PAKISTAN CHEST SOCIETY

Interstitial Lung Diseases

Guideline Document on Diagnosis and Management of ILDs in Pakistan

ILD Advisory Board and Guideline Committee
4/7/2016

THE ILD ADVISORY BOARD AND GUIDELINE COMMITTEE

CHAIRMAN:

DR. MOSAVIR ANSARIE

MEMBERS:

DR. ALI ZUBAIRI	Aga Khan University Hospital, Karachi
PROF. ARSHAD JAVAID	Lady Reading Hospital, Peshawar
GEN. JAWAD ANSARI	Armed Forces Medical College, Rawalpindi
DR. MUKHTIAR Z. AFRIDI	Khyber Medical College, Peshawar
DR. SAQIB SAEED	King Edward Medical College, Lahore
DR. SHERIN KHAN	Bolan Medical College, Quetta
DR. TALHA MEHMOOD	Sheikh Zayed Hospital, Lahore
PROF. ZUBAIR SHAHEEN	Nishter Medical College, Multan

REVIEWERS:

PROF. NADEEM RIZVI	Jinnah Postgrad Med Center, Karachi
PROF. SOHAIL AKHTER	Ziauddin Medical University, Karachi

ACKNOWLEDGEMENT OF CONTRIBUTION

Special gratitude is expressed to:

Dr. Muhammad Azeemuddin -
Radiology- AKUH
(Major contribution on HRCT)

Dr. Sadia Ashraf & Dr. Asif Naseem
(Documentation and Coordination)

Dr. Aneeka M Kasmani & Ms. Anum Fatima
(Research, References and Manuscript)

Dr. Azfar Abbas Haidrie
(Organization and Publication)

The committee gratefully acknowledges the support provided by Ms. Hinoon Laboratories during the development and publication of this document.

DISCLOSURE

None of the committee members have any personal financial disclosures to reveal.

Message From The President PCS

Societies at large flourish in an environment of academics and learning, they perish when the frivolous overwhelms the sanctity of the pen and the book. So is with the societies of professionals, scientists, artists and men who matter.

I am genuinely happy to see that there has been this productive activity in our tenure. Reading through this document makes one feel the effort involved in its formulation.

Interstitial lung diseases especially pulmonary fibrosis is a scourge for the suffering patients and the understanding of its pathogenesis and development of a treatment has seen great strides in the contemporary period of time and thus this guideline.

I wish to congratulate Dr. Mosavir Ansarie and the members of his team who formed The ILD Guideline Committee for this admirable task that they have completed in the form of this guideline.

I hope that this document would be read by most pulmonologists of the country and remain with them as a useful guide book on the subject.

Prof. Kamran K. Chima
President
Pakistan Chest Society

PREFACE

The **objective** of this guideline is to present to Pakistani fellow physicians and pulmonologists, a concise edition of updated knowledge on Interstitial Lung Diseases (ILDs) with references from current literature. This also encompasses the diagnostic algorithms in current use as well as management strategies which have recently undergone significant improvement with the advent of new anti-fibrotic drugs.

A **Resource group** consisting of prominent pulmonologists from different parts of the country who had a known interest in the subject, collected in the form of an ILD Advisory Group to deliberate over relevant literature and produce a National Guideline for the Pakistan Chest Society, in line with those published by it before on other subjects.

The **Resource data** emanated from different ILD registries spread over the last decade mostly European, that have gathered invaluable information on its epidemiology [1, 2, 3]. Despite lack of published data, there is evidence of online national registries in this subcontinent which would soon enable us to use local data in refining our knowledge on the profile of disease in our part of the world [3, 4].The group also undertook a combined study of the ATS/ERS/JRS/ALAT consensus document of 2011 in which nomenclature and diagnostic criteria were sharpened and redefined and also the 2015 update in the form of a 'yes'/ 'no' answer statement to some contentious questions on IPF [5, 6]. Also studied was the 2014 French guideline which is an equally elaborate document[7].

The results of the PANTHER trial and subsequent changes in the treatment after the successful ASCEND trial were also discussed [8, 9]. Experience was shared on one of the two FDA approved anti-fibrotic drugs with input from the members who have been using it for a reasonable time.

These deliberations were documented after consensus of the committee members for future discussions and publications. Non-committee peer review was also solicited.

The **Presentation** before you is the first published edition of the National ILD Guideline endorsed by the Pakistan Chest Society which is a singular professional body of pulmonologists in Pakistan.

It pertains to Definitions, Pathophysiology, Epidemiology, Classification, Clinical manifestations and diagnostic workup of ILDs as a whole to give the reader a broad picture of the disease spectrum (Part A I-V). This is followed by a section that would be of great help to Fellows and Pulmonologists as it would assist them to understand the High Resolution CT scan which is indispensible to identifying, managing and monitoring ILD (Part B).

It then deals with Interstitial Pulmonary Fibrosis (IPF) specifically and in its entirety (Part C). Guidelines on other interstitial lung diseases will be prepared by the committee for future presentations.

I wish to express my gratitude to all members of the Guideline Committee who helped me in the formulation of this document at all stages, conceptual and tangible and to others who donated time and energy purely with the intent to propagate knowledge. JazaakAllah May He grant us knowledge that is profitable and cure for all ailments. Allahumma inna nas'aluka ilm annafe'a wa shifa min kulli da'a. Amen.

Dr. Mosavir Ansarie
Chairman, ILD Guideline Committee

CONTENTS

A-I. DEFINITIONS:

The **interstitial lung diseases (ILDs)** are a heterogeneous group of pulmonary disorders, classified together because of similar clinical, radiologic, physiologic or pathologic features[10]. ILDs comprises more than 200 entities, many uncommon and many of unknown etiology[11].

The term **interstitium** is confined to the microscopic anatomic space bounded by the basement membranes of epithelial and endothelial cells and inflammatory-fibrotic process extends well beyond the interstitium into the alveolar space, acini, bronchiolar lumen and bronchioles [12]. Hence, a more appropriate descriptive term used is Diffuse Parenchymal Lung Diseases (DPLDs).Despite the long standing misnomer of 'interstitial' in ILDs, it seems appropriate to use the term as long as the scope of the diseases is appreciated.

A-II. PATHOPHYSIOLOGY OF ILD

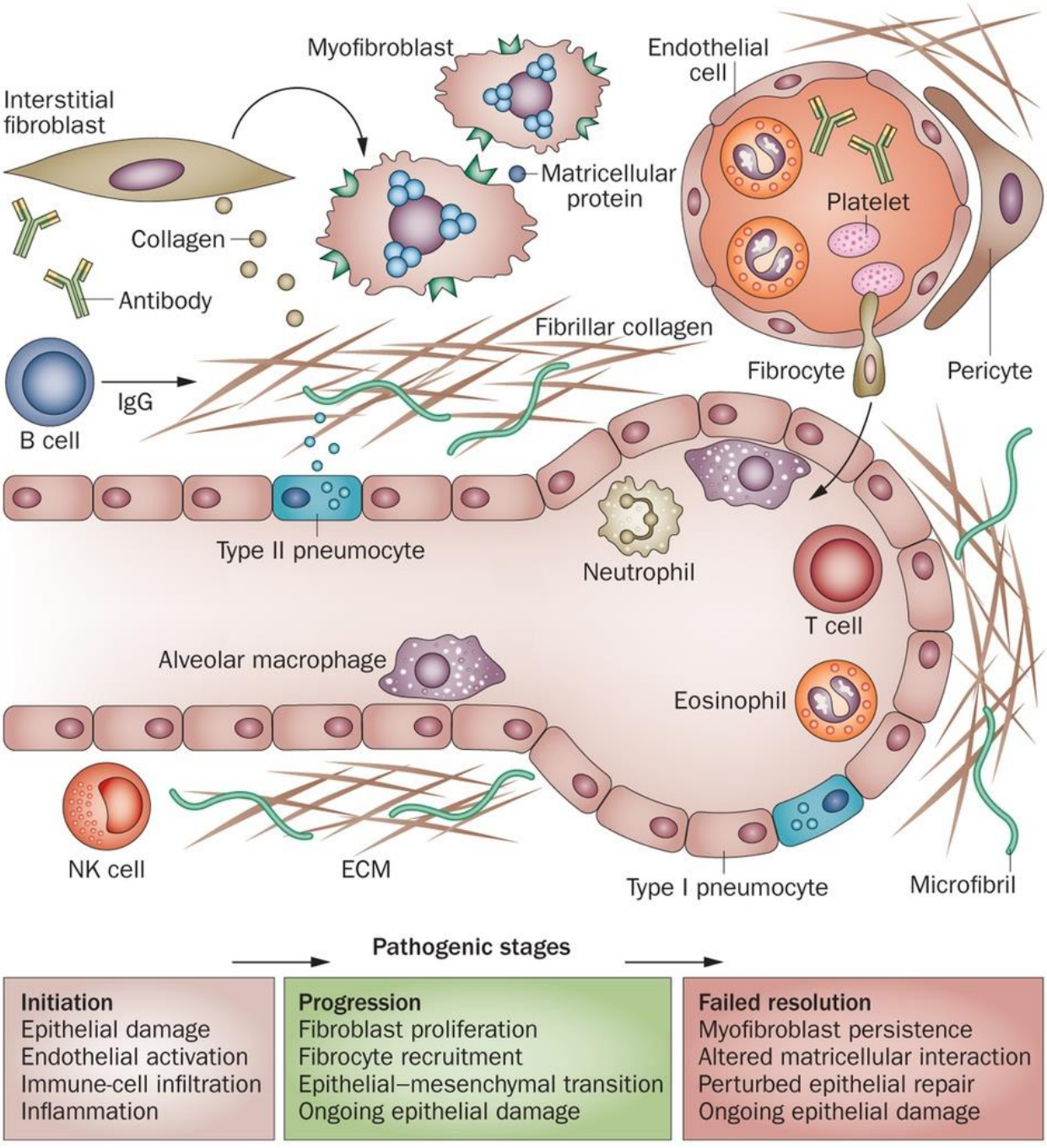


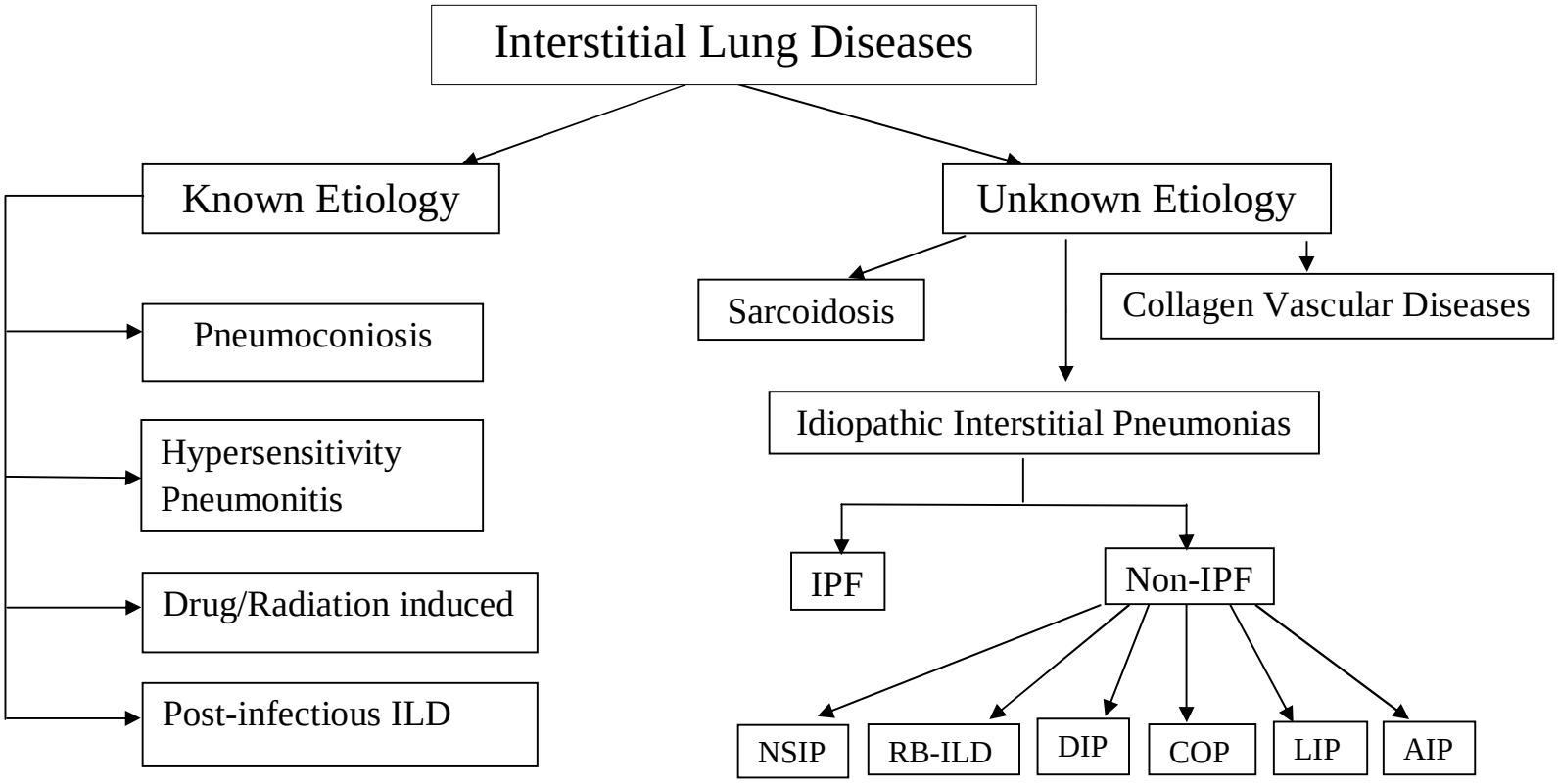
Figure 1. Pathophysiology of ILDs [13]

A-III. Epidemiology

Epidemiology of the ILDs has always been uncertain. As in the beginning these were not understood and identified for a long time until the advent of HRCT, when more clear identification and classifications could be made. A landmark study in the epidemiology of ILD was the first registry in Bernalillo County, New Mexico[1] was published in 1994 and then much later a number of registries in major European countries were established[2]. However, the results of these registries and individual research work remained confounded until 2011, when definitions and identifiable clinical features became more clear and stratified, leading to the possibility of a global approach of identification and classification of the disease. The European registries in Italy, Belgium, Germany, Spain, Greece, Finland, Denmark added invaluable information to the epidemiology of the subject[3,14-18]. This led to the information that various types of ILD had different incidences and prevalences in these registries.

The global data available estimates the prevalence of all ILDs in the US at about 500,000 out of which IPF afflicts between a 132000 to 200000 people[10, 19]. Approximately 50,000 new cases are diagnosed each year and as many as 40,000 people die from IPF each year[19]. Another recent study estimates IPF affects 1 out of 200 adults over the age of 65 in the United States[20]. The current estimate of the incidence of IPF in the EU is between 30,000 to 40,000 people and in the UK more than 5,000 new cases are diagnosed each year[3]. Data from a local registry suggests that the burden of ILD stands at 5.1% of all pulmonary referrals and IPF constitutes 33% of these.[21] Extrapolating the latest US estimation of prevalence, it can be assumed that there are 67,000 IPF patients over the age of 55 years in Pakistan. The total estimated ILD population would hence be much higher.

A IV- CLASSIFICATION OF ILDs: DILUTING THE ALPHABET SOUP



*AIP= Acute Interstitial Pneumonia
*COP=Cryptogenic Organizing Pneumonia,
*DIP= Desquamative Interstitial Pneumonia
*IPF=Idiopathic Pulmonary Fibrosis
* LIP=Lymphocytic Interstitial Pneumonia,
* NSIP= Non-Specific Interstitial Pneumonia,
*RB-ILD= Respiratory Bronchiolitis-ILD

Figure 2: Classification of ILDs

A-V. CLINICAL PRESENTATION AND ESSENTIALS OF DIAGNOSIS:

To reach an accurate diagnosis of a patient suspected of having an ILD, the following should be explored:

DEMOGRAPHICS:

Age and Gender – Some of the ILDs are more common in certain age groups or have a gender predominance. The majority of patients with sarcoidosis, connective tissue disease-associated interstitial lung disease (CTD-ILD), lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), and inherited forms of ILD (familial IPF, Gaucher's disease) present in young ages between 20 and 40 years.[22] In contrast, most patients with idiopathic pulmonary fibrosis (IPF) are over age 50.[10,23] LAM is a disease specific to females. Men are more likely to have pneumoconioses because of occupational exposure and ILD associated with rheumatoid arthritis (RA) is also more common in males.[23]

PRESENTING SYMPTOMS:

Dyspnea which is usually progressive is the most frequent and bothersome symptom. Grading the level of dyspnea is useful as a method to gauge the severity of the disease and to follow its course. Sudden worsening of dyspnea, particularly if associated with pleural pain, may indicate a spontaneous pneumothorax which may occur with underlying ILD.[2]

Cough, mostly dry is the next most common symptom of ILDs and in conditions that affect smaller airways, such as sarcoidosis, bronchiolitis obliterans with or without organizing pneumonia (OP), respiratory bronchiolitis, PLCH, hypersensitivity pneumonitis (HP), lipoid pneumonia, and lymphangitic carcinomatosis (LC).[23] A productive cough is unusual for most ILDs; but maybe seen with secondary bronchiectasis. Rarely, an excessive mucoid, salty-tasting sputum may be a characteristic of bronchoalveolar cell carcinoma mimicking ILD.[24]

Hemoptysis is a rare presentation in ILD. The new onset of hemoptysis in a patient with known ILD may suggest a complicating malignancy or maybe associated with some conditions like vasculitides (GPA) and LAM.[25]

Wheezing and Chest Pain: wheezing and chest pain are uncommon manifestations of ILDs. Wheezing may be heard in eosoniphillic lung diseases. Acute onset of pleuritic chest pain may indicate a pneumothorax.[10,22,23]

Extrapulmonary symptoms may include musculoskeletal pain, weakness, fatigue, fever, joint pains or swelling, photosensitivity, Raynaud phenomenon, pleuritis, dry eyes, and dry mouth. However, the absence of these symptoms does not exclude CTD, as the pulmonary manifestations occasionally precede the more typical systemic manifestations by months or years (especially in RA, SLE, and polymyositis-dermatomyositis).[26]

Onset of Symptoms – The duration of symptoms prior to presentation may help focus the differential diagnosis.[22] The acute or subacute (days to several weeks) processes (e.g., acute interstitial pneumonia (AIP) formerly known as Hamman-Reich syndrome, cryptogenic organizing pneumonia, diffuse alveolar hemorrhage syndromes, HP) often share confusing features with atypical infectious pneumonias. ILDs with a chronic or indolent presentation (e.g., IPF, sarcoidosis, pneumoconioses and chronic HP) need to be differentiated from each other and from other chronic pulmonary diseases.[23]

Past and Personal History

Any past medical or surgical history of CTD, inflammatory bowel disease, or malignancy might be a clue to an associated ILD, either due to the underlying disease or to drugs used to treat the disease.[23]

Some ILDs (eg, PLCH, desquamative interstitial pneumonitis, respiratory bronchiolitis-interstitial lung disease, and IPF) are associated with current or tobacco smoking, while there are few which are found predominantly among never or former smokers.[10,23] Among cigarette smokers with Good pasture syndrome, there are 100% chances of developing DAH, compared to 20% in non smokers.[27] There is increased risk of asbestosis in exposed smokers almost 13 times compared to nonsmoking asbestos workers.[23]

Occupational and environmental exposures

Occupational history should be recorded in a strict chronological fashion of the patient's entire lifelong employment, including specific duties and known exposures to dusts, gases, and chemicals.[28] Family members may develop disease as a result of "passive" exposure to dusts.[23] In HP, there is often a strong temporal relationship between the symptoms and abnormal chest X-ray (CXR) to repeated exposures at the workplace (farmer's lung) or to a hobby (bird fanciers lung).[28] Strong evidence of prolonged exposure to avian antigens because of pigeon infested environment has been noted in coastal areas where it may cause chronic HP and also be associated with IPF making it difficult to differentiate between the two conditions.[29,30]

Drug History

A detailed history of drugs used in the recent and distant past is important. A number of medications used to treat cardiac diseases have been associated with ILD, notably amiodarone but also procainamide, hydrocholorothiazide and ace-inhibitors. Anti-microbials like amphotericin-b, isoniazid, nitrofurantoin. Anti-inflammatory agents used in rheumatology like methotrexate, penicillamine, infliximab, gold. Chemotherapeutic agents bleomycin, busulfan, cyclophosphamide, interferons. Uncommonly, lung disease may appear weeks to years after the drug has been discontinued (eg, nitrofurantoin or carmustine). [31,32]

Radiation-induced lung injury is directly related to the volume of irradiated lung and the cumulative dose of therapeutic irradiation. Symptoms associated with acute radiation pneumonitis usually develop approximately 4-12 weeks following irradiation, whereas symptoms of late or fibrotic radiation pneumonitis develop after 6-12 months.[10,31] Radiation recall pneumonitis can occur months to years after irradiation, when certain antineoplastic agents (eg, adriamycin, paclitaxel, erlotinib, etoposide) are administered to a patient having history of therapeutic lung irradiation.[32]

Family History

Familial associations with an autosomal dominant pattern have been identified in cases of IPF, sarcoidosis, tuberous sclerosis, and neurofibromatosis.[23]

PHYSICAL EXAMINATION:

Respiratory system examination in most forms of ILDs reveals the typical physical finding of bibasilar inspiratory crackles **(velcro rales)**, although they are less likely to be heard in sarcoidosis.[23,33] Crackles may precede the development of radiographic abnormalities on the chest radiograph in early ILDs. It is helpful to listen at the lung bases in the posterior axillary line, as crackles may be audible only in this location in early ILD.[33] Scattered late inspiratory high-pitched rhonchi, so-called **inspiratory squeaks**, are frequently heard in patients with bronchiolitis, but may also be heard in patients with traction bronchiectasis due to interstitial pulmonary fibrosis.[33]

Cardiovascular examination is usually normal except in advanced fibrosis leading to chronic hypoxemia and signs of pulmonary hypertension and cor pulmonale characterized by peripheral edema, tachycardia, loud P2, right-sided parasternal lift and right-sided gallop rhythm. [23]

Clubbing of the digits is typically a late manifestation in the course of ILD and suggests advanced fibrosis of the lung.[33] It is common in some ILDs like idiopathic or familial IPF, asbestosis, chronic HP and rarely in sarcoidosis & PLCH.[33] However, the appearance of digital clubbing in a patient with an established case of ILD could also indicate an underlying bronchogenic carcinoma.[23]

Table 1: Extrapulmonary Physical Findings & Clinical Manifestations in ILDs[23]

Erythema nodosum	**Sarcoidosis; connective tissue disease; Behçet syndrome**
Maculopapular rash	Drug-induced; amyloidosis; lipoidosis; connective tissue diseases; Gaucher disease
Heliotrope rash	Dermatomyositis
Albinism	Hermansky-Pudlak syndrome
Discoid lupus	Systemic lupus erythematosus
Neurofibroma	Neurofibromatosis
Telangiectasia	Scleroderma
Raynaud phenomenon	Connective tissue disease
Cutaneous Vasculitis	Systemic vasculitides; connective tissue disease
Subcutaneous nodules	Neurofibromatosis; rheumatoid arthritis
Calcinosis	Dermatomyositis; scleroderma; amyloidosis
Uveitis	Sarcoidosis; Behçet syndrome; ankylosing spondylitis
Scleritis	Systemic vasculitis; SLE; scleroderma; relapsing polychondritis; sarcoidosis
Keratoconjunctivitis sicca	Lymphocytic interstitial pneumonia (Sjögren syndrome)
Salivary gland enlargement	Sarcoidosis, lymphocytic interstitial pneumonia (Sjögren syndrome)
Peripheral lymphadenopathy	Sarcoidosis; lymphangitic carcinomatosis; lymphocytic interstitial pneumonia; lymphoma
Hepatosplenomegaly	Sarcoidosis; pulmonary Langerhans cell histiocytosis; connective tissue disease; amyloidosis; lymphocytic interstitial pneumonia
Pericarditis	Radiation pneumonitis; connective tissue disease; systemic Vasculitis
Myositis	Connective tissue disease; drugs (L-tryptophan)
Bone involvement	Pulmonary Langerhans cell histiocytosis; sarcoidosis; Gaucher disease; lymphangitic carcinomatosis
Arthritis	Connective tissue disease; systemic vasculitis; sarcoidosis
Diabetes insipidus	Pulmonary Langerhans cell histiocytosis; sarcoidosis
Glomerulonephritis	Systemic vasculitis; connective tissue disease; Goodpasture syndrome; sarcoidosis
Nephrotic syndrome	Amyloidosis; drug-induced (gold, penicillamine); systemic lupus erythematosus
Renal mass	Lymphangioleiomyomatosis; tuberous sclerosis

THE CHEST RADIOGRAPH:

CXR is usually the first investigation in the work up of an ILD. Although HRCT chest is superior to CXR (normal in 10% individuals particularly HP), radiological abnormalities on CXR should be carefully evaluated as they may provide a useful clue to etiology of ILD. Abnormalities on CXR are generally divided into two radiological patterns including alveolar, and interstitial (having further sub types of nodular and linear or reticular).[34] The commonest abnormality is a reticular pattern however, nodular or mixed patterns may be seen in patients with ILDs.[35] Decreased lung volume may be suggestive of disease severity as in IPF and increased lung volume may be seen in ILD with COPD or in LAM. Prominent hilar shadows may be seen in lymphadenopathy (e.g. sarcoidosis) or dilated pulmonary artery in pulmonary hypertension.

PULMONARY FUNCTION TESTS (PFT) :

Complete lung function testing (spirometry, lung volumes, diffusing capacity) and resting and exercise pulse oximetry (depending upon the availability) should be carried out in all patients.[36]

LUNG FUNCTION TEST

Physiologic Parameters	Direction of Change
FVC	↓ ↔
FEV_1/FVC	↑ ↔
DL_{co}	↓
TLC	↓ ↔
Exercise $P(A\text{-}a)O_2$ difference	↑

ANCILLARY LAB TESTS:

In any patient suspected of having an ILD, baseline biochemical tests should be conducted including liver, renal functions (may be abnormal in renopulmonary syndromes), urinalysis and CBC with differential blood count to check for evidence of anemia, polycythemia, leukocytosis, or eosinophilia.[33]
Serologic studies are obtained to ensure that subclinical rheumatic disease is not overlooked. Anti-nuclear antibodies (ANA) and a rheumatoid factor can be used for

screening purposes.[37] Additional serological testing should be reserved for suspected other rheumatic disorders.

BRONCHOALVEOLAR LAVAGE (BAL) & LUNG BIOPSY:

BAL is a minimally invasive procedure performed during bronchoscopy to obtain a sample of alveolar cells. Analysis of BAL, cell counts, cytology, and culture provides insights into immunologic, inflammatory, neoplastic, and infectious processes occurring at the level of alveoli.[38]

In patients with various ILDs, BAL can be diagnostic in the following situations including opportunistic infections, pulmonary alveolar proteinosis (PAP) (milky appearance, alveolar macrophages filled with periodic acid-Schiffï positive material & lamellar bodies), alveolar hemorrhage, diffuse malignant infiltrate, eosinophilic lung disease (> 25% eosinophils in acute and > 40% in chronic eosinophilic pneumonia.[39] BAL lymphocytosis (>35% lymphocytes) most commonly predominates in some diseases including sarcoidosis, HP and others include LIP, pulmonary lymphoma, berylliosis, and some drug-induced ILDs.[23]

Transbronchial lung biopsy (TBLB)

TBLB is often the biopsy procedure of choice when the suspected ILD is likely to have a centrilobular location and when a diagnosis can be made from small samples of lung tissue.[33] Examples include LC, sarcoidosis, HP, rejection after lung transplantation (obliterative bronchiolitis), and mycobacterial and invasive fungal infections presenting as DPLD[23,38] It may also be diagnostic in diffuse malignancies, LIP (lymphocytic infiltration), CEP (eosinophilic microabscesses, low-grade vasculitis, and interstitial fibrosis) and alveolar proteinosis.[39] Potential complications include pneumothorax (0.7 to 10 percent) and hemorrhage (> 50 ml in 4%). Pulmonary hypertension increases the risk of hemorrhage. TBLB is safe in patients receiving aspirin, but clopidogrel should be withheld 5ï 7 days before the test.[39]

Transbronchial cryobiopsy (cryo-TBB) under moderate sedation appears to have a better diagnostic yield and safety profile, is a technique to obtain biopsy samples of lung parenchyma that exceeds the size and quality of conventional forceps biopsy samples.[40]

Surgical or VATS lung biopsy gives the highest yield but is invasive and costly and available only in a few centers in Pakistan. It should be performed if the clinical, and BAL data and TBLB, remain inconclusive and the patient is not at high risk for general anesthesia or the procedure.[23]

Before commencing on any type of lung biopsy, it is important to ensure that adequate pathology service is available and the pathologist is well aware of various interstitial disease histopathological classification and abnormalities. Besides, the outcome of the patient improves if there is liaison between pulmonologist, radiologist, thoracic surgeon and the pathologist (multidisciplinary approach).

Part B. HRCT IN ILD

UNDERSTANDING THE PULMONARY STRUCTURE

Secondary lobule

Knowledge of the lung anatomy is essential for understanding HRCT. The secondary lobule is the basic anatomic unit of pulmonary structure and function. Interpretation of interstitial lung diseases is based on the type of involvement of the secondary lobule. It is the smallest lung unit that is surrounded by connective tissue septa. It measures about 1-2 cm and is made up of 5-15 pulmonary acini, that contain the alveoli for gas exchange. The secondary lobule is supplied by a small bronchiole (terminal bronchiole) in the center, that is paralleled by the centrilobular artery. Pulmonary veins and lymphatics run in the periphery of the lobule within the interlobular septa.

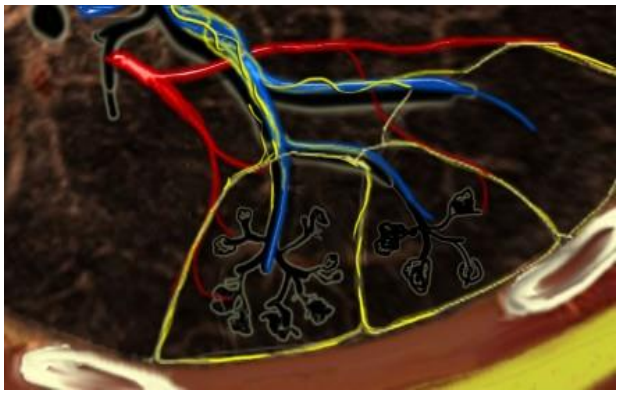


Figure 3.

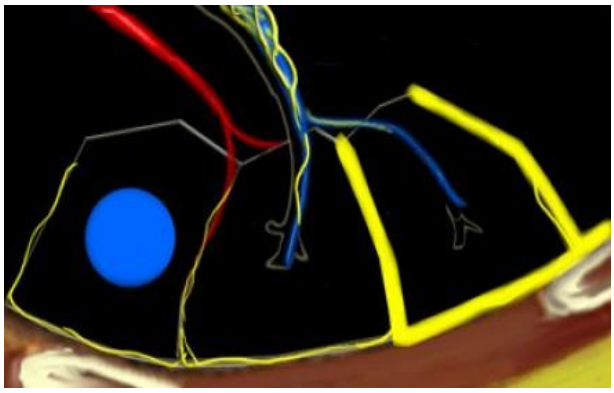


Figure 4.

The centrilobular artery (blue)with oxygen-poor blood and the terminal bronchiole run in the center while lymphatics and veins (red) with oxygen-rich blood run within interlobular septum (Figure 3). Figure 4 shows the centrilobular area in blue (left) and peri-lymphatic area in yellow (right).

Centrilobular area is the central part of the secondary lobule. It is usually the site of diseases, that enter the lung through the airways (i.e. hypersensitivity pneumonitis, respiratory bronchiolitis, centrilobular emphysema).

Perilymphatic area is the peripheral part of the secondary lobule. It is usually the site of diseases, that are located in the lymphatics of the interlobular septa (i.e. sarcoid, lymphangitic carcinomatosis, pulmonary edema). These diseases are usually also located in the central network of lymphatics that surround the bronchovascular bundle.

Basic Interpretation

A structured approach to interpretation of HRCT involves the following questions:

- What is the dominant HR-pattern?
- Reticular Nodular High attenuation (ground-glass, consolidation) Low attenuation (emphysema, cystic)
- Where is it located within the secondary lobule (centrilobular, perilymphatic or random)?
- Is there an upper versus lower zone or a central versus peripheral predominance?
- Are there additional findings (pleural fluid, lymphadenopathy, traction bronchiectasis)?

HRCT Basic Interpretation	
Dominant pattern	**Reticular, Nodular, High density, Low density**
⇩	
Distribution in sec lobule	**Centrilobular, Perilymphatic, Random**
⇩	
Distribution within lung	**Upper zones, Lower zones, Central or peripheral**

RETICULAR PATTERN:

In the reticular pattern there are too many lines, either as a result of thickening of the interlobular septa or as a result of fibrosis as in honeycombing.

Septal thickening

Thickening of the lung interstitium by fluid, fibrous tissue or infiltration by cells results in a pattern of reticular opacities due to thickening of the interlobular septa.
Although thickening of the interlobular septa is relatively common in patients with interstitial lung disease, it is uncommon as a predominant finding and has a limited differential diagnosis

Septal Thickening
Smooth • **Lymphangitic spread of carcinoma or lymphoma** • **Interstitial pulmonary edema** • **Alveolar proteinosis** **Nodular or Irregular** • **Lymphangitic spread of carcinoma or lymphoma** • **Sarcoidosis and silicosis.**

NODULAR PATTERN

The distribution of nodules shown on HRCT is the most important factor in making an accurate diagnosis in the nodular pattern. In most cases small nodules can be placed into one of three categories: perilymphatic, centrilobular or random distribution.

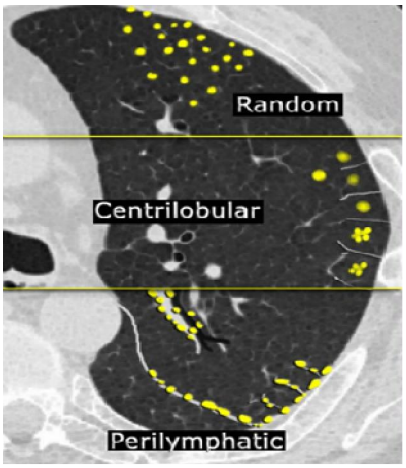


Figure 5. Types of nodules

Perilymphatic distribution
In patients with a perilymphatic distribution, nodules are seen in relation to pleural surfaces, interlobular septa and the peribronchovascular interstitium. Nodules are almost always visible in a subpleural location, particularly in relation to the fissures.

Centrilobular distribution
In certain diseases, nodules are limited to the centrilobular region. Unlike perilymphatic and random nodules, centrilobular nodules spare the pleural surfaces. The most peripheral nodules are centered 5-10mm from fissures or the pleural surface.

Random distribution Nodules are randomly distributed relative to structures of the lung and secondary lobule. Nodules can usually be seen to involve the pleural surfaces and fissures, but lack the subpleural predominance often seen in patients with a perilymphatic distribution.

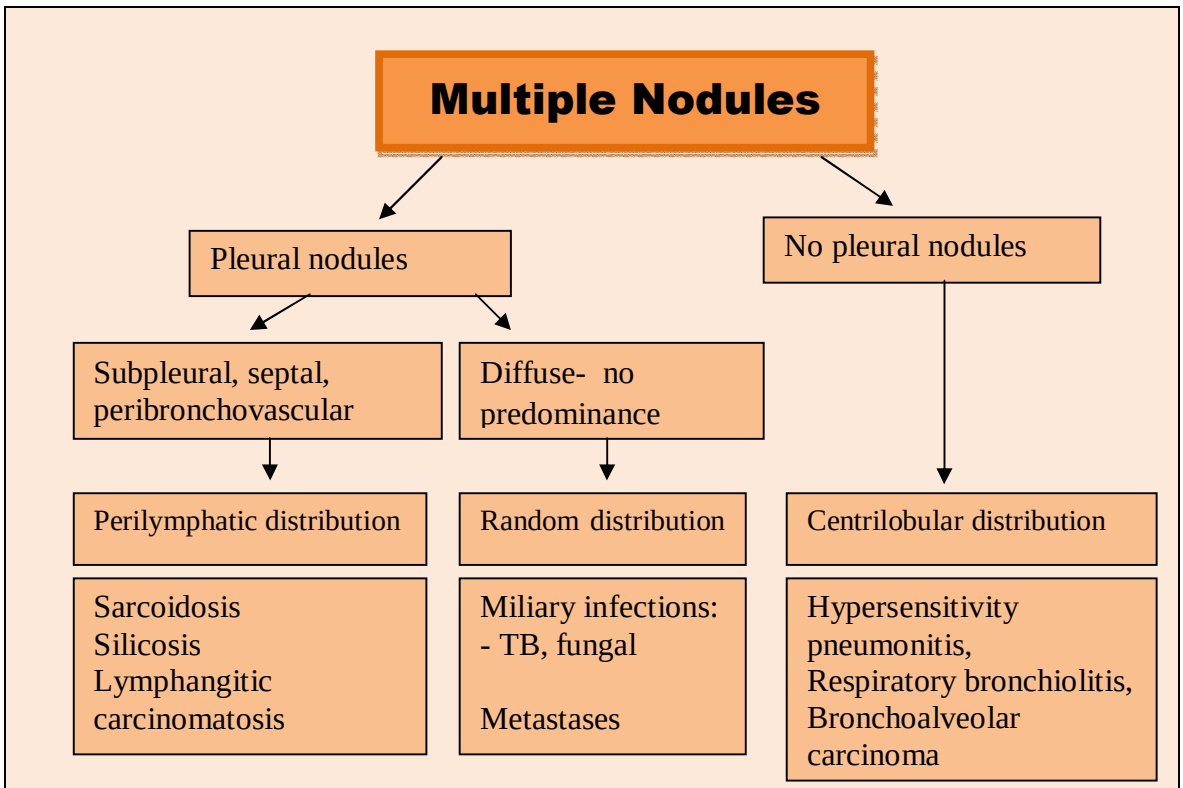


Figure 6. Identifying the pattern of nodules

Perilymphatic Nodules
• **Sarcoidosis** • **Lymphangtic spread of carcinoma** • **Silicosis & coal workers' pneumoconiosis** • **Lymphoid interstitial pneumonitis (rare)** • **Amyloidosis (rare)**

Tree-in-bud

In centrilobular nodules the recognition of 'tree-in-bud' is of value for narrowing the differential diagnosis.
Tree-in-bud describes the appearance of an irregular and often nodular branching structure, most easily identified in the lung periphery.
It represents dilated and impacted (mucus or pus-filled) centrilobular bronchioles.

Tree in Bud
• **Infection – Tuberculosis, MAC (mycobacterium avium), bacterial, fungal** • **Airways disease (i.e cystic fibrosis or bronchietasis)** • **ABPA (Allergic bronchopulmonary aspergillosis (rare)**

HIGH ATTENUATION PATTERN

Ground-glass opacity

Ground-glass opacity (GGO) represents:

- Filling of the alveolar spaces with pus, edema, hemorrhage, inflammation or tumor cells.
- Thickening of the interstitium or alveolar walls below the spatial resolution of the HRCT as seen in fibrosis.

So ground-glass opacification may either be the result of air space disease (filling of the alveoli) or interstitial lung disease (i.e. fibrosis).

The location of the abnormalities in ground glass pattern can be helpful:

- Upper zone predominance: Respiratory bronchiolitis, Pneumocystis Carinii Pneumonia (PCP).
- Lower zone predominance: UIP, NSIP, DIP.
- Centrilobular distribution: Hypersensitivity pneumonitis, Respiratory bronchiolitis

Ground glass opacity	
Acute	**Chronic**
Pulmonary edema	**Hypersensitivity pneumonitis**
- ***Heart failure***	**Organizing pneumonia (BOOP, COP)**
- ***ARDS***	**Chronic Eosinophilic pneumonia**
Pulmonary hemorrhage	
Pneumonia	**Alveolar proteinosis**
- ***Viral***	**Lung fibrosis**
- ***Mycoplasma***	***- UIP***
- ***PCP***	***-NSIP***
Acute Eosinophilic pneumonia	**Bronchoalveolar carcinoma**

MOSAIC ATTENUATION

The term 'mosaic attenuation' is used to describe density differences between affected and non-affected lung areas. There are patchy areas of black and white lung. The role of the radiologist is to determine which part is abnormal.

When ground glass opacity presents as mosaic attenuation consider:

- Infiltrative process adjacent to normal lung
- Normal lung appearing relatively dense adjacent to lung with air-trapping
- Hyperperfused lung adjacent to oligemic lung due to chronic thromboembolic disease

It can be difficult to distinguish these three entities. There are two diagnostic hints:

- Look at expiratory scans for air trapping
- Look at the vessels

If the vessels are difficult to see in the 'black' lung as compared to the 'white' lung, then it is likely that the 'black' lung is abnormal.

Then there are two possibilities: obstructive bronchiolitis or chronic pulmonary embolism. Sometimes these can be differentiated with an expiratory scan.

If the vessels are the same in the 'black' lung and 'white' lung, then you are looking at a patient with infiltrative lung disease, like the one on the right with the pulmonary hemorrhage.

Mosaic Attenuation
• **Asthma** • **Bronchiolitis** • **Hypersensitivity pneumonitis** • **Pulmonary embolism**

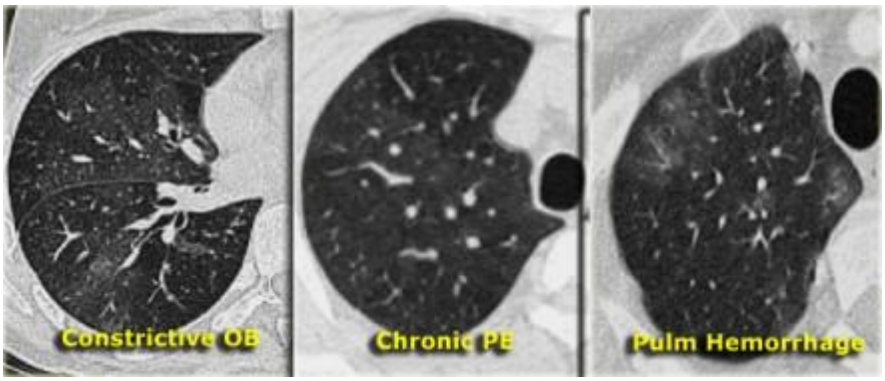


Figure 7. Three different causes of mosaic attenuation

CRAZY PAVING

Crazy Paving is a combination of ground glass opacity with superimposed septal thickening.

It was first thought to be specific for alveolar proteinosis, but later was also seen in other diseases.

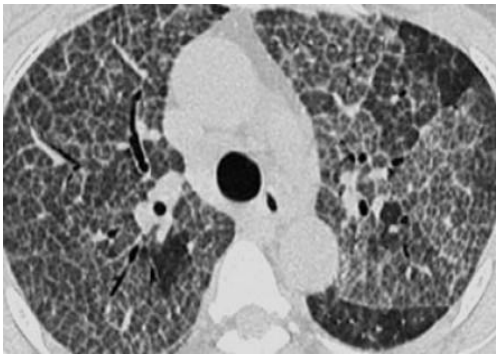


Figure 8.Crazy Paving in a patient with AP.

LOW ATTENUATION PATTERN

The fourth pattern includes abnormalities that result in decreased lung attenuation or air-filled lesions.
These include:

- Emphysema
- Lung cysts (LAM, LIP, Langerhans cell histiocytosis)
- Bronchiectasis
- Honeycombing

Emphysema

Emphysema typically presents as areas of low attenuation without visible walls as a result of parenchymal destruction.

- **Centrilobular emphysema**
  - Most common type
  - Irreversible destruction of alveolar walls in the centrilobular portion of the lobule
  - Upper lobe predominance and uneven distribution
  - Strongly associated with smoking.
- **Panlobular emphysema**
  - Affects the whole secondary lobule
  - Lower lobe predominance
  - In alpha-1-antitrypsin deficiency, but also seen in smokers with advanced emphysema
- **Paraseptal emphysema**
  - Adjacent to the pleura and interlobar fissures
  - Can be isolated phenomenon in young adults, or in older patients with centrilobular emphysema
  - In young adults often associated with spontaneous pneumothorax

Cystic lung disease

Lung cysts are defined as radiolucent areas with a wall thickness of less than 4mm.

Cavities are defined as radiolucent areas with a wall thickness of more than 4mm and are seen in infection (TB, Staph, fungal, hydatid), septic emboli, squamous cell carcinoma and Wegener's disease.

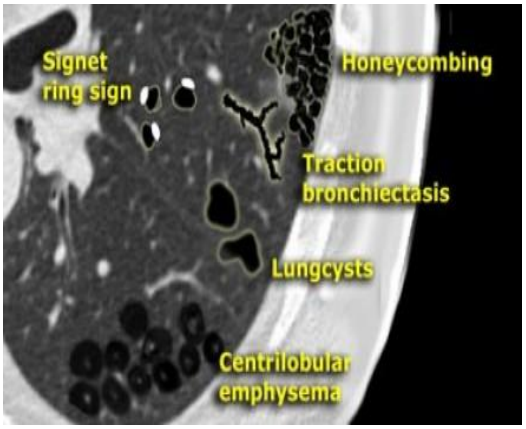


Figure 9. Cystic Lung Disease

Cystic Lung Diseases
• **Lymphangioleiomyomatosis** • **Langerhans cell histiocytosis** • **Lymphocytic interstitial pneumonia** • **Pneumatoceles (PCP)** • **Honeycombing**

BRONCHIECTASIS

Bronchiectasis is defined as localized bronchial dilatation.
The diagnosis of bronchiectasis is usually based on a combination of the following findings:

- bronchial dilatation (signet-ring sign)
- bronchial wall thickening
- lack of normal tapering with visibility of airways in the peripheral lung
- mucus retention in the bronchial lumen
- associated atelectasis and sometimes air trapping

A signet-ring sign represents an axial cut of a dilated bronchus (ring) with its accompanying small artery (signet).
Bronchiectasis may mimic cystic lung disease and bullous emphysema.
Bronchiectasis caused by primary airway disease should be differentiated from traction bronchiectasis as a result of fibrosis.

HONEYCOMBING

Honeycombing is defined by the presence of small cystic spaces with irregularly thickened walls composed of fibrous tissue. Honeycomb cysts often predominate in the peripheral and subpleural lung regions regardless of their cause. Subpleural honeycomb cysts typically occur in several contiguous layers. This finding can allow honeycombing to be distinguished from paraseptal emphysema in which subpleural cysts usually occur in a single layer.

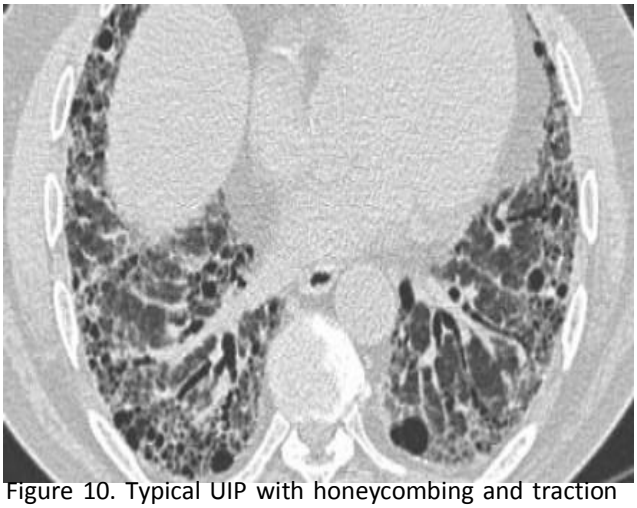


Figure 10. Typical UIP with honeycombing and traction bronchiectasis in a patient with idiopathic pulmonary fibrosis (IPF)

DISTRIBUTION WITHIN THE LUNG

Upper lung zone preference is seen in:

- Inhaled particles: pneumoconiosis (silica or coal)
- Smoking related diseases (centrilobular emphysema
- Respiratory bronchiolitis (RB-ILD)
- Langerhans cell histiocytosis
- Hypersensitivity pneumonitis
- Sarcoidosis

Lower zone preference is seen in:

- UIP
- Aspiration
- Pulmonary edema

Central distribution is seen in

- sarcoidosis and
- cardiogenic pulmonary edema.

Peripheral distribution is mainly seen in

- Cryptogenic organizing pneumonia (COP),
- Chronic eosinophilic pneumonia and
- UIP.

Honeycombing
○ **UIP or Interstitial fibrosis** • **IPF** • **RA, scleroderma** • **drug reaction** • **asbestosis** ○ **End stage hypersensitivity pneumonitis** ○ **End stage sarcoidosis**

IDIOPATHIC INTERSTITIAL PNEUMONIAS

Idiopathic interstitial pneumonias	
UIP	**Basal and peripheral reticular opacities Honeycombing Traction bronchiectasis**
NSIP	**Basal ground-glass opascities Traction bronchiectasis in advanced disease**
COP	**Patchy peripheral or peribronchovascular consolidation**
RB-ILD, DIP	**Centrilobular nodules ground-glass opacities**
AIP fibrosis	**Diffuse consolidation and ground-glass Progresses to**
LIP lesions	**Ground-glass opacities, Often in combination with cystic**

These diseases have specific patterns of morphologic findings on HRCT and histology. Before we call these findings idiopathic or cryptogenic, we should realize, that these patterns are also common findings in collagen vascular diseases (e.g., scleroderma, rheumatoid arthritis) and drug-related lung diseases. For instance in patients with rheumatoid arthritis findings of NSIP, UIP, OP and LIP have been reported.

UIP

Usual Interstitial Pneumonitis (UIP) is a histologic diagnosis.
UIP has distinctive HRCT findings. If the UIP pattern is of unknown cause (i.e. idiopathic), the disease is called **Idiopathic pulmonary fibrosis (IPF)**

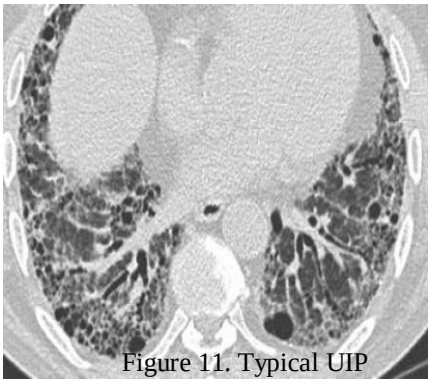


Figure 11. Typical UIP

HRCT findings in UIP

- Honeycombing consisting of multilayered thick-walled cysts.
- Architectural distortion with traction bronchiectasis due to fibrosis.
- Predominance in basal and subpleural region.
- Mild mediastinal lymphadenopathy

Differential diagnosis of UIP.

- Chronic Hypersensitivity Pneumonitis
- End stage Sarcoidosis
- NSIP

- Chronic HP may be indistinguishable. It is suspected if there is a mosaic pattern with sparing of the lung bases or when there are centrilobular nodules.
- Sarcoidosis is a more likely diagnosis if the fibrosis is located in the posterior parts of the upper lobes or in the perihilar area and if there are also nodules in a perilymphatic distribution or if there is extensive mediastinal lymphadenopathy.
- The presence of pleural plaques helps for the differentiation between IPF and asbestosis.

NSIP

NSIP is a very inhomogeneous group. NSIP ranges from type I which is a cellular pattern seen as ground glass opacity on HRCT to type IV with a fibrotic pattern, which may be indistinguishable from UIP.

.

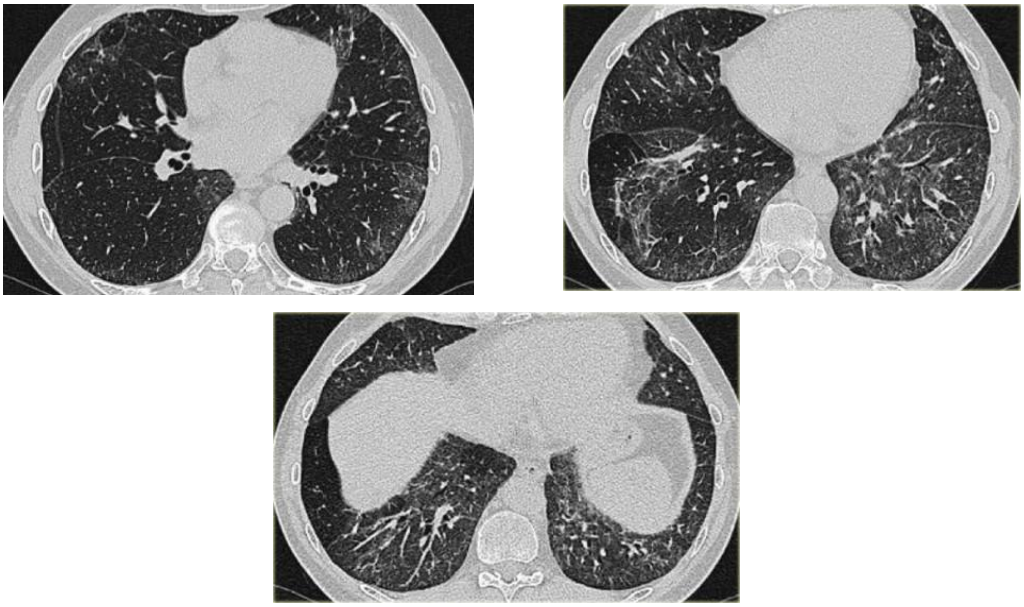


Figure 12. HRCT images of a patient with a NSIP

*Adopted from: Radiology Assistant
Author: Robin Smithuis, Otto van Delden and Cornelia Schaefer-Prokop. Radiology Department of the Rijnland Hospital, Leiderdorp and the Academical Medical Centre, Amsterdam, the Netherlands

Note: For further learning of the HRCT differential diagnosis of variuos ILDs, the pulmonologist is recommended to keep a copy of an ILD atlas at his clinic and refer to it as frequently as possible. Recommended reading: Diffuse lung diseases M. Maffessanti, G. Dalpiaz - Springer 2006.

Part C INTERSTITIAL PULMONARY FIBROSIS

C- I. Definition of IPF

Idiopathic Pulmonary Fibrosis is defined as a specific form of chronic, progressive fibrotic interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP (refer table 2 and 3). The definition of IPF requires the exclusion of all other forms of interstitial pneumonia including other idiopathic interstitial pneumonias and ILD associated with environmental exposure, medication, or systemic disease.[41]

C-II. CLINICAL PRESENTATION

Consider **IPF** in any gender if:

- unexplained dry cough
- unexplained chronic exertional dyspnea
- bibasal end-inspiratory crackles classically of the "velcro" type
- finger clubbing

It is seen more in age greater than 50 years, typically past 60 years, and among male smokers.

C-III. INCIDENCE AND PREVALENCE

Refer to Part A-III.

C-IV. POTENTIAL RISK FACTORS

Although idiopathic pulmonary fibrosis by definition is a disease of unknown etiology, a number of potential risk factors have been identified as under.

1. **Cigarette Smoking**
   Strong association especially more than 20 pack years history
2. **Environmental Exposures** ï
   Exposure to metal dusts (brass, lead, steel), Wood dust, Vegetable dust, Animal dust and occupational exposures like agricultural, farming, bird raising, livestock exposure or hair dressing may be associated.

3. Microbial Agents

Chronic viral infections- Hep-C, CMV, Herpes virus including EBV, HHV 7 and HHV 8

4. Gastro Esophageal Reflux

Lately many studies have suggested that abnormal Gastro Esophageal Reflux (GER) because of micro aspiration, is a risk for developing IPF. This GER may not necessarily be symptomatic. It is specially noted in patients with lung fibrosis associated with scleroderma. Alkaline GERD may also be relevant to IPF, studies are going on in this regard.[6]

5. Genetic Risk Factors / Familial IPF

IPF affecting two or more members of the same biological family account for around less than 5% of total population. Clinical presentation of familial IPF is identical with sporadic IPF. Familial IPF is an autosomal dominant type of genetic transmission with variable penetrance and a linkage of chromosome 14. Genetic testing in patients with either familial or sporadic IPF as part of routine clinical evaluation is not recommended.[6]

C-V. DIAGNOSIS

- Careful exclusion of alternative etiologies through multi-disciplinary discussion between pulmonologists, radiologists, and pathologists experienced in the diagnosis of ILD is of the utmost importance to form an accurate diagnosis.
- In situations in which multidisciplinary discussion is not feasible, it is recommended that patients be referred to experienced clinical experts in ILD for consultation.
- Given the high-quality evidence regarding HRCT specificity for the recognition of histopathologic UIP pattern, surgical lung biopsy is not essential [42-45]. In the appropriate clinical setting as described in Part A-V a thorough medical, occupational/environmental and family history, physical examination, physiological testing, and laboratory evaluation, the presence of a UIP pattern on HRCT is sufficient for the diagnosis of IPF.

C-VI. DIAGNOSTIC CRITERIA

The diagnosis of IPF requires the following:

1. Exclusion of other known causes of ILD: domestic/occupational environmental exposures, connective tissue disease, and drug toxicity).
2. The presence of a typical UIP pattern on HRCT (Table 3).
3. Specific combinations of possible UIP on HRCT and histopathologic pattern on surgical lung biopsy (Tables 2,3). (The decision regarding surgical lung biopsy must be tailored to the clinical situation of the patient.)
4. Multidisciplinary discussion in case of discordant HRCT and histopathologic patterns.

TABLE: 2 Histopathological Features[6]

UIP Pattern (All Four Criteria)	Probable UIP Pattern	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
• Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly sub pleural/ paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis. • Presence of fibroblast foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	• Evidence of marked fibrosis / architectural distortion, ± honeycombing. • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column) OR • Honeycomb changes onlyÿ	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation. • Absence of other criteria for UIP (see UIP PATTERN column) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	• Hyaline membranes* • Organizing pneumonia*À • GranulomasÀ • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes • Other features suggestive of an alternate diagnosis

Definition of abbreviations:
HRCT= high-resolution computed tomography;
UIP = usual interstitial pneumonia.
* Can be associated with acute exacerbation of idiopathic pulmonary fibrosis.
À An isolated or occasional granuloma and/or a mild component of organizing pneumonia pattern may rarely be coexisting in lung biopsies with an otherwise UIP pattern.
ÿ This scenario usually represents end-stage fibrotic lung disease where honeycombed segments have been sampled but where a UIP pattern might be present in other areas. Such areas are usually represented by overt honeycombing on HRCT and can be avoided by pre-operative targeting of biopsy sites away from these areas using HRCT.

TABLE: 3 HRCT Diagnostic Features[6]

UIP Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (Any of the Seven Features)
• Sub pleural, basal predominance • Reticular abnormality • Honeycombing with or without traction bronchiectasis • Absence of features listed as inconsistent with UIP pattern (see third column)	• Sub pleural, basal predominance • Reticular abnormality • Absence of features listed as inconsistent with UIP pattern (see third column)	• Upper or mid-lung predominance • Peribronchovascular predominance • Extensive ground glass abnormality (extent> reticular abnormality). • Profuse micro nodules (bilateral, predominantly upper lobes) • Discrete cysts (multiple, bilateral, away from areas of honeycombing) • Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes) • Consolidation in Broncho pulmonary segment(s)/lobe(s)

C-VII. DIAGNOSTIC ALGORITHM

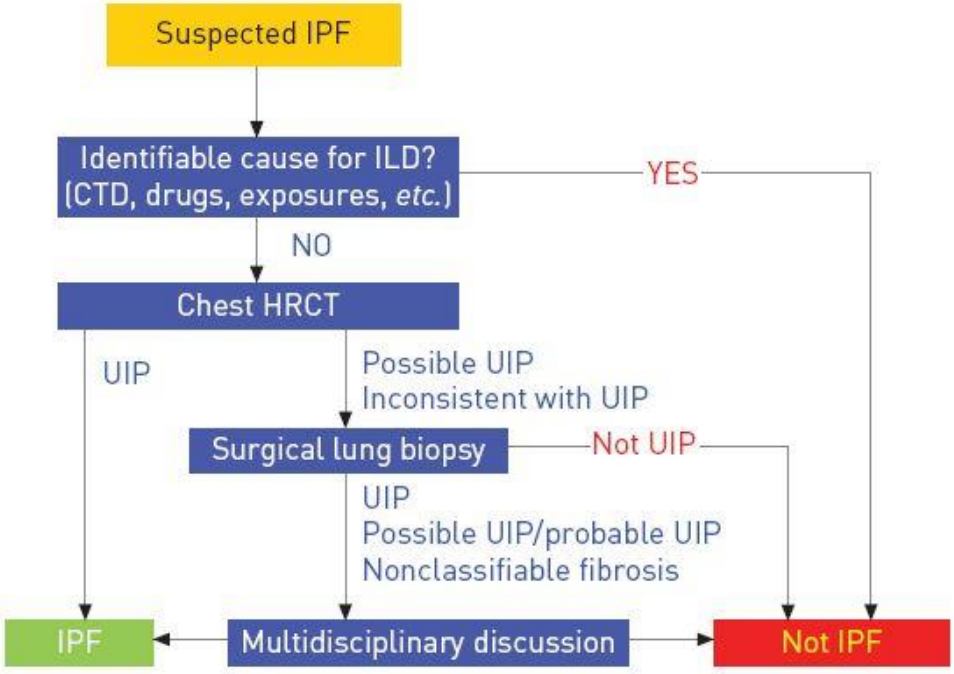


Figure 13. Diagnostic algorithm for idiopathic pulmonary fibrosis (IPF). Patients with suspected IPF (i.e., patients with unexplained dyspnea on exertion and/or cough with evidence of interstitial lung disease [ILD]) should be carefully evaluated for identifiable causes of ILD. In the absence of an identifiable cause for ILD, an HRCT demonstrating UIP pattern is diagnostic of IPF. In the absence of UIP pattern on HRCT, IPF can be diagnosed by the combination of specific HRCT and histopathological patterns. The accuracy of the diagnosis of IPF increases with multidisciplinary discussion (MDD) among ILD experts. [8]

C-VIII. EXCLUSION OF OTHER KNOWN CAUSES

Chronic Hypersensitivity Pneumonitis can mimic IPF and in doubt may need investigation using BAL and possibly a surgical lung biopsy. Index of suspicion for connective tissue disorder (CTD) should be high especially in young females (less than 50 years of age). CTD can present with a UIP pattern, hence serological testing (RA, Anti-CCP, ANA) should be performed in majority of patients. Other tests (ENA) maybe performed if there is presence of extra thoracic symptoms.

C-IX. NATURAL HISTORY OF IPF AND RISK OF MORTALITY

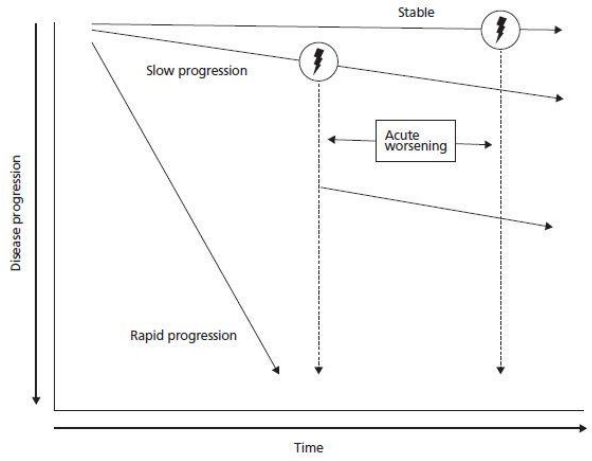


Figure 14. Natural history of IPF[6]

TABLE 4 . SELECTED FEATURES ASSOCIATED WITH INCREASED RISK OF MORTALITY IN IDIOPATHIC PULMONARY FIBROSIS[6]

Baseline factors

Level of dyspnea

DlCo < 40% predicted

Desaturation Ò88% during 6MWT

Extent of honeycombing on HRCT

Pulmonary hypertension

Longitudinal factors

Increase in level of dyspnea

Decrease in Forced Vital Capacity by Ó10% absolute value

Decrease in DlCo by Ó15% absolute value

Worsening of fibrosis on HRCT

Natural History Of Disease

For a given patient, the natural history is unpredictable at the time of the diagnosis but the majority of patients demonstrate a slow, gradual progression over many years. Some patients remain stable while others have an accelerated decline [46,47]. Some patients may experience episodes of acute respiratory worsening. It is unknown if these different natural histories represent distinct phenotypes of IPF or if the natural history is influenced by geographic, ethnic, cultural, racial, or other factors. Other comorbid conditions such as emphysema and pulmonary hypertension may impact the disease course [48-50].

Risk Of Mortality Assessment

Prognostic features at the time of diagnosis and the increased risk of mortality at baseline as well as periodic assessment on the basis of longitudinal factors can give the clinician an idea of the course of disease. (Table 4)

C-X. TREATMENT RECOMMENDATIONS

NOT RECOMMENDED FOR USE IN IPF PER SE

- Anticoagulation (warfarin)
- Imatinib (tyrosine kinase inhibitor against PDGF
- Combination therapy (prednisone, azathioprine and N- acetyl cysteine)
- Endothelin receptor antagonists (bosentan)
- Phosphodiesterase-5 inhibitor (sildenafil)
- N-Acetyl cysteine monotherapy

CONDITIONAL RECOMMENDATION FOR USE IN IPF

- Antiacids
- Anti fibrogenic therapy

ANTI FIBROGENIC TREATMENT:

Goal of Therapy:
It is important that both clinicians and patients understand at the outset of therapy that the goal of treatment is not to recover lung function and improve symptoms but it is to slow disease progression and thus stall the deterioration of dyspnea and delay the development of respiratory failure.

Previously, immune suppression was considered important in the treatment of IPF. Patients were treated with combination of Prednisolone, Azathioprine, and N-Acetylcysteine . However, post PANTHER trial, the updated ATS/ERS Clinical Practice Guidelines published in 2015 recommend against the use of triple drug combination in IPF [7,9]. These recommendations, may not necessarily be generalized to other forms of interstitial lung diseases.

Recently two anti fibrogenic drugs have been approved in Europe and USA for the treatment of IPF. Randomised clinical trials demonstrate that patients with mild-to-moderate IPF benefit from anti fibrogenic therapy with reduced lung function decline and improved survival [51,52.]

PIRFENIDONE:

Introduction:

Pirfenidone was approved by the European Medicines Agency in March 2011, becoming the first licensed therapy for IPF in Europe. The US Food and Drug Administration (FDA) approved pirfenidone, simultaneously with Nintedanib, as a treatment for IPF in the USA in October 2014.

Pirfenidone is a small, orally available molecule that demonstrates anti-inflammatory and anti-fibrotic effects. It results in dose-related reductions in fibrosis through modulation of cytokines and growth factors, including transforming growth factor-ɓ and tumour necrosis factor-Ŭ.

Phase III trials CAPACITY and ASCEND have shown that Pirfenidone treatment reduced lung function decline, improved progression-free survival and reduced both all-cause mortality at 1 year [51,52].

Given the different inclusion criteria for the pirfenidone trials, these results cannot necessarily be generalized to patients with IPF with more severe impairment in PFTs or for patients with other significant comorbidities. The evidence does not offer suggestions about the optimal duration of therapy, and it is uncertain how long the treatment effect endures with ongoing drug therapy.

Indications And Recommendations For Treatment:

- It is currently recommended to treat patients with **mild-to-moderate IPF.**
- This treatment should be initiated and supervised by a physician experienced in the diagnosis and management of IPF.
- **Mandatory baseline PFT** should be performed prior to beginning treatment. Ideally the patient should have **FVC_o ≥50% predicted and $DLCO_o$ ≥35% predicted)**. [8] However in Pakistan Dlco testing facilities are rarely available and a majority of IPF have FVC <50% predicted at the time of diagnosis. While it may be unjustified to keep all these patients away from treatment, strict follow-up with monitoring of PFT at a periodic interval of 4-6 months should be mandatory. If there is a decline in FVC of >10% at the end of 1 year the medication should be discontinued.
- Clinical tolerance and liver enzymes should be monitored during the treatment. The patient must be advised not to smoke and also warned against UV exposure.[8]

Dose:

Drug may be started in a dose of 600mg (one tab three times daily along with meals) initially to check tolerability and within 2 weeks increased to 1200mg and further increased to an optimum dose of 2400mg per day. However, an optimum dose of 1800mg daily should be continued if drug is not tolerated in a higher dose.

Side Effects:

Pirfenidone is generally well tolerated; the most common side effects observed in clinical trials were gastrointestinal and skin-related. In order to reduce these side effects patients should take pirfenidone with food. If symptoms persist, patients may be

instructed to interrupt treatment for 1ï 2 weeks to allow symptoms to resolve. Prokinetic agents or proton-pump inhibitors may be added to manage gastrointestinal symptoms.

NINTEDANIB:

Nintedanib, the second anti-fibrogenic drug, is an intracellular inhibitor of several tyrosine kinases that targets multiple growth factor receptors, including vascular endothelial growth factor, fibroblast growth factor, and platelet derived growth factor (PDGF) [53, 54]. This drug is not yet available in Pakistan.

C-XI. ACUTE EXACERBATION OF IPF (AE-IPF)

There is no universal definition of an AE-IPF. An AE-IPF is suspected when there is a sudden deterioration in the clinical status of the disease [55,56.] Recent observations have suggested that acute respiratory worsening occurs in a small minority of patients with IPF annually (approximately 5ï 10%) [57-59]. Acute exacerbation can occur at any point in the course of IPF and occasionally can be its presenting manifestation [60-63]. Worsened cough, fever, and/or increased sputum have been observed [60,61,64]. While there are no known risk factors for acute exacerbation of IPF, there have been reports of acute respiratory decompensation after thoracic surgery [65-69]and broncho alveolar lavage [60,70]. It is unclear whether or not these events represent true acute exacerbations or complications of the respective procedures.

Diagnostic Criteria:

Standard criteria have been proposed to diagnose AE-IPF[8,56]. These criteria include:

1. A previous or concurrent diagnosis of IPF with unexplained worsening or development of dyspnea within 30 days
2. Exclusion of other etiologies including infection, left-sided heart failure, pulmonary embolism, pneumothorax and an identifiable cause of acute lung injury.
3. New bilateral ground-glass abnormality and/ or consolidation superimposed on a background reticular/honeycomb pattern consistent with usual interstitial pneumonia (UIP) on high-resolution computed tomography (HRCT).
4. Worsening of hypoxaemia is common (10 mmHg decrease of PaO_2).

MANAGEMENT

The management of AE-IPF is a challenging task because of lack of expertise, resources, diagnostic difficulties and limited therapeutic options. Still the main treatment options remain supportive care and corticosteroids [6,8].

Corticosteroids:

Despite the lack of convincing evidence, corticosteroids are used as the mainstay of the treatment of AE-IPF [6,8,71]. The dosage is usually selected according to the severity of the exacerbation. A mild or moderate exacerbation is treated with 0.5-1mg/kg of prednisone tapered over weeks; while the severe exacerbation may initially be treated with pulse Methylprednisolone (0.5 ï 1gm/day I/V) for three days followed by oral steroids.

Antibiotics:

Though the diagnosis of the AE-IPF requires the exclusion of infection as the cause of deterioration but it is not often possible to exclude infections by BAL because of marked hypoxia and respiratory distress. Therefore depending on the clinical judgement of the physician and the usual antibiogram spectrum of the ICU, broad spectrum antibiotics should be prescribed. Where the facility is available and affordable the initiation and duration of the antibiotics can be d by serum procalcitonin level which is a recent surrogate marker for bacterial infection [72].

Oxygen Therapy

Oxygen should be supplemented to keep oxygen saturation more than 88%.[6,8] This can be done more easily by using an oxygen concentrator.

Non Invasive Ventilation (NIV)

NIV can be used to alleviate symptoms and reduce the need for mechanical ventilation and can be tried in selected patients [8,73]

Invasive Ventilation

Invasive mechanical ventilation is associated with high mortality rate and is not recommended in the majority of patients with AE-IPF [74-76]. However invasive mechanical ventilation maybe suitable where patients are planned for lung transplantation, patients with an identified reversible cause like infection, pulmonary embolism or pneumothorax (these patients are usually not classified as AE-IPF).

Other immunosuppressive drugs

In addition to corticosteroids many other immunosuppressive agents (including cyclosporine A, cyclophosphamide, Tacrolimus, sivelestat) have been used with variable results [77-80.] The French guidelines have given possible recommendation for the use of cyclophosphamide after a promising study which included a small number of patients [8,77.] All these agents require more studies before they can be generally recommended.

C-XII. PULMONARY REHABILITATION (PR)

Pulmonary rehabilitation includes conditioning; exercise training and breathing exercises; anxiety, stress, and depression management; nutritional counseling; education; and other components. The goal of pulmonary rehabilitation is to restore the patientôs ability to function without extreme breathlessness, therefore should be offered to patients with stable IPF.[81] PR can improve the walking distance and quality of life. [8, 82] The patients with advanced disease may not be suitable candidates for PR [8].

Using a multidisciplinary approach, palliative care can involve physical, psychosocial, and spiritual factors as a part of management plan.

C-XIII. LUNG TRANSPLANTATION

IPF is now the leading indication for lung transplantation in many large transplant centers of the world. Transplantation can improve both longevity and the quality of life in properly selected patients who have no other significant health problems. Previously, it was uncommon for individuals over the age of 65 to receive transplants. However, as surgical techniques and outcomes have improved more centers are performing transplants in individuals over age 65. Transplantation is not without risk; patients should discuss all of the potential risks and benefits of lung transplantation with their physician.[81] The facility of lung transplantation is not available in Pakistan.

REFERENCES

1. Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. Am J RespirCrit Care Med 1994;150: 967-72
2. Thomier MJ, Costabel U, Rizzato G, Poletti V, Demedts M. Comparison of registries of interstitial lung diseases in three European countries. Euro Resp Journal ERJ. 2001;18 (32): 114-18
3. Navaratnum V, Fleming KM, West J, Smith CJP, Jenkins RG, Fogarty A et al. The rising incidence of idiopathic pulmonary fibrosis in the UK. Thorax 2011, April, 27;66:462ï 67
4. ILDPAK Registry [cited 2016 March 24] available from http://www.ildpak.com
5. ILD India Registry [cited 2016 march 24] available from http://www.ildindiaregistry.com
6. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK et al. An official ATS/ERS/JRS/ALAT statement: Idiopathic Pulmonary Fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011; 183:788ï 824.
7. Raghu G, Rochwerg B, Zhang Y, Garcia CAC, Azuma A, Behr J, et al. 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;192: e3ï 19.
8. Cottin V, Crestani B, ValeyreD, Wallaert B, Cadranel J, DalphinJC. Diagnosis and management of idiopathic pulmonary fibrosis: French practical guidelines. Eur Respir Rev 2014; 23: 193ï 214
9. Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Mrtinez FJ. Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis. N Engl J Med. 2012 May 24; 366 (21) 1968- 77
10. King TE Jr. Clinical advances in the diagnosis and therapy of interstitial lung diseases. Am J Respir Crit Care Med 2005 Aug 1; 172 (3):268-279
11. Cushley MJ, Davison AG, DuBois RM et al. The diagnosis, assesment and treatment of the diffuse parenchymal lung disease: British thoracic Society recommendations. Thorax.1999:54(1): S1-30
12. Baughman RP, Du Bois RM, Lynch JP, Wells AU. Diffuse Lung Disease- A practical approach. Great Britain: Arnold; 2004.
13. Wells AU, Denton CP. Interstitial Lung disease in connective tissue disease-mechanisms and management. Nat Rev Rheum 2014; 10: 728ï 739
14. Agostini C, Albera C, Bariffi F, DePalma M, Harari S, Lusuardi M et al. First report of the Italian register for diffuse infiltrative lung disorders (RIPID). Monaldi Arch Chest Dis 2001; 56 (4): 364ï 8.

15. Lopez-Campos JL, Rodriguez-Becerra E. Incidence of interstitial lung diseases in the south of Spain 1998-2000: the RENIA study. Eur J Epidemiol 2004; 19: 155ï 161.
16. Karakatsani A, Papakosta D, Rapti A, Antoniou KM, Dimadi M, Markopulou A et al. Epidemiology of interstitial lung diseases in Greece. Respir Med 2009(103); 1122ï 9.
17. Hodgson U, Laitinen T, Tukiainen P. Nationwide prevalence of sporadic and familial idiopathic pulmonary fibrosis: evidence of founder effect among multiplex families in Finland. Thorax. 2002; 57(4):338-42.
18. Kornum JB, Christensen S, Grijota M, Pedersen L, Wogelius P, Beiderbeck A et al. The incidence of interstitial lung disease 1995ï 2005: a Danish nationwide population-based study. BMC Pulmon Med 2008 Nov 4; 8: 24ï 30.
19. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2006;174:810ï 6.
20. Raghu G, Chen SY, Yeh WS, Maroni B, Li Q, Lee YC et al. Idiopathic pulmonary fibrosis is US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001ï 11. Lancet Respir Med 2014 Jul; 2(7):566ï 72.
21. Ansarie M, Naseem A, Kasmani A, Ahmed R, Azeemuddin M. Profile of Interstitial Lung Diseases in Pakistan, Karachi Pulmonolgy Clinics Registry Data-Jan 2012- Aug 2013. Chest 2014 Mar 1;145(3) 241A
22. Mahmud T, Ahmad S. Comparing Apples with Apples- Clinico-radiological Diagnosis of Multiple Cystic Lung Diseases. Pak J Chest Med. 2012 Oct-Dec;18 (4);7-22
23. Broaddus VC, Mason RJ, Ernst JD, King TE Jr, Lazarus SC, Murray JF et al. Murray and Nadelôs Textbook of Respiratory Medicine. 6th edition. USA: Elsevier; 2016
24. Thompson WH. Bronchioloalveolar carcinoma masquerading as pneumonia. Respir Care. 2004 Nov; 49(11):1349-53.
25. Antoniou KM, Tomassetti S, Tsitoura E, Vancheri C. Idiopathic pulmonary fibrosis and lung cancer: a clinical and pathogenesis update. Curr Opin Pulm Med. 2015 Nov; 21(6):626-33.
26. Papiris SA, Manali ED, Kolilekas L, Kagouridis K, Maniati M, Borie R et al. Investigation of Lung Involvement in Connective Tissue Disorders. Respiration. 2015; 90 (1):2-24.
27. Donaghy M, Rees AJ. Cigarette smoking and lung haemorrhage in glomerulonephritis caused by autoantibodies to glomerular basement membrane. Lancet. 1983; 2:1390ï 3
28. Glazer CS, Newman LS. Occupational interstitial lung disease. Clin Chest Med 2004; 25:467

29. Morell F, Villar A, Montero MA, Munoz X, Colby TV, Pipvath S et al. Chronic hypersensitivity pneumonitis in patients diagnosed with IPF: a prospective case-cohort study. The Lancet Resp Med. 2013 Oct 21; 1 (9)685-94
30. Ansarie M, Kasmani A, Naseem A, Azeemuddin M, Fatima A. Presentation of Idiopathic Pulmonary Fibrosis & Hypersensitivity Pneumonitis in an Avian Exposed Segment of Urban Population. Chest 2016 April 1
31. Restrepo CS, Carrillo JA, Martínez S, Ojeda P, Rivera AL, Hatta A. Pulmonary complications from cocaine and cocaine-based substances: imaging manifestations. Radiographics 2007 July-Aug; 27(4):941-56
32. Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol 2009 Jan 1; 27(1):127-45
33. Wells AU, Hirani N, Bradley B, Branley H, Egan JJ, Harrison K et al. BTS Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008; 63: v1-58.
34. Ziskind MM, Weill H, Buechner HA, Brown M: Recognition of distinctive radiologic patterns in diffuse pulmonary disease. Arch Intern Med. 1964; 114: 108ï 12
35. Pipavath S, Godwin JD. Imaging of interstitial lung disease. Clin Chest Med 2004; 25:455
36. Martinez FJ, Flaherty K. Pulmonary function testing in idiopathic interstitial pneumonias. Proc Am Thorac Soc 2006; 3:315.
37. Mittoo S, Gelber AC, Christopher-Stine L, et al. Ascertainment of collagen vascular disease in patients presenting with interstitial lung disease. Respir Med 2009; 103:1152.
38. Helmers RA, Dayton CS, Floerchinger C, Hunninghake GW. Bronchoalveolar lavage in interstitial lung disease: effect of volume of fluid infused. J Appl Physiol 1989; 67:1443.
39. Stephanie YC. ATS Pulmonary Medicine Board Review. 2015. Chapter 8 Common Respiratory Symptoms, Pulmonary Imaging, and Procedures pp 390-1.
40. Babiak A, Hetzel J, Krishna G, et al. Transbronchial cryobiopsy: a new tool for lung biopsies. Respiration 2009; 78:203.
41. American Thoracic Society. Idiopathic pulmonary ýbrosis: diagnosis and treatment: international consensus statement. American Thoracic Society (ATS) and the European Respiratory Society (ERS). Am J RespirCrit Care Med 2000 Feb;161(2):646ï 64

42. Hunninghake GW, Zimmerman MB, Schwartz DA, King TE Jr, Lynch JP III, Hegele R et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. Am J RespirCrit Care Med 2001;164: 193ï 6.
43. Raghu G, Mageto YN, Lockhart D, Schmidt RA, Wood DE, Godwin JD. The accuracy of the clinical diagnosis of new-onset idiopathic pulmonary fibrosis and other interstitial lung disease: A prospective study. Chest 1999;116:1168ï 74
44. Flaherty KR, Thwaite EL, Kazerooni EA, Gross BH, Toews GB, Colby TV et al. Radiological versus histological diagnosis in UIP and NSIP: survival implications. Thorax 2003; 58:143ï 8.
45. Quadrelli S, Molinari L, Ciallella L, Spina JC, Sobrino E, Chertcoff J. Radiological versus histopathological diagnosis of usual interstitial pneumonia in the clinical practice: does it have any survival difference? Respiration 2010; 79:32ï 7.
46. Raghu G. Idiopathic pulmonary fibrosis: a rational clinical approach. Chest 1987; 92:148ï 54.
47. Selman M, Carrillo G, Estrada A, Mejia M, Becerril C, Cisneros J et al. Accelerated variant of idiopathic pulmonary fibrosis: clinical behavior and gene expression pattern. P LoS ONE 2007; 2: e482
48. Mejia M, Carrillo G, Rojas-Serrano J, Estrada A, Suarez T, Alonso Det al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest 2009; 136:10ï 5.
49. Wells AU, Desai SR, Rubens MB, Goh NSL, Cramer D, Nicholson AGet al. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. Am J RespirCrit Care Med 2003;167: 962ï 9
50. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006;129:746ï 52
51. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011 May 21; 377(9779): 1760ï 9
52. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014 May 29; 370 (22): 2083ï 92
53. Richeldi L, Costabel U, Selman M, Soon D, Hansell DM, Nicholson AG et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011 Sep 22;365:1079ï 87
54. Richeldi L, duBois RM, Raghu G, Azuma A, Brown KK, Costabel U et al.; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014 May 29;370(22):2071ï 82

55. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur Respir J 2011 Feb;37(2):356-63
56. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbation of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2007;176:636-43
57. King TE Jr, Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2008 Jan 1;177(1):75ï 81
58. Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE Jr et al Idiopathic Pulmonary Fibrosis Clinical Research Network Investigators. Acute exacerbations of idiopathic pulmonary fibrosis. Am J RespirCrit Care Med 2007 Oct 1;176(7):636ï 43
59. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J RespirCrit Care Med 2005 May 1;171(9):1040ï 7
60. Kim DS, Park JH, Park BK, Lee JS, Nicholson AG, Colby T. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. EurRespir J 2006; 27:143ï 150
61. Parambil JG, Myers JL, Ryu JH. Histopathologic features and outcome of patients with acute exacerbation of idiopathic pulmonary fibrosis undergoing surgical lung biopsy. Chest 2005; 128: 3310ï 5
62. Sakamoto K, Taniguchi H, Kondoh Y, Ono K, Hasegawa Y, Kitaichi M. Acute exacerbation of idiopathic pulmonary fibrosis as the initial presentation of the disease. EurRespir Rev 2009;18:129ï 32
63. Kondoh Y, Taniguchi H, Kataoka K, Kato K, Suzuki R, Ogura T et al Tokai Diffuse Lung Disease Study Group. Prognostic factors in rapidly progressive interstitial pneumonia. Respirology 2010 Feb;15(2):257ï 64
64. Ambrosini V, Cancellieri A, Chilosi M, Zompatori M, Trisolini R, Saragoni L et al. Acute exacerbation of idiopathic pulmonary fibrosis: report of a series. Eur Respir J 2003; 22:821ï 26
65. Kumar P, Goldstraw P, Yamada K, Nicholson AG, Wells AU, Hansell DM et al. Pulmonary fibrosis and lung cancer: risk and benefit analysis of pulmonary resection. J Thorac Cardiovasc Surg 2003;125:1321ï 7
66. Yuksel M, Ozyurtkan MO, Bostanci K, Ahiskali R, Kodalli N. Acute exacerbation of interstitial fibrosis after pulmonary resection. Ann ThoracSurg 2006; 82:336ï 8
67. Utz JP, Ryu JH, Douglas WW, Hartman TE, Tazelaar HD, Myers JL . High short-term mortality following lung biopsy for usual interstitial pneumonia. EurRespir J 2001;17:175ï 9

68. Zegdi R, Azorin J, Tremblay B, Destable MD, Lajos PS, Valeyre D. Videothoracoscopic lung biopsy in diffuse infiltrative lung diseases: a 5-year surgical experience. Ann ThoracSurg 1998;66:1170ï 3
69. Kondoh Y, Taniguchi H, Kitaichi M, Yokoi T, Johkoh T, Oishi T et al. Acute exacerbation of interstitial pneumonia following surgical lung biopsy. Respir Med 2006;100:1753ï 9
70. Hiwatari N, Shimura S, Takishima T, Shirato K. Bronchoalveolar lavage as a possible cause of acute exacerbation in idiopathic pulmonary fibrosis patients. Tohoku J Exp Med 1994;174: 379ï 86
71. Spagnolo P, Nunes H, Wuyts WA. Pharmacological treatment of idiopathic pulmonary fibrosis - an update. EMJ Respir 2013;1:108-21
72. Ding J, Chen Z, Feng K. Procalcitonin-guided antibiotic use in acute exacerbations of idiopathic pulmonary fibrosis. Int J Med Sci 2013;10: 903-7
73. Yokoyama T, Kondoh Y, Taniguchi H, et al. Noninvasive ventilation in acute exacerbation of idiopathic pulmonary fibrosis. Intern Med 2010;49:1509-14
74. Al-Hameed FM, Sharma S. Outcome of patients admitted to the intensive care unit for acute exacerbation of idiopathic pulmonary ýbrosis. Can Respir J J Can Thorac Soc. 2004;11(2):117ï 22.
75. Cerri S, Spagnolo P, Luppi F, Richeldi L. Management of idiopathic pulmonary ýbrosis. Clin Chest Med. 2012;33(1):85ï 94.
76. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary ýbrosis: incidence, risk factors and outcome. Eur Respir J. 2011;37:356ï 63
77. Morawiec E, Tillie-Leblond I, Pansini V, et al. Exacerbations of idiopathic pulmonary fibrosis treated with corticosteroids and cyclophosphamide pulses. Eur Respir J 2011; 38: 1487ï 9
78. Horita N, Akahane M, Okada Y, et al. Tacrolimus and steroid treatment for acute exacerbation of idiopathic pulmonary fibrosis. Intern Med 2011;50:189-95
79. Sakamoto S, Homma S, Miyamoto A, et al. Cyclosporin A in the treatment of acute exacerbation of idiopathic pulmonary fibrosis. Intern Med 2010;49:109-15
80. Nakamura M, Ogura T, Miyazawa N, Tagawa A, Kozawa S, Watanuki Y et al. Outcome of patients with acute exacerbation of idiopathic interstitial fibrosis (IPF) treated with sivelestat and the prognostic value of serum KL-6 and surfactant protein D. Nihon Kokyuki Gakkai Zasshi 2007;45(6):455-9
81. Cosgrove GP, Lederer DJ, et al. Pulmonary fibrosis patient information guide. Pulmonary Fibrosis Foundation. 2015
82. Swigris JJ, Fairclough DL, Morrison M, MakeB, Kozora E, Brown KK et al. Benefits of Pulmonary Rehabilitation in Idiopathic Pulmonary Fibrosis. Respir Care. 2011 June; 56(6): 783ï 9

ABBREVIATIONS

AE-IPF Acute Exacerbation of Idiopathic Pulmonary Fibrosis
AIP Acute interstitial pneumonitis
ALAT Latin America Thoracic Association
ANA Anti nuclear antibody
Anti CCP Anti cyclic citrullinated peptide antibody
ARDS Acute respiratory distress syndrome
ATS American Thoracic Society
BAL Broncho alveolar lavage
BOOP Bronchiolitis obliterans organizing pneumonia
CBC Complete blood count
CEP Chronic eosinophilic pneumonia
CMV CytoMegalo Virus
COP Cryptogenic organizing pneumonia
COPD Chronic obstructive pulmonary disease
CTD Connective tissue disease
CXR Chest x- ray
DAH Diffuse alveolar haemorrhage
DIP Desquamative interstitial pneumonia
DPLD Diffuse parenchymal lung diseases
EBV Epstein bar virus
ENA Extractable nuclear antigens
ERS European Respiratory Society
EU European Union
FDA Food and Drug Administration
FVC Forced vital capacity
GER Gastroeophageal Reflux
GGO Ground Glass Opacity
GPA Granulomatosis with polyangiitis
HHV Human herpes virus
HP Hypersensitivity pneumonitis
HRCT High resolution computed tomography
IIP Idiopathic interstitial pneumonias
ILD Interstitial lung disease
IPF Idiopathic pulmonary fibrosis
JRS Japanese Respiratory Society
LAM lymphangioleiomyomatosis
LC Lymphangitic carcinomatosis
LIP Lmphocytic interstitial pneumonia
MDD Multidisciplinary discussion
NIV Non invasive ventilation
NSIP Non specific interstitial pneumonia
PAP Pulmonary alveolar proteinosis
PCP Pneumocystis carinii pneumonia
PDGF Platelet derived growth factor
PFT Pulmonary function tests
PLCH Pulmonary Langerhans cell histiocytosis
PR Pulmonary rehabilitation
RA Rheumatoid Arthritis
RB-ILD Respiratory Bronchiolitis Interstitial lung disease
SLE Systemic lupus erythematosus
TB Tuberculosis
TBB Transbronchial biopsy
TBLB Transbronchial lung biopsy
UIP Usual interstitial pneumonia
VATS Video assisted thoracoscopic surgery

EPILOGUE

We end this document
With a sense of immense thankfulness
To the Bearer of Infinite Knowledge
Who lends us some of it,
And gratitude to the people
Who help fellow humans receive a measure of it.

The next publication in this series would be related to the non-IPF interstitial lung diseases consisting of NSIP, CTD/CVD related ILD, Hypersensitivity pneumonitis, Sarcoidosis and Pneumoconiosis.
The Guideline Committee has already accumulated resource material on the topics.