EU-PFF
EUROPEAN PULMONARY FIBROSIS FEDERATION

THE EU-PFF CONSULTATION GUIDE

A guide to **treating** fibrotic ILDs

1 INFORMATION ABOUT FIBROTIC ILDS (fILDs)[1]

Interstitial lung diseases (ILDs) encompass a large number of conditions, with a wide range of causes, clinical manifestations, and imaging and pathological features in the lung interstitium, as well as variable outcomes.

EPIDEMIOLOGY

Idiopathic pulmonary fibrosis (IPF) is the most common fILD. It occurs more commonly in men than in women and in people older than 60 years of age. IPF is a chronic and irreversible disease, usually progressing to respiratory failure and death, with a median interval between diagnosis and death of 3 years. In contrast to IPF, other fILDs are characterised by a younger median age at presentation of 20–60 years and a more balanced sex ratio.

Overall prevalence of fILD is estimated to be up to 76.0 cases per 100,000 people in Europe. Sarcoidosis, connective-tissue disease (CTD)–associated ILDs, and IPF are the most common fILDs, with an estimated prevalence of 30.2, 12.1, and 8.2 cases per 100,000, respectively. Among all patients with fILDs other than IPF, 13 to 40 % have a progressive fibrosing phenotype, representing up to 20 patients per 100,000 people.

PATHOPHYSIOLOGY OF FIBROTIC ILDS[2]

Despite the heterogeneity of this group of diseases, in most of them, the pulmonary alveolar walls are infiltrated by various combinations of inflammatory cells, fibrosis, and proliferation of certain cells that make up the normal alveolar wall. The formation of fibrosis is an essential response of the body against pathogens and in normal wound healing.

In fILD, various and often disease-specific triggers set off exaggerated cascades of inflammatory and fibrotic responses, leading to downstream fibrotic tissue remodeling and extracellular-matrix deposition which in turn perpetuate fibrosis formation.

Much is still unknown about the pathophysiology of specific disease entities and the factors that differentiate normal wound repair from progression to fibrosis. Although triggers, susceptibility, and initial inflammatory responses vary among diseases, the current assumption is that in later phases, common mechanisms play a role.

76 cases per **100,000** people

median interval between diagnosis & death **3yrs**

more common in **men**

WHAT ARE THE SYMPTOMS?

The symptoms of fILD develop over time and can vary from person to person. The most common symptoms of fILD are **dyspnoea** along with the following:

- **dry chronic cough**
- **loss of appetite**
- **gradual, unexplained weight loss**
- **fatigue, tiredness and generally feeling unwell**
- **thorax pain**
- **aching joints and muscles**

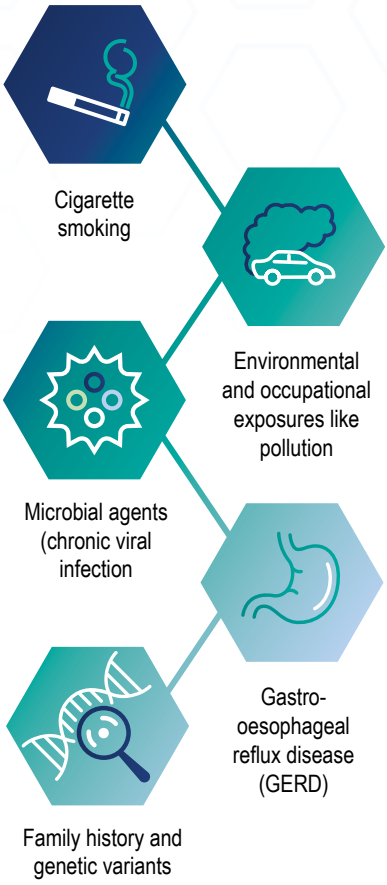
At physical examination, **"velcro-like" crackles** in the lungs of a patient with lung fibrosis may be heard and about half of patients with fILD may also experience **finger clubbing**. Although other sounds can also be heard, depending on the form of fibrosis, for instance so-called squeaks in fibrotic hypersensitivity pneumonitis.

[1] *The term* **fibrotic ILD (fILD)** *will hereinafter be used synonymously with fibrosing ILDs as well as* **Pulmonary Fibrosis (PF)**.

[2] *Wijsenbeek M, Cottin V. Spectrum of Fibrotic Lung Diseases. N Engl J Med. 2020 Sep 3;383(10):958-968. doi: 10.1056/NEJMra2005230. PMID: 32877584.*

WHAT ARE THE PREDISPOSING FACTORS?

We don't know exactly what causes people to develop fILD. However, there are several recognized risk factors for developing fILD. They include:



2 HOW ARE fILDs DIAGNOSED?

The key symptoms of fILD, exertional breathlessness and coughing, are like those of other, more common chronic lung diseases.

Unfortunately, this means that diagnosis is often delayed and misdiagnosis occurs frequently. The average time to diagnosis with fILD is 7–8 months, with 40% of patients taking over a year. To avoid this delay, patients with suspected fILD should be referred to ILD specialist centres. If a patient is suspected of having fILD, a multidisciplinary team to confirm diagnosis should at least include an expert pulmonologist, a radiologist, a pathologist and ideally a specialist nurse. Attendance of other disciplines, such as a rheumatologist, an occupational physician or a geneticist, may be of additional help.

As a first step, the pulmonologist will – most likely – conduct the following diagnostic tests to confirm the diagnosis and/or refer the patient to a centre with expertise in fILD:

PULMONARY FUNCTION TESTING (PFT):

The most common type of PFT is spirometry, used to obtain lung volumes (FVC= forced vital capacity, TLC= total lung capacity) and lung diffusing capacity (DLCO). Blood gas analysis may still be normal at rest, but can be significantly reduced under exercise, indicating a need for supplemental oxygen. To this aim, the six-minute walk test is widely used to measure the clinical status and has been demonstrated to be independently associated with the risk of mortality in patients with IPF.

CHEST X-RAY:

Not suitable for determining if a patient has fILD. As 5-15% (IPF) of patients with significant scarring will still have a normal chest X-ray, patients with a suspected fILD should be referred directly to a HRCT.

BLOOD TESTS:

The detection of specific autoantibodies serves a critical role in the diagnosis of other known causes of ILD such as connective tissue disease (CTD) and also carries value predicting outcomes and guiding pharmacological management (=serologic testing in CTD).

SURGICAL LUNG BIOPSY:

Is usually performed in a minimally surgical fashion (video assisted thoracic surgery, VATS), resulting in shorter recovery times and hospital stay as compared to the previously done open surgery. Biopsies obtained during VATS are still regarded as gold standard for diagnosis of fILD, and surgical lung biopsy will be considered if the preceding diagnostic work-up including HRCT and bronchoscopy did not yield a safe and specific diagnosis. Although being safe in general, there is a small, but measurable risk of developing an exacerbation and significant clinical deterioration.

BRONCHOSCOPY FOR TRANS-BRONCHIAL BIOPSY AND CRYOBIOPSY:

A small, flexible tube called bronchoscope is inserted through a patient's nose or mouth under local or general anaesthesia. There are risks associated with a bronchoscopy and – even more – when conducting a biopsy during bronchoscopy, and these include infection, bleeding and pneumothorax, an accumulation of air in the pleural space. However, the overall tolerability and safety of bronchoscopy or cryobiopsy, i.e. a biopsy through immediate freezing of the lung tissue, with biopsy seems to be better as compared to surgical lung biopsy, which is why this investigation is preferred as a first invasive procedure.

HIGH-RESOLUTION COMPUTED TOMOGRAPHY (HRCT):

A High-Resolution Computed Tomography scan is the most important imaging study used to diagnose fILD. High resolution means that image slices are thin, generally under 2 millimetres. In half of all cases, a HRCT is enough to confirm a diagnosis of fILD, and no lung biopsy is necessary.

BRONCHOALVEOLAR LAVAGE (BAL):

A minimally invasive procedure, essentially a bronchoscopy with instillation and recovery of a small amount of fluid, that can be very helpful to exclude or confirm other interstitial lung diseases by counting cell populations through optic microscopy or by applying specific staining.

GENETIC COUNSELLING:

Genetic counselling could be useful for patients with a family history of lung fibrosis. In case it is decided to do further genetic testing, blood tests will be done.

3 WHAT TREATMENTS ARE AVAILABLE FOR fILDs?

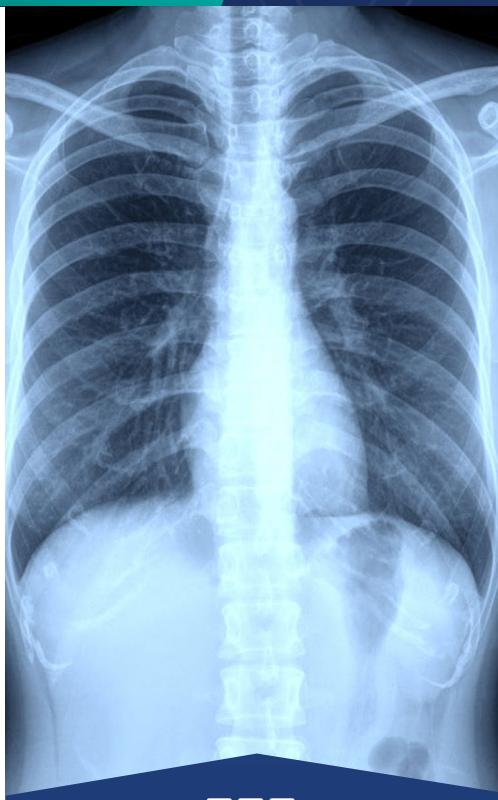
To manage fILD, both pharmacological and non pharmacological treatments are recommended. Furthermore, regular check-ups and medical examinations are advisable.

As soon as a patient is diagnosed with fILD, they should be offered psychological support and be provided with information on patient organisations.

A PHARMACOLOGICAL TREATMENTS

Decisions about pharmacological treatment are guided by the underlying diagnosis and the disease course. For persons with IPF, treatment with antifibrotic drugs (Pirfenidone or Nintedanib) is now recommended to slow down disease progression.

In the majority of persons affected with fILD other than IPF, immunomodulation (glucocorticoids, immunosuppressive therapy, or both) is generally used as first-line therapy if an inflammation-driven disease is suspected. In those who develop disease progression despite appropriate first-line therapy, antifibrotic therapy such as Nintedanib is now approved as an effective treatment. The appropriate timing and sequence of these treatments remain to be elucidated.



Clinical trials

You can find information on on-going clinical trials using **ClinicalTrials.gov** (worldwide), the **EU-PFF clinical trial finder** or the **EU Clinical Trials Register**.

Some **30%** of lung transplants are performed on patients with fILD

Only **5%** of all patients with fILD qualify for a lung transplant

B NON-PHARMACOLOGICAL TREATMENTS

While a lung transplant is the only effective cure for someone with fILD, there are several non-pharmacological treatments which can help improve patients' quality of life:

Pulmonary rehabilitation

Pulmonary rehabilitation improves functional exercise capacity, dyspnoea and quality of life in the short term, with benefits also probable in fILD. Although short-term benefits of pulmonary rehabilitation are well documented, the longevity of those benefits remains unclear. The challenge of sustaining long-term behaviour change for exercise is likely a contributor. Patients with less severe disease (e.g., higher FVC) are more likely to maintain benefits at 6 months after program completion, reinforcing the need for early referral of people with fibrotic ILD.[3]

Oxygen therapy

Patients may experience hypoxemia while resting, sleeping or exercising. To deal with the effects of hypoxemia, they may be given extra oxygen through a concentrator (home-based or mobile), oxygen cylinders (portable or on wheels) or liquid oxygen.

Lung transplantation

Lung transplantation is the only surgical intervention procedure which can reverse the progression of fILD, improve quality of life and life expectancy. Some 30% of lung transplants worldwide are performed on patients with fILD. Unfortunately, only 5% of all patients with fILD qualify for a lung transplant, since the criteria for selection as a viable transplant candidate are quite strict. These consider a range of factors such as a patient's age, general health, comorbidities, severity and progression of fILD. In case of lung transplantation, timely referral to a transplant center is crucial as the procedure takes time.

Post-transplant treatment

After lung transplantation, patients must take antimicrobial, antifungal, and antiviral medications in the initial phase and additional immunosuppressive medications for the rest of their lives.

[3] *Dowman L, Hill CJ, May A, Holland AE. Pulmonary rehabilitation for interstitial lung disease. Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD006322. DOI: 10.1002/14651858.CD006322.pub4.*

Palliative and end-of-life care

The majority of patients with chronic fILD have poor access to a specialist in palliative medicine. That is due to several barriers such as a misunderstanding by patients and providers of its purpose and a lack of ability to integrate into other modalities of care.

Non-pharmacological therapies might include relationship building, bed-adjustments, noninvasive ventilation, high-flow oxygen via nasal cannula and pulmonary rehabilitation, whereas **pharmacological therapies** include oxygen, anxiolytics, opioids and antidepressants.

Palliative care consultation may improve communication among patients, caregivers and providers regarding treatments, prognosis, and end of life planning.[4]

Learning to manage breathlessness and cough

Palliative care is focused on symptom management and can help patients to manage episodes of breathlessness and cough. It is very important that patients learn how to minimise, cope and manage breathlessness as it can make a big difference to their quality of life. Emotions can affect breathing and being anxious about breathlessness can make patients‘ breathing even worse. Being able to handle cough plays an important role in managing fILD as it can make patients feel isolated and embarrassed.

Relaxation can help to reduce breathlessness and it is useful for relieving anxiety

Palliative care addresses symptoms like dyspnea, intractable cough, depression, anxiety and pain which are commonly experienced by patients with fILD.

[4] *Wijsenbeek MS, Holland AE, Swigris JJ, Renzoni EA. Comprehensive Supportive Care for Patients with Fibrosing Interstitial Lung Disease. Am J Respir Crit Care Med. 2019 Jul 15;200(2):152-159. doi: 10.1164/rccm.201903-0614PP. PMID: 31051080.*

DISEASE COURSE AND PROGRESSION 4

Progression is disease-specific, varies from person to person and is reflected in a decline in lung function, worsening of symptoms and deterioration in health-related quality of life. It is impossible to predict exactly how rapidly fILD will progress for an individual.

Many people with fILD experience a slow, but steady worsening of their disease. If fILD is progressing slowly, patients could have the symptoms for a long time before being diagnosed, and then the disease might still progress relatively slowly. While IPF is almost always progressive, in other forms of fILD similar progression is seen in about one third of patients.[5]

Some patients may experience unpredictable acute worsening of their disease, called acute exacerbations, which can happen at any time. An event like this may be fatal or may leave a patient with substantially worsened disease. Sometimes a person is not diagnosed with fILD until their first acute exacerbation. The main risk factor for acute exacerbation of fILD is advanced disease.

Other conditions patients with fILD might have (comorbidities)

FILD can be a debilitating condition as on top of the adverse effects of fILD, most fILD patients have other associated conditions (comorbidities). They can have a negative effect on quality of life and prognosis. This is why doctors also need to identify and treat any comorbidities patients may develop. These conditions can affect the lungs (pulmonary comorbidities like lung cancer and emphysema) or other parts of the body (non-pulmonary comorbidities like gastro-oesophageal reflux disease and cardiovascular diseases).

The danger of an acute exacerbation makes regular monitoring by professionals essential so they can track how the disease is progressing and see how a patient is responding to treatment.

[5] George PM, Spagnolo P, Kreuter M, et al. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. Lancet Respir Med 2020; 8: 925–34; Wijsenbeek M, Kreuter M, Olson A et al. Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management. Curr Med Res Opin. 2019; 35: 2015-2024

5 CENTRES OF EXPERTISE FOR INTERSTITIAL LUNG DISEASES

Centres of Expertise (CEs) are expert centres for the management and care of rare disease (RD) patients. ILD/PF centres of expertise specialise in ILDs. They aim to provide patients with ILD/PF (among others) with the highest standards of care and to deliver timely diagnosis, appropriate treatments and follow up. They also contribute to research and collaborate with different stakeholders, including patient organisations.

What is more, the European Commission has organised European Reference Networks (ERNs), aimed at tackling complex or rare diseases and conditions that require highly specialised treatment and resources. They unite several CEs and provide expert opinions, advice and referral for cross-border care when appropriate.

An ERN on respiratory diseases including fILDs was launched in March 2017: the ERN-LUNG. The ERN-LUNG (find more information **here**) is made up of many European Expert Centres (**see here**), but not all. We strongly recommend that you ask your local patient group or GP about your nearest nationally recognised centre.

HOW CAN PEOPLE AFFECTED TAKE CARE OF THEMSELVES?

6

FILD is a highly complex condition which needs to be managed along with its symptoms and it is essential that patients manage some parts of the condition themselves. This allows them to control their care, set realistic goals and prepare for their future.

A doctor should advise patients on how to deal with the challenges associated with their condition, but there are lifestyle changes that can improve their quality of life. Giving up smoking or avoiding exposure to second-hand smoke can increase oxygen levels in the blood, lower blood pressure and heart rate and reduce the risk of cancer and heart diseases.

Patients need to work closely with their care team to take an active and positive role in their treatment pathway and outcomes.

Stay active

Regular, moderate exercise not only helps maintain a healthy weight, but also strengthens the muscles and keeps the body working efficiently. This can include guided exercise with a physiotherapist, but also exercising independently. Daily activity should be adapted to the patient's performance status and lung function. For patients with respiratory failure receiving supplemental oxygen, physical exertion should be minimal.

Eat healthily

A balanced, nutritious diet is usually recommended. In patients taking antifibrotic drugs, different side effects related to the gastrointestinal tract, such as diarrhea, nausea, bloating, decreased appetite and weight loss which is associated with worse outcomes of fILD, may occur. In such a situation, changing the diet may be crucial, e.g. avoiding raw vegetables or diary products. In addition, diet adjustments may be advised depending on treatment (e.g., risk of diarrhea with Nintedanib).

Get plenty of rest

Sleep is essential for boosting the immune system and improving the overall sense of well-being. What is more, the risk of obstructive sleep apnea is increased in IPF, even in the absence of obesity.

Stay up to date with vaccinations

It is especially important that patients stay up to date with influenza, pneumonia, pneumococcus and Covid-19 vaccines. They should also avoid exposure to infections as they can make fILD worse. Patients taking immunosuppressants should keep their herpes zoster virus vaccinations up to date.

Avoid stress

Being physically and emotionally relaxed may help patients to avoid excessive oxygen consumption. Relaxation techniques can also teach patients to manage the panic that can occur with shortness of breath.

Relaxation and mindfulness

There are different relaxation techniques that can help patients cope with the emotional and psychological challenges that may come with the fILD diagnosis. Mindfulness can help manage the physical and lifestyle challenges of living with fILD and to calm patients when they are distressed, discouraged, scared, or in pain.

Yoga and similar activities

Yoga or other activities, for example Pilates, Tai Chi or Qi Gong, are beneficial for patients with fILD as they can stimulate the lungs through focused breathing and also train the diaphragm. Simple breathing exercises can improve lung function and relieve breathing problems.

7 PSYCHOLOGICAL SUPPORT AND PEER SUPPORT

Psychological support can help patients accept the treatment and the drug's side effects as well. In an advanced stage, it can help them in end-of-life planning and choosing hospice care or the comfort of their home. It is important for patients to involve friends and family members in the psychological support programme as they can help manage the condition.

Whenever possible and desired, doctors should refer patients to a psychologist.

8 REFER PATIENTS TO PATIENT ORGANISATIONS AND/OR PATIENT SUPPORT GROUPS

Finding out as much as possible about fILD can help patients feel more in control. Patient organisations are a good place to start as they provide information dedicated to people living with fILD. Joining a local support group can be helpful for patients, as they can meet other patients and discuss and share their experiences.

Support from family and friends is essential, but reaching out to fellow patients going through the same experience can be particularly beneficial. Whenever possible and desired, doctors should refer patients to a support group or a patient organisation.

A list of patient organisations can be found on the EU-PFF **website.**

This booklet is kindly sponsored by

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