Current approach to idiopathic pulmonary fibrosis and considerations on diagnostic and treatment advances in Romania

Abstract
Idiopathic pulmonary fibrosis, a chronic, progressive and irreversible fibro-proliferative condition of unknown origin, exclusively affecting the lungs, is eliciting a growing interest in the past decade due to its increasing annual incidence and to the recent advances in developing precise diagnostic tools and in obtaining new specific anti-fibrosis therapies. Moreover, these diagnostic and treatment advances are available in Romania, starting with 2017. This review article summarizes the most important aspects of approaching patients with idiopathic pulmonary fibrosis regarding known risk factors, disease pathogenesis, diagnostic and treatment in general terms. In the same time, more thorough consideration is given to diagnostic controversies, overview of existing clinical practice guideline recommendations and to management principles shared in the literature. Finally, current recommended therapeutic approach for Romanian patients is revised, with highlights on treatment enrollment and on treatment monitoring criteria.

Keywords: idiopathic pulmonary fibrosis, interstitial pneumonia, high resolution computed tomography, fibroblast foci, anti-fibrotic therapy

Rezumat
Fibroza pulmonară idiopatică este o boală fibroproliferativă cronicană, progresivă și irreversible, cu etiologie necunoscută, ce afectează exclusiv plămânii. În ultimul deceniu s-a constatat un interes crescut pentru această boală, în urma incidenței în creștere, a progreselor recente în definirea instrumentelor de diagnostic și a apariției noilor terapii antifibrotice. Mai mult, aceste noi instrumente de diagnostic și tratament au devenit disponibile și în România începând cu anul 2017. Această sinteză sumarizează cele mai importante aspecte ale abordului pacienților cu fibroză pulmonară idiopatică, precum factorii de risc cunoscuți, patogenia bolii și liniiile generale ale diagnosticului și tratamentului acestei boli. O atenție specială este acordată controverselor diagnosticului; totodată, se trec în revistă ghidurile de practică actuale și principiile de tratament descrise și în literatură. Nu în ultimul rând, sunt prezentate și recomandările curente de tratament în România, cu accentuare critériilor de includere și de monitorizare a tratamentului.

Cuvinte-cheie: fibroza pulmonară idiopatică, pneumonie interstțială, tomografie computerizată de înaltă rezoluție, focare fibroblastice, tratament antifibrotic

Disease definition and general context
Idiopathic pulmonary fibrosis (IPF) is a rare and severe disease that belongs to the vast group of interstitial lung diseases (ILD), generally described as acute and chronic bilateral parenchyma infiltrative lung diseases, with variable degrees of tissue inflammation and fibrosis, when they occur in immune-competent hosts without infection or neoplasm(1). They are usually manifested by exertional dyspnea, pulmonary infiltrates, both lung function and gas transfer abnormalities, with inflammatory and immune cell accumulation in the interstitial and distal airways areas. The ILDs tend to evolve over months to years, and include disorders of both known and unknown origins.

Among the ILDs with known causes or associations, there are pneumoconiosis, ILD associated with connective tissue disease (CTD-ILD), and hypersensitivity pneumonitis (HP). Among the ILDs of unknown cause, there are sarcoidosis and idiopathic interstitial pneumonias (IIP), a far-reaching heterogeneous group of ILDs of unknown etiology, that includes idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), respiratory bronchiolitis with interstitial lung disease (RBILD), acute interstitial pneumonia (AIP), cryptogenic organizing pneumonia (COP), and lymphoid interstitial pneumonia (LIP)(2).
IPF occurs frequently in men, ex-smokers, aged 45–65 and over 65. It only affects the lungs and unlike other interstitial idiopathic pneumonias, it has a radiological and histopathological pattern of usual interstitial pneumonia (UIP)\(^{(10)}\).

**Epidemiology and risk factors**

Overall, the annual incidence of IPF is increasing and especially increases with age (4.6 and 16.3 per 100 000 people), the prevalence being 13 to 20 cases per 100 000\(^{(13-16)}\). Despite its clinical relevant picture, few data are available about IPF’s prevalence, probably due to the numerous challenges in both recruiting patients for large scale epidemiological studies and in harmonizing criteria for diagnostic confirmation.

Data from Europe suggest IPF prevalence ranged from 1.25 to 23.4 cases per 100 000 population, while in the US, a higher prevalence was reported\(^{(7)}\): 14-27.9/100 000 population (by narrow case definition) to 42.7-63 per 100 000 population (by broad case definition).

The overall prevalence of IPF estimated in 2006 by Raghu et al.\(^{(8)}\) was 14 and 42.7 per 100 000 person-years using their narrow and broad case definition, respectively, while the prevalence estimated by Fernandez-Perez et al. in 2010\(^{(9)}\) was 27.9 and 63 per 100 000 person-years by their narrow and broad case definition criteria, respectively.

In Japan, only one study has been conducted to investigate the epidemiology of IPF\(^{(10)}\), and the obtained results imply that in 2008 the prevalence and incidence appears to be 10 and 2.2 per 100 000 person-years.

In a large population based survey, in Italy, based on healthcare administrative databases of Lombardy Healthcare System and on adopting three algorithms, such as generic case definition (GCD), broad case definition (BCD) and narrow case definition (NCD), Harari and colleagues identified IPF cases according to diagnoses reported in inpatient and outpatient claims occurred during 2000-2010. They reported the estimated mean annual incidence rate of IPF variable between 2.3 and 5.3 per 100 000 person-years, and the estimated prevalence rate varying between 12.6 and 35.5 per 100 000 person-years, depending on the case definition used to identify IPF patients\(^{(11)}\).

There is a predominance in men versus women (1/5 to 1/7.1)\(^{(16)}\). A complex contribution of both environmental and host factors is thought to contribute to the development of IPF, although the inciting factors remain elusive and the disease pathogenesis is incompletely understood\(^{(12-14)}\). Most frequently invoked environmental factors are tobacco smoking, chronic silent microaspiration\(^{(15)}\) and exposure to metal and wood dust. Family-related IPF and genetic transmission in 0.5-3.7%\(^{(10)}\) are also cited. Gene-expression signatures have indicated that, in the case of IPF, the most highly expressed are matrix metalloproteinase 7 (MMP7), MMP1 and MMP2\(^{(16)}\). Some intriguing reports imply that herpes virus and/or hepatitis C virus is implicated in the etiology of IPP\(^{(17)}\).

**Understanding the actual concept about IPF pathogenesis**

The pathogenesis of fibrosis is complex and poorly understood, and may be specific for different agents\(^{(18)}\). Initially considered an inflammatory condition, the pathogenesis of IPF has considerably advanced in the past ten years. Currently the inflammatory process is described as mild and consisting of a patchy interstitial infiltrate of lymphocytes and plasma cells\(^{(19,20)}\).

**Epithelial injury and activation: genetic and environmental interactions**

Cigarette smoking is an environmental factor that can determine epithelial injury and apoptosis, and there are more such factors, also chronic microaspiration\(^{(21)}\).

Alterations in unfolded protein response occur in some familial cases of pulmonary fibrosis that have mutations in surfactant protein C, a hydrophobic protein expressed exclusively by AEC type II (AEC II)\(^{(22)}\). Short-deletion mutations of this protein result in epithelial cell injury. Familial interstitial pneumonia and sporadic IPF have been associated with a common polymorphism in the promoter region of mucin 5B gene (MUC5B)\(^{(23)}\).

In injured tissues, fibroblasts are activated and differentiate into myofibroblasts, which are specialized contractile cells with higher profibrotic potential than fibroblasts. The large extracellular matrix deposit (which causes the destruction of the lung structure) is caused by these cells, in the fibroblastic foci. The source of fibroblasts and myofibroblasts and the reasons why they organize in morphologically distinct foci in IPF are unclear. The source of pathological fibroblast foci could be the differentiation of resident fibroblast, transdifferentiation of epithelial cells into pathological fibroblast phenotypes and recruitment of circulating fibroblast precursor\(^{(24)}\).

Epithelial and mesenchymal markers in histological specimens obtained from patients with IPF are suggesting a role for epithelial to mesenchimal transition in pulmonary fibrosis, in a process similar to cell differentiation occurred during embryogenesis\(^{(25)}\).

In addition, an increased angiogenic activity was described, as such an imbalance between angiogenic chemokines (IL-8 and ENA-78) and angiostatic chemokines (IP-10) has been proposed to explain angiogenesis in the development of progressive pulmonary fibrosis\(^{(26)}\).

Depending on the disease progression pattern, different pathological findings are described. In a study aiming to define clinical and functional progress in 73 IPF patients, referred for a possible transplant indication, Balestro and colleagues have noted important differences in lung pathology among slow and rapid progressing patients, consisting mainly of the presence of an extensive degree of innate and adaptive immune inflammation in the rapid group, more prominent than in the slow one\(^{(27)}\).
Diagnostic approach

Typically, middle aged or elderly patients address for a disease limited to the lungs, with a radiological and histopathological picture resembling usual interstitial pneumonia (UIP). UIP pattern is defined by reticular opacities +/- traction bronchiectasis and honeycombing on the chest X-ray, plus histological aspects of patchy interstitial fibrosis alternating with areas of normal lung tissue/architectural distortions due to honeycombing/heterogeneity of fibrosis with scarring and fibroblastic foci30.

CLINICAL MANIFESTATIONS

In general, IPF patients accuse slowly (average, six months to two years) progressive dyspnea on exertion and dry cough. Slow onset of symptoms is causing a delayed diagnostic, and frequent confusion with cardiovascular dyspnea, COPD, tuberculosis or lung cancer is not uncommon28. In 90% of cases, gastroesophageal acid reflux is revealed, but symptomless. Other general symptoms, like fever, weight loss and diffuse joint pain, are rare and not specific29. End-inspiratory (“velcro-like”) crackles at chest auscultation and digital clubbing are common findings at physical exam.

Most patients describe such slow, progressive disease course, still some follow an alternative pattern with stable disease stages followed by episodic acute exacerbations or even a quick progressive route29.

Acute exacerbations

Worsening of dyspnea in the past 30 days, vital capacity or gas exchange deterioration and new pulmonary infiltrates detected at radiological exam describe an acute exacerbation of IPF, after careful exclusion of any other differential diagnosis like pulmonary embolism, pneumonia, acute heart failure, etc. A disease exacerbation can intervene in both onset and in the long run.

Coexisting conditions

Most encountered morbid associations in IPF are pulmonary hypertension in 32-84% of cases30, lung cancer, regarded as an independent risk factor for IPF, and pulmonary emphysema in 35% of IPF patients. In the early stages of IPF, the pulmonary pressure during exercise usually increases. Values between 23 and 28 mmHg are the normal values of the pulmonary artery pressure at rest. A pressure greater than 30 mmHg has a negative influence on the prognosis31.

The couple IPF – pulmonary emphysema has smoking as a common ground risk factor and appears like upper lobe emphysema and lower lobe fibrosis, with pronounced decrease of the diffusion capacity32.

Patients with IPF and arterial oxygen saturation of less than 90% have a higher chance of manifest sleep disorder31.

Facts for optimizing approach of patients with idiopathic pulmonary fibrosis

How can clinicians better understand IPF patients’ needs and how could they better help them?

Duck and colleagues approached this aspect by assessing IPF patients’ needs, experiences and perceptions and found that they face three major problems: “struggling to get a diagnosis”, “loss of the life I previously had” and “living with idiopathic pulmonary fibrosis”. That’s why these authors concluded on the urgent need to establish properly funded regional Idiopathic Pulmonary Fibrosis networks with experienced staff conducting multidisciplinary teams to secure a timely diagnosis and treatment opportunities for patients, but also to ease early access to specialists who can provide information about the disease, discuss prognosis realistically and support them till death33.

BASIC LABORATORY INVESTIGATIONS

Except non-specific inflammation markers, there are only few abnormal findings at blood test examination, such as polycythemia in advanced stages of the disease.

Spirometry shows restrictive respiratory dysfunction, due to reduced pulmonary compliance determined by parenchyma fibrosis, with decreased values of forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), while the ratio of FEV1/FVC is normal or increased.

Gas exchange at rest and during exercise. The diffusing capacity of the lung for carbon monoxide (DLCO) is reduced and may actually forego the reduction of lung volume. The reduction in the DLCO is probably caused both by a contraction of the pulmonary capillary volume and by ventilation and perfusion abnormalities. With exercise, the alveolar-arterial O2 gradient (AaPO2) widens, and the arterial O2 pressure (PaO2) and arterial O2 saturation (SaO2) fall. The most sensitive parameter that can be used for assessing the disease clinical progression has been shown to be the gas exchange during exercise31,34.

If cardiovascular comorbidities or pulmonary hypertension is not associated, the electrocardiogram generally is normal31.

IMAGISTIC INVESTIGATIONS

Chest radiography and high resolution computed tomography are the key exams to diagnose idiopathic pulmonary fibrosis. A standard chest X-ray may reveal interpretable abnormalities in 50-70% of the patients (see Figures 1a and 1b), while it can be normal in approximately 10%. Radiologic aspect of the lungs in IPF shows linear- reticular, bilateral opacities, predominant in the lower lobes, asymmetrically disposed. A honeycombing pattern (reticular lines juxtaposed between areas of focal round translucency) can be seen in advanced stages35.

The gold standard investigation to confirm an imagistic diagnosis of idiopathic pulmonary fibrosis is high resolution computed tomography (HRCT), which provides useful information about the transforming processes taking place in the parenchyma of the lung.

The HRCT picture in IPF consists of patchy, predominantly peripheral, predominantly subpleural and necessarily bibasilar reticular opacities (Figures 2a and 2b). Other findings may consist of: ground-glass infiltrates with various limited localizations, “traction bronchiec tasis” and honeycombing (defined on HRCT as strictly
The presence of traction bronchiectasis and thickened interlobular septae increases specificity for a diagnosis of IPF. Together, these findings constitute a radiographic pattern that is termed “confident” or “certain” IPF.

The usefulness of HRCT has been proved also to differentiate IPF pattern from other similar entities, such as heart failure (ground-glass), hypersensitivity pneumonitis (upper lobe and central distribution), granulomatous infection or lymphangitis (fine multiple nodules), sarcoidosis, lung infection or malignancy (hilar limphadenopathy), and pneumoconiosis, histiocytosis or rheumatoid nodules (upper lobes involvement).

**BRONCHOSCOPIC EXAMINATION**

A bronchoscopic examination will not reveal any macroscopic endobronchial signs specific for idiopathic

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**Figure 1.** Idiopathic pulmonary fibrosis reticular-nodular pattern predominant in the lower right lobe; a) Anterior-Posterior Chest X-ray; b) Lateral right Chest X-ray

**Figure 2a.** HRCT – (sub-carina level): Idiopathic pulmonary fibrosis: reticular pattern with typical peripheral distribution, irregular interlobular septal thickening, traction bronchiectasis, areas of honeycombing, centrilobular and paraseptal emphysema

**Figure 2b.** HRCT – Idiopathic pulmonary fibrosis (lower lung level): extensive and marked reticular opacities, traction bronchiectasis and honeycomb cysts
pulmonary fibrosis, but will prove very useful for excluding other diagnostics (cancer, sarcoidosis, pneumoconiosis, etc.) and to perform bronchoalveolar lavage (BAL) or transbronchial biopsy (TBB). Occasionally, suggestive aspects are found even in bronchial secretion samples (Figure 3).

Bronchoalveolar lavage is a safe, well tolerated procedure and it gained more and more acceptance as IPF diagnostic tool in the last two decades. Main BAL information useful in clinical practice refers to total cell count, type of cells, and lymphocytes subtyping.

It has been recognized that only about 30% of IPF patients can undergo a lung biopsy procedure, due to certain limitations for the performance of a surgical biopsy, such as in the case of: elderly patients with IPF, including severely impaired pulmonary function, acute exacerbations or significant comorbidities. So, from this perspective, BAL analysis represents a potential tool to plead for a diagnosis of interstitial lung disease, mostly in situations when lung biopsy cannot be performed.

In the case of patients with IPF, BAL shows an increase in polymorphonuclear leukocytes (PMNs), neutrophil products, eosinophils, eosinophil products, activated alveolar macrophages, alveolar macrophage products, cytokines, growth factors for fibroblasts and immune complexes.

In a study aiming to evaluate the diagnostic contribution of BAL cell differentials in patients with clinical-radiological suspected IPF, Ohshimo and colleagues showed that a cut-off level of 30% for lymphocytes in BAL demonstrated a favorable discriminative power for the diagnosis of IPF and that the absence of a lymphocytosis is consistent with the diagnosis of IPF.

The American Thoracic Society Clinical Practice Guideline recommends a differential cell count to be performed on the BAL fluid. This includes lymphocyte, neutrophil, eosinophil and mast cell counts. The remaining sample may be used for microbes, viruses and/or malignant cell cytology laboratory testing, if clinically indicated.

Transbronchial biopsy
Using TBB does not confirm UIP, although it is abnormal in many cases. Also, these exams should not be used to evaluate the degree of fibrosis or inflammation, because the sample prelevated is small in size (2 to 5 mm). TBB can be used to identify a specific diagnosis other than UIP (malignancy, infections, sarcoidosis, hypersensitivity pneumonitis, etc.).

In diffuse parenchyma lung disease, histological support for a specific diagnosis can be obtained using TBB in 29-79% of cases only, in majority UIP and IPF. A study by Votava et al. reveals that in two out of every three cases (67%), surgical lung biopsy (SLB) may change the diagnosis reached by TBB.

Histological diagnosis (surgical lung biopsy)
Lung biopsy, considered the gold standard for the diagnosis of diffuse lung disease, was conducted in about 30-60% of the cases, included in large clinical trials performed in the last decade. The biopsy should be performed from minimum two lobes, since there is a great histological variability.

The IPF histopathological pattern is known as usual interstitial pneumonia (UIP) that combines normal lung architecture with patchy areas of histological apparent pulmonary parenchyma fibrosis, with a scar appearance. Fibrosis takes the form of alveolar septal thickening with marked involvement of the subpleural regions; also, hypertrophy of the smooth muscle is described (Figure 4).

In the most severely affected areas, the lung exhibits complete distortion of normal architecture, with sheets of dense collagen replacing normal tissue and occasional cystic structures (Figure 5).
At a closer inspection, minute foci of immature fibroblastic proliferation are detected at the edge of dense fibrosis in the place where this interacts with normal lung tissue (Figure 6).

The number of fibroblast foci in surgical lung biopsy has been shown to correlate with survival in several studies(44).

DIAGNOSTIC CONTROVERSIES AND THE NEED FOR A MULTIDISCIPLINARY DIAGNOSTIC APPROACH

There are many difficulties in confirming an IPF diagnosis, as required by the gold standard criteria. The interpretation of the HRCT may rise different positions in front of a radiological pattern suggestive for both IPF and non-IPF lesions, and literature describes an interobserver agreement of 80% amongst radiologists (45). But the most sensitive question is related to histopathology confirmation, for which there is a much lower interobserver agreement between pathologists, of only 50% (46). The main controversy is related to the distinction between the NSIP (homogenously thickened interstitial spaces that contain accumulated fibrosis and inflammation) and UIP aspect. Evidence showed that UIP and NSIP are different ends of a spectrum resulting from the same disease, or even that NSIP may represent an early stage of IPF (47). It has been shown, in one study, that 26% of patients with IPF had in one lobe NSIP pathology, while in a sample from another lobe they were exhibiting UIP (48).

To establish the diagnosis of IPF, a multidisciplinary team (a chest physician, pathologist and radiologist) should be formed, because the appearance of UIP pattern in lung biopsies alone is insufficient and the differentiation from other interstitial pneumonias is difficult (49).

Differential diagnosis of IPF

The differential diagnosis of IPF includes other idiopathic interstitial pneumonias. HRCT is useful for excluding diseases with predominantly ground-glass opacities or nodular patterns. Nonspecific interstitial pneumonia (NSIP) will always remain in the differential and, in some cases, can only be excluded by biopsy (24).

Connective tissue diseases such as systemic sclerosis, polymyositis or rheumatoid arthritis can mimic IPF, both clinically and radiologically (24,50).

Some undifferentiated connective tissue diseases can resemble IPF, being defined by one or more symptoms (Raynaud’s syndrome, proximal muscle weakness or sicca-like symptoms) linked with systemic inflammation (antinuclear and other specific autoantibodies) (51).

Chronic hypersensitivity pneumonitis (52) and other environmental (sometimes occupational) exposures can also be difficult to differentiate. The clinical history can serve to discriminate this condition. Through the initial assessment of IPF, consideration should be given to previous exposure to asbestos, grain dust or mold, also to any history of radiation pneumonitis, drug toxicities (e.g., amiodarone, bleomycin, methotrexate, nitrofurantoin) or congenital disorders (e.g., dyskeratosis congenita) (24).

Some prognostic landmarks

Early studies looking at the prognosis of IPF showed that some factors such as age, male gender, considerable dyspnea, advanced fibrosis and inadequate response to therapy could predict a shortened survival (53).

To predict the survival in IPF patients, some investigators came to the conclusion that FVC can be used for this purpose. A 10% FVC drop after 6 or 12 months showed a poor prognosis, and was more precise than predictions using baseline physiologic parameters (54).

Honeycombing predicted the worst survival in patients with biopsy-confirmed IPF undergoing a three years HRCT follow-up (55).

Treatment of idiopathic pulmonary fibrosis

Since idiopathic pulmonary fibrosis has been recognized as an independent disease, there have been numerous approaches of the treatment, aiming to improve symptoms and survival, by addressing either inflammation, at first supposed to cause this disease, or fibrosis...
progression, afterwards, as progress in understanding pathogenesis has been made.

So, at the time of ATS-ERS consensus in 2000, the standard care for IPF was considered to be corticosteroids (prednisone starting at 0.5 mg/kg and tapered to a maintenance level of 0.125 mg/kg), combined with a cytotoxic agent (either azathioprine, or cyclophosphamide; the dose targeted to 2-3 mg/kg) for carefully selected IPF patients. More complex regimens were recommended as well, like corticosteroid + two immunosuppressive therapies (azathioprine, cyclophosphamide or methotrexate) + N-acetylcysteine. Combination therapy was suggested for a period of at least six months, with clinical and physiological response used to guide further management.

Nonetheless, later the PANTHER study, comparing the triple therapy with placebo and N-acetylcysteine alone, had to be stopped early because of the higher mortality and hospital admissions in the triple therapy arm compared to placebo. Current guidelines recommend against the use of immunosuppressive agents in IPF.

N-acetylcysteine (NAC), a molecular precursor to the antioxidant glutathione, was considered a potential treatment for IPF. The lung of patients with IPF consumes glutathione. Oral NAC repletes glutathione deposits and restores natural oxidant/antioxidant balance attempting to prevent oxidative injury which precedes fibroproliferation. Unfortunately, NAC proved no supplemental benefits for IPF patients, compared to placebo.

Trials related to new drug treatments have been conducted over the years. The year 2014 has been marked by the emergence of two promising drugs, namely pirfenidone and nintedanib.

The newly licensed drugs for the treatment of IPF, showing first evidence for a slowing in disease progression, are pirfenidone and nintedanib.

Pirfenidone is an anti-fibrotic drug approved in EU, used in patients with mild to moderate IPF. This new drug’s mechanism of action is not known, but it was demonstrated that it can reduce the production of key profibrotic cytokines like transforming growth factor, interleukin-1 and fibroblast growth factor (FGF) in a murine model of fibrosis. Also, lung collagen content and fibrosis scores were demonstrated to drop, and the proliferation of fibroblasts was attenuated, indicating that pirfenidone acts by inhibiting important fibrogenic pathways.

The clinical use of pirfenidone was preceded by a decade of clinical trials that implicated the recruitment of over 1,700 patients into five trials designed to test its safety and efficacy. After initial phase II and III studies undergoing in Japan, it was showed that pirfenidone significantly reduced the decline in FVC over a year compared to placebo. Then, the CAPACITY trials recruited patients in the US, Europe and Australia to receive high or low-dose pirfenidone or placebo, for a 72-week period. In the patients treated with high-dose treatment, it was observed a change in FVC from baseline (the primary end-point) and prolonged progression-free survival time.

For the treatment of IPF, pirfenidone was approved in Europe in 2011, while in the US, FDA approved its use in October 2014. Commonly reported treatment-related adverse events include nausea, diarrhea, dyspepsia, tiredness and fatigue, rash, photosensitivity reaction and anorexia.

Nintedanib is an intracellular triple tyrosine kinase inhibitor that binds competitively to receptors of vascular endothelial growth factor, platelet-derived growth factor and fibroblast growth factor, blocking downstream signaling pathways. The inhibition of fibroblast function is thought to be the central mechanism that nintedanib uses to modulate the disease processes in IPF. There were three clinical trials in which the safety and efficacy of this drug were assessed, on approximately 1,500 IPF patients receiving various doses of nintedanib versus placebo.

The primary outcome (slowing FVC decline over one year) was reached, so this medication was approved for use in the US also in 2014. The common adverse effects of nintedanib are: nausea, abdominal discomfort and vomiting, mild to moderate diarrhea and in rare cases liver function abnormalities.

The efficacy profiles of pirfenidone and nintedanib are similar, with equivalent slowing of disease progression, so the decision regarding which treatment to initiate requires careful judgement. There is more data available on the long-term effect of pirfenidone, if pirfenidone seems to have significant mortality benefits, in the case of nintedanib until now insufficient data are available. If one must decide which anti-fibrotic drug to indicate in IPF, consideration should be given to specific prescribing criteria, financial arguments and manageable side effects.

Imatinib is an inhibitor of PDGF, which has been implicated in the pathogenesis of IPF, but has an actual recommendation against its use.

Antiacid therapy (either proton-pump inhibitors or H2 blockers) is efficient for the abnormal gastroesophageal reflux (GER), including clinically silent GER, that is highly prevalent in patients with IPF. However, more studies are needed to provide evidence for long-term usefulness of this treatment in IPF patients.

Sildenafil stabilizes the second messenger of nitric oxide determining pulmonary vasodilation and for the treatment of pulmonary arterial hypertension is authorized to be used alone or in association with other medication.

Anticoagulation. A procoagulant state locally (in the lung tissue) and also systemically is present in IPF, so it was hypothesized that anticoagulation treatment would be beneficial in IPF. Studies have focused on anticoagulation with vitamin K antagonists and low molecular weight heparins.

Though, a recent study proved no efficacy of warfarin in IPF, anticoagulation being associated with a higher mortality than placebo. This makes anticoagulant treatment not recommended for IPF.
Newer direct oral anticoagulants have not been studied yet for use in IPF, but the contribution of coagulation and the profibrotic effect of platelets are being investigated.

Dual endothelin receptor antagonists, like bosentan and macitentan, have been examined in a few randomized controlled trials (RCTs) for use in IPF patients, regardless of pulmonary hypertension. Ambrisentan, a selective type A endothelin receptor blocker, was not recommended in IPF.

Other treatment indications
Comorbidities like ischemic heart disease and heart failure might cause additional breathlessness that will need specific treatments.

Smoking cessation should be attempted in smoker patients with IPF who continue to smoke after diagnosis.

Lung transplant. According to the NICE guidelines, the option of lung transplant should be discussed with patients who do not have absolute contraindication, in the first 3-6 months after diagnosis. The NHS Blood and Transplant Authority set of absolute contraindications include: untreated psychiatric conditions or poor social support network, severe dysfunction of other organs, cancer in the past five years, unstable critical condition, poor compliance with the treatment, drug abuse.

Pulmonary rehabilitation. A significant 6-minute walk test (6MWT) improvement was noted following rehabilitation interventions.

Oxygen therapy
The recent British Thoracic Society oxygen therapy guidelines advise the use of ambulatory oxygen, because it may be beneficial as a palliative adjunctive therapy in IPF patients with severe dyspnea but without evidence of hypoxemia.

Acute exacerbations of IPF
Patients with IPF may experience an exacerbation, defined as new infiltrates on HRCT, deterioration of dyspnea over 30 days or less, in the absence of other causes such as heart failure, pulmonary emboli and infection. This is resulting in increased breathlessness and hospital admission in the majority of cases. IPF exacerbation is a severe condition, with a mortality higher than 50%. One of the triggering factors of acute exacerbations of IPF was shown to be thoracic surgery, so the choice of a lung biopsy in these patients should be made with extreme caution.

The treatment for acute exacerbation is currently very limited and entirely without an evidence base. Antibiotics are invariably prescribed to treat possible infection, regardless of the clinical findings, and in the majority of cases, patients are treated with high-dose prednisolone, usually in the form of pulsed methylprednisolone for three days, to overcome any inflammatory component within the scarred lung. Mechanical ventilation, probably by increasing the alveolar pressure and further stretching the fibrotic lung, didn’t bring any benefit to these patients.

Overview of clinical practice guideline recommendations
The definition, diagnostic criteria and treatment recommendations have been subject of several consensus of experts in the past two decades, the most important being the result of a collaborative effort from the American Thoracic Society (ATS), European Respiratory Society (ERS) and the American College of Chest Physicians (ACCP). As such, in 2000, a panel of experts has approved a number of key recommendations, focusing on disease definition, clinical criteria, indications for surgical lung biopsy and best therapeutic approach.

Due to small body of evidence at that time, these recommendations were mainly based on experts’ opinions consensus, without using standard procedures for guideline development. Even so, this guidance paper represented a reference point for future documents arising in this field, by setting a gold standard for the clinical-radiological-pathological correlation with the diagnosis in IPF, based on:

- Surgical lung biopsy revealing a histological pattern for UIP.
- Eliminating other causes of interstitial lung disease.
- Abnormal pulmonary physiology during exercise, showing signs of restriction and/or impaired gas exchange.

A pattern of “confident” or “possible” IPF on HRCT. Following next decade’s scientific progresses, an update in diagnostic and treatment recommendations for IPF patients was made in 2011 by Raghu and colleagues. Its major novelty consisted of guideline development based on GRADE (Grading of Recommendations Assessment, Development and Evaluation) evidence-based approach, but also of providing first evidence-based treatment recommendations for this rare respiratory disease. The 2011 guidelines, named “An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management”, draw six summary conclusions and recommendations about the definition, diagnosis, natural outcome and coexisting conditions of IPF.

In the same time, based on available evidence before 2011, treatment recommendations for and against specific therapies in IPF and its complications or comorbid conditions were released for the first time. The document statement agreed that there was no specific pharmacological treatment in IPF, and formulated strong recommendations against the following therapies in IPF: corticosteroid monotherapy, colchicine, cyclosporine A, combined corticosteroid and immune-modulator therapy.

The most recent clinical practice guideline for the treatment of idiopathic pulmonary fibrosis was produced in 2015 as an update to the previous 2011 clinical practice guideline, being a result of several systematic reviews and meta-analyses summarizing all available evidences pertinent to the clinical questions raised by the precedent version.
There were 12 treatment recommendations, transcribed below(75):

1. Clinicians should not use warfarin anticoagulation in patients with IPF who do not have a known alternative indication for its use.

2. Clinicians should not use imatinib in patients with IPF.

3. Clinicians should not use the combination therapy of N-acetylcysteine, azathioprine, and prednisone in patients with IPF.

4. Clinicians should not use ambrisentan in patients with IPF, regardless of the presence or absence of PH.

5. Clinicians should use nintedanib in patients with IPF.

6. Clinicians should use pirfenidone in patients with IPF.

7. Clinicians are suggested to use regular antiacid treatment for patients with IPF.

8. Clinicians are suggested not to use sildenafil for the treatment of IPF.

9. Clinicians are suggested not to use bosentan or macitentan for the treatment of IPF.

10. Clinicians are suggested not to use N-acetylcysteine monotherapy in patients with IPF.

11. In patients with IPF the committee did not make a recommendation regarding single versus bilateral lung transplant. As for this clinical decision, the committee established that there is need for supplementary evidence.

12. Regarding treatment of PH in patients with PF, the committee did not make a suggestion, as further evidence is needed.

Overall management principles in IPF

Like in many other chronic illnesses, the healthcare needs of an IPF patient must be addressed by an ILD specialist team, including a pulmonologist with ILD expertise, a respiratory physiotherapist, a nurse specialist and a pharmacist. Close liaison with the general practitioner and involvement of community nursing and palliative care teams will be required in time, especially during the later stages of illness.

Three approaches to management have been proposed(63):

a) Watch and wait approach

Patients with early disease stages, or who have combined emphysema and IPF, will not qualify for anti-fibrotic therapy under NICE guidance if they have preserved lung function tests, which currently prescribe the use of therapy if FVC is between 50% and 80% of predicted value. Other patients may have minimal symptoms and wish to delay treatment due to concerns about the impact that potential side effects could have on their quality of life. In these cases, a careful monitoring strategy is recommended and by repeated lung-function tests every 3-6 months the clinician will be capable to detect evidence of worsening disease. Indicators of significant disease are the progression of FVC of >10% or transfer factor for carbon monoxide (TLCO) of >15%.

b) Active disease-directed treatment

Pirfenidone and nintedanib are available in many European countries for patients with an FVC between 50% and 80% of predicted value and in respect with national treatment inclusion criteria.

c) Symptom-based approach

A subset of patients address with advanced disease stages or having extensive comorbidities that preclude the use of anti-fibrotic therapy. Symptomatic relief of breathlessness, low-dose corticosteroids or codeine for intractable cough and supportive care are essential, in addition to palliative care.

Recent treatment advances for Romanian patients diagnosed with idiopathic pulmonary fibrosis

In the last decade, most reference pulmonary disease clinics in Romania have succeeded to create access to new, modern laboratory and imagistic investigations like HRCT, complete bronchoscopy evaluation with BAL and TBB, thoracic surgery diagnostic procedures, or full parameters lung function testing, all these being indispensable for an accurate diagnosis of IPF. This progress has made possible to advance with IPF screening in the Romanian population and to shape first patient databases in few such reference centers like Bucharest and Timișoara(30).

Starting with 2017, pirfenidone and nindetanib are available in Romania for IPF patients with mild to moderate forms of disease, under fully reimbursed prescription, according to a national treatment program for orphan lung diseases. As such, in accordance with ATS-ERS criteria, those IPF patients with either a histopathological diagnosis confirmed through lung biopsy or TBB, or a probable histopathological aspect of UIP + a HRCT aspect of UIP or even a typical HRCT aspect of UIP with or without a lung biopsy with an UIP aspect can qualify to receive this anti-fibrosis medication. Additionally, IPF patients must be non-smokers or former smokers for at least 3 months and have the confirmation of the IPF diagnosis since no more than 5 years before treatment enrollment. Lung function must have a FVC of 50-90% of predicted value, a DLCO of 30-90% of predicted and a FEV/FVC ratio higher than normal.

Shaping future research directions in idiopathic pulmonary fibrosis

Even though so many progresses were done in the past decade in the diagnostic methods and new therapeutic agents, still IPF remains a disease with unknown etiology, the pathogenesis is not yet completely understood and disease clinical course may pose numerous challenges to clinicians. There is no definitive consensus for its treatment approach and large multi-center clinical trials to sustain effectiveness of targeted pharmacological therapy would much more ease management of this difficult category of patients.

In a comprehensive review of the pharmacological treatment of IPF, Kreuter and colleagues, after full over-
view of all therapeutic options up to date, formulated the following open questions:  
**Should we start anti-fibrotic treatment as early as possible?**

**Answer:** After the diagnosis of IPF, it makes sense to start the treatment as rapidly as possible, so the pulmonary function to be preserved and to prolong survival(77).

**Which drug should we use as first-line treatment for IPF?**

**Answer:** Both pirfenidone and nintedanib have been demonstrated to slow the decline in FVC in IPF patients with mild to moderate functional impairment with acceptable safety profiles.

**How do we treat more severe IPF?**

**Answer:** FDA authorized pirfenidone and nintedanib(78) use irrespective of disease severity (and the European Medicines Agency authorized nintedanib with the same directive), but there are no studies regarding the safety and efficacy of pirfenidone and nintedanib in patients with more severe functional impairment (e.g., FVC<50%). For patients with DLCO<35% of predicted, echocardiographic evidence of right ventricular dysfunction, and no contraindications to the drug, a trial of sildenafil may be a reasonable therapeutic option(79).

**How do we treat patients with IPF and lung cancer?**

**Answer:** It is well known that patients with IPF are at high risk of developing lung cancer. No specific guidelines exist on this association, so Kreuter and colleagues suggest to make decisions on a case-by-case basis after a careful assessment of the benefits and the risks(80).

**How do we treat elderly IPF patients?**

**Answer:** The management of elderly patients with IPF should be as personalized as possible, in order to prevent functional decline and disease progression, but also for limiting the risk of treatment-related adverse events(81).

**Conclusions and future perspectives**

The future development of state-of-the-art management for idiopathic pulmonary fibrosis is directly linked to sustained and extensive efforts of the researchers to both developing more accurate and easily applied diagnostic tools(82), and to maximizing patient’s therapeutic benefits.

It was initially considered that combination therapy of the two drugs available for IPF should be avoided(77). Recently, a randomized, double-blind, placebo-controlled phase II, dose escalation trial has been conducted to assess the safety, tolerability and pharmacokinetics of nintedanib, alone and when added to ongoing pirfenidone therapy in Japanese patients with IPF. Regarding the administration of pirfenidone and nintedanib combination in patients with IPF, investigators noticed a tendency towards reduced exposure to nintedanib when administrated together with pirfenidone and recommended additional studies to evaluate the safety and tolerability profile of using this combination in IPF patients(83).

Another add-on pirfenidone to nintedanib study proved a better outcome in preventing disease progression, with no supplemental side effects, with full-dose use of both molecules(84).

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References


References
