Idiopathic lung fibrosis

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List of abbreviations:

AE ILF- Acute exacerbation of ILF

ATS-American thoracic society

BAL- Bronchoalveolar lavage

CPAP- Continuous positive airway pressure

CTD- Connective tissue disease

DAD-Diffuse alveolar damage

DLCO-Diffusing capacity for carbon monoxide

ECM- Extracellular matrix

EMT-Epithelial-to-mesenchymal Transformation

EPC- Endothelial progenitor cells

ER- Endoplasmatic reticulum

ERS-European respiratory society

FVC-Forced vital capacity

FEV1-Functional expiratory volume in 1 second

FPF-Familial pulmonary fibrosis

GERD- Gastroesophageal reflux disease

ILF-Idiopathic lung fibrosis

IPF-Idiopathic pulmonary fibrosis

IIP-Idiopathic interstitial pneumonias

ILD-Interstitial lung disease

PFT-Pulmonary function test

SPPL2C- Signal peptide peptidase like 2C

TERT-Telomerase reverse transcriptase

TERC-Telomerase RNA

TOLLIP-Toll-interacting protein

UIP- Usual interstitial pattern

VATS- Video-assisted thoracoscopic surgery

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1.SUMMARY

Idiopathic Lung Fibrosis

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Idiopathic lung fibrosis is a chronic disease affecting the pulmonary interstitium or parenchyma. As such it has signs typical of other interstitial lung diseases such as dyspnea, hypoxia, chronic cough and clubbing of fingers. It typically affects older patients with a history of smoking or exposure to some occupational pollutants as well as patients with a positive family history. Multiple hypotheses are present that would explain this condition, including both genetic factors and environmental factors such as smoking or air pollutants. It is safe to say that this disease is caused by an interplay of various factors and not one single cause. It is a relatively rare disease with a very poor prognosis. Diagnosis is complex and involves a multidisciplinary approach. In addition to proper anamnesis and physical exam other more advanced procedures such as high-resolution computerized tomography imaging. Cryobiopsy and bronchoalveolar lavage are also needed for excluding differentials and for establishing a diagnosis. Important treatment breakthroughs have been made in recent decades owing to newly discovered antifibrotic drugs. These have greatly impacted our treatment procedures for idiopathic lung fibrosis, by helping to prologue life and improve symptoms. Because of this they have injected a newfound optimism into treatment of this difficult condition. Another important consideration in idiopathic lung fibrosis are the various comorbidities associated with this condition. As with most chronic conditions we have numerous comorbidities such as lung cancer, esophageal reflux, heart failure and pulmonary embolism that must be recognized and treated because they can significantly alter the patient's outcome.

Key Words: Idiopathic, Pulmonary, Lung, Fibrosis, Review

1.SAŽETAK

Idiopatska Plućna Fibroza

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Idiopatska plućna fibroza je kronična bolest koja zahvaća plućni intersticij ili parenhim. Klinička slika odgovara simptomima karakterističnim za intersticijske bolesti pluća poput dispneje, hipoksemije, kroničnog kašlja i batićastih prstiju. Obično zahvaća starije pacijente koji imaju povjest pušenja ili su izloženi raznim zagađivačima, a dokazana je i genetska predispozicija odnosno može biti prisutna i pozitivna obiteljska povijest. Postoji nekoliko hipoteza o uzroku ove bolesti koje uključuju genetske zajedno s okolišnim faktorima poput pušenja i okolišnih zagađivača. Relativno je rijetka bolest s vrlo lošom prognozom. Postavljanje dijagnoze je vrlo složeni proces koji zahtijeva multidisciplinarni pristup. Potrebna je detaljna anamneza i fizikalni pregled kao i naprednije procedure poput kompjutorizirane tomografije visoke rezolucije. Kriobiopsija i bronhoalveolarna lavaža su također potrebni u pojedinim slučajevima za postavljanje dijagnoze i isključivanje drugih diferencijalnih dijagnoza. Posljednjih desetak godina dostupnošću dvije vrste antifibrotika u liječenju idiopatske plućne fibroze poboljšala se značajno kvaliteta života i smanjila smrtnost pacijenta s navedneom bolešću. Potrebno je naglasiti da treba potvrditi i liječiti moguće komorbiditete kao što su tumori pluća, plućna hipertenzija, srčano zatajenje i plućna embolija jer oni također utječu na tijek bolesti. Njihovo rano prepoznavanje i liječenje pospješuje kvalitetu života bolesnika.

Ključne riječi: Idiopatska, Plućna, Fibroza, Pregled

2.INTRODUCTION

Idiopathic lung fibrosis (ILF) is a chronic, fibrosing interstitial pneumonia of unknown etiology (1). It is part of a larger group of diseases known as idiopathic interstitial pneumonias (IIP) (2). Primarily it effects the older population and has a very poor prognosis. It is characterized by chronic clinical progression with episodes of acute exacerbation (AE ILF). Although ILF is a rare disease, because of its poor prognosis and insidious onset it is very important to recognize this entity in its early stage and initiate treatment promptly.

Various environmental factors as well as intrinsic genetic factors are now thought to play a role in pathogenesis of ILF. The fact that we have a familial and sporadic form lend support to this conclusion. This area of ILF research is still undergoing extensive investigation and various hypotheses have been proposed for explanation of ILF, but we can say that it is likely that a combination of these various factors is responsible.

ILF may be very difficult to diagnose and the list of differential diagnoses is extensive as will be shown later in the text. The main difficulties come from nonspecific symptoms that have an insidious onset, and even with the proper diagnostic tools the results may overlap with other interstitial pneumonias or chronic pulmonary diseases. Nevertheless, diagnosis is easier now than in the past because we now have a more sophisticated understanding of ILF as well as precise clinically defined diagnostic criteria. In combination with this we also have newer diagnostic methods such as HRCT and cryobiopsy that are also available worldwide. Professionals from different medical fields are also working in concert to ascertain the diagnosis and guide management. In very difficult cases all of these elements must be harmonized in order to establish the diagnosis.

In recent years we have had breakthroughs in the treatment of the ILF. Several antifibrotic therapies have been approved that show a marked improvement over previous treatment options. This novel area of pharmacological therapy for ILF is especially emphasized in the text below. Several nonpharmacological therapeutic methods are also available including lung transplantation in severe cases. It must be mentioned that even with all of the available treatment options ILF remains a terminal disease with a very poor prognosis.

Finally, several comorbid conditions are usually found to accompany ILF. This is expected since any severe chronic disease will have various comorbid conditions associated with it, especially in the later stages. Identification of these comorbid conditions is also necessary as they may complicate treatment and significantly alter disease outcomes.

3.EPIDEMIOLOGY

Although a rare disease in its own right, ILF is known for being the most prevalent form of IIP (2). It is a challenge to give a precise estimate of prevalence and incidence of this particular disease owing to a sundry list of difficulties. In the past we had no exact uniform classification of ILF, and many interstitial lung diseases overlapped in their definitions which made it very difficult to calculate the prevalence and incidence of the disease. Today we have an exact clinical definition so classification is more standardized (1). Secondly, different diagnostic methodologies have been used by different studies ranging from differences in physician experience to the use of different International Classification of Disease (ICD) codes. Lastly each study has its own peculiarities that make it difficult to do a comparison, such as differences in population (3). According to the European ILF registry the incidence is heavily dependent on age, and rises in proportion to it. It reports an incidence of 2.7/100,000 in 35 to 44-year-olds and in patients that are over 75 a significantly higher rate of 175/100,000 (4). It acknowledges that there are difficulties with estimating a total incidence but concludes that an „average incidence of 7-10/100,000 is likely“ (4). These numbers are confirmed by other registers that get their data from various trials, for instance a trial in Northern California used a traditional ILF algorithm to identify 2608 cases of ILF in at-risk adults. They give an annual incidence of 6.8/100,000, and the incidence is higher in patients that are older, male and Caucasian, higher rates were also found in older populations being as high as 494/100,000 in the USA (5,16). Similar incidences are found in registries from Finland (6) and other European countries (7). Japan has shown slightly lower rates of 2.23/100,000 (8). It is possible to find studies that report much higher rates of ILF than the ones listed; this is mostly due to a disaccord of their inclusion criteria and methodologies, as well as regional differences among the population. In order to better appreciate the incidence of the disease over various geographical regions refer to Table 1.

As mentioned above it is a disease of advanced age with a mean age of onset in the late 60s and early 70s (10). A comprehensive data analysis from the European ILF registry sets the mean age of onset at 68.1 years (11). A similar study in the UK gives the highest incidence for the disease in the age group over 65; with a sharp decline in incidence in patients over 85 (14). From this data we can conclude that the majority of cases appear between 60 and 70 years of age.

All of the previously mentioned studies and registries agree that ILF is more common in males than in females. One study conducted in the USA shows a 20% higher prevalence of ILDs in males than in females; with a smaller but significant increase in the incidence among males as well (13). The most common ILD in this study among both sexes was ILF. Similar findings that show an increased incidence among males can be seen in studies conducted in the UK (14). Although the exact number by which the disease is more prevalent in males differ from study to study, this is to be expected due to international variations in population, among other incongruences as mentioned above.

In studies conducted in Europe we can see that the prevalence and incidence of ILF is on the rise, especially among older males (15). Data from the USA also shows that incidence and prevalence are increasing in recent years (16). It must be noted that diagnostic criteria have recently undergone significant revisions, which might explain the cause of this upward trend in the prevalence and incidence.

The mortality of ILF is very high, with estimations of mean survival after diagnosis being 3-6 years (9). Mortality is dependent on different baseline factors that are estimated at the time of diagnosis including CT findings and pulmonary function tests. In recent years mortality for ILF has shown a slight increase, or at least no improvement (9,16).

Table 1. Incidence of ILF by country (5,6,7,8,16)

Country	Incidence
UK (1)	7.44/100 000
Denmark (2)	1.3/100 000
USA-New Mexico (3)	10.7/100000 in males, and 7.4/100000 in females
USA-Minnesota (4)	8.8/100000
Norway (5)	4.3/ 100 000
Czech Republic (6)	0.74–1.28/100000
South Korea (7)	1.7/100 000
Japan (8)	2.23/100 000

4.PATHOGENESIS

The pathogenesis of ILF is very complex and a complete understanding of all of its intricacies has not yet been achieved. Nevertheless, various risk factors and molecular pathways have been identified that can help us to better understand the pathological processes that underlie this condition. Various environmental and genetic factors play a role, as well as the natural physiological process of ageing. The basic hypothesis for the mechanism of disease is described as follows; chronic microscopic injury to the alveolar epithelium initiates a cascade of signaling cytokines and growth factors which initiate repair of the tissue (190). For various genetic and environmental causes this repair process may be aberrant, and will cause abnormal fibrosis and remodeling of the alveolar epithelium leading to ILF (190).

4.1.Gastro Esophageal Reflux Disease

One of the most important proposed mechanisms to discuss is the association between GERD and ILF. GERD is extremely common in patients with ILF prevalence being as high as 87%, which is much higher than in the general population (71). About half of these patients have occult forms of GERD while the others have more prominent symptoms such as heartburn (115). We see a higher proportion of asymptomatic GERD in ILF patients than in GERD without ILF, so this is important to keep in mind for diagnosis (115). The proposed mechanism of pathogenesis is via microaspiration of acidic particles which cause damage to the lungs and induce fibrosis and abnormal remodeling (115). This association is strengthened by studies linking a fibrotic response in mice to aspirated gastric fluid mediated by T cells in conjunction with various interleukins, TGF-β and TNF-α (116,117). In humans we also have studies showing a more acidic aspirate in ILF when bronchoalveolar lavage was performed, which further strengthens the association between GERD and ILF (118). Treatment with PPIs has also shown to be of some benefit in patients with ILF, however we should also note that certain studies have demonstrated no or negative impact on disease progression with this therapy (81,119). It is also thought that ILF may favor the development of GERD by way of increased negative intrathoracic pressure (115). This shows that we do not yet have a full understanding of the complex relationship between GERD and ILF, therefore further research is needed. Similar conflicting findings regarding its impact on ILF have been found in patients that underwent surgery for GERD (115). For an illustration of the relationship between GERD and ILF refer to graph. 1.

4.2.Genetics

Numerous genetic polymorphisms and mutations have recently been identified that are associated with ILF, both in the familial and sporadic form. One of these mutations was located in the TERT and TERC genes region, which encode different telomerase components. These mutations result in shortened telomeres which restrict the capacity for renewal of the epithelial cells in the lungs and are associated with familial ILF (FPF) and to a lesser degree sporadic ILF (17). Another important mutation was identified in the region encoding for suftactanct protein A2, which plays a role in surfactant production in the epithelial cells of the lungs; the gene in question is SFTPA2. Two different missense mutations in this region were found to be associated with both ILF and lung cancer. It is thought that these mutations cause the production of unstable proteins that are retained in the endoplasmatic reticulum of the cell (18). Another frequent mutation associated with FPF is found in the gene encoding for surfactant protein C, which likewise potentiates protein retention in the ER (14). Large genome-wide association studies have discovered a common polymorphism in the promoter region of the MUC5B gene that is associated with both sporadic and FPF forms of the disease (19). This gene is pivotal for maintaining normal lung clearance by mucociliary secretion, and is shown to contribute to normal lung immune homeostasis in mice; inhibition of the gene resulted in numerous infections (20). Additional variants found to be associated with susceptibility for ILF are polymorphisms of TOLLIP and SPPL2C, with one novel variant of TOLLIP also associated with a higher mortality (21). These genes are important regulators of the innate immune response pathways, especially for lung epithelial cells, and polymorphisms of these genes can result in susceptibility to various infections and subsequent lung damage (21). Analysis has shown us a trend of genes causing changes at the genetic level (TERT,TERC), as well as genes influencing the normal function of the alveolar epithelial cells (MUC5B, TOLLIP, SFTPA2), subsequently increasing susceptibility for ILF. Refer to Table 2. for an overview of all of the main genetic factors influencing ILF and their proposed mechanism of effect.

Table 2. Mutations and polymorphisms associated with ILF

Mutation Region	Effect
TERT and TERC	- Shortened telomeres results in restricted potential for cell renewal - Associated with familial and sporadic pulmonary fibrosis (less often).
SFTPA2	- Misfolding of proteins which leads to cellular stress - Associated with familial pulmonary fibrosis or lung cancer
MUC5B	- Abnormal mucociliary secretion, results in multiple infections - Associated with familial and sporadic pulmonary fibrosis
TOLLIP and SPPL2C	- Abnormal regulation of innate immunity, results in epithelial damage and susceptibility to infections

4.3.Environment

Although a direct causal link has not been established, environmental agents may have an aetiological role in the development of ILF. Numerous epidemiological investigations have been undertaken with the goal of exposing a causal relationship between various environmental factors and ILF. The data has shown a strong association between cigarette smoking, metal dust and ILF (22); even after smoking cessation some genes will remain altered and will not revert to pre-smoker levels and thus pose a continuous risk for development of ILF and other pulmonary diseases (23). Other environmental exposures associated with the disease are linked to several occupations such as agriculture and farming, or prolonged exposure to wood dust and sand dust, however these studies admit to certain limitations and conclude that the cause of ILF is likely heterogeneous (24).

There is mounting evidence that microbial agents play a notable role in ILF pathogenesis. Viruses belonging to the family of human herpes viruses such as herpes simplex virus type 1, Epstein-Barr virus and cytomegalovirus; which are frequently found in patients with ILF are thought to occasion ER stress and apoptosis of alveolar epithelial cells (25,26). Such processes are shown to be associated with ILF development (25). Other information that supports this hypothesis is found in studies analyzing the effects of antiviral therapy on ILF patients. Although such studies are few in number, they show improvements in patients treated with antiviral therapy, and while it cannot replace standard treatment for ILF it is seen as adjunctive (27). The role of bacteria has not been as thoroughly developed, although it is known that ILF predisposes the patient to bacterial infections it is difficult to say whether or

thought they play a role in the initiation of the disease (28,29). Further studies regarding the role of bacteria are needed to provide more conclusive results.

4.4.Endoplasmic reticulum stress

The ER is an organelle with many functions including protein packaging and secretion. When there is an increased demand for protein processing in the cell, the ER will respond by activating various signaling pathways known as UPR which is a physiological mechanism by which it meets the increased demands for protein folding. If the ER is unable to meet the increased requirements it will be put under severe stress in which case UPR will lead to apoptosis of the cell (30). ER stress is found in patients with ILF and evidence suggests that it contributes to its pathogenesis (25). Characteristic UPR markers were found in both sporadic and FPF, particularly in type II alveolar epithelial cells (25). The causes of ER stress are various; studies show that the above mentioned mutations SFTPA2 and SFTPC are strongly associated with an ER stress response. The heterozygous mutation in the SFTPA2 gene results in a buildup of proteins in the ER that cannot be properly folded and secreted. SFTPC mutation causes similar abnormalities in protein folding resulting in subsequent buildup leading to apoptosis of the cell (31,32). Viruses have also been found to activate the UPR response and their presence in patients with ILF has been documented (33,25). In addition, cigarette smoke, which is an important potential cause of ILF, also been linked with signaling pathways involved with ER stress (23,34).

4.5.TGF-β activation

Increased activation of TGF-β is one of the most important operations that underlies ILF pathogenesis. TGF-β in its inactive or latent form is bound to a latency associated peptide; this complex is attached to the extracellular matrix (35). During development of lung fibrosis alveolar cells, which have undergone lung injury and inflammation, are known to produce an alpha(v)beta6 molecule that binds to the latency associated peptide that is bound to the latent TGF-β (36), resulting in an activation of the latent TGF-β. This leads to abnormally high levels of active TGF-β because under conditions of lung injury or inflammation alveolar epithelial cells are shown to upregulate alpha(v)beta6 molecule expression (36). The effects of TGF-β on the lungs are numerous and its activity is qualified by the tyrosine kinase receptor (37). This interaction of TGF-β with its receptor leads to activation of profibrotic pathways (37), alveolar epithelial apoptosis and inhibition of their proliferation (37), and promotion of

the transition from epithelial cells to mesenchymal cells (38). All of these mechanisms are thought to contribute to ILF pathogenesis.

4.6.Epithelium-to-mesenchyme transformation

EMT is the process by which fully differentiated epithelial cells undergo transformation into a mesenchymal cell phenotype (38). What is meant by this is that cells that undergo EMT typically express markers associated with fibroblasts, or more specifically activated fibroblasts known as myofibroblasts, which are cell types derived from primitive mesenchyme. However, there are difficulties in classifying these EMT cells as fibroblasts themselves based on these markers alone; as is illustrated below (39). One of the markers in question is αSMA; this marker is not shown in all myofibroblasts and hence is not universally specific (39). Other markers such a vimentin and type I collagen also suffer this problem of specificity (39). Regardless of the exact specification of the EMT cells it is known that this process occurs in adult organs and is associated with tissue injury and fibrosis (40,41), just how much this process contributes to the development of lung fibrosis remains unknown. Even so, given that EMT is associated with fibrosis in adult organs and that alveolar epithelial cells in mice have shown to be progenitors for fibroblasts which contribute to fibrogenesis (42), this pathway could potentially play a role in pathogenesis and must be further researched to elucidate possible treatment targets. It is prudent to mention that TGF-β, which is increased in ILF, is involved in inducing the EMT process (38). Further UPR is also shown to initiate EMT (43), and UPR itself was shown to be increased in ILF due to certain genetic mutations such as SFTPC and SFTPA2 (32). Give all this data we can say that EMT probably contributes to some of the fibrinogenesis in ILF by having the aberrant alveolar epithelial cells interact with the local fibroblasts in the lungs and cause a profibrotic response, although it is unlikely that is serves as a source of newly developed myofibroblasts.

4.7.Epigenetics

Epigenetics is the process by which gene activity is altered without changing the underlying DNA. The main mechanisms of epigenetics are changes in DNA methylation, microRNA expression and histone modification, these modifications are heritable but they do not alter the DNA sequence as mentioned above (44). Such changes are shown to occur in ILF; studies indicate that an important microRNA cluster miR-17~92 responsible for normal alveolar homeostasis in the lungs is suppressed in ILF due to increased DNA methylation of the miR-17~92 promoter region, with a concurrent upregulation of DNA methyltransferase (45). This

is an example of epigenetic changes in the ILF alveolar epithelium. Other studies have found a number of other genes in ILF lungs that had a severely altered DNA methylation profile in contrast to normal lung tissue, and ILF samples in general had a higher expression of DNA methyltransferase (46). The main causes of epigenetic modification in ILF are thought to be cigarette smoking and ageing. Cigarette smoke is a known inducer of epigenetic changes in epithelial cells (47), considering its association with ILF (22) we can conjecture that it contributes to some of the epigenetic alteration seen in this disease. As for ageing, genome wide studies have shown a stochastic DNA methylation drift affecting gradual upregulations and downregulations at various loci in ageing stem cells (48). This results in phenomena known as epigenetic mosaicism, which can be defined as a change in the epigenotype in different cells sharing a common lineal zygote (49). Such changes will derive altered phenotypes that lose their plasticity and contribute to proliferative defects and various diseases including cancer (48). It is thought that this mechanism of stochastic methylation involved with ageing cells could help explain the prevalence of ILF in the older population (11).

4.8.Fibrocytes and Fibroblasts

Fibrocytes are mesenchymal cell progenitors derived from the bone marrow. Identified by their precursor markers CD34, CD45 and type I collagen, they are involved with the physiological repair of damaged tissue (50). They are normally found in the circulation, but in ILF they can be found in the lungs as well (51,54). Fibrocytes are thought to participate in lung fibrosis by secreting collagen types I and type III, by way of profibrotic mediators and by differentiating into fibroblasts and myofibroblasts, all of these mechanisms potentiate fibrosis of the lungs (51,54). Fibrocytes are especially prone to conversion into fibroblasts in the presence of TGF-β, which has been shown to be increased in ILF (36). Moreover pulmonary epithelium in ILF is shown to express an escalated number of chemokine CXCL12, which mediates the recruitment of fibrocytes from the circulation into the lungs and promotes their transformation into fibroblasts (51,52).To further strengthen this relation between fibrocytes and ILF the number of circulating fibrocytes was shown to be a predictor of mortality in ILF, and the number also increased in acute exacerbations (53). Taken together this data indicates that fibrocytes contribute to ILF (54).

Fibroblasts are tissue mesenchymal cells found in the lung and contribute to tissue repair by secreting matrix proteins such as collagen, while myofibroblasts are the primary phenotype present in ILF that excessively secretes matrix proteins which may lead to pathologic fibrosis

of the lungs (55). In addition to their excessive secretory activity myofibroblasts will contract and this ultimately leads to formation of stiff scar tissue (56). TGF-β is a potent mediator for differentiation of fibroblasts to myofibroblasts and in addition to this; contraction of myofibrobalsts releases TGF-β which leads to a feedback loop potentiating further lung fibrosis (56,36). In normal lung healing excess fibroblasts and extracellular matrix components are removed via apoptosis (57). This process fails in ILF as the fibroblasts are resistant to apoptosis and they will continue secreting fibrotic components leading to an abnormal ECM and injury to alveolar cells (59). The reason for this apoptotic resistance is thought to be molecular modification by SPARC and survivin production among others (59,58). Another question is why fibroblasts are sequestered to the lungs so aggressively in ILF; to emphasize this facet some have compared them to cancer cells (60). Researchers have sought for the answer in one of the signaling pathways known as alpha4beta1, which if inhibited will confer a more migratory and invasive phenotype in comparison to normal lung fibroblasts (61). This inhibition was shown to occur in ILF (61). Another feature associated with the more aggressive phenotype is overexpression of HA synthase 2 and expression of hyaluronan receptor CD44, blocking of these receptors showed a decrease in fibrotic activity in the lungs of mice (62).

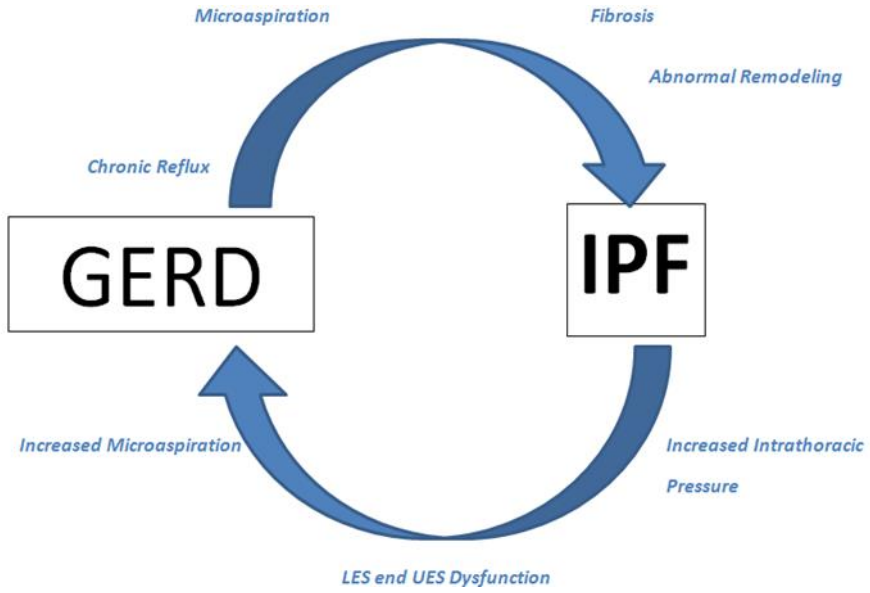
4.9.Synthesis of the pathological factors

ILF is a disease with a chronic progressive course, characterized by progression of fibrosis (60); given the large number of contributing factors we can attempt to offer explanations for why this is so. One hypothesis is that this unremitting character of the disease is due to constant microinjury of the lungs (60). This would explain why GERD is seen in many patients with ILF, since microaspiration of these acidic particles could cause microscopic damage to the lower parts of the lungs (63). Other potential sources of this protracted damage to the lungs are cigarette smoke and infections (23,25,63). However, the kind of diffuse histological damage that follows such exposures is not seen in all patents with ILF, and is more common in patients with acute exacerbation of ILF (60,64). Thus, alternative explanations must be sought out for these cases.

For alternative explanations we should look at some of the genetic changes mentioned above (SFTPA2,SFTPC,MUC5B), these changes will activate other prominent mechanism related to ILF and that is UPR (31,32). These changes will be chronic and persistent and will result in apoptosis of normal lung tissue and remodeling into aberrant extracellular matrix formation and development of fibroblasts. TGF-β is also activated by UPR, which is upregulated in the

lungs through activation of the integrin system alpha(v)beta6 (36). This will also lead to EMT and further propagate fibroblast recruitment into the lungs (43). Another possible cause of ILF without the classic histological signs of damage to the lower lung could be sought in the epigenetic sources we have mentioned, this would have a similar pathological pathway to the genetic mutations described above. Thus, we see how all of the previously mentioned factors are interconnected and we can further appreciate the complex nature of ILF pathogenesis.

We should also mention the role of aberrant wound repair in ILF. Once damage has been done to the alveolar epithelium it will result in a disruption of the basement membrane which will result in clot formation in part mediated by EPCs (65). In ILF levels of EPCs are decreased, which is thought to stifle wound repair and recovery in the lungs. This is thought to initiate a profibrotic response, and also to induce EMT, which will have further negative downstream effects illustrated to us above (65).



Graph 1.Relation between GERD and ILF, adapted from Ghisa et al. (115)

5.CLINICAL PICTURE AND PROGRESSION

ILF is found predominantly in male patients of advanced age, with the mean age of onset being above 60 (1,10). The disease is rare below the age of 50 (1). The early phase of the disease has non-specific signs such as dyspnea, fatigue, malaise, inspiratory crackles and finger clubbing (66). A dry cough is also present, especially on exertion such as walking uphill (66). Something more specific that should prompt the physician to think of ILF is the

presence of bibasilar inspiratory crackles that are described as „velcro type "(67). Finger clubbing is present in 25-50% of patients (68). Given the older population that this disease is associated with patients will have various comorbidities, and at late stages of the disease cyanosis and right ventricular failure (68).

Risk factors for ILF are cigarette smoke, wood dust, metal dust, and jobs in agriculture and farming (24,72). Comorbidities commonly seen in ILF include obstructive sleep apnea, diabetes mellitus, infection with herpes virus and GERD (26,69-71). Recently a positive family history for ILF was reported as the most important risk factor (72). Given the extensive genetic changes linked with ILF this comes as no surprise.

Lung function tests should be performed in all suspected ILF patients. Here a notable decline in the FVC will be noted. A marked decrease in FVC of more than 10% predicted is associated with an increased mortality as well as increased risk of AE ILF (91,92). The 6 minute walking test should also be performed, ILF will present with deterioration here. A reduction in the distance walked of more than 50 m in 24 weeks is associated with a threefold increase in mortality over the concurrent year (92). Later on in the disease supplemental oxygen will be needed in any kind of physical exertion and finally upon rest as well (92).

Disease progression can be classified into different clinical forms. We have subclinical ILF where the symptoms of the disease will be preceded by radiographic evidence (191). This is followed by a symptomatic period; the rate of decline is relatively slow in the subclinical model (191). The classic pattern of decline is slow steady progression followed by death within several years (192). We also have patients with an aggressive rapid progression of the disease, associated with smoking and male sex as well as expression of certain genes that are not present in the more benign clinical variants (193). Finally, a mixed progression with periods of stability interposed with periods of precipitous decline in which AE ILF is frequent, they also have a poorer outcome relative to the slower progressing cases (194).

5.1.Acute Exacerbation of ILF

AE ILF has been defined as clinically significant acute deterioration of previously stable chronic ILF, of undefinable cause (73). The exact criteria for AE ILF include deterioration (dyspnea and hypoxemia etc.) of less than 30 days duration, new bilateral consolidation and opacification on CT and the deterioration is not explained by cardiac failure or overload of fluid (1,73-75). Aetiology of AE ILF is uncertain, it is now recognized that a myriad of external factors including surgery, microaspiration, biopsy and infections could be possible

triggers (76-81). Risk factors are never having smoked, reduced FVC, poor baseline oxygenation, poor 6 minute walking test result, pulmonary hypertension and high baseline KL-6 a mucinous glycoprotein expressed by alveolar type II cells (82,83). Potential risk factors are increased BMI, young age and coronary artery disease comorbidity (73). The incidence is around 10%, but varies according to ethnicity (73). AE ILF has a very high mortality rate; about 46% of all ILF patients die from this entity (73,84). Biomarkers have been recognized for outcome prediction such as lactate dehydrogenase, KL-6 and C-reactive protein and can help us recognize patients at higher risk for AE ILF (73,84,85).

Diagnosis of AE ILF must be prompt; other emergencies such as heart failure, pulmonary embolism, pneumothorax or infection should be ruled out (1). Diagnosis is made in part by clinical signs such as worsening dyspnea, finger clubbing and cyanosis that have a rapid onset of less than 30 days. Additionally, fever, cough, sputum production and flu like symptoms may occur (86). To quantify these signs arterial blood gas should be drawn to assess gas exchange, a low PaO2 (<75 mmHg) or an abnormal PaO2/FiO2 (<225 mmHg) is expected (87). FVC must be measured and 6 minute walking test should be conducted and compared with previous measurements if they are available; precipitous deterioration in either of these can point to AE ILF (88,89). Markers such as lactate dehydrogenase, C-reactive protein and KL-6 should also be measured when possible, since they are increased in AE ILF (73,84,84). Imaging with HRCT is the most important component of AE ILF diagnosis. Here the typical finding is new bilateral alveolar infiltrates (1). These infiltrates are described as consolidation and ground glass opacification in the literature (73). Subsequent scans should be compared with the earlier ones. If this is the patient's first HRCT scan and no previous images are available for comparison the appearance of bilateral ground glass opacification and/or consolidation superimposed on findings typical of ILF such as UIP will suffice for diagnosis (73).

We should also mention the histological pattern associated with AE ILF. The typical pathologic feature is DAD, which it shares with ARDS (1,74). It can also appear as an organizing pneumonia histologically but this is rarer (1). This will be superimposed over the regular histologic signs of ILF like honeycombing and reticular densities which are discussed below (74).

6.DIAGNOSIS

The diagnosis of ILF has long been an area of controversy due to its complexity and therefore the 2000 ATS/ERS 2011 statement and the 2011 ATS/ERS/JRS/ALAT revision were so important because they offered standardized criteria for diagnosis of ILF using the best evidence available at the time (1). The 2011 ATS/ERS/JRS/ALAT revision is the most recent and authoritative review of the guidelines and recommendations for ILF and it is mainly this data that we will draw from in this review. It must be said at the outset that diagnosis of ILF is very complex and requires a robust multidisciplinary approach. Before we discuss the updated diagnostic criteria it would be prudent to give a basic overview of the differential diagnoses related to ILF. We will then discuss the diagnostic procedures proper as well as the multidisciplinary approach.

6.1.Differential Diagnosis

An important part of establishing ILF involves ruling out other possible causes of lung fibrosis, because diagnosis of ILF is partly a diagnosis of exclusion. A careful history and physical examination, as well as HRCT imaging is indispensable for discerning the probable cause as many other causes can present with UIP which is the characteristic finding of ILF. Here we will mention a few of the most important differentials that are frequently seen in clinical practice and how to differentiate them from ILF.

Combined pulmonary fibrosis and emphysema syndrome is seen as the coexistence of IIPs with emphysema. This is a relatively novel entity with a poor prognosis and limited treatment options. The main feature to distinguish it from ILF is emphysema located in the upper lobes on imaging (120). Even if it has UIP on the basal area of the lungs, emphysema of the upper lobes will exclude ILF.

Asbestosis is an insidious chronic pulmonary disease caused by small asbestos fibers that are deposited in the lungs. It is most commonly linked to some occupation or living conditions that provide exposure to the material. Differentiating between asbestosis and ILF can be very difficult since both present with bilateral pleural thickening and honeycombing. Also, no significant difference in history is observable (121). The main point of differentiation is the presence of subpleural dotlike or branching opacities, curvilinear lines, and bandlike opacities which are all suggestive of asbestosis. Basal and dorsal localization of the lesions is suggestive of asbestosis. These findings are also centrilobular in asbestosis as opposed to ILF (121).

Autoimmune diseases are another category presenting similar to ILF. Here serologic testing is useful and should be performed. On HRCT straight edge signs, lesions in the upper lobes, and exuberant honeycombing (>70% of fibrotic area) are associated with autoimmune diseases (105,122). The most specific sign is the straight edge sign; also less emphysema is seen and pleural and pericardial effusions may be present (105,123).

Chronic hypersensitivity pneumonitis can also be confused with any IIP unless exposure is evident. Here specification can be done via clinical, HRCT and pathological findings. HRCT findings suggestive of hypersensitivity pneumonitis are centrilobular nodules, mosaic air trapping and upper lobe involvement (90). Pathologically bronchiolocentric distribution and poorly formed granulomas is the key to diagnosis (90). BAL with predominance of lymphocytosis can also help to make the diagnosis of hypersensitivity pneumonitis (1). Finally, an inquiry as to possible sources of exposure is necessary in these patients.

6.2.PFT and 6 Minute Walk test

PFTs are a key component for monitoring and diagnosis of ILF, and are one of the first tests that should be ordered. Indeed, changes in PFT results can be a potent predictor of disease mortality as stated above (91,124). The main variables that are evaluated are FVC and DLCO. FVC should be evaluated at regular intervals usually every 6 to 12 months (125). Declines in FVC of 10% or DLCO of 15% over 6 months predict mortality in the subsequent year (126). Even smaller absolute declines in FVC of 5% can indicate a worse diagnosis (126). These findings must be contextualized with the larger clinical picture, since in isolation they are not specific to ILF.

6MWT is another test used to predict prognosis in ILF, however these results are also nonspecific and therefore can't be used for diagnosis and must be contextualized (1). The key variables measured here are oxygen saturation and distance walked. Changes in oxygen saturation during testing to below 88% may be significant but an exact cut-off point to determine outcomes has not been determined (127). When we consider distance walked, a distance of less than 207 m walked or a more than 50 m decline within 24 weeks may be significant (128,129). These measurements should be conducted every few months to determine if these are any changes and to monitor disease progression while keeping in mind the context of the larger clinical picture.

6.3.Laboratory Testing

Given the wide range of connective tissue diseases that may have a similar presentation to that of ILF serologic testing is used to help differentiate between these different etiologies. The guidelines suggest that such testing should be done in the majority of patients and should include the following: rheumatoid factor, anti-cyclic citrullinated peptide and anti-nuclear antibody and pattern (1). Other antibodies such as antisynthestase antibodies, Sjogren's antibodies, creatine kinase and aldolase and scleroderma antibodies may be useful in specific cases (1,93). We should note that at this time there is no biological marker that allows for a diagnosis of ILF. A slight increase in anti-nuclear antibody and rheumatiod factor may be seen in ILF (1). Such patients should not have any of the accompanying signs of CTD and no other positive serological findings for ILF to be safely diagnosed (1). Other studies report an increase in SP-A, SP-D as well as free circulating DNA (94,95). The clinical utility of these findings is vague however, and at best it can serve for excluding other IDLs but not for diagnosis.

6.4.Bronchoalveolar Lavage

The role of BAL in ILF diagnosis is controversial. This procedure is usually used for diagnosis of various ILDs by analyzing the cellular and protein content of the obtained fluid. Hypersensitivity pneumonia is one of the differentials that can be excluded in this way (1). It can also be used to narrow the diagnosis between other ILDs mainly by evaluating the cellular content of the sample (1,96). The drawbacks are that it cannot establish the diagnosis of ILF in isolation from other tests as the findings may overlap with other ILDs (98). It also carries with it a risk of provoking AE ILF (97). BAL also has no value in predicting disease prognosis or outcomes (1,98). All of this taken together, the guidelines recommend that BAL should not be used in a majority of patients for diagnostic purposes (1,98). It has a more prominent role in evaluation of suspected infection, malignancy or AE ILF where BAL may be diagnostic (98).

6.5.Imaging

Chest x ray can show a bilateral reticular pattern, predominantly in the basal areas, cystic airspaces may also be present (93). However this is usually present in later stages of the disease, in early stages x ray images may be completely normal. Such findings are non-specific and should be placed in the larger context of the clinical picture. It is therefore necessary to use HRCT for establishing a definitive diagnosis in patients that are suspected of

ILF. According to the latest guidelines HRCT findings characteristic for ILF are sufficient to establish a diagnosis in concurrence with other characteristic clinical findings mentioned above, lung biopsy is not required for diagnosis (1). Imaging should be obtained during maximal inspiration in the supine position and reconstructed with a high spatial resolution reconstruction algorithm using thin slices (<2mm) (1,93,99). Volumetric imaging is the preferred mode of imaging as it improves the characterization of the findings (99). Prone imaging may also be done to evaluate the posterior lobes and to elucidate any dependent opacification that may be mimicking ILF (93,99). Expiratory imaging can be used to detect air trapping which may suggest an ulterior diagnosis (93,99).

The defining pattern of ILF on HRCT is UIP. This pattern is essential for establishing a diagnosis according to the latest guidelines (1). Radiological UIP is defined by the presence of reticular opacities and honeycombing, with or without traction bronciectasis, with a peripheral, subpleural and basal distribution, in the absence of other findings inconsistent with UIP (1,93). Recognizing these various signs is important for diagnosis but also for disease prognosis, indeed traction bronchiectasis and honeycombing are associated with lower survival (100,101).

Honeycombing is the most specific UIP finding and occurs in up to 90% of cases, it is found on radiological examination in the dorsal, basal, subpleural and can be seen in the upper lungs (93,102,103). According to the latest guidelines it presents as clustered, thick-walled, cystic spaces of uniform diameters measuring 3-5mm, occasionally they can be a big as 25 mm (1,99). The number of such cysts varies depending on disease progression, but 2-3 contiguous cysts are adequate for identification of honeycombing (99). Much smaller cysts termed micro-honeycombing may be seen on histological samples in ILF, these cannot be seen by HRCT and do not correlate with CT findings (102). Recently there has been discussion over the visualization of honeycombing by physicians, and is now recognized as one of the greatest challenges in ILF diagnosis (93). Interobservational variations are seen, mainly due to the large number of entities that can be indistinguishable from honeycombing according to its current definition. For instance, traction bronchiectasis can present as rounded pockets of air with thick walls, and if they appear in clusters differentiation from honeycombing is near impossible (93,99). In addition, histopathological studies have shown that honeycombing and bronchiectasis can overlap on CT further complicating differentiation (93). Other entities that may cause confusion in diagnosis are emphysema, overlapping ground glass opacities and any

pulmonary cystic disease (93). A careful evaluation of sequential multiplanar images is required in these cases.

Traction bronchiectasis is common to all forms of lung fibrosis. It manifests as dilation of the airways due to fibrosis and distortion of the surrounding parenchyma (99). It has a more peripheral distribution in ILF. Since it is not specific for ILF, traction bronchiectasis must be differentiated from honeycombing which is more specific. It usually overlaps with honeycombing so telling the two apart is difficult as mentioned above, and requires an experienced radiologist (93,99). Thin section multiplanar image reformations and minimum intensity projections are recommended for visualization of bronchiectasis (104).

Reticular pattern is defined as linear opacities related to septal thickenings, interlobar lines, or the walls of honeycomb cysts (105). Characteristically it will look like a network of fine lines that are irregularly spaced (99). Something to note is that extension of reticularities into the upper parts of the lungs is a predictor of UIP at histology (105).

Ground glass opacities are thickenings or attenuations of lung tissue (105). This entity can appear in various diseases and is not usually a feature of UIP but it can be included if it is found in areas of fibrosis (99,105). Different aetiologies should be sought if ground glass opacities are found in isolation (99,105). Appearance of this entity bilaterally in the context of a worsening clinical picture for less than one month is associated with AE ILF (93). Please refer to image 1 (page 31) for typical x-ray findings of ILF.

6.6.Classification of HRCT findings

Recently a review paper has published a new system for stratification of CT findings that builds off the 2011 guidelines and expert opinion (1,99). The main groups are typical UIP CT pattern, probable UIP CT pattern, CT pattern indeterminate for UIP and CT pattern most consistent with a non-ILF diagnosis (99). For the precise criteria required for admission to each group see Table 3. The main difference between these criteria and the 2011 ones is the addition of the indeterminate group. This group covers those cases without a typical UIP pattern that have positive histological findings (99). For instance, areas of variable or diffuse attenuation is not consistent with the typical picture of UIP but cannot be used to exclude ILF, therefore it is termed indeterminate according to these guidelines (99). Probably the most important category is typical UIP because if we can satisfy the criteria for this group, then any need for surgical biopsy or other invasive procedures is excluded because of its excellent specificity (1,99,101). Indeed, studies show that usual UIP findings are predictable for UIP

biopsy findings in more than 95% of cases (106). The predictability is even higher in patients with other typical clinical signs (93,107). The main finding to look for is honeycombing which is highly predictive of UIP pattern on histology, even if honeycombing is found in small traces (106). Traction bronchiectasis are also of importance for diagnosis as it is closely associated to honeycombing and may even be part of the same histopathological process (93). Probable UIP pattern is associated with absence of honeycombing with all of the other required findings, this group still has a high probability of a definite or probable histopathological UIP pattern and it can provide a diagnosis in conjunction with all of the typical clinical findings according to latest guidelines (99). The guidelines also recommend surgical biopsy if the criteria for typical UIP or probable UIP pattern on HRCT with typical clinical findings is not satisfied, although a biopsy is usually done in the latter case (1,93,99). Please refer to image 2 (page 32) for typical CT findings of ILF.

Table 3. Classification of HRCT findings adapted from Lynch et al. (99)

Typical UIP	Probable UIP	Indeterminate for UIP	Non-IPF diagnosis
-Subpleural and basal distribution predominant; often heterogeneous -Honeycombing present with or without bronchiectasis and peripheral traction	-Subpleural and basal distribution predominant; often heterogeneous -Reticular pattern with peripheral traction or bronchiectasis - Ground glass opacities may be present	-Subpleural and basal distribution predominant -Subtle reticulation; mild ground glass opacities may be present -CT features with or without a distribution of lung fibrosis that does not present any specific etiology	Findings that suggest some alternative diagnosis: ❖ CT ➢ Cysts ➢ Mosaic attenuation ➢ Predominant ground glass opacities ➢ Profuse micronodules ➢ Centrilobular nodules ➢ Consolidation ❖ Predominant distribution ➢ Peribronchovascular ➢ Perilymphatic ➢ Upper or mid-lung ❖ Other ➢ Pleural plaques (asbestosis) ➢ Dilated esophagus (CTD) ➢ Dilated clavicular erosion (consider RA) ➢ Extensive lymph node enlargement ➢ Pleural effusions, pleural thickenings (consider CTD/drugs)

6.7.Biopsy and Histological Findings

Surgical biopsies should be considered in patients with inconsistent and indeterminate HRCT findings or in patients that are under consideration for an alternative diagnosis (93). Surgical biopsies are the gold standard for acquiring lung tissue samples. Diagnostic yields are as high as 95% according to certain studies (93). Ideally the biopsy is taken from multiple lobes and should not target areas that are heavily affected by the disease (99,108). Biopsy should measure 2-3 cm along the pleural axis and be 1-2 cm deep (99). Open lung biopsies carry with them a high risk of mortality, up to 16%, and therefore VATS biopsies are sought as a safer alternative (109,110). However, VATS itself is not a benign procedure and has a mortality rate between 2-4% in ILD patients, especially in patients that have other risk factors such as pulmonary hypertension (111). Classically, transbronchial lung biopsy has shown to be unreliable for diagnosis of ILF; a new alternative to this procedure is transbronchial lung cryobiopsy (1,112). It has a lower mortality compared to surgical biopsy and can acquire a higher surgical yield than transbronchial biopsy; this comes at the price of increased incidences of hemorrhage and pneumothorax (93,112). Today the role of cryobiopsy is becoming more prominent, and for the reasons mentioned above it is preferred to open biopsy (112).

All samples provided by the biopsy should be examined by an experienced pathologist. The histological features consistent with UIP in ILF are heterogeneous presentation with alternating areas of normal tissue intermixed with fibrosis and honeycombing (93,99). The fibrotic areas consist of foci made up of proliferating fibroblasts (93). Honeycombing on histology differs from the honeycombing on HRCT, and can appear in the absence of the latter (113). It is described as „1 to 2 mm dilated bronchioles surrounded by airless fibrotic lung on a pathologic specimen“ however some clinicians consider cyst larger than a centimeter as radiological honeycombing (99,113). Obviously, this causes some overlap with radiologic honeycombing but the two should be differentiated. The histologic criteria for determining the significance of the pathological findings are shown in Table 4. The histological diagnosis of ILF can only be made in the presence of UIP pattern or probable UIP pattern in the absence of some other known cause for the changes (93). The typical histological UIP/ILF pattern requires the presence of four findings including dense fibrotic remodeling and honeycombing, patchy lung involvement, fibroblastic foci and a subpleural or paraseptal distribution (99). If DAD is seen on histology this is indicative of AE ILF, and should be treated accordingly (74).

Table 4. Histologic criteria for ILF diagnosis adapted from Lynch et al. (99)

Definite UIP/IPF	Probable UIP/IPF	Indeterminate for UIP/IPF	Features that suggest an alternative diagnosis
No features suggesting a diagnosis other than IPF are found, and all of the listed criteria are present ➢ Dense fibrosis causing architecture remodeling with frequent honeycombing ➢ Patchy lung involvement by fibrosis ➢ Subpleural and/or paraseptal distribution ➢ Fibroblast foci at the edge of dense scars	***Sample falls short of showing all of the findings for definite UIP/IPF but an alternative diagnosis is unlikely*** ➢ Dense fibrosis causing architecture remodeling with frequent honeycombing ➢ Patchy lung involvement by fibrosis ➢ Fibroblastic foci at the edge of dense scars may or may not be present OR ➢ Only honeycomb fibrosis	***There is a fibrosis process present, but other features suggest a non-UIP pattern, or UIP associated with some other entity besides IPF***	***a)UIP not present*** ***b)UIP present but other factors strongly suggest an alternative diagnosis to IPF***

6.8.Multidisciplinary Approach

A multidisciplinary approach is essential for diagnosis of ILF simply because the diagnostic procedure involves other specialties from the outset. What this entails is collaboration between radiologists, pathologists and pulmonary specialist according to the 2011 guidelines (1). Other specialties such as rheumatologists might also be consulted for exclusion of other causes (99). Overall the multidisciplinary approach has shown to have less variances between observers during in establishing diagnosis of ILF, and allows for a greater confidence when establishing the diagnosis (114). This is expected because the additional input provided by the specialties, especially from pathologists, forces the clinicians to review their initial impressions and to try to come to a consensus with the other specialties. Indeed, studies show that both pathologists and radiologists would change their initial diagnosis when presented with information from their colleagues in other specialties (114). For these reasons a discussion and dialogue between the specialties is recommended by the guidelines, but not all cases require this approach (1). For instance, a case with typical HRCT findings and clinical findings consistent with ILF will not need the multidisciplinary approach to establish a diagnosis. This approach has the most utility when applied to those cases with indeterminate features where it can provide a higher confidence for the diagnosis or establish a preliminary working diagnosis. The participants of the multidisciplinary approach must use the latest

standardized criteria as a starting point, and from there work out how to best classify non-standardized features and come to a diagnostic consensus (99). This can be very time-consuming and difficult to coordinate in a hospital setting and these difficulties must be taken into account when making a treatment plan. Despite this setback the multidisciplinary approach when conducted by experienced physicians and when applied correctly can reduce diagnostic inaccuracy in atypical cases of ILF and other ILDs (99,114).

7.TREATMENT

In recent years we have seen some new developments in the area of ILF treatment. However, none of the new treatments are curative, they can only slow progression of the disease. Previously treatment was aimed at suppressing inflammation and slowing the progression of disease (131). We now know that the lesions in ILF may be of a more fibrotic nature than inflammatory and therefore this type of treatment was inadequate. Indeed, previous treatment regimens were associated with similar outcomes compared to placebo (132). Treatment will depend on the severity of the disease, comorbid conditions and the patient's wishes or compliance. Furthermore, treatment is usually complex and involves a combination of medical therapy, patient education, ongoing monitoring and supportive care (1).

7.1.Pharmacological therapy

Today we have two antifibrotic drugs that are prominently in use for treatment of ILF. Nintedanib and pirfenidone are now considered as the first line of ILF therapy.

Nintedanib is one of the drugs that has changed the paradigm of ILF treatment and is now one of the first line drugs used for ILF treatment. It is a receptor blocker for various tyrosine kinases (131). Initially it was conceived as an anti-tumor drug until it was discovered to have antifibrotic properties (130). Its antifibrotic effect is thought to be due to its inhibition of profibrotic mediators including platelet-derived growth factor, TGF-β, fibroblast growth factor and vascular endothelial growth factor which all have tyrosine kinase receptors (133). Nintedanib should be given in a dose of 150 mg twice daily 12 h apart (1,134). Trials have shown a reduction in the rate of decline in lung function measured by FVC compared to placebo and a lower incidence of AE ILF (134). A reduction in all-cause mortality was also observed (134). This drug is also shown to have beneficial effects irrespective of age, gender, smoking status and expected FVC. Indeed, it is effective even among patients with more severe forms of the disease (135). The drawbacks are side effects of that may be so severe as to lead to discontinuation of treatment (134). These include diarrhea (62%), nausea (24%),

vomiting (12%), an elevation in liver function tests and bleeding (10.3%) (134,136). This is why monitoring of liver function tests as well as patients taking anticoagulation therapy is necessary. Depending on monitoring results dose modification or discontinuation may be implemented (136).

Pirfenidone is a novel antifibrotic agent that inhibits TGF-β stimulated collagen synthesis, and attenuates and downregulates fibroblast activity (137,138). The dose is fixed and titrated over a period of three weeks, in the first week we give 1 capsule 3x per day (801 mg/day), the second week we give 2 capsules 3x per day (1602 mg/day), and the third week we reach the maximum dose of 3 capsules 3x per day (2403 mg/day) (142). Various trials have been conducted using pirfenidone and they have shown a survival benefit, reduction in lung function decline and a decrease in mortality in favor of pirfenidone treatment in mild to moderate cases of ILF (139,140). An extensive safety profile has been constructed for pirfenidone based on these trials. It is considered to be well tolerated drug with infrequent serious adverse events, and any adverse effects that do occur may be managed by adjustment of the dose (141-143). The main side effects reported are rash, diarrhea, fatigue, photosensitivity and nausea, with nausea being the most common (140,143). If severe photosensitive reaction occurs then topical creams with steroids or silver sulfadiazine should be applied (141). In severe cases of ILF the efficacy of pirfenidone is not well established, but the data available shows a limited benefit with a diminishment of efficacy after 6 months (144).

Immune suppression was previously considered important in ILF treatment. Before the advent of newer drugs various combinations of prednisone, azathioprine and N-acetylcysteine were used in ILF therapy. Recently studies have shown that combinations of such drugs have a greater mortality and hospitalization rate than placebo, and the guidelines therefore do not recommend these drugs (1,145).

Since GERD is a major co-morbidity of ILF, it is no wonder that the role of PPIs has been widely considered in ILF treatment. The guidelines give a weak recommendation in favor of PPIs based on several studies that show a decrease in disease progression (1,146). This data has recently been revised and the effect of PPIs on disease progression has been brought into question. The data suggested a slight increase in pneumonia for patients taking antacid therapy, and no difference in mortality was shown (147). Nevertheless, there is a bias for

employing antacid therapy, especially if cough or other symptoms of reflux are present (1,148).

7.2.Lung Transplantation

Lung transplantation is the only procedure that has proven survival benefit in patients with end-stage ILF so far (149,153). Indeed, a study in the Netherlands showed a median survival rate of up to 10 years post transplantation in ILF patients (151). This finding however, is the ideal and we should temper our expectations given that ILF patients tend to have worse post-transplantation outcomes than transplant patients with other diseases (154,155). Overall lung transplantation patients have a 54% 5-year survival rate (151,152). This low survival rate is mostly due to rejection, and the survival rate in ILF patients will greatly depend on the presence of graft dysfunction and infection (152,154). The most important contraindications are comorbidities such as recent malignancy, chronic extra-pulmonary infections and incurable major dysfunctions of other organ systems (149). Because of this, patients referred to transplantation must be closely monitored for development of comorbidities, especially for lung cancer as these may exclude the possibility of transplantation (149). HLA testing and extracorporeal membrane oxygenations have served to improve recipient selection standards and may preserve patients till transplantation is available (150). Because of the rapid deterioration of ILF as well as the occurrence of AE ILF early referral for lung transplantation is essential, indeed if the patient meets the criteria laid out in table 3, he should be referred as soon as possible (149). The latest guidelines recommend lung transplantation in severely affected patients, but they have no consensus on weather single or bilateral lung transplantation is preferable (1). This is an area of controversy, and the literature seems to suggest that the choice should be based on the experience of the transplant teams, the age of the patients and recipient and the presence of comorbidities (155,156).

7.3.Other Non-Pharmacological Therapies

Pulmonary rehabilitation has recently shown to have a positive effect on ILF patients. A systematic review of the relevant literature showed an increase in exercise tolerance and improvement in the overall quality of life for patients (157). Oxygen therapy is also recommended for patients in whom hypoxemia is present (1). It has been shown to improve exercise tolerance and may have a survival benefit in long term use (158,159).

8.COMMORBIDITIES

Almost 90% of ILF patients have some comorbidity (149). They can be both respiratory and non-respiratory, knowledge of these is important since they play a large role in the patient's quality of life and prognosis.

8.1.Pulmonary Hypertension

Pulmonary hypertension is defined as mean pulmonary arterial pressure (mPAP) more than 20 mmHg on right heart catheterization (160). It is a well know comorbidity of ILF, however the exact prevalence is difficult to ascertain given the variations in methodology and interpatient variations. Between 20-60% of patients with advanced ILF will develop pulmonary hypertension (161). Suspicion should be drawn to pulmonary hypertension when the patient displays signs of right heart failure, additionally hypoxia and desaturation during 6MWT that is disproportionate to their current status (162-164). Disproportionate decrease in the DLCO should also bring pulmonary hypertension under consideration (162,163). Other ways of assessing pulmonary hypertension are echocardiography and CT of the chest where arterial enlargement is seen (162,163). These are more difficult to analyze and right heart catheterization is the gold standard (165). Pulmonary hypertension is an important predictor of mortality, especially when pulmonary arterial pressure is higher than 50 mmHg (162). Here mortality will be significantly higher. Unfortunately, effective treatment is lacking for this comorbidity and the guidelines do not have an official recommendation regarding treatment for this comorbidity (1). Various treatment options have been considered but none have established a valid treatment option, although in select patients sildenafil may have some benefit on quality of life (166). Further trials are needed to illuminate the inclusion of sildenafil in standard therapy of ILF with pulmonary hypertension as comorbidity (1).

8.2.Gastro Esophageal Reflux Disease

Microaspiration of acidic particles has been long been considered as a potential causal factor in ILF pathogenesis, and is considered to be one of the risk factors for developing lung damage which might lead to ILF (63,69-71). The prevalence of both symptomatic and asymptomatic GERD among ILF patients exceeds 80%, with up to one half being asymptomatic (167). This staggering prevalence would lend credence to the causal hypothesis, however a direct causal link is difficult if not impossible to establish as correlation in no way means causation (168).

8.3.Pulmonary Embolism

In a retrospective study conducted in America on ILF patients the incidence of pulmonary embolism was three times higher than in patients without ILF (169). It is important to exclude pulmonary embolism when there is a worsening of symptoms, since it may mimic some of the ILF symptoms. Anticoagulation is not recommended in ILF, given some results that show an increased mortality in patients with anticoagulation therapy (170). Even patients taking anticoagulation for other non-ILF related indications may have negative effects (171).

8.4.Lung Cancer

These is an increased risk of lung cancer in ILF, the increase is proportionate to the duration of the disease (172). It is thought that both epigenetic and genetic factors as well as cellular transformation into a mesenchymal phenotype that occurs in ILF plays a role in lung cancer pathogenesis in ILF (42,173). Abnormalities in the telomerase enzymes TERT and TERC are also involved with lung cancer, but as we have mentioned they also play a role in ILF (17,180). Surgery can be curative in patients with this comorbidity, but overall an increased mortality and acute exacerbations are seen, and it has also been shown that chemotherapy may have an increased incidence of acute exacerbations (174,175,177). There is no official recommendation, but annual screening with HRCT for lung cancer is something to be considered (1,176). Furthermore, some studies have shown that therapy with pirfenidone and nintedanib have may improve survival in certain patients with lung cancer (178,179).

8.5.Other Comorbidities

Emphysema and COPD are comorbidities that have some of the same risk factors as ILF such as smoking. The prevalence of these conditions varies, with emphysema being in up to 27% of patients and COPD ranging from 6% to 67% (181). When ILF is found together with emphysematous signs it is known as combined pulmonary fibrosis emphysema (CPFE) and this condition must be treated as emphysema with bronchodilators, corticosteroids and antibiotics (182). Smoking cessation should be encouraged and oxygen therapy together with pulmonary rehabilitation is also recommended (164).

Cardiovascular complications such as heart failure, hypertension, arrhythmias/atrial fibrillation and coronary artery disease are also noticed (183). Coronary artery disease is the most frequent cardiovascular comorbidity associated with ILF, but the prevalence is very difficult to gage with estimates ranging as high as 65% (184). Coronary artery disease is associated with worse outcomes for the patients and should be monitored carefully (184).

Obstructive sleep apnea has a complex relationship with ILF. Studies show that restrictive changes consistent with ILF may facilitate the development of apnea (185). On the other hand, apnea may lead to GERD which may lead to fibrosis, so a causal relationship is difficult to establish (187). Whatever the case we can see that obstructive sleep apnea is prevalent in ILF, and should be diagnosed with polysomnography (186,188). Treatment should be initiated with CPAP, and this is a case where treatment of comorbidity will have an improvement on quality of life and mortality in ILF patients (189).

9.CONCLUSION

Significant advancements have been made thanks to novel antifibrotic drugs. Despite this ILF remains a terminal condition and treatment is rather thankless; especially given the complexity involved in all stages of the disease from diagnosis to death. It remains an entity that only specialized multidisciplinary teams of clinicians can adequately treat. Further research that is focused on finding reliable biomarkers for early diagnosis and novel treatment options that might halt fibrosis is currently underway and should be followed carefully for any further advancement (195).

Images:

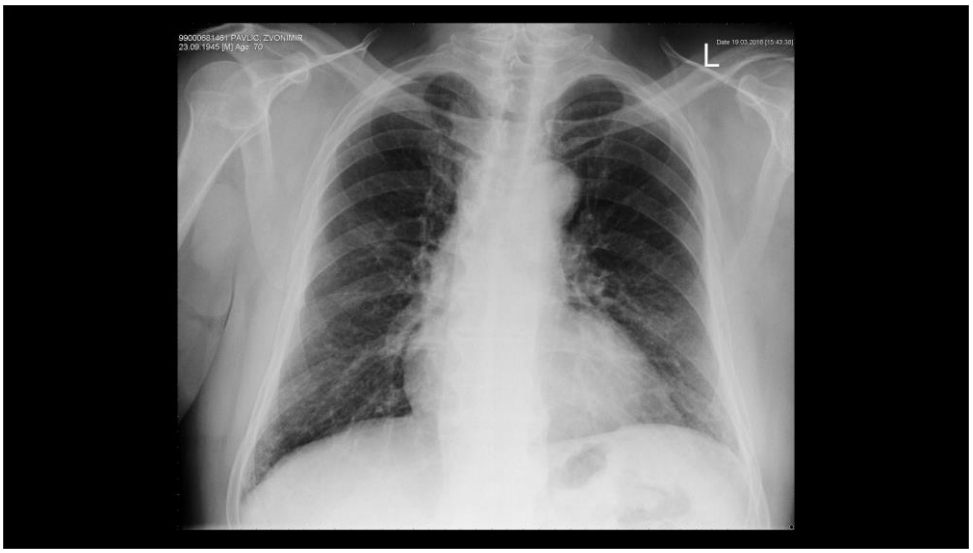


Image 1. Typical chest x-ray findings in ILF. Notice the bilateral reticular changes.

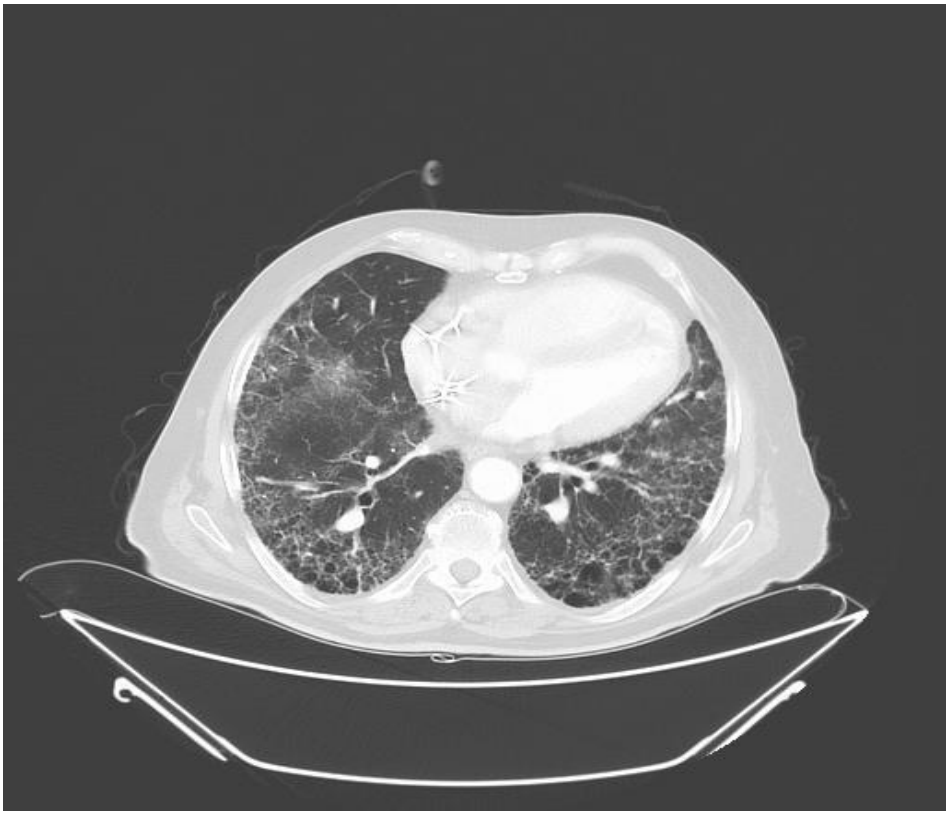


Image 2. Typical CT findings of ILF. Notice the bilateral cystic pattern in the basal areas, this is a typical of honeycombing in ILF.

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11.REFRENCES:

1- Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, Brozek JL, Collard HR, Cunningham W, Homma S, Johkoh T, Martinez FJ, Myers J, Protzko SL, Richeldi L, Rind D, Selman M, Theodore A, Wells AU, Hoogsteden H, Schünemann HJ; American Thoracic Society; European Respiratory society; Japanese Respiratory Society; Latin American Thoracic Association.An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline.Am J Respir Crit Care Med. 2015 Jul 15;192(2):e3-19. doi: 10.1164/rccm.201506-1063ST.

2- Katerina M. Antoniou, George A. Margaritopoulos, Sara Tomassetti, Francesco Bonella, Ulrich Costabel, Venerino Poletti. Interstitial lung disease. European Respiratory Review 2014 23: 40-54; DOI: 10.1183/09059180.00009113

3-Giacomo Sgalla, Alice Biffi, Luca Richeldi. Idiopathic pulmonary fibrosis: Diagnosis, epidemiology and natural history.Respirology. 2016 Apr; 21(3): 427–437.

4-European IPF Registry. 2008. Available at-http://www.pulmonary-fibrosis.net/index.php/european-ipf-registry-and-biobank/information-for-clinicians/idiopathic-pulmonary-fibrosis-ipf

5- Ley B, Urbania T, Husson G, Vittinghoff E, Brush DR, Eisner MD, et al. Code-based diagnostic algorithms for idiopathic pulmonary fibrosis: case validation and improvement. Ann Am Thorac Soc. 2017;14:880–887.

6-Ferrara G, Carlson L, Palm A, Einarsson J, Olivesten C, Sköld M, et al. Idiopathic pulmonary fibrosis in Sweden: report from the first year of activity of the Swedish IPF-Registry. Eur Clin Respir J. 2016;3:31090.

7-John Hutchinson, Andrew Fogarty, Richard Hubbard, Tricia McKeever. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. European Respiratory Journal 2015 46: 795-806; DOI: 10.1183/09031936.00185114

8- Natsuizaka M., Chiba H., Kuronuma K., Otsuka M., Kudo K., Mori M., Bando M., Sugiyama Y., Takahashi H. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. Am. J. Respir. Crit. Care Med. 2014;190:773–779. doi: 10.1164/rccm.201403-0566OC.

9- Joseph P. Lynch, III. John A. Belperio. Idiopathic Pulmonary Fibrosis. Diffuse Lung Disease. 2011 Jul 12 : 171–194.

10-Poletti V. Ravaglia C. Buccioli M. Tantalocco P. Piciucchi S. Dubini A. Carloni A. Chilosi M. Tomassetti S. Idiopathic Pulmonary Fibrosis: Diagnosis and Prognostic EvaluationRespiration 2013;86:5-12

11- Guenther A, Krauss E, Tello S, Wagner J, Paul B, Kuhn S, et al. The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. Respir Res. 2018;19:141. doi: 10.1186/s12931-018-0845-5.

12-Gribbin J, Hubbard RB, Le Jeune I, Smith CJP, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax. 2006;61:980–5.

13-Coultas DB, Zumwalt RE, Black WC, et al. The epidemiology of interstitial lung diseases. Am J Respir Crit Care Med 1994;150:967–72. 10.1164/ajrccm.150.4.7921471

14- van Moorsel CH1, van Oosterhout MF, Barlo NP, de Jong PA, van der Vis JJ, Ruven HJ, van Es HW, van den Bosch JM, Grutters JC.Surfactant protein C mutations are the basis of a significant portion of adult familial pulmonary fibrosis in a dutch cohort.Am J Respir Crit Care Med. 2010 Dec 1;182(11):1419-25.

15-Harari, S., Davì, M., Biffi, A. et al.Epidemiology of idiopathic pulmonary fibrosis: a population-based study in primary care. Intern Emerg Med. 2019. doi: 10.1007/s11739-019-02195-0.

16-Raghu G, Chen S-Y, Yeh W-S, Maroni B, Li Q, Lee Y-C, Collard HR. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence and survival, 2001–11. Lancet Respir. Med. 2014; 2: 566–572.

17- Alder JK, Chen JJ, Lancaster L, Danoff S, Su SC, Cogan JD, Vulto I, Xie M, Qi X, Tuder RM, Phillips JA 3rd, Lansdorp PM, Loyd JE, Armanios MY. Short telomeres are a risk factor for idiopathic pulmonary fibrosis. Proc Natl Acad Sci USA. 2008 Sep 2; 105(35):13051-6.

18- Wang Y, Kuan PJ, Xing C, Cronkhite JT, Torres F, Rosenblatt RL, DiMaio JM, Kinch LN, Grishin NV, Garcia CK. Genetic defects in surfactant protein A2 are associated with pulmonary fibrosis and lung cancer.Am J Hum Genet. 2009 Jan; 84(1):52-9.

19- Seibold MA, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE, Fingerlin TE, Zhang W, Gudmundsson G, Groshong SD, Evans CM, Garantziotis S, Adler KB, Dickey BF, du Bois RM, Yang IV, Herron A, Kervitsky D, Talbert JL, Markin C, Park J, Crews AL, Slifer SH, Auerbach S, Roy MG, Lin J, Hennessy CE, Schwarz MI, Schwartz DA. A common MUC5B promoter polymorphism and pulmonary fibrosis.N Engl J Med. 2011 Apr 21; 364(16):1503-12.

20-Roy MG, Livraghi-Butrico A, Fletcher AA, McElwee MM, Evans SE, Boerner RM, Alexander SN, Bellinghausen LK, Song AS, Petrova YM, Tuvim MJ, Adachi R, Romo I, Bordt AS, Bowden MG, Sisson JH, Woodruff PG, Thornton DJ, Rousseau K, De la Garza MM, Moghaddam SJ, Karmouty-Quintana H, Blackburn MR, Drouin SM, Davis CW, Terrell KA, Grubb BR, O'Neal WK, Flores SC, Cota-Gomez A, Lozupone CA, Donnelly JM, Watson AM, Hennessy CE, Keith RC, Yang IV, Barthel L, Henson PM, Janssen WJ, Schwartz DA, Boucher RC, Dickey BF, Evans CM. Muc5b is required for airway defence.Nature. 2014 Jan 16; 505(7483):412-6.

21- Noth I, Zhang Y, Ma SF, Flores C, Barber M, Huang Y, Broderick SM, Wade MS, Hysi P, Scuirba J, Richards TJ, Juan-Guardela BM, Vij R, Han MK, Martinez FJ, Kossen K, Seiwert SD, Christie JD, Nicolae D, Kaminski N, Garcia JGN. Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study.Lancet Respir Med. 2013 Jun; 1(4):309-317.

22-Taskar V, Coultas D. Exposures and idiopathic lung disease.Semin Respir Crit Care Med. 2008 Dec; 29(6):670-9.

23- Spira A, Beane J, Shah V, Liu G, Schembri F, Yang X, Palma J, Brody JS.Effects of cigarette smoke on the human airway epithelial cell transcriptome.Proc Natl Acad Sci U S A. 2004 Jul 6;101(27):10143-8.

24-Taskar VS, Coultas DB.Is idiopathic pulmonary fibrosis an environmental disease?Proc Am Thorac Soc. 2006 Jun;3(4):293-8.

25-Lawson WE, Crossno PF, Polosukhin VV, Roldan J, Cheng DS, Lane KB, Blackwell TR, Xu C, Markin C, Ware LB, Miller GG, Loyd JE, Blackwell TS.Endoplasmic reticulum stress in alveolar epithelial cells is prominent in IPF: association with altered surfactant protein processing and herpesvirus infection.Am J Physiol Lung Cell Mol Physiol. 2008 Jun;294(6):L1119-26. doi: 10.1152/ajplung.00382.2007.

26-Calabrese F, Kipar A, Lunardi F, Balestro E, Perissinotto E, Rossi E, Nannini N, Marulli G, Stewart JP, Rea F.Herpes virus infection is associated with vascular remodeling and pulmonary hypertension in idiopathic pulmonary fibrosis.PLoS One. 2013;8(2):e55715. doi: 10.1371/journal.pone.0055715.

27- Egan JJ, Adamali HI, Lok SS, Stewart JP, Woodcock AA.Ganciclovir antiviral therapy in advanced idiopathic pulmonary fibrosis: an open pilot study.Pulm Med. 2011;2011:240805. doi: 10.1155/2011/240805.

28- Richter AG, Stockley RA, Harper L, et al. Pulmonary infection in Wegener granulomatosis and idiopathic pulmonary fibrosis. Thorax 2009; 64: 692–697

29- Chioma OS, Drake WP.Role of Microbial Agents in Pulmonary Fibrosis. Yale J Biol Med. 2017 Jun; 90(2):219-227.

30- Walter P, Ron D.The unfolded protein response: from stress pathway to homeostatic regulation.Science. 2011 Nov 25;334(6059):1081-6. doi: 10.1126/science.1209038.

31- Maitra M, Wang Y, Gerard RD, Mendelson CR, Garcia CK.Surfactant protein A2 mutations associated with pulmonary fibrosis lead to protein instability and endoplasmic reticulum stress.J Biol Chem. 2010 Jul 16;285(29):22103-13. doi: 10.1074/jbc.M110.121467.

32- Surafel Mulugeta, Vu Nguyen, Scott J. Russo, Madesh Muniswamy, and Michael F. Beers.A Surfactant Protein C Precursor Protein BRICHOS Domain Mutation Causes Endoplasmic Reticulum Stress, Proteasome Dysfunction, and Caspase 3 Activation. Am J Respir Cell Mol Biol. 2005 Jun; 32(6): 521–530.

33-Jennifer A. Isler, Alison H. Skalet, and James C. Alwine. Human Cytomegalovirus Infection Activates and Regulates the Unfolded Protein Response.J Virol. 2005 Jun; 79(11): 6890–6899.

34- Hengstermann A, Müller T.Endoplasmic reticulum stress induced by aqueous extracts of cigarette smoke in 3T3 cells activates the unfolded-protein-response-dependent PERK pathway of cell survival.Free Radic Biol Med. 2008 Mar 15;44(6):1097-107.

35-Annes JP, Munger JS, Rifkin DB.Making sense of latent TGFbeta activation.J Cell Sci. 2003 Jan 15;116(Pt 2):217-24.

36-Munger JS, Huang X, Kawakatsu H, Griffiths MJ, Dalton SL, Wu J, Pittet JF, Kaminski N, Garat C, Matthay MA, Rifkin DB, Sheppard D.The integrin alpha v beta 6 binds and activates latent TGF beta 1: a mechanism for regulating pulmonary inflammation and fibrosis.Cell. 1999 Feb 5;96(3):319-28.

37-Grimminger F, Günther A, Vancheri C.The role of tyrosine kinases in the pathogenesis of idiopathic pulmonary fibrosis.Eur Respir J. 2015 May; 45(5):1426-33.

38-Willis BC, Borok Z.TGF-beta-induced EMT: mechanisms and implications for fibrotic lung disease.Am J Physiol Lung Cell Mol Physiol. 2007 Sep;293(3):L525-34.

39-Raghu Kalluri and Eric G. Neilson. Epithelial-mesenchymal transition and its implications for fibrosis. J Clin Invest. 2003 Dec 15; 112(12): 1776–1784.

40-Kalluri R, Neilson EG. Epithelial-mesenchymal transition and its implications for fibrosis. J Clin Invest 112: 1776–1784, 2003.

41-Iwano M, Plieth D, Danoff TM, Xue C, Okada H, Neilson EG. Evidence that fibroblasts derive from epithelium during tissue fibrosis. J Clin Invest 110: 341–350, 2002.

42- Kim KK, Kugler MC, Wolters PJ, Robillard L, Galvez MG, Brumwell AN, Sheppard D, Chapman HA.Alveolar epithelial cell mesenchymal transition develops in vivo during pulmonary fibrosis and is regulated by the extracellular matrix.roc Natl Acad Sci U S A. 2006 Aug 29;103(35):13180-5.

43-Harikrishna Tanjore, Dong-Sheng Cheng, Amber L. Degryse, Donald F. Zoz, Rasul Abdolrasulnia, William E. Lawson, and Timothy S. Blackwell.Alveolar Epithelial Cells Undergo Epithelial-to-Mesenchymal Transition in Response to Endoplasmic Reticulum Stress. J Biol Chem. 2011 Sep 2; 286(35): 30972–30980.

44- Rabinovich EI, Selman M, Kaminski N. Epigenomics of idiopathic pulmonary fibrosis: evaluating the first steps. Am J Respir Crit Care Med. 2012 Sep 15; 186(6):473-5.

45-Dakhlallah D, Batte K, Wang Y, Cantemir-Stone CZ, Yan P, Nuovo G, Mikhail A, Hitchcock CL, Wright VP, Nana-Sinkam SP, Piper MG, Marsh CB.Epigenetic regulation of miR-17~92 contributes to the pathogenesis of pulmonary fibrosis. Am J Respir Crit Care Med. 2013 Feb 15; 187(4):397-405.

46-Sanders YY, Ambalavanan N, Halloran B, Zhang X, Liu H, Crossman DK, Bray M, Zhang K, Thannickal VJ, Hagood JS. Altered DNA methylation profile in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2012 Sep 15; 186(6):525-35.

47- Liu F, Killian JK, Yang M, Walker RL, Hong JA, Zhang M, Davis S, Zhang Y, Hussain M, Xi S, Rao M, Meltzer PA, Schrump DS. Epigenomic alterations and gene expression profiles in respiratory epithelia exposed to cigarette smoke condensate.Oncogene. 2010 Jun 24; 29(25):3650-64.

48- Issa JP.Aging and epigenetic drift: a vicious cycle. J Clin Invest. 2014 Jan; 124(1):24-9.

49- Sazhenova, E.A., Lebedev, I.N. Epigenetic Mosaicism in Genomic Imprinting Disorders. Russ J Genet 55, 1196–1207 (2019) doi:10.1134/S1022795419100119

50-Bucala R, Spiegel LA, Chesney J, Hogan M, Cerami A.Circulating fibrocytes define a new leukocyte subpopulation that mediates tissue repair.Mol Med. 1994 Nov;1(1):71-81.

51-Robert M. Strieter, Ellen C. Keeley, Molly A. Hughes, Marie D. Burdick, and Borna Mehrad. The role of circulating mesenchymal progenitor cells (fibrocytes) in the pathogenesis of pulmonary fibrosis. J Leukoc Biol. 2009 Nov; 86(5): 1111–1118.

52-Mehrad B, Burdick MD, Zisman DA, Keane MP, Belperio JA, Strieter RM. Circulating peripheral blood fibrocytes in human fibrotic interstitial lung disease.Biochem Biophys Res Commun. 2007 Feb 2;353(1):104-8. Epub 2006 Dec 11.

53-Moeller A, Gilpin SE, Ask K, Cox G, Cook D, Gauldie J, Margetts PJ, Farkas L, Dobranowski J, Boylan C, O'Byrne PM, Strieter RM, Kolb M.Circulating fibrocytes are an indicator of poor prognosis in idiopathic pulmonary fibrosis.Am J Respir Crit Care Med. 2009 Apr 1;179(7):588-94. doi: 10.1164/rccm.200810-1534OC.

54-Andersson-Sjöland A, de Alba CG, Nihlberg K, Becerril C, Ramírez R, Pardo A, Westergren-Thorsson G, Selman M.Fibrocytes are a potential source of lung fibroblasts in idiopathic pulmonary fibrosis.Int J Biochem Cell Biol. 2008;40(10):2129-40.

55-Scotton CJ, Chambers RC.Molecular targets in pulmonary fibrosis: the myofibroblast in focus.Chest. 2007 Oct;132(4):1311-21.

56-Hinz B. Mechanical aspects of lung fibrosis: a spotlight on the myofibroblast.Proc Am Thorac Soc. 2012 Jul;9(3):137-47.

57-A. Desmoulière, M. Redard, I. Darby, and G. Gabbiani. Apoptosis mediates the decrease in cellularity during the transition between granulation tissue and scar.Am J Pathol. 1995 Jan; 146(1): 56–66.

58- Sisson TH, Maher TM, Ajayi IO, King JE, Higgins PD, Booth AJ, Sagana RL, Huang SK, White ES, Moore BB, Horowitz JC. Increased survivin expression contributes to apoptosis-resistance in IPF fibroblasts. Adv Biosci Biotechnol. 2012 Oct; 3(6A):657-664.

59- Chang W, Wei K, Jacobs SS, Upadhyay D, Weill D, Rosen GD.SPARC suppresses apoptosis of idiopathic pulmonary fibrosis fibroblasts through constitutive activation of beta-catenin. J Biol Chem. 2010 Mar 12; 285(11):8196-206.

60- Paul J. Wolters, Harold R. Collard, and Kirk D. Jones. Pathogenesis of Idiopathic Pulmonary Fibrosis. Annu Rev Pathol. 2014; 9: 157–179.

61-White ES, Thannickal VJ, Carskadon SL, Dickie EG, Livant DL, Markwart S, Toews GB, Arenberg DA.Integrin alpha4beta1 regulates migration across basement membranes by lung fibroblasts: a role for phosphatase and tensin homologue deleted on chromosome 10.Am J Respir Crit Care Med. 2003 Aug 15;168(4):436-42.

62- Li Y, Jiang D, Liang J, Meltzer EB, Gray A, Miura R, Wogensen L, Yamaguchi Y, Noble PW.Severe lung fibrosis requires an invasive fibroblast phenotype regulated by hyaluronan and CD44.J Exp Med. 2011 Jul 4;208(7):1459-71.

63- Coward WR, Saini G, Jenkins G. The pathogenesis of idiopathic pulmonary fibrosis. Ther Adv Respir Dis. 2010 Dec; 4(6):367-88.

64- Rice AJ, Wells AU, Bouros D, du Bois RM, Hansell DM, Polychronopoulos V, Vassilakis D, Kerr JR, Evans TW, Nicholson AG.Terminal diffuse alveolar damage in relation to interstitial pneumonias. An autopsy study.Am J Clin Pathol. 2003 May;119(5):709-14.

65- Malli F, Koutsokera A, Paraskeva E, Zakynthinos E, Papagianni M, Makris D, Tsilioni I, Molyvdas PA, Gourgoulianis KI, Daniil Z.Endothelial progenitor cells in the pathogenesis of idiopathic pulmonary fibrosis: an evolving concept.PLoS One. 2013;8(1):e53658.

66-King TE Jr, Tooze JA, Schwarz MI, Brown KR, Cherniack RM.Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model.Am J Respir Crit Care Med. 2001 Oct 1;164(7):1171-81.

67- Cottin V, Cordier JF. Velcro crackles: the key for early diagnosis of idiopathic pulmonary fibrosis? Eur. Respir. J. 2012; 40: 519–521.

68- Giacomo Sgalla, Alice Biffi, Luca Richeldi. Idiopathic pulmonary fibrosis: Diagnosis, epidemiology and natural history. Respirology. 2016 Apr;21(3):427-37.

69-Lancaster LH, Mason WR, Parnell JA, Rice TW, Loyd JE, Milstone AP, Collard HR, Malow BA.Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. Chest. 2009 Sep; 136(3):772-778.

70-Enomoto T, Usuki J, Azuma A, Nakagawa T, Kudoh S.Diabetes mellitus may increase risk for idiopathic pulmonary fibrosis.Chest. 2003 Jun; 123(6):2007-11.

71-Raghu G, Freudenberger TD, Yang S, Curtis JR, Spada C, Hayes J, Sillery JK, Pope CE 2nd, Pellegrini CA.High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. Eur Respir J. 2006 Jan; 27(1):136-42.

72- García-Sancho C, Buendía-Roldán I, Fernández-Plata MR, Navarro C, Pérez-Padilla R, Vargas MH, Loyd JE, Selman M.Familial pulmonary fibrosis is the strongest risk factor for idiopathic pulmonary fibrosis.Respir Med. 2011 Dec;105(12):1902-7.

73- Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. Am J Respir Crit Care Med 2016; 194: 265–275.

74- Kim DS, Park JH, Park BK, Lee JS, Nicholson AG, Colby T. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. Eur Respir J. 2006;27(1):143–150.

75-Yasuhiro Kondoh, Vincent Cottin, Kevin K. Brown.Recent lessons learned in the management of acute exacerbation of idiopathic pulmonary fibrosis. European Respiratory Review 2017 26: 170050

76- Huie TJ, Olson AL, Cosgrove GP, Janssen WJ, Lara AR, Lynch DA, Groshong SD, Moss M, Schwarz MI, Brown KK, Frankel SK.A detailed evaluation of acute respiratory decline in patients with fibrotic lung disease: aetiology and outcomes.Respirology. 2010 Aug;15(6):909-17.

77- Johannson KA, Vittinghoff E, Lee K, Balmes JR, Ji W, Kaplan GG, Kim DS, Collard HR. Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. Eur Respir J 2014; 43: 1124-1131.

78- Ghatol A, Ruhl AP, Danoff SK. Exacerbations in idiopathic pulmonary fibrosis triggered by pulmonary and nonpulmonary surgery: a case series and comprehensive review of the literature. Lung 2012; 190: 373-380.

79- Bando M, Ohno S, Hosono T, Yanase K, Sato Y, Sohara Y, Hironaka M, Sugiyama Y. Risk of Acute Exacerbation After Video-assisted Thoracoscopic Lung Biopsy for Interstitial Lung Disease. J Bronchology Interv Pulmonol 2009; 16: 229-235.

80-Wootton SC, Kim DS, Kondoh Y, Chen E, Lee JS, Song JW, Huh JW, Taniguchi H, Chiu C, Boushey H, Lancaster LH, Wolters PJ, DeRisi J, Ganem D, Collard HR. Viral infection in acute exacerbation of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011; 183: 1698-1702.

81- Lee JS, Collard HR, Anstrom KJ, Martinez FJ, Noth I, Roberts RS, Yow E, Raghu G, Investigators IP. Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials. Lancet Respir Med 2013; 1: 369-376.

82- Song J.W., Hong S.B., Lim C.M., Koh Y., Kim D.S. Acute exacerbation of idiopathic pulmonary fibrosis: Incidence, risk factors and outcome. Eur. Respir. J. 2011;37:356–363. doi: 10.1183/09031936.00159709.

83- Ohshimo S., Ishikawa N., Horimasu Y., Hattori N., Hirohashi N., Tanigawa K., Kohno N., Bonella F., Guzman J., Costabel U. Baseline KL-6 predicts increased risk for acute exacerbation of idiopathic pulmonary fibrosis. Respir. Med. 2014;108:1031–1039. doi: 10.1016/j.rmed.2014.04.009.

84- Tomoo Kishaba. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. Medicina 2019, 55(3), 70

85-Kishaba T., Nei Y., Momose M., Nagano H., Yamashiro S. Clinical Characteristics Based on the New Criteria of Acute Exacerbation in Patients with Idiopathic Pulmonary Fibrosis. Eurasian J. Med. 2018;50:6–10. doi: 10.5152/eurasianjmed.2018.17330.

86- Kim DS, Park JH, Park BK, Lee JS, Nicholson AG, Colby T. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. Eur Respir J (2006) 27:143–50.10.1183/09031936.06.00114004

87- Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE, Jr, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med (2007) 176:636–43.10.1164/rccm.200703-463PP

88- Reichmann WM, Yu YF, Macaulay D, Wu EQ, Nathan SD. Change in forced vital capacity and associated subsequent outcomes in patients with newly diagnosed idiopathic pulmonary fibrosis. BMC Pulm Med 2015;15:167.

89- Collard HR, Yow E, Richeldi L, Anstrom KJ, Glazer C; IPFnet investigators. Suspected acute exacerbation of idiopathic pulmonary fibrosis as an outcome measure in clinical trials. Respir Res 2013;14:73.

90- Travis W.D., Costabel U., Hansell D.M., King T.E., Jr., Lynch D.A., Nicholson A.G., Ryerson C.J., Ryu J.H., Selman M., Wells A.U., et al. ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am. J. Respir. Crit. Care Med. 2013;188:733–748. doi: 10.1164/rccm.201308-1483ST.

91- Paterniti MO, Bi Y, Rekić D, Wang Y, Karimi-Shah BA, Chowdhury BA. Acute exacerbation and decline in forced vital capacity are associated with increased mortality in idiopathic pulmonary fibrosis. Ann Am Thorac Soc. 2017 Sep;14(9):1395–402.

92- Wuyts WA, Wijsenbeek M, Bondue B, Bouros D, Bresser P, Robalo Cordeiro C, Hilberg O, Magnusson J, Manali ED, Morais A, Papiris S, Shaker S, Veltkamp M, Bendstrup E.Idiopathic Pulmonary Fibrosis: Best Practice in Monitoring and Managing a Relentless Fibrotic Disease.Respiration. 2020;99(1):73-82.

93- Myriam Aburto, Inmaculada Herráez, David Iturbe, Ana Jiménez-Romero. Diagnosis of Idiopathic Pulmonary Fibrosis: Differential Diagnosis. Med Sci (Basel). 2018 Sep 4;6(3). pii: E73

94- Ohnishi H, Yokoyama A, Kondo K, Hamada H, Abe M, Nishimura K, Hiwada K, Kohno N.Comparative study of KL-6, surfactant protein-A, surfactant protein-D, and monocyte chemoattractant protein-1 as serum markers for interstitial lung diseases.Am J Respir Crit Care Med. 2002 Feb 1;165(3):378-81.

95- Casoni GL, Ulivi P, Mercatali L, Chilosi M, Tomassetti S, Romagnoli M, Ravaglia C, Gurioli C, Gurioli C, Zoli W, Silvestrini R, Poletti V.Increased levels of free circulating DNA in patients with idiopathic pulmonary fibrosis.Int J Biol Markers. 2010 Oct-Dec;25(4):229-35.

96- Ohshimo S, Bonella F, Cui A, Beume M, Kohno N, Guzman J, Costabel U.Significance of bronchoalveolar lavage for the diagnosis of idiopathic pulmonary fibrosis.Am J Respir Crit Care Med. 2009 Jun 1;179(11):1043-7.

97- Sakamoto K, Taniguchi H, Kondoh Y, Wakai K, Kimura T, Kataoka K, Hashimoto N, Nishiyama O, Hasegawa Y.Acute exacerbation of IPF following diagnostic bronchoalveolar lavage procedures.Respir Med. 2012 Mar;106(3):436-42. doi: 10.1016/j.rmed.2011.11.006.

98- Pesci A, Ricchiuti E, Ruggiero R, De Micheli A.Bronchoalveolar lavage in idiopathic pulmonary fibrosis: what does it tell us?Respir Med. 2010 Jul;104 Suppl 1:S70-3. doi: 10.1016/j.rmed.2010.03.019.

99- Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JR, Goldin JG, Hansell DM, Inoue Y, Johkoh T, Nicholson AG, Knight SL, Raoof S, Richeldi L, Ryerson CJ, Ryu JH, Wells AU.Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper.Lancet Respir Med. 2018 Feb;6(2):138-153.

100- Chung JH, Montner SM, Adegunsoye A, Lee C, Oldham JM, Husain AN, MacMahon H, Noth I, Vij R, Strek ME.CT Findings, Radiologic-Pathologic Correlation, and Imaging Predictors of Survival for Patients With Interstitial Pneumonia With Autoimmune Features.AJR Am J Roentgenol. 2017 Jun;208(6):1229-1236.

101- Sumikawa H, Johkoh T, Colby TV, Ichikado K, Suga M, Taniguchi H, Kondoh Y, Ogura T, Arakawa H, Fujimoto K, Inoue A, Mihara N, Honda O, Tomiyama N, Nakamura H, Müller NL.Computed tomography findings in pathological usual interstitial pneumonia: relationship to survival.Am J Respir Crit Care Med. 2008 Feb 15;177(4):433-9.

102- Chung JH, Chawla A, Peljto AL, Cool CD, Groshong SD, Talbert JL, et al. CT scan findings of probable usual interstitial pneumonitis have a high predictive value for histologic usual interstitial pneumonitis. Chest. 2015 Feb;147(2):450-9.

103- Lynch DA, Godwin JD, Safrin S, et al. ; Idiopathic Pulmonary Fibrosis Study Group. High-resolution computed tomography in idiopathic pulmonary fibrosis: diagnosis and prognosis. Am J Respir Crit Care Med. 2005;172(4):488-493.

104- Beigelman-Aubry, C, Hill, C, Guibal, A, Savatovsky, J, Grenier, P.A.Multi-detector row CT and postprocessing techniques in the assessment of diffuse lung disease. Radiographics 2005, 25, 1639–1652.

105- Mohning MP, Richards JC, Huie TJ. Idiopathic pulmonary fibrosis: the radiologist's role in making the diagnosis. Br J Radiol. 2019;92(1099):20181003. doi:10.1259/bjr.20181003

106- Raghu G, Lynch D, Godwin JD, Webb R, Colby TV, Leslie KO, Behr J, Brown KK, Egan JJ, Flaherty KR, et al. Diagnosis of idiopathic pulmonary fibrosis with high-resolution CT in patients withlittle or no radiological evidence of honeycombing: Secondary analysis of a randomised, controlled trial. Lancet Respir. Med. 2014, 2, 277–284.

107- Brownell R, Moua T, Henry TS, Elicker BM, White D, Vittinghoff E, Jones K D,Urisman A, Aravena C, Johannson KA, et al. The use of pretest probability increases the value of high-resolution CT in diagnosing usual interstitial pneumonia. Thorax 2017, 72, 424–429.

108- Qureshi RA, Ahmed TA, Grayson AD, Soorae AS, Drakeley MJ, Page RD. Does lung biopsy help patients with interstitial lung disease? Eur J Cardiothorac Surg. 2002 Apr;21(4):621-6.

109- Park JH, Kim DK, Kim DS, et al. Mortality and risk factors for surgical lung biopsy in patients with idiopathic interstitial pneumonia. Eur J Cardiothorac Surg. 2007;31:1115–1119.

110- Utz JP, Ryu JH, Douglas WW, et al. High short-term mortality following lung biopsy for usual interstitial pneumonia. Eur Respir J. 2001;17:175–179.

111- Kreider ME, Hansen-Flaschen J, Ahmad NN, Rossman MD, Kaiser LR, Kucharczuk JC, Shrager JB.Complications of video-assisted thoracoscopic lung biopsy in patients with interstitial lung disease.Ann Thorac Surg. 2007 Mar;83(3):1140-4.

112- Lodhi T, Hughes G, Stanel S, Chaudhuri N, Hayton C.Transbronchial Lung Cryobiopsy in Idiopathic Pulmonary Fibrosis: A State of the Art Review.Adv Ther. 2019 Sep;36(9):2193-2204.

113- Arakawa H, Honma K. Honeycomb lung: history and current concepts. American Journal of Roentgenology 2011; 196: 773–82. doi: 10.2214/AJR.10.4873

114- Flaherty KR, King TE Jr, Raghu G, Lynch JP III, Colby TV, Travis WD, Gross BH, Kazerooni EA, Toews GB, Long Q, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med 2004;170:904–910.

115- Ghisa M, Marinelli C, Savarino V, Savarino E. Idiopathic pulmonary fibrosis and GERD: links and risks. Ther Clin Risk Manag. 2019;15:1081–1093. Published 2019 Sep 5. doi:10.2147/TCRM.S184291

116- Downing TE, Sporn TA, Bollinger RR, Davis RD, Parker W, Lin SS.Pulmonary histopathology in an experimental model of chronic aspiration is independent of acidity.Exp Biol Med (Maywood). 2008 Oct;233(10):1202-12.

117- Appel JZ, Lee SM, Hartwig MG, et al. Characterization of the innate immune response to chronic aspiration in a novel rodent model. Respir Res. 2007;8(1):87. doi:10.1186/1465-9921-8-87

118- Mise J, Lozo M, Mise K, et al. Bronchoalveolar pH and inflammatory biomarkers in newly diagnosed IPF and GERD patients: a case-control study. Med Sci Monit. 2014;20:255–261. doi:10.12659/MSM.889800

119- Costabel U, Behr J, Crestani B, et al. Anti-acid therapy in idiopathic pulmonary fibrosis: insights from the INPULSIS® trials. Respir Res. 2018;19(1):167. doi:10.1186/s12931-018-0866-0

120- Lin H, Jiang S. Combined pulmonary fibrosis and emphysema (CPFE): an entity different from emphysema or pulmonary fibrosis alone. J Thorac Dis. 2015;7(4):767–779. doi:10.3978/j.issn.2072-1439.2015.04.17

121- Akira M, Yamamoto S, Inoue Y, Sakatani M. High-resolution CT of asbestosis and idiopathic pulmonary fibrosis.AJR Am J Roentgenol. 2003 Jul;181(1):163-9.

122- Jonathan H Chung, Christian W Cox, Steven M Montner, Ayodeji Adegunsoye, Justin M Oldham, Aliya N Husain, Rekha Vij, Imre Noth, David A Lynch, Mary E Strek. CT Features of the Usual Interstitial Pneumonia Pattern: Differentiating Connective Tissue Disease–Associated Interstitial Lung Disease From Idiopathic Pulmonary Fibrosis. American Journal of Roentgenology. 2018;210: 307-313. 10.2214/AJR.17.18384

123- Luo YF, Robbins IM, Karatas M, Brixey AG, Rice TW, Light RW.Frequency of pleural effusions in patients with pulmonary arterial hypertension associated with connective tissue diseases.Chest. 2011 Jul;140(1):42-47. doi: 10.1378/chest.10-0227.

124- Latsi PI, du Bois RM, Nicholson AG, Colby TV, Bisirtzoglou D, Nikolakopoulou A, Veeraraghavan S, Hansell DM, Wells AU.Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends.Am J Respir Crit Care Med. 2003 Sep 1;168(5):531-7.

125- Collard HR, King TE Jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK.Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis.Am J Respir Crit Care Med. 2003 Sep 1;168(5):538-42.

126- Plantier L, Cazes A, Dinh-Xuan AT, Bancal C, Marchand-Adam S, Crestani B.Physiology of the lung in idiopathic pulmonary fibrosis.Eur Respir Rev. 2018 Jan 24;27(147). pii: 170062. doi: 10.1183/16000617.0062-2017.

127- Lama VN, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, Murray S, Kazerooni EA, Gross BH, Lynch JP 3rd, Martinez FJ.Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia.Am J Respir Crit Care Med. 2003 Nov 1;168(9):1084-90.

128- du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, Lancaster L, Noble PW, Sahn SA, Szwarcberg J, Thomeer M, Valeyre D, King TE Jr.Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference.Am J Respir Crit Care Med. 2011 May 1;183(9):1231-7.

129- Lederer DJ, Arcasoy SM, Wilt JS, D'Ovidio F, Sonett JR, Kawut SM.Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis.Am J Respir Crit Care Med. 2006 Sep 15;174(6):659-64.

130- Wollin L, Maillet I, Quesniaux V, Holweg A, Ryffel B.Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis.J Pharmacol Exp Ther. 2014 May;349(2):209-20.

131- Rivera-Ortega P, Hayton C, Blaikley J, Leonard C, Chaudhuri N. Nintedanib in the management of idiopathic pulmonary fibrosis: clinical trial evidence and real-world experience. Ther Adv Respir Dis. 2018;12:1753466618800618. doi:10.1177/1753466618800618

132- Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ.Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis.N Engl J Med. 2012 May 24;366(21):1968-77. doi: 10.1056/NEJMoa1113354.

133- Wollin L, Wex E, Pautsch A, Schnapp G, Hostettler KE, Stowasser S, Kolb M.Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis.Eur Respir J. 2015 May;45(5):1434-45. doi: 10.1183/09031936.00174914.

134- Richeldi L, Cottin V, du Bois RM, Selman M, Kimura T, Bailes Z, Schlenker-Herceg R, Stowasser S, Brown KK.Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS(®) trials.Respir Med. 2016 Apr;113:74-9. doi: 10.1016/j.rmed.2016.02.001.

135- Costabel U, Inoue Y, Richeldi L, Collard HR, Tschoepe I, Stowasser S, Azuma A.Efficacy of Nintedanib in Idiopathic Pulmonary Fibrosis across Prespecified Subgroups in INPULSIS.Am J Respir Crit Care Med. 2016 Jan 15;193(2):178-85. doi: 10.1164/rccm.201503-0562OC.

136- Corte T, Bonella F, Crestani B, et al. Safety, tolerability and appropriate use of nintedanib in idiopathic pulmonary fibrosis. Respir Res. 2015;16:116. Published 2015 Sep 24. doi:10.1186/s12931-015-0276-5

137- Hisatomi K, Mukae H, Sakamoto N, Ishimatsu Y, Kakugawa T, Hara S, Fujita H, Nakamichi S, Oku H, Urata Y, Kubota H, Nagata K, Kohno S.Pirfenidone inhibits TGF-β1-induced over-expression of collagen type I and heat shock protein 47 in A549 cells.BMC Pulm Med. 2012 Jun 13;12:24. doi: 10.1186/1471-2466-12-24.

138- Jin J, Togo S, Kadoya K, Tulafu M, Namba Y, Iwai M, Watanabe J, Nagahama K, Okabe T, Hidayat M, Kodama Y, Kitamura H, Ogura T, Kitamura N, Ikeo K, Sasaki S,

Tominaga S, Takahashi K.Pirfenidone attenuates lung fibrotic fibroblast responses to transforming growth factor-β1.Respir Res. 2019 Jun 11;20(1):119. doi: 10.1186/s12931-019-1093-z.

139- King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, Lederer DJ, Nathan SD, Pereira CA, Sahn SA, Sussman R, Swigris JJ, Noble PW; ASCEND Study Group.A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis.N Engl J Med. 2014 May 29;370(22):2083-92. doi: 10.1056/NEJMoa1402582.

140- Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, King TE Jr, Lancaster L, Sahn SA, Szwarcberg J, Valeyre D, du Bois RM; CAPACITY Study Group.Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials.Lancet. 2011 May 21;377(9779):1760-9. doi: 10.1016/S0140-6736(11)60405-4.

141- Lancaster LH, de Andrade JA, Zibrak JD, Padilla ML, Albera C, Nathan SD, Wijsenbeek MS, Stauffer JL, Kirchgaessler KU, Costabel U.Pirfenidone safety and adverse event management in idiopathic pulmonary fibrosis.Eur Respir Rev. 2017 Dec 6;26(146). pii: 170057. doi: 10.1183/16000617.0057-2017.

142-https://www.ema.europa.eu/en/documents/product-information/esbriet-epar-product-information_hr.pdf

143- Koschel D, Cottin V, Skold M, et al. Pirfenidone post-authorisation safety registry (PASSPORT) – Interim analysis of IPF treatment. Eur Respir J 2014; 44: Suppl. 58, 1904.

144- Tzouvelekis A, Ntolios P, Karampitsakos T, Tzilas V, Anevlavis S, Bouros E, Steiropoulos P, Koulouris N, Stratakos G, Froudarakis M, Bouros D.Safety and efficacy of pirfenidone in severe Idiopathic Pulmonary Fibrosis: A real-world observational study.Pulm Pharmacol Ther. 2017 Oct;46:48-53. doi: 10.1016/j.pupt.2017.08.011.

145- Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ.Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis.N Engl J Med. 2012 May 24;366(21):1968-77. doi: 10.1056/NEJMoa1113354.

146- Lee JS, Ryu JH, Elicker BM, Lydell CP, Jones KD, Wolters PJ, King TE Jr, Collard HR.Gastroesophageal reflux therapy is associated with longer survival in patients with idiopathic pulmonary fibrosis.Am J Respir Crit Care Med. 2011 Dec 15;184(12):1390-4. doi: 10.1164/rccm.201101-0138OC.

147- Kreuter M, Wuyts W, Renzoni E, Koschel D, Maher TM, Kolb M, Weycker D, Spagnolo P, Kirchgaessler KU, Herth FJ, Costabel U. Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis.Lancet Respir Med. 2016 May;4(5):381-9. doi: 10.1016/S2213-2600(16)00067-9.

148- Saito S, Alkhatib A, Kolls JK, Kondoh Y, Lasky JA. Pharmacotherapy and adjunctive treatment for idiopathic pulmonary fibrosis (IPF). J Thorac Dis. 2019;11(Suppl 14):S1740–S1754. doi:10.21037/jtd.2019.04.62

149- Balestro E, Cocconcelli E, Tinè M, et al. Idiopathic Pulmonary Fibrosis and Lung Transplantation: When it is Feasible. Medicina (Kaunas). 2019;55(10):702. Published 2019 Oct 19. doi:10.3390/medicina55100702

150- Vandervest K.M., Zamora M.R. Recipient risk factors and lung transplant outcomes. Curr. Opin. Organ. Transplant. 2013;18:531–536. doi: 10.1097/MOT.0b013e32836519ec.

151- ten Klooster L, Nossent GD, Kwakkel-van Erp JM, van Kessel DA, Oudijk EJ, van de Graaf EA, Luijk B, Hoek RA, van den Blink B, van Hal PT, Verschuuren EA, van der Bij W, van Moorsel CH, Grutters JC.Ten-Year Survival in Patients with Idiopathic Pulmonary Fibrosis After Lung Transplantation.Lung. 2015 Dec;193(6):919-26. doi: 10.1007/s00408-015-9794-7.

152- Chambers DC, Yusen RD, Cherikh WS, Goldfarb SB, Kucheryavaya AY, Khusch K, Levvey BJ, Lund LH, Meiser B, Rossano JW, Stehlik J; International Society for Heart and Lung Transplantation.The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Lung And Heart-Lung Transplantation Report-2017; Focus Theme: Allograft ischemic time.J Heart Lung Transplant. 2017 Oct;36(10):1047-1059. doi: 10.1016/j.healun.2017.07.016.

153- Thabut G., Mal H., Castier Y., Groussard O., Brugière O., Marrash-Chahla R., Lesèche G., Fournier M. Survival benefit of lung transplantation for patients with idiopathic pulmonary fibrosis. J. Thorac. Cardiovasc. Surg. 2003;126:469–475. doi: 10.1016/S0022-5223(03)00600-7.

154- Laporta Hernandez R, Aguilar Perez M, Lázaro Carrasco MT, Ussetti Gil P. Lung Transplantation in Idiopathic Pulmonary Fibrosis. Med Sci (Basel). 2018;6(3):68. Published 2018 Aug 23. doi:10.3390/medsci6030068

155- Puri V., Patterson G.A., Meyers B.F. Single versus bilateral lung transplantation: Do guidelines exist? Thorac. Surg. Clin. 2015;25:47–54. doi: 10.1016/j.thorsurg.2014.09.007.

156- Kumar A., Kapnadak S.G., Girgis R.E., Raghu G. Lung transplantation in idiopathic pulmonary fibrosis. Exp. Rev. Respir. Med. 2018;12:375–385. doi: 10.1080/17476348.2018.1462704.

157- Gomes-Neto M, Silva CM, Ezequiel D, et al. Impact of Pulmonary Rehabilitation on Exercise Tolerance and Quality of Life in Patients With Idiopathic Pulmonary Fibrosis: A SYSTEMATIC REVIEW AND META-ANALYSIS. J Cardiopulm Rehabil Prev 2018;38:273-8.

158- Morrison DA, Stovall JR. Increased exercise capacity in hypoxemic patients after long-term oxygen therapy. Chest 1992;102:542–550.

159- Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Ann Intern Med 1980;93:391–398.

160- Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019; 53: 1801913.

161- Raghu G, Amatto VC, Behr J, et al. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. Eur Respir J 2015; 46: 1113–1130.

162- Castria D, Refini RM, Bargagli E, et al. Pulmonary hypertension in idiopathic pulmonary fibrosis: prevalence and clinical progress. Int J Immunopathol Pharmacol 2012; 25: 681–689.

163- Nadrous HF, Pellikka PA, Krowka MJ, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Chest 2005; 128: 2393–2399.

164- Caminati A, Lonati C, Cassandro R, Elia D, Pelosi G, Torre O, Zompatori M, Uslenghi E, Harari S.Comorbidities in idiopathic pulmonary fibrosis: an underestimated issue.Eur Respir Rev. 2019 Oct 1;28(153). pii: 190044. doi: 10.1183/16000617.0044-2019.

165- Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015; 46: 903–975.

166- Han MK, Bach DS, Hagan PG, et al. Sildenafil preserves exercise capacity in patients with idiopathic pulmonary fibrosis and right-sided ventricular dysfunction. Chest 2013; 143: 1699–1708.

167- Raghu G, Freudenberger TD, Yang S, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. Eur Respir J 2006; 27: 136–142.

168- Kahrilas IJ, Kahrilas PJ.Reflux Disease and Idiopathic Lung Fibrosis: Association Does Not Imply Causation.Chest. 2019 Jan;155(1):5-6. doi: 10.1016/j.chest.2018.08.1062.

169- Collard HR, Ward AJ, Lanes S, et al. Burden of illness in idiopathic pulmonary fibrosis. J Med Econ 2012; 15: 829–835.

170- Noth I, Anstrom KJ, Calvert SB, et al. A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2012; 186: 88–95.

171- Tomassetti S, Ruy JH, Gurioli C, et al. The effect of anticoagulant therapy for idiopathic pulmonary fibrosis in real life practice. Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 121–127.

172- Ozawa Y, Suda T, Naito T, et al. Cumulative incidence of and predictive factors for lung cancer in IPF. Respirology 2009; 14: 723–728.

173- Tzouvelekis A, Gomatou G, Bouros E, et al. Common pathogenic mechanisms between idiopathic pulmonary fibrosis and lung cancer. Chest 2019; 156: 383–391.

174- Watanabe A, Higami T, Ohori S, et al. Is lung cancer resection indicated in patients with idiopathic pulmonary fibrosis? J Thorac Cardiovasc Surg 2008; 136: 1357–1363.

175- Suzuki H, Sekine Y, Yoshida S, Suzuki M, Shibuya K, Yonemori Y, Hiroshima K, Nakatani Y, Mizuno S, Takiguchi Y, Yoshino I.Risk of acute exacerbation of interstitial pneumonia after pulmonary resection for lung cancer in patients with idiopathic pulmonary fibrosis based on preoperative high-resolution computed tomography.Surg Today. 2011 Jul;41(7):914-21. doi: 10.1007/s00595-010-4384-z.

176- National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365: 395–409

177- Kenmotsu H, Naito T, Kimura M, et al. The risk of cytotoxic chemotherapy-related exacerbation of interstitial lung disease with lung cancer. J Thorac Oncol 2011; 6: 1242–1246.

178- Mediavilla-Varela M, Boateng K, Noyes D, et al. The anti-fibrotic agent pirfenidone synergizes with cisplatin in killing tumor cells and cancer-associated fibroblasts. BMC Cancer 2016; 16: 176.

179- Miura Y, Saito T, Tanaka T, et al. Reduced incidence of lung cancer in patients with lung cancer treated with pirfenidone. Respir Invest 2018; 56: 72–79.

180- Calado R, Young N. Telomeres in disease. F1000 Med Rep 2012; 4: 8.

181- Kurashima K, Takayanagi N, Tsuchiya N, et al. The effect of emphysema on lung function and survival in patients with idiopathic pulmonary fibrosis. Respirology 2010; 15: 843–848.

182- Lin H, Jiang S.Combined pulmonary fibrosis and emphysema (CPFE): an entity different from emphysema or pulmonary fibrosis alone.J Thorac Dis. 2015 Apr;7(4):767-79. doi: 10.3978/j.issn.2072-1439.2015.04.17.

183- Hubbard RB, Smith C, Le Jeune I, et al. The association between idiopathic pulmonary fibrosis and vascular disease: a population-based study. Am J Respir Crit Care Med 2008; 178: 1257–1261.

184- Nathan SD, Basavaraj A, Reichner C, Shlobin OA, Ahmad S, Kiernan J, Burton N, Barnett SD.Prevalence and impact of coronary artery disease in idiopathic pulmonary fibrosis.Respir Med. 2010 Jul;104(7):1035-41. doi: 10.1016/j.rmed.2010.02.008.

185- Heinzer RC, Stanchina ML, Malhotra A, et al. Lung volume and continuous positive airway pressure requirements in obstructive sleep apnea. Am J Respir Crit Care Med 2005; 172: 114–117.

186- Mermigkis C, Chapman J, Golish J, et al. Sleep-related breathing disorders in patients with idiopathic pulmonary fibrosis. Lung 2007; 185: 173–178.

187- Raghu G. The role of gastroesophageal reflux in idiopathic pulmonary fibrosis. Am J Med 2003; 115: 60–64.

188- Thomas Gille, Morgane Didier, Marouane Boubaya, Loris Moya, Angela Sutton, Zohra Carton, Fanny Baran-Marszak, Danielle Sadoun-Danino, Dominique Israël-Biet, Vincent Cottin, Frederic Gagnadoux, Bruno Crestani, Marie-Pia d'Ortho, Pierre-Yves Brillet, Dominique Valeyre, Hilario Nunes, Carole Planès. Obstructive sleep apnoea and related comorbidities in incident idiopathic pulmonary fibrosis. European Respiratory Journal 2017 49: 1601934; DOI: 10.1183/13993003.01934-2016

189- Mermigkis C, Bouloukaki I, Antoniou K, et al. Obstructive sleep apnea should be treated in patients with idiopathic pulmonary fibrosis. Sleep Breath 2015; 19: 385–391.

190- Selman M1, King TE, Pardo A; American Thoracic Society; European Respiratory Society; American College of Chest Physicians.Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy.Ann Intern Med. 2001 Jan 16;134(2):136-51.

191- Rosas IO, Ren P, Avila NA, Chow CK, Franks TJ, Travis WD, McCoy JP Jr, May RM, Wu HP, Nguyen DM, et al. Early interstitial lung disease in familial pulmonary fibrosis. Am J Respir Crit Care Med 2007;176:698–705.

192- King TE Jr, Tooze JA, Schwarz MI, Brown K, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis. Scoring system and survival model. Am J Respir Crit Care Med 2001;164:1171–1181.

193- Selman M, Carrillo G, Estrada A, Mejia M, Becerril C, Cisneros J, Gaxiola M, Perez-Padilla R, Navarro C, Richards T, et al. Accelerated variant of idiopathic pulmonary fibrosis: clinical behavior and gene expression pattern. PLoS ONE 2007;2:e482.

194- Ley B, Collard HR, King TE Jr.Clinical course and prediction of survival in idiopathic pulmonary fibrosis.Am J Respir Crit Care Med. 2011 Feb 15;183(4):431-40. doi: 10.1164/rccm.201006-0894CI.

195- Shaney LB, Andrew C, Conal H, Nazia C. Idiopathic Pulmonary Fibrosis (IPF): An Overview. J Clin Med. 2018 Aug; 7(8): 201.

12.BIOGRAPHY

I was born 16.12.1994 in Zagreb. I attended elementary school in the Šestine Elementary School and high school at VI Gymnasium of Zagreb. I was enrolled in the Split School of Medicine in 2013, I subsequently transferred to the Zagreb School of medicine in 2016. I am fluent in English and Croatian and have a basic knowledge of German. My interests include theology and philosophy which I study in my spare time. Concerning my further medical bearing I am interested in the field of family medicine.