Interstitial Lung Disease

(Diffuse Parenchymal Lung Disease)

Focusing on Idiopathic Pulmonary Fibrosis

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Preface:

Interstitial lung disease (ILD) (also known as Diffuse Parenchymal Lung Disease) is a broad – term / blanket – term that describes a group of as many as 200 chronic progressive lung disorders that share similar characteristics of alveolar septal thickening, fibroblast proliferation, collagen deposition and, most often, pulmonary scarring (fibrosis). This set of disorders can further be classified as acute or chronic, primary or secondary, secondary to a known cause or of unknown causes (idiopathic), granulomatous or non-granulomatous, etc… Interstitial Lung Disease is also sometimes synonymously referred to as *pulmonary fibrosis*, but not all ILD's are fibrotic in nature.

The diagnostic difficulties of ILD are the result of the commonalities between the individual diseases. All interstitial lung diseases are similar in basic description, as in they share similar characteristics. Investigative persistence not only aids in diagnostics but also allows the medical team build a patient – specific treatment plan designed especially for the individual case being presented.

ILD is broken down into 4 main sub-groups, or sub-categories, based on probable/possible causes and certain characteristics. Table-1 below lists these sub categories in order of prevalence.

Interstitial Lung Disease **(Diffuse Parenchymal Lung Disease)**			
Idiopathic Interstitial Pneumonia	Known Cause ILD	Granulomatous ILD	Other Forms of ILD

Table 1: The 4 Sub-Groups of Interstitial Lung Disease in Order of Prevalence

Causes of Interstitial Lung Disease

While the causes of ILD are many, and many more remain unknown today, most of the known causes are long term exposure to certain irritants such as asbestos, coal dust, silica dust, etc… Also, some autoimmune diseases are known to cause ILD. These include, but are not limited to lupus, rheumatoid arthritis, and scleroderma. Still, even with what the medical community knows more than 50% of the cases of interstitial lung disease are in fact *idiopathic* – of unknown causes. Table-2 below lists some of the known causes of ILD:

Some Known Causes of Interstitial Lung Disease

Long Term Exposure – Regular exposures to known irritants either at work or play can lead to alveolar epithelial cell injury, eventually causing interstitial lung disease. Some of these irritants include, but are NOT limited to those listed here;
* ***Of note:*** some cancers can spread throughout the lungs via the lymphatic system and masquerade as interstitial lung disease. This marks the importance of investigative persistence and tissue biopsy. Also, congestive heart failure (CHF) and renal failure both can cause excess fluid to buildup in the spongy tissue of the lungs and present as interstitial lung disease; thus the importance of a multidisciplinary approach.

a. Asbestos
b. Certain Autoimmune diseases such as lupus, rheumatoid arthritis, scleroderma.
c. Bacteria, viruses, and fungi are known to cause interstitial pneumonia's
d. Bird proteins – such as from exotic birds, chickens, or pigeons
e. Certain medications, including amiodarone and even some cancer-fighting chemotherapies
f. Coal dust, or various other metal dusts from working in the mining industry
g. Genetic diseases – some genetic diseases can cause ILD mainly due to the effects of the individual diseases.
h. Grain dust from farming
i. Infections: *Mycoplasma pneumoniae* is one of the most common causes of interstitial inflammation, a signature of interstitial lung disease. Some viruses, bacteria, and fungi can also cause chronic interstitial inflammation.
j. Mold
k. Radiation therapy
l. Silica dust
m. Talc
n. Tobacco smoke – Primary and/or secondary exposure poses equal risk of occurrence.

Interstitial Lung Disease resulting from exposure to known causing irritants is sometimes referred to as hypersensitivity pneumonitis

Table 2: Some known causes of interstitial lung disease – Listed in alphabetical order, NOT necessarily in order of prevalence.

Idiopathic Interstitial Pneumonia's

Idiopathic Interstitial Pneumonia (IIP) is the largest, and most commonly diagnosed, of the 4 sub-categories of Interstitial Lung Disease. There are 7 main disease states within the IIP group. They are all radiographically and clinically similar, cause dyspnea, show varying degrees of inflammation and show non-specific changes on standard CXR. Most often a high-resolution Lung CT and surgical lung biopsy are required for a definitive diagnosis to be made. This is important because treatment varies by specific type, as does prognosis – ranging from excellent to fatal. Table-3 lists the Idiopathic Interstitial Pneumonia's in order of prevalence.

Idiopathic Interstitial Pneumonias
1. Idiopathic Pulmonary Fibrosis – (with Usual Interstitial Pneumonia)
2. Desquamative Interstitial Pneumonia
3. Nonspecific Interstitial Pneumonia
4. Cryptogenic Organizing Pneumonia
5. Respiratory Bronchiolitis-Associated ILD
6. Acute Interstitial Pneumonia
7. Lymphoid Interstitial Pneumonia

Table 3: Idiopathic Interstitial Pneumonia's listed in order of prevalence.

Idiopathic Pulmonary Fibrosis

Idiopathic Pulmonary Fibrosis (*IPF*) (also known as *cryptogenic fibrosing alveolitis*) is a chronic progressive fibrotic lung disease of unknown origin that causes fibrous scar tissue to grow throughout the lungs. It is the most commonly diagnosed and most fatal of all Interstitial Lung Diseases in the United States, residing at the top of the list of the Idiopathic Interstitial Pneumonia's (IIP's). As with most interstitial lung disease the original characteristics are vague and non-specific, making diagnosis exceedingly challenging. IPF is characterized by gradually worsening shortness of breath either with exertion or at rest, and a chronic dry hacking cough of unknown origin. The diagnosis of IPF requires a multi-disciplinary approach and must include a pattern of usual interstitial pneumonia as seen by high resolution chest computed tomography, a surgical lung tissue biopsy and the ruling out of all known causes.

Histologically IPF damages alveolar epithelial cells causing alveolar septal thickening, fibroblast and myofiborblast proliferation, and near irreversible inflammation and fibrosis (scarring).

Epidemiology of IPF

It is estimated that IPF effects about 5 million people worldwide, primarily affecting the middle-aged to older adult population – usually effecting those in their late 40's to early 50's, but epidemiology is difficult to interpret because most studies of the disease were done here in the United States, and in a handful of the European countries. It appears to affect males more so than females by a ratio of approximately 1.53:1 respectively, with a diagnostic incidence of approximately 20 per 100,000 males and 13 per 100,000 females, as suggested by many of the United States studies. One study in the UK suggests that IPF affects 62% male vs. 38% female, and the incidence of IPF has more than doubled between 1990 and 2003, but it is not believed to be due to the aging UK population. A more current UK study said that the incidence reports >5000 new cases of IPF diagnosed annually.

In another study (Qunn L, et al. Hyperplastic epithelial foci in honeycomb lesions in idiopathic pulmonary fibrosis. Virchow's Arch 2002; 441:271–278) IPF appears to have a higher incidence of primary lung cancer than patients who do not have IPF.

Data According to the Coalition for Pulmonary Fibrosis: (http://www.coalitionforpf.org)
• 40,000 People die from Pulmonary Fibrosis each year in the United States. This is equal to the number of fatalities from breast cancer. • Adult between ages 30 – 80 are at higher risk, with risk usually increasing with age, but anyone can get Pulmonary Fibrosis • There is NO current effective cure or treatment for Pulmonary Fibrosis. There are some therapies that are shown only to slow the progression of the disease • As scar tissue and fibrosis progresses breathing gradually gets more and more difficult • In the United States the number of cases of IPF has increased 156% since 1999 • As many as 50% of patients are misdiagnosed for the first year or more • A relentless and progressive disease – most patients die within 2 – 5 years of diagnosis • There are 4 times as many fatalities from IPF as there are from Cystic Fibrosis • Lung transplantation is the only means to extend life expectancy but few are candidates, and many patients who actually make it on the transplant list (as many as 50%) die before receiving a lung.

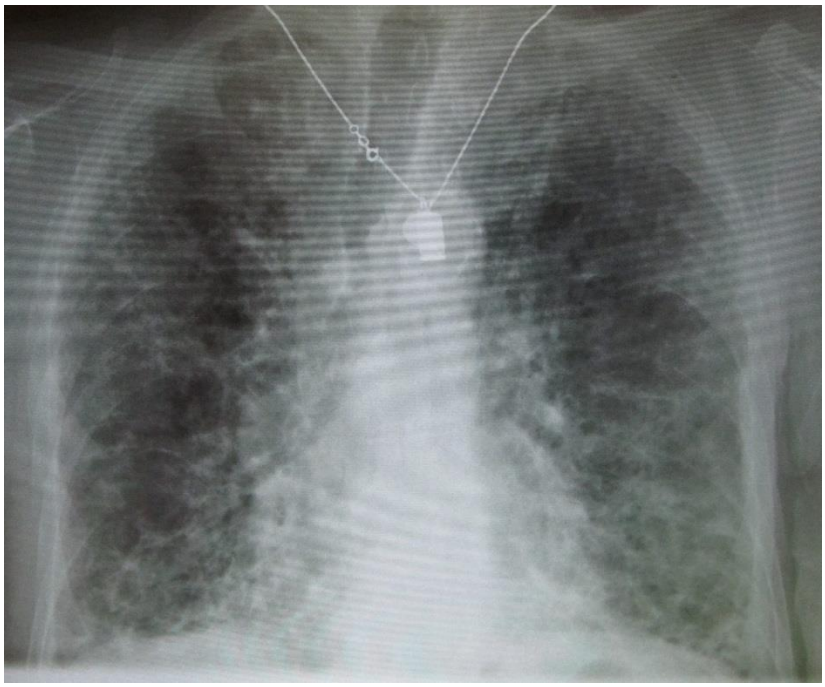
Table 4: This data was obtained from the Coalition for Pulmonary Fibrosis (http://www.coalitionforpf.org)

Etiology, Pathology and Risk Factors of IPF

The etiology of IPF is mostly unknown but there is a growing list of risk factors and common exposures associated with the disease. Some of the more prominent risk factors are listed in Table-5. Diagnosing IPF requires the positive diagnosis of interstitial lung disease by High Resolution Chest CT showing a pattern of Usual Interstitial Pneumonia (UIP), surgical lung tissue biopsy, and the ruling out of all known causes. As noted, this requires a multidisciplinary approach so diagnosis and treatment can be specific to the individual patient.

Some Known Risk Factors Associated With Idiopathic Pulmonary Fibrosis
a. Cigarette Smoking (Regular smokers of >20 packs/year) b. Livestock exposure c. Silica exposure d. Asbestos exposure e. Long term exposure to metal dust (brass, steel, lead) f. Long term exposure to wood dust g. Construction of wooden houses h. GERD – Microaspiration from GERD is a risk factor for the predisposition and progression of IPF

Table 5: Some Known Risk Factors Associated With Idiopathic Pulmonary Fibrosis



Fibrosis is mostly seen along the inferior portions of the lower lobes, showing a cobblestone appearance often referred to as honeycombing, with patches of ground glass infiltrate. This honeycombing pattern is also seen along the pleural lining in later phases of the disease.

Figure 1: PA Chest X-Ray of advanced idiopathic pulmonary fibrosis. Note the cobblestone appearance commonly referred to as gross honeycombing along the bases and lung periphery.

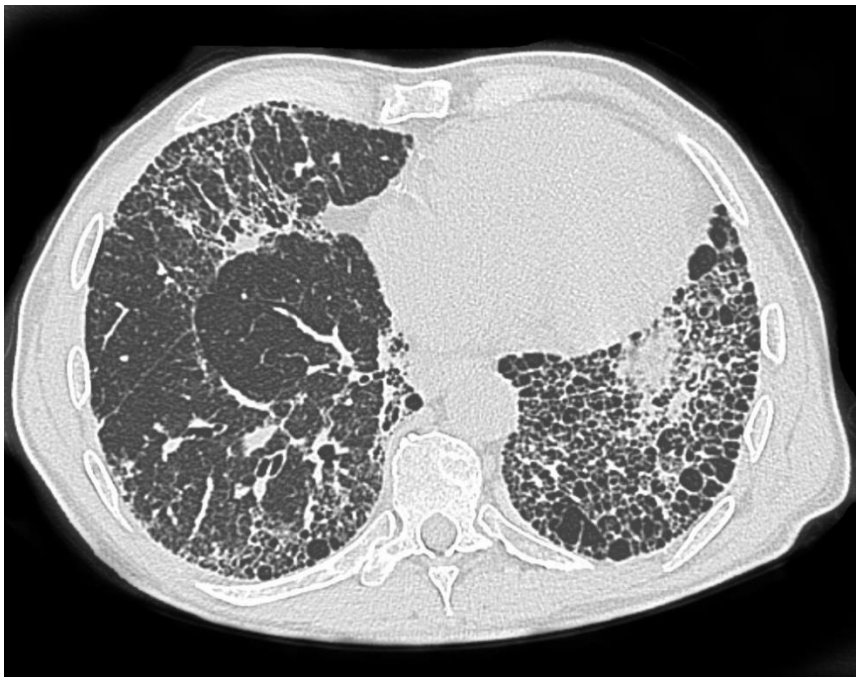


Figure 2: HRCCT of a patient with idiopathic pulmonary fibrosis. Note the cobblestone appearance commonly referred to as gross honeycombing.

The current belief is that IPF is the result of an aberrant healing process of injured alveolar epithelial cells. This alveolar injury is usually the result of long term exposure of inhaled foreign material such as cigarette smoke, asbestos, metal dust, etc… There is, however, some evidence of a hereditary predisposition to IPF in a very small percentage of patients. Further studies are needed to better understand the possibility of a hereditary relationship.

Following alveolar epithelial injury is the proliferation of pro-inflammatory cells (due to a chemokine gradient), cytokines, fibroblasts, and myofiborblasts. The result is near unstoppable and unforgiving interstitial inflammation, the abnormal growth of fibrotic scarring, and the alteration of pulmonary architecture. These effects continue to grow and spread throughout the interstitial tissue, slowly and gradually decreasing gas exchange and increasing dyspnea. Up to 59% of patients with end stage IPF develop pulmonary hypertension, making symptoms even worse. It is also not uncommon for patients with IPF to have other chronic lung diseases concomitantly.

Differential Diagnosis

Because the symptoms of IPF are mostly vague and non-specific it is easy to misdiagnose IPF for many other diseases or disorders. It is also easy to misdiagnose other diseases for IPF. Again, this stresses the importance for persistence and a multidisciplinary approach to diagnostics. Some of the differential diagnoses are listed below.

Differential Diagnoses of Idiopathic Pulmonary Fibrosis

- **Acute Interstitial Pneumonia**
- **Asbestosis**
- **Bronchoalveolar Carcinoma**
- **Drug Induced Interstitial Lung Disease** – There are many drugs (prescription & illicit drugs) that have an increased risk of precipitating interstitial lung disease including pulmonary fibrosis.
- **Eosinophilic Pneumonia**
- **Farmer's Lung**
- **Histoplasmosis**
- **Interstitial Lung Disease other than IPF**
  - Acute Interstitial Pneumonia
  - Desquamative Interstitial Pneumonia
  - Histiocytosis
  - Nonspecific Interstitial Pneumonia
  - Sarcoidosis
- **Mycoplasma Pneumonia**
- **Nonidiopathic Pulmonary Fibrosis**
- **Nonspecific Interstitial Pneumonitis** – Pneumonitis that is frequently secondary to various autoimmune diseases such as Rheumatoid Arthritis or Scleroderma
- **Pneumonitis of Various Origins**
  - Aspiration Pneumonitis
  - Hypersensitivity Pneumonitis
  - Radiation Pneumonitis
  - Viral or bacterial pneumonitis
- **Pulmonary Edema of Various Origins**
  - Cardiogenic Pulmonary Edema
  - High Altitude Pulmonary Edema
  - Neurogenic Pulmonary Edema

Table 6: Differential diagnoses of Interstitial Lung Disease

Treatment & Prognosis of IPF

Currently there are no known cures or effective therapies for IPF. It is common practice to use agents such as the corticosteroid *prednisone*, and the immunomodulatory agent *azathioprine* but that has been notably ineffective. A recent trial added the antioxidant *acetylcysteine* to the mix but the trial was stopped prematurely due to increased mortality.

Because a significant number of IPF patients develop pulmonary arterial hypertension the increased workload of the right ventricle of the heart, and eventual right ventricular dysfunction,

cause a significant increase in dyspnea as well as other complications. Sildenafil, a phosphodiesterase type-5 (PDE5) inhibitor, was approved by the US Food & Drug Administration in June of 2005 under the brand name Revatio. It relaxes the smooth muscle within the pulmonary arterial walls which decreases pulmonary blood pressure. This, in turn, relieves some of the some of the dyspnea associated with pulmonary hypertension. As a word of caution the clinician must be aware that sildenafil does nothing for idiopathic pulmonary fibrosis. The decrease in dyspnea is strictly a result of the decrease in pulmonary arterial blood pressure.

Currently the antifibrotic/anti-inflammatory agent pirfenidone seems to be the golden nugget in the treatment of IPF. In animal studies, and 2 phase-III clinical trials (the CAPACITY & ASCEND trials) the use of pirfenidone showed little improvement vs placebo, but a meta-analysis of 4 other studies involving a total of 1,155 patients showed up to a 30% improvement in FVC, a significant improvement in the 6-minute walk test, and a significant decrease in the rate of progression of inflammation and fibrotic scarring. The US Food & Drug Administration approved pirfenidone for use in IPF in October of 2014 under the brand name Esbriet.

Scientists and drug makers are now focusing on fibroproliferation and fibrogenesis. In addition, a recent pilot trial was conducted by Physicians from the University of Pittsburgh using therapeutic plasma exchange and rituximab. The goal was to reduce autoantibodies that are believed to play a role in acute exacerbations of IPF. The results of their pilot trial was published online in PLoS One on June 17, 2015. This pilot trial has shown dramatic results that go well beyond any currently approved therapy for IPF but more studies are needed to better understand the role of autoantibodies, and the role of TPE therapy in the treatment of IPF.

It is hopeful, and likely, that in the coming decade the medical community will begin to see more effective, and safer treatments for IPF. While we remain hopeful for better results in the near future, IPF remains a relentless, progressive fatal disease.

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