Interstitial Lung Diseases : Current Trends in Diagnosis and Treatment

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ABSTRACT

Most of the studies have found that idiopathic pulmonary fibrosis is the most common form of ILD followed by ILDs due to collagen vascular disorders, inorganic and organic exposure, related to smoking and drugs and certain granulomatous ILDs. Diagnosis of ILD is based on detailed clinical history, laboratory data, chest radiology, pulmonary function tests, diffusion capacity for CO, HRCT and histopathological co-relations. Recent guidelines have quoted standard of care that includes early referral for lung transplantation, home oxygen therapy, palliative care, and conditional recommendations for the treatment with novel agents such as perfinidone and nintedanib as well as antacids for treatment of IPF. Treatment of ILDs due to known causes such as collagen vascular diseases, drug induced and organic and inorganic exposure depends on underlying etiology.

This article briefly summarises the current trends in diagnosis & management of Interstitial lung disease

Keywords : Interstitial Lung Disease, IPF, Perfinidone, Nintedanib, Lung Function Testing.

Introduction :

Interstitial Lung Diseases (ILD) are a heterogeneous group of diseases with varied etiology, therapy and prognosis. ILDs are classified according to time course (acute, sub-acute, chronic) the cause (known or unknown), and presence or absence of extra pulmonary or systemic disease manifestation.[1] Idiopathic pulmonary fibrosis (IPF) is most common of all the ILDs with worst prognosis, followed by ILDs due to collagen vascular disorders, inorganic and organic exposure, related to smoking and drugs and certain granulomatous ILDs.[1] Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive diffuse parenchymal lung disease of unknown origin with median survival estimates ranging from 3 to 5 years after diagnosis.[2,3] The diagnostic process involves integration of clinical, laboratory, radiological, and histological evidence. In the last 2-3 decade, our understanding of the mechanisms of pathogenesis of IPF has greatly evolved. Historically, IPF was considered an inflammatory or autoimmune condition. IPF is a complex disease characterized by abnormalities in multiple pathways involved in normal wound healing following alveolar epithelial cell injury that results in scarring of lung, architectural distortion, and irreversible loss of function.[4]

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Classification Of ILDS :

The American Thoracic Society (ATS) / European Respiratory Society (ERS) consensus panel classification system was published in 2001 and has recently been revised. ***(Fig.1)***[1] In classification of ILDs it is often important to integrate patients history, clinical, radiological and histopathological features. It is important to distinguish patients with known cause of ILD (CTDs, occupational and environmental exposure) from those with unkonwn cause (eg IPF, Sarcoidosis).

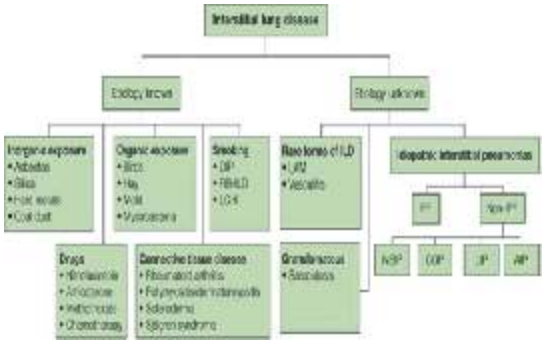


Fig. 1. **Classification of ILDs** (AIP, acute interstitial pneumonia; COP, cryptogenic organizing pneumonia; DIP, desquamative interstitial pneumonia; LAM, lymphangioleomyomatosis; LCH, langerhan cell histiocytosis; LIP, lymphocytic interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease) (Data Source ATS/ERS Classification 2013)[1]

Approach to diagnosis of Interstitial Lung Disease

The diagnostic strategy in patient with ILD is based on considerations regarding dynamic time course, the cause, and the context of disease at presentation ie presence of pulmonary and extra pulmonary manifestations. The diagnostic approach of ILD includes Clinical evaluation; Lung function test including Diffusion capacity; HRCT and Surgical Lung Biopsy.

Clinical Evaluation : Detailed history taking is of paramount importance for the diagnosis of ILD.

Assessment of Symptoms : Dyspnea on exertion is the predominant symptom of most ILDs. The degree of dyspnea is linked to disease severity and prognosis. It is also necessary to exclude non respiratory symptoms as a cause of exercise limitations like joint pain, muscle pain or weakness. Cough is the second most frequent syndrome in patient with ILD. In IPF cough is usually dry in nature. Dry cough is indicative of airway centered disease such assarcoidosis, hypersensitivity pneumonitis(HP) or organizing pneumonia. Wheeze is infrequent in ILD but can occur with certain systemic disease like Churg-strauss syndrome, HP or Airway stenotic sarciodosis.[5] Pleural pain and effusion is also seen in ILD with connective tissue disease.[4] Hemoptysis is an alarming symptom and indicate pulmonary haemorrhagic syndrome. GERD is another symptom that exacerbates ILD.

Extra pulmonary manifestation may give clue to the correct diagnosis, therefore joint pain and swelling (rheumatoid arthritis), cutaneous thickening, raynauds phenomenon, dysphagia (systemic sclerosis), oculocutaneous albinism and colitis (hermanskypudlak syndrome), chronic granulomatous sinusitis (GPA and churgstrauss syndrome) renal failure (Good pastuer syndrome) renal angiolipoma (LAM)[2,4,5.] Clinical features of IIPs are summarized in ***Table 1.***

History taking should include 1) smoking history 2) hobbies 3) occupations 4) travel 5) drug history and 6) treatments (eg radiation therapy).[4,6] Various occupational exposures leading to ILD are summarized in ***Table 2.***

Table 1 : **Clinical Features of the Idiopathic Interstitial Pneumonias**

Features	UIP	DIP	RB-ILD	AIP	NSIP	COP
Mean age at onset (yr)	60s	40s	40s	50s	50s	50s
Onset	Insidious	Insidious	Insidious	Acute	Subacute, insidious	Acute or subacute
History of cigarette smoking	About two thirds	Most	Most	Not known	Not known	About half
Mortality rate (mean survival)	68% (56 yr)	27% (12 yr)	0%	62% (1-2 mo)	11% (17 mo)	10% in 5 years
Response to steroids	Poor	Good	Good	Poor	Good	Excellent
Complete recovery Possible	No	Yes	Yes	Yes	Yes	Yes (up to 70% of patients)

AIP, acute interstitial pneumonia; COP, cryptogenic organizing pneumonia; DIP, desquamative interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease; UIP, usual interstitial pneumonia.

Data source Murray and Nadel's Textbook of Respiratory Medicine)[8]

Table 2 : **Occupational exposure and ILDs :**

Occupation	Type of ILD	Exposure
Electrician Plumber Pipe fitter Construction worker Ship builder Insulation installer	Asbestosis	Asbestos
Stone cutter Miner Sand blaster	Silicosis	Crystalline silica dust
Metal grinder	Giant cell interstitial pneumonia Hard metal lung disease	Hard metals Cobalt Tungsten carbide
Metal worker Factory workers Nuclear weapons Aircrafts Electronics Ceramics Golf clubs Bicycle frames	Berylliosis	Beryllium
Coal worker	Coal worker's pneumoconiosis	Coal dust
Paint sprayer Plastic worker	Chemical worker's lung	Isocyanates
Bird breeder	Bird breeder's lung	Bird droppings Bird feathers
Farm worker Haying Mushroom compost	Farmer's lung Mushroom worker's lung	Thermophilic bacteria
Office worker	Humidifier lung Ventilation pneumonitis	Fungi/Molds
Lifeguard	"Hot tub" hypersensitivity pneumonitis	*Mycobacteria*

(Data source Fishman's Pulmonary Diseases and Disorders)[7]

Risk Factors For Idiopathic Pulmonary Fibrosis (IPF) :

Although IPF is defined as idiopathic disease several epidemiologic studies have identified several risk factors including environmental[9] and occupational exposures associated with the diagnosis. Several case control studies found association between smoking and IPF.[10,11] It has been hypothesized that environmental or occupational exposures (asbestosis, silicosis and coal worker pneumoconiosis) may be associated with IPF. Several studies have shown association between nickel, silicon and aluminum levels and IPF. Agriculture and live stock related exposures have been found to be associated with IPF.[9]

Physical Examination :

On physical examination, inspection may reveal various findings like skin thickening and acralnecrosis (scleroderma), oculocutaneous albinism (Hermansky Pudlak syndrome), clubbing (upto 40% of all ILDs) cutaneous vasculitis (churg-strauss syndrome) and edematous cyanotic skin (dermatomyositis).[2,4,5]

Palpation may reveal lymphadenopathy, hepato-splenomegaly pointing at sarcoidosis, HIV infection or connective tissue disease.

Auscultation reveals symmetric fine "Velcro-like" late inspiratory crackles in more than 90% patients with IPF and about 60% of patients with CTD related ILD.

Laboratory Testing :

Laboratory testing allow exclusion or suggestion of an associated hematologic ,liver or kidney disease in systemic disease (sarcoidosis, vasculitis, amyloidosis), malignancy (eg. lymphoma) or infection (eg. Tuberculosis, HIV). Other laboratory testing like ANA ,RA factor, scl70, jo1 for CTD; Immunoglobulins for immunodeficiency; c-ANCA, p-ANCA for vasculitis; Antiglomerular basement membrane antibody for Good pasture syndrome help to rule out other associated conditions along with ILDs. Various seriological markers for connective tissue disease are summarized ***(Table 3).***[5]

Pulmonary Function Testing :

In patients with ILD, PFT should include arterial blood gas analysis at rest and on exertion, spirometry, body plethysmography and DLCO.[4,12] Lung function usually reveals restrictive ventilator defect, impaired gas exchange as well as reduced compliance. Some diseases like LAM, LCH, sarcoidosis and HP may present with airway obstruction and or hyperinflation as part of underlying disease process.[4,5] During follow-up ,changes in lung function are helpful for disease monitoring.[2,4,12]

Table 3 : **Serological Testing in ILD. (Data source Fishman's Pulmonary Diseases and Disorders)**[7]

Serologic Testing in ILD	
Test	**Disease**
ANA	Scleroderma, SLE, MCTD
SSA	Sjögren syndrome, Polymyositis
SSB	Sjögren syndrome
CK Aldolase Jo-1 Myositis-associated antibodies	Polymyositis, dermatomyositis
Jo-1 Myositis-associated antibodies	Antisynthetase syndrome
Scl-70 Anticentromere antibody	Scleroderma
RF CCP	Rheumatoid arthritis
RNP Antihistone antibody	Mixed connective tissue disease
p-ANCA, c-ANCA	ANCA-associated vasculitis

ANA, antinuclear antibody; CK, creatine kinase; ESR, erythrocyte sedimentation rate; SSA, anti-Ro antibody; SSB, anti-La antibody; RF, rheumatoid actor; CCP, cyclic citrullinated peptide; RNP, ribonucleoprotein; CRP, C-reactive protein; ANCA, antineutrophil cytoplasmic antibody.

Radiologic Assessment :

Abnormal chest radiograph is often the initial finding in patients with ILD. Most common findings are diffuse reticulonodular pattern, ground glass opacities, or both ***(fig. 2).*** Various patterns and radiologic appearances are summarized in ***Table 4.***[2,4,5] HRCT is the key diagnostic procedure and is sufficient for diagnosis in a significant number of patients with IPF ***(fig. 3).*** The criteria for making a confident diagnosis are presented in ***Table 5.***[2] HRCT findings suggestive of alternative diagnosis other than IPF are shown in ***Table 6.***

Table 5. **HRCT findings for diagnosis of IPF :**

a) UIP pattern (All 4 patterns) :

1. Subpleural basal predominance
2. Reticular abnormality
3. Honeycombing with or without traction bronchiectasis
4. Absence of features listed as inconsistent with UIP pattern.

b) Possible UIP pattern : 1,2 and 4

c) Inconsistent with UIP pattern (any of 7 features) :

1. Upper lung or midlung predominance
2. Peribronchovascular predominance
3. Extensive ground glass abnormality
4. Profuse micronodules
5. Diffuse mosaic attenuation/air trapping.
6. Discrete cysts
7. Consolidation in bronchopulmonary segments / lobes.

(Data source Fishman's Pulmonary Diseases and Disorders)[7]

Table 4 : **Chest radiograph findings in various ILDs**

Normal	HP, NSIP, CTD - assocaiated ILD, RBILD, Bronchiolitis, Sarcoidosis
Low lung volumes	IPF, CTD - related ILD, chronic HP, asbestosis, chronic drug induced fibrosis
Preserved / Increased lung volumes	RBILD, IPF plus Emphysema, LCH, LAM, Sarcoidosis
Upper zone predominance	Sarcoidosis, silicosis, coal worker pneumoconiosis
Lower zone predominance	IPF, CTD ILD, asbestosis, chronic HP
Peripheral predominance	IPF, COP, CEP
Honeycombing	IPF, asbestosis, CTD-ILD, chronic HP, sarcoidosis
Mediastinal / Hilar lymphadenopathy	Sarcoidosis, malignancy, silicosis, infection

(Data source Fishman's Pulmonary Diseases and Disorders)[7]

Table 6 : **Radiological features of ILDs.**[13]

Distribution of ILD	
Upper lung zone	**Lower lung zone**
Sarcoidosis	Usual interstitial pneumonia (UIP/IPF)
Silicosis	Nonspecific interstitial pneumonia (NSIP)
Coal worker's pneumoconiosis	Connective tissue disease–associated ILD
Hypersensitivity pneumonitis	Asbestosis
Langerhans cell histiocytosis	Desquamative interstitial pneumonia (DIP)
Berylliosis	
Chronic eosinophilic pneumonia	
Pattern of ILD	
Peripheral reticular	**Ground glass**
Idiopathic pulmonary fibrosis/usual interstitial pneumonia	NSIP
Nonspecific interstitial pneumonia	Cryptogenic organizing pneumonia
	Eosinophilic pneumonia (chronic or acute)
	Pulmonary edema
Nodular	Infection (opportunistic or viral)
Sarcoidosis	Alveolar hemorrhage
Berylliosis	Hypersensitivity pneumonitis
Hypersensitivity pneumonitis	Desquamative interstitial pneumonia
Langerhans cell histiocytosis	Sarcoidosis
Silicosis	Pulmonary alveolar proteinosis
Metastatic disease	
Talcosis	**Cystic**
Granulomatous polyangiitis (formerly known as Wegener's granulomatosis)	Lymphangioleiomyomatosis
Respiratory bronchiolitis ILD	Langerhans cell histiocytosis
	Lymphocytic interstitial pneumonia
	Pneumocystis jiroveci pneumonia (PCP)

Source: Data from Diagnostic Thoracic Imaging, Miller W. McGraw Hill; 2006.

Role of Bronchoscopy :

In patients with ILD, bronchoscopy can be performed to obtain materials for microbiological, cytological and histological analyses. various techniques includebronco - alveolar ravage (BAL), trans-bronchial lung biopsy (TBLB), and transbronchail needle aspiration (TBNA) for cytological or histologicalanalyses.[2,4] With use of BAL, TBNA, TBLB a diagnosis of Sarcoidosis, lymphangitiscarcinomatosa, eosinophilic Pneuomonia, alveolar proteinosis, LCH, LIP and several bacterial, viral, fungal infections can be confirmed.

Role of Surgical Lung Biopsy :

Surgical lung biopsy, performed during VATS is the most invasive diagnostic procedure used for diagnosis of ILD. However ,it is associated with significant morbidity and mortality and hence should be reserved for patients in whom management and treatment could change depending on result of biopsy.[2,4,15] The multidisciplinary discussion involving the pulmonologists, radiologists and pathologists has become the gold standard for diagnosis.[2,16]

Therapeutic Approach :

Therapeutic approach for management of IPF includes both pharmacological and non pharmacological management strategies. ***(Table 7)***

Table 7 : **Therapeutic Approach For ILDs**

Pharmacological Management
Perfinidone
Nintedanib
Anti-coagulants
Anti acids
Interferon gamma
Anti-inflammatory and Vasodilators
Non-Pharmacological Management
Oxygen Therapy
Lung Transplantation
Pulmonary Rehabilitation

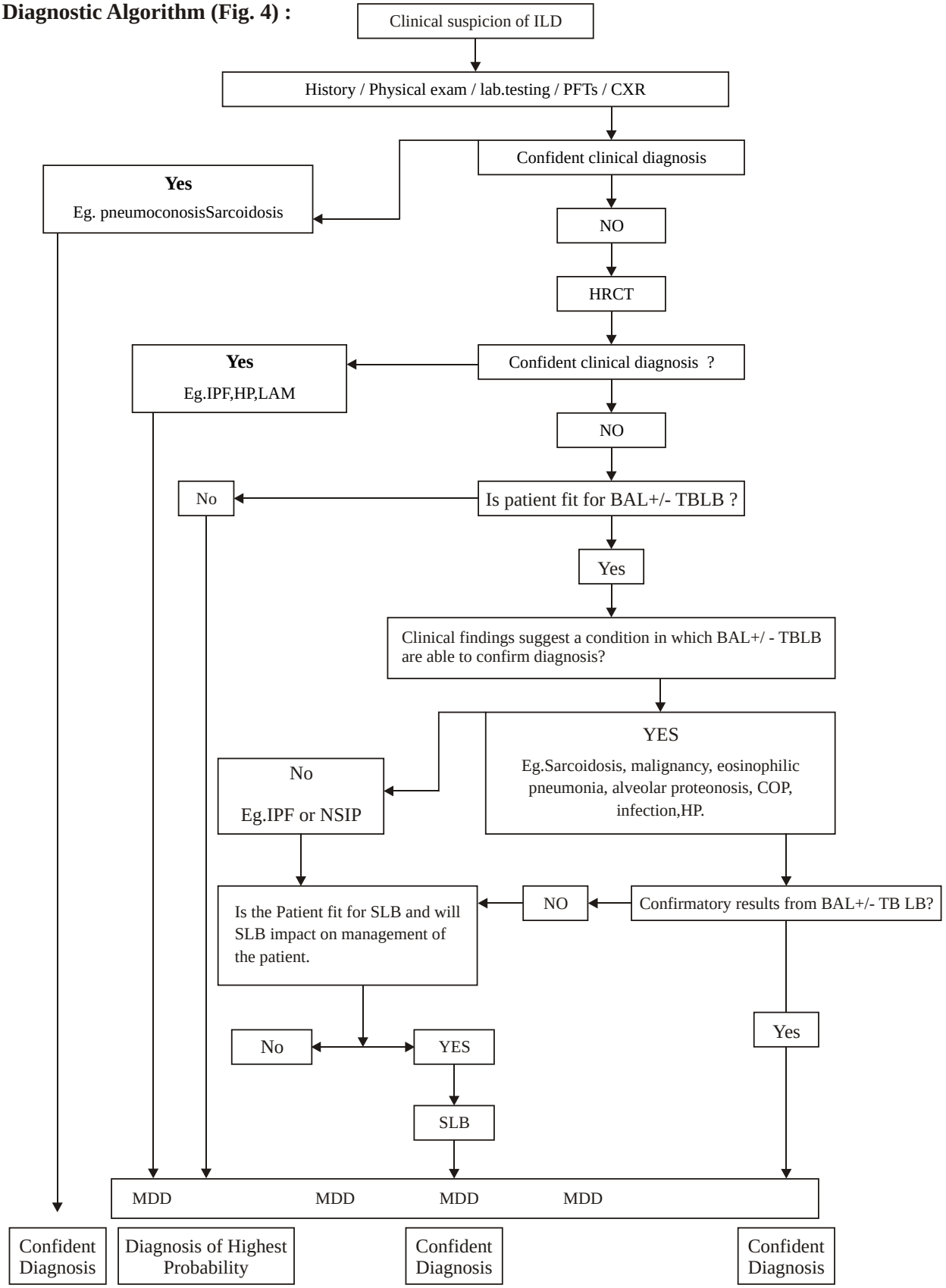
Pharmacological Management :

After number of randomized clinical trials ***(Table 8)*** two drugs have received FDA approval vizperfinidone and nintedanib. Many new molecules are under clinical trial important among them are perfinidone and nintedanib.

Perfinidone :

Perfinidone is an oral drug with antifibrotic and anti inflammatory properties. Various RCTs have evaluated safety and efficacy of perfinidone in IPF

Diagnostic Algorithm (Fig. 4) :



patients. Original observation regarding its potential benefit paved the way for the undertaking of three RCTs, one in Japan and two multinational, involving centers in the USA, Europe, and Australia. A meta-analysis of all three studies showed a reduction in the risk of disease progression of approximately 30% com- pared with placebo. However, while pirfenidone reduced the rate of decline in vital capacity in the Japanese trial,[17] it produced a similar beneficial effect in the rate of decline of the percentage of forced vital capacity (FVC) in only one of two CAPACITY studies (ie, Study 004).[18] The drug was approved for the treatment of IPF in patients with mild to moderate functional impairment in Europe and Japan; conversely, these controversial results prompted the US Food and Drug Administration to request an additional trial to support the approval of pirfenidone. In the recent ASCEND trial, 555 patients with IPF were randomized to receive either the maximum oral dose of pirfenidone (2,403 mg/day) or placebo.[19] Pirfenidone significantly reduced disease progression, as measured by changes in the mean decline of absolute (193 mL) or percent predicted (45%) FVC and changes in the 6-minute walking test (6MWT). Moreover, pirfenidone reduced disease progression or death by 43% compared with placebo. Although there was no statistically significant difference in rates of all-cause mortality.

Adverse Effects : Gastrointestinal adverse effects include nausea, dyspepsia, anorexia, and gastroesophageal reflux. Skin-related adverse events (eg, photosensitivity rash) are also more common. Finally, elevations in levels of alanine or aspartate aminotransferase that were three or more times the upper limit of the normal range occurred more frequently in the pirfenidone group.

Nintedanib :

Nintedanib (BIBF1120) is an intracellular multiple tyrosine kinase inhibitor that targets receptors of platelet-derived growth factor, vascular endothelial growth factor and fibroblast growth factor all thought to be involved in the pathogenesis of IPF.[20] An earlier Phase IIb study (TOMORROW) of 432 patients with mild to moderate disease (FVC >50%) reported that treatment with 150 mg of nintedanib twice daily was effective in reducing FVC decline and preventing acute exacerbations, while preserving quality of life.[21]

Adverse events : In all the trialsmost common side effect associated with nintedanib was diarrhea followed by nausea and vomiting. Other side effect included elevation of alanine and aspartate aminotransferase.

Anti-Acids : Chronic microaspiration has been implicated to trigger development of the IPF. Abnormal acid gastroesophageal reflux has been reported in as many as 88% of patients with IPF. A retrospective study by Lee et al reported a statistically significant difference in the decline of FVC and fewer exacerbations in a large cohort of patients with IPF (n=242) under treatment with anti-acid agents (proton pump inhibitors or histamine 2-receptor antagonists).[28] Hence, recent guidelines recommend regular antacid treatment for patients with IPF.

Table 8 : **Overview of the most recent randomized controlled trials performed in idiopathic pulmonary fibrosis**

Study drug (author / trial acronym)	Patients (n)	Primary endpoint	Outcome / comments	Reference
Pirfenidone (Taniguchi et al)	267	Change in VC (relative)	Primary endpoint met	17
Pirfenidone (CAPACITY 004)	435	Change in FVC (absolute)	Primary endpoint met	18
Pirfenidone (CAPACITY 006)	344	Change in FVC (absolute)	Primary endpoint not met	18

Pirfenidone (ASCEND)	555	Change in FVC (relative)	Primary endpoint met	19
Nintedanib (TOMORROW)	432	Annual rate of decline in FVC (relative)	Primary endpoint not met Nintedanib 150 mg twice daily was associated with a trend toward a reduction In FVC decline	21
Nintedanib (INPULSIS-1)	513	Annual rate of decline in FVC (relative)	Primary endpoint met	22
Nintedanib (INPULSIS-2)	548	Annual rate of decline in FVC (relative)	Primary endpoint met	22
Warfarin (ACE)	145	Composite outcome of time to death, Hospitalization, or a □ 10% absolute decline in FVC	Primary endpoint not met Trial terminated early	26
NAC + AZA + CS versus AZA + CS (IFIGENIA)	182	Change in VC and DLCO (relative)	Primary endpoint met	23
NAC versus placebo Versus NAC+AZA +CS (PANTHER)	236	Change in FVC (relative)	Primary endpoint not met Trial terminated early	24
NAC versus placebo (PANTHER)	264	Change in FVC (relative)	Primary endpoint not met	25
IFN γ-1b (INSPIRE)	826	Overall survival	Primary endpoint not met Trial terminatedearly	29
Etanercept (Raghu et al)	88	Change in FVC (Absolute)	Primary endpoint not met	30
Bosentan (BUILD-1)	158	Change in 6MWD	Primary endpoint not met	31
Bosentan (BUILD-3)	616	Time to IPF worsening (decline in FVC □ 10% and decline in DLCO □ 15% or acute exacerbation) or death	Primary endpoint not met	32
Macitentan (MUSIC)	178	Change in VC (relative)	Primary endpoint not met	33
Ambrisentan (ARIES)	492	Time to disease progression (death, decline in FVC □ 10%, decline in DLCO □ 15% or acute exacerbation)	Primary endpoint not met Trial terminated early	34
Sildenafil (STEP)	180	Proportion of patients with an increase in 6MWD of >20%	Primary endpoint not met Positive treatment effect in secondary endpoints	35

Abbreviations : 6MWD, 6-minute walking distance; AZA, azathioprine; CS, corticosteroids; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; IFN, interferon; NAC, N-acetylcysteine; TLC, total lung capacity; VC, vital capacity.

Non-Pharmacological Management

Oxygen Therapy :

Long-term oxygen treatment is recommended for all IPF patients with resting or nocturnal hypoxemia.[2,36]

LUNG TRANSPLANTATION :

Lung transplantation is recommended as the most effective and reliable treatment for the management of IPF.[1]

Pulmonary Rehabilitation :

Pulmonary rehabilitation (PR) is regarded as the standard of care for chronic lung diseases because of its efficacy in alleviating symptoms, and improving exercise tolerance, functional capacity, and dyspnea scores. In patients with IPF, PR has been associated with a significant improvement in 6MWT, dyspnea, and quality of life.[1,37]

Discussion :

According to current guidelines,1the standard of care for patients with IPF includes early referral for lung transplantation, palliative care, and enrollment into therapeutic clinical trials. Recent guidelines have given conditional recommendation for treatment with novel agents such as perfinidone and nintedanib as well as antacids for treatment of IPF.[19,22,28] However there is absolute need for further long term studies to determine safety and efficacy of treatment options for IPF. It is clear that treatment with warfarin[27] is not beneficial in patients with IPF without other indication. Triple therapy with prednisone, azathioprine and NAC is harmful.[23] Ambrisentan, a selective ERA is not recommended as it was associated with decline in respiratory function.[34] However further studies should be dictated towards role of dual ERAs in patients with IPF with PH. Use of antacids is recommended as strong association has been found between abnormal acid GER and IPF. However further studies are recommended for determining role of surgical correction to eliminate or decrease GER, conservative measures to prevent or decrease the risks of insults to lung by micro aspiration. Strategies should be designed for early detection and treatment of co morbidities like PAH, emphysema, airflow obstruction, sleep apnea, GERD.

More emphasis should be given on end of life care for patients who are terminally ill. Palliative care for symptoms of dyspnea, fatigue and cough should be an essential part of care of patient.

Conclusion and Future Directives : Finally approaches based on individualized treatment of patient according to various biomarkers found in circulation or in lung and studies with pharmacogenomics and pharmacoeconomics should be the target for further studies. Thus with collaboration between various multinational organizations and availability of adequate resources and fund newer treatment options can be designed to halt the disease progression and ultimately curing the disease.

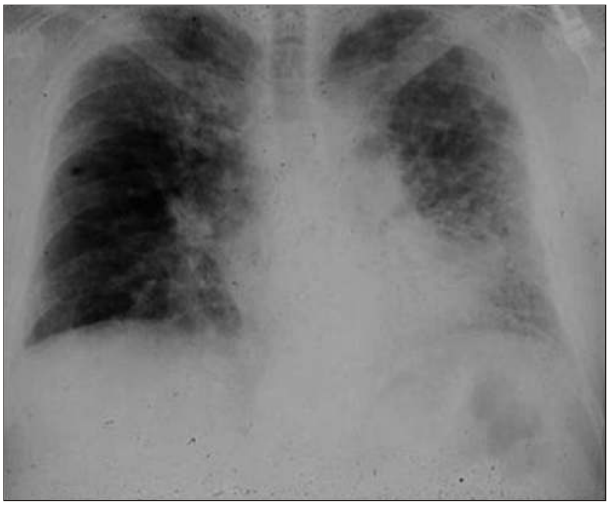


Figure 2 : Posteroanterior chest radiograph of a 67-year-old man with progressive dyspnearevealing bilateral reticular infiltrates with lower lobe predominance.

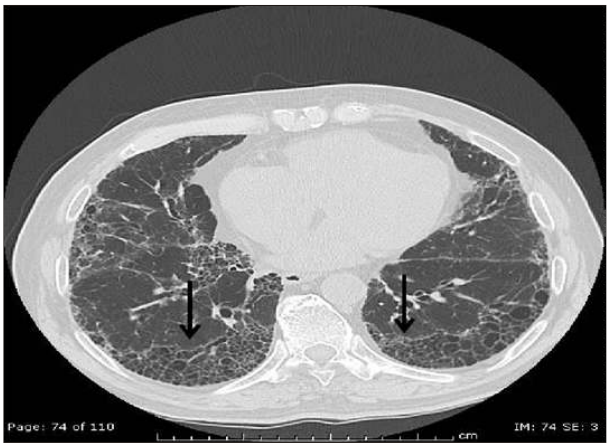


Figure 3 : High-resolution computed tomography image demonstrating usual interstitial pneumonia pattern, with bilateral, basal, and subpleural predominant reticular abnormality and honeycombing (arrows).

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