)	• Unknown half life and clearance mechanisms in the lower respiratory tract
• **Bronchoalveolar lavage (BAL)** 65	Directed sampling of lung via bronchoscopy	• Samples the lining fluid of the lower respiratory tract	• Semi-invasive • Potential risk for exacerbation of IPF • Dilution
• **Exhaled breath condensate (EBC)** 66-69	Non-invasive method of sampling the respiratory tract	• Rapid • Non-invasive • In-expensive	• Final sample may be affected by oropharyngeal components • Some biomarkers in EBC do not correlate with BAL • Dilution

Abbreviations: BAL – bronchoalveolar lavage, CT – computed tomography, EBC – exhaled breath condensate, IPF – idiopathic pulmonary fibrosis