PAKISTAN CHEST SOCIETY

Interstitial Lung Diseases Guideline

Idiopathic and CTD Associated NSIP

ILD Advisory Board and Guideline Committee

Guideline Document on ILD
Idiopathic and CTD Associated NSIP

ILD Advisory Board and Guideline Committee
March, 2018

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

Message from the President Pakistan Chest Society

It is a matter of personal satisfaction for me that the PCS ILD Guideline Committee is successfully pursuing their agenda of formulating national guidelines on the subject. The first PCS Guideline on Interstitial Lung Disease with a focus on IPF was published and circulated in the last 12th Biennial Conference held in 2016. This was followed by the first PCS-ILDPAK Registry Report in June 2016 and having persevered with the collection of data at a national level, hopefully it is ready with yet another report before the 13th Biennial Conference that is being held in March 2018.

With the publication of the previous ILD Guideline on IPF, it was announced that next in the series would be a guideline on NSIP and CTD/CVD related ILD and I am glad to note that they have lived up to their promise. Reading through the document makes one feel the great effort involved in formulating a lucid presentation on an extremely difficult topic which is still in a phase of consensus development throughout the world. I wish to congratulate Dr. Mosavir Ansarie and the members of his team in the ILD Guideline committee for accomplishing this arduous task. I am sure that the National Guidelines and Registry would prove to be historic landmarks in the understanding and management of Interstitial Lung Diseases in Pakistan.

Dr. Arshad Javaid
President
Pakistan Chest Society

PREFACE

This Presentation is the second guideline document on Interstitial Lung Diseases (ILD) following our first publication in 2016 that discussed the ILD in general and Idiopathic Pulmonary Fibrosis (IPF) in particular. The present document is meant to be a Guideline on Non Specific Interstitial Pneumonia (NSIP) and deals with both Idiopathic Non Specific Pneumonia (iNSIP) and Connective Tissue Disease related NSIP (CTD-NSIP) in one volume.

The Objective of this Guideline is to present before Pakistani fellow physicians and pulmonologists, a concise edition of updated knowledge on more common and important types of ILD, encompassing the current diagnostic and management strategies.

A Resource Group comprising of prominent pulmonologists from different parts of the country who had a known interest in the subject collected again as an ILD Advisory Group with a similar agenda and modus operandi as with the previous ILD-IPF guideline. This time a majority of them were also active participants of the ongoing PCS-ILDPAK National Registry under the auspices of Pakistan Chest Society (PCS) ILD Guideline Committee.

Resource Data consisting of relevant literature published in 2017 and earlier was collected, shared and reviewed with committee members along with local experience. Templates were presented by key contributors (TM, SS, AZ, MA) which were approved after deliberation by the committee members. Following incorporation of data, edition and referencing this document was peer reviewed in the final stage.

The First Part of this document encompasses iNSIP. Since Katzenstein and Fiorelli described NSIP in 1994, several cases of IPF were reclassified as NSIP and since then the two have been considered as separate entities. However, it is often difficult to differentiate between the fibrosing NSIP and IPF where a grey area of overlap may exist. NSIP still remains a hard nut to crack for Radiologists, Pulmonologists and Pathologists and this is not just academic because there is a distinct corticosteroid response and better prognosis in NSIP as against IPF.

The Second Part of this document reviews Connective Tissue Disease Associated Interstitial Lung Disease (CTD-ILD). Not minimizing the importance of ILD occurring in established CTD, it is looking beyond the frontier that is so important and interesting when despite the lung interstitium being a major target of CTD associated auto immunity, the lung is over looked during the diagnosis of CTD. Also, ILD cases having a rheumatologic flavor may not meet criteria of the definite CTD although a quarter of them would progress to CTD in the future.

Hence in approaching ILDs, it is essential to consider the possibilities of CTD as an etiologic agent and screened for extra pulmonary manifestations and auto antibodies.

The objective of this document is to provide updated knowledge of definitions, epidemiology, classification, clinical manifestations, diagnostic workup and treatment strategies for managing Idiopathic and CTD-NSIP.

I wish to express my gratitude to all members of ILD Guideline Committee who helped in the formulation of this document at various stages, conceptual and tangible and to other members of my team for donating time and energy purely to propagate knowledge. Jazak Allah, may He grant us knowledge that is profitable and cure for all ailments. Allahhumma inna nas'aluka ilm annafe'a wa shifa min kulli da'a. Amen

Dr. Mosavir Ansarie
Chairman, ILD Guideline Committee
Pakistan Chest Society

CONTENTS

Part A INTRODUCTION TO ILD

A-I. DEFINITION

The **Interstitial Lung Diseases (ILDs)** are a heterogeneous group of pulmonary disorders, classified together because of similar clinical, radiologic, physiologic or pathologic features[1]. ILDs comprise more than 200 entities, many uncommon and many of an unknown etiology[2].

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[3]. 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. **CLASSIFICATION OF ILDs: DILUTING THE ALPHABET SOUP**

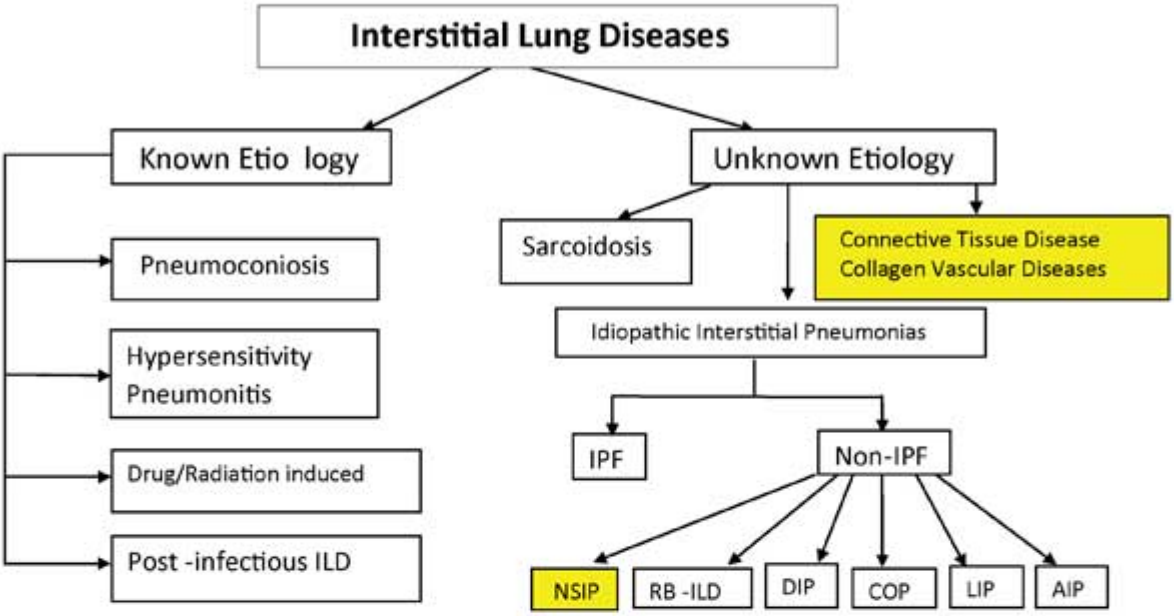

Figure 1. Classification of ILDs

*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

Part B NON SPECIFIC INTERSTITIAL PNEUMONIA

B-I. DEFINITION

Non Specific Interstitial pneumonia (NSIP) is a type of idiopathic interstitial pneumonia (IIP) which by definition cannot be classified into any other category of IIPs. The term 'Non-specific' implies that although it presents similarly to other IIPs, but lacks the histopathologic features that characterize the individual disorders[4].

B- II. NSIP - A Pattern or Entity?

Before the era of histopathologic classification of IIPs, IPF and NSIP were considered the same disease. Katzenstein (1994) first proposed the idea of NSIP, as it did not fit any pattern of known IIP. In 1998 he described re-evaluation of IIPs which were diagnosed earlier as UIPs but later classified as NSIP.

NSIP was initially a 'provisional disease' in the 2002 American Thoracic Society/European Respiratory Society (ATS/ERS) classification but finally considered as a defined disease in the 2013 ATS/ERS classification. NSIP is the name of a morphologic pattern which may present as clinical-pathologic overlaps for example with Idiopathic Pulmonary Fibrosis (IPF), Organizing Pneumonia (OP) and Hypersensitivity Pneumonia (HP) but when no specific cause is defined, then the clinical, radiological and pathological diagnosis of 'idiopathic NSIP'(iNSIP) is rendered.

B- III. EPIDEMIOLOGY

The true incidence of NSIP is unknown. It constitutes 14-36% of cases of IIPs, and is therefore second most common IIP, following IPF[5,6,7].
Local data is available on the relative frequency of ILD in Pakistan. This suggests that the frequency of iNSIP is 14- 20 %[8,9].

B-IV. **DIAGNOSTIC APPROACH**

Recommended Steps

1. Clinical assessment
2. Pulmonary function tests (PFTs)
3. Radiology- Chest X Ray and HRCT chest
4. Serology
5. Broncho Alveolar Lavage (BAL)
6. Histopathology/ biopsy

Multi Disciplinary Consultation

Correct IIP Diagnosis needs team work and experience

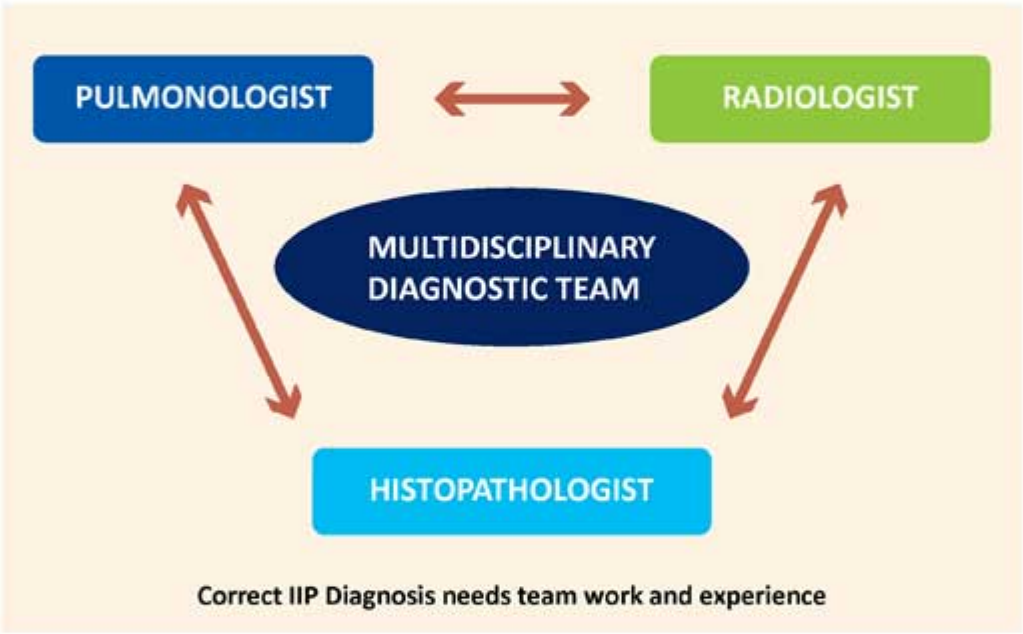

Figure 2. Multi disciplinary approach to diagnosis

B-V. CLINICAL FEATURES

The mean onset of disease occurs in 40-50 years of age[5,6]. There is a slight female preponderance and no association with cigarette smoking has been observed[10].
A patient with NSIP presents with cough and shortness of breath, typically dyspnea on exertion along with non specific symptoms such as fatigue and weight loss[11,12].
Chest examination will usually reveal bibasilar end inspiratory fine crackles and only 10-35% have clubbing[13].

B- VI. PULMONARY FUNCTION TESTS (PFTS)

PFTs show a restrictive pattern (decreased Forced vital capacity: FVC) and reduced gas transfer [decreased Diffusing Capacity of the Lung for carbon monoxide (D_{LCO})][5,10].
While PFT is not essential for making the diagnosis, it is required for assessment of functional impairment, disease progression, response to therapy and prognosis.

B-VII. RADIOLOGY

1. Chest X Ray

Chest radiograph can be normal in early stages. There may be ill-defined or ground glass opacities with lower lobe distribution or consolidation in a patchy, reticulonodular or mixed pattern. A bilateral pulmonary infiltrative pattern with volume loss of lower lobes may be seen in those with advanced disease.

2. HRCT Chest

Although no single high-resolution CT finding is diagnostic, the presence of multiple findings can help suggest the diagnosis in the right clinical setting.

a. **Ground Glass Abnormality**
Ground glass opacities remain the most obvious HRCT feature in the typical patient with NSIP and is found in nearly 76%-100% of all cases[14,15,16].

b. **Reticular Abnormality**
Fine reticular abnormality is seen with fibrotic NSIP and represents areas of fibrosis. This is seen in 80%–94% of patients with NSIP[14,15,16].

c. **Traction Bronchiectasis**

Traction bronchiectasis is almost universal in patients with fibrotic NSIP and is most prominent in the lower lung zones. Recent studies demonstrated traction bronchiectasis in 93 to 100% of patients with NSIP[17,18,19].

d. **Symmetric Lower Lobe Distribution**

Symmetric Lower Lobe Distribution is one of the key factors in helping one make the diagnosis of NSIP. It has been described in 84%- 95% of cases with NSIP[17,20]. Lower lobe peribronchovascular predominance with subpleural sparing, is quite suggestive in NSIP.

e. **Lower Lobe Volume Loss**

Lower lobe volume loss is often seen in patients with a fibrotic NSIP.

f. **Cystic Changes**

In advanced NSIP, sub-pleural cysts can be found, but compared to those of Usual Interstitial Pneumonia (UIP), these cysts are smaller and limited in extent. They are referred to as microcystic honeycombing' (as opposed to the macrocystic honeycombing seen in UIP). Microcystic honeycombing is a feature exclusively seen in patients with fibrotic NSIP.

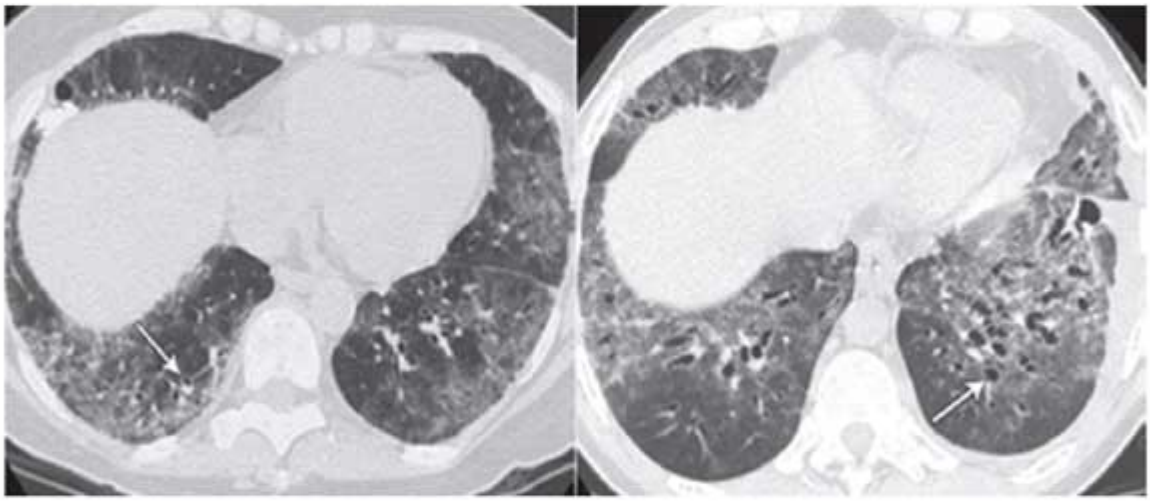

Figure 3. High resolution CT images of NSIP show bilateral symmetric lower lobe predominant ground glass opacities with reticular abnormalities and traction bronchiectasis (arrows). Relative sparing of the immediate subpleural lung can be suggestive of NSIP although it's absence does not allow exclusion of the diagnosis.

B-VIII. **DIFFERENTIATING NSIP FROM UIP BASED ON HRCT**

The major CT differential diagnosis for NSIP is UIP. The key CT features that favor the diagnosis of NSIP over UIP are

1. Homogeneous lung involvement without an obvious apicobasal gradient,
2. Extensive ground-glass abnormalities,
3. Fine reticular pattern,
4. Micro nodules.

Follow-up CT also demonstrate that in patients with NSIP, ground-glass opacities usually do not progress to areas of honeycombing, even if there is associated bronchiectasis. However, in patients with UIP, progression of ground-glass attenuation to honeycombing is common and indicates irreversible fibrosis.

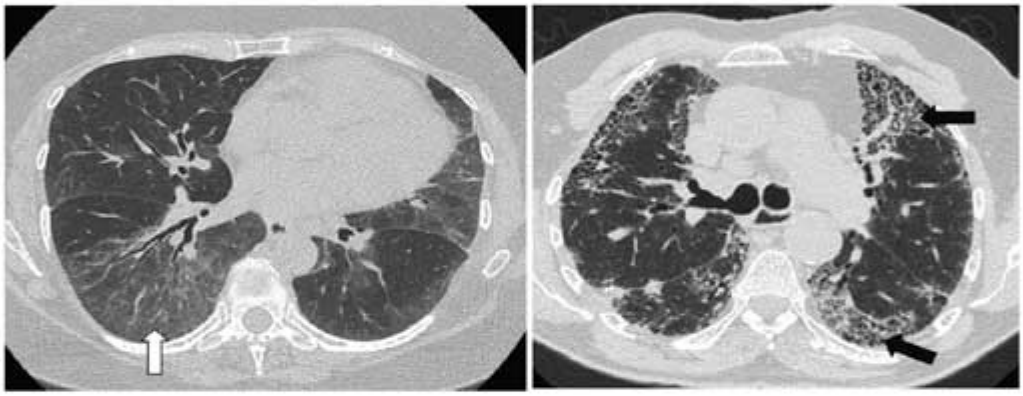

Figure 4. (A). NSIP: Bilateral ground glass opacities (white arrow)

(B). UIP: Bilateral ground glass with sub-pleural honeycombing (black arrows)

The diagnosis of NSIP remains one of the biggest challenges and studies show correct diagnosis by chest radiologists varies between 65-85%. Data shows a wide variety of CT findings in biopsy proven NSIP patients:

Ground glass attenuation	76%
Irregular Linear opacities	46%
Traction Bronchiectasis	36%
Honeycombing	30%
Consolidation	16%
Nodular opacities	14%
Interlobular septal thickening	6%

Table 1. HRCT findings in biopsy proven NSIP patients[21]

B-IX. **SEROLOGY**

NSIP may be idiopathic or may be associated with connective tissue disease, certain drugs, human immunodeficiency virus (HIV) infection, and hypersensitivity pneumonitis.
Appropriate investigations [e.g. HIV/ Anti Nuclear Antibodies (ANA), Extractable Nuclear Antigen Antibodies (ENA) and so on] should be made to rule out known causes before classifying the disease as idopathic. (for details of investigations in CTD, refer to part C-Vc of this document.)

B-X. **BRONCHOALVEOLAR LAVAGE (BAL)**

The role of BAL to distinguish iNSIP from IPF is controversial. Some studies show that BAL lymphocytosis is more likely suggestive of NSIP rather than IPF[22], and that BAL neutrophilia is more suggestive of IPF, whereas other studies show that BAL findings do not help to differentiate between NSIP and IPF[23,24].
BAL is not always required in the assessment of the IIPs. However, BAL may be used to exclude malignancy and/or infections.

B-XI. **HISTOPATHOLOGY**

NSIP has two main subtypes

1. **Cellular Non Specific Interstitial Pneumonia**

Less common; interstitial thickening is mainly secondary to infiltration of inflammatory cells and type II pneumocyte hyperplasia. Lung architecture is preserved

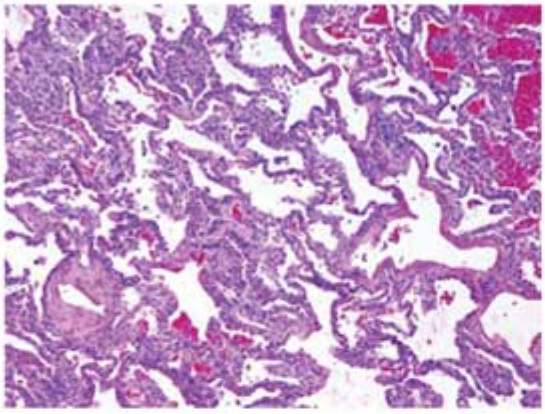

Figure 5. Cellular NSIP- Note the widespread thickening of the alveolar septa by a cellular infiltrate

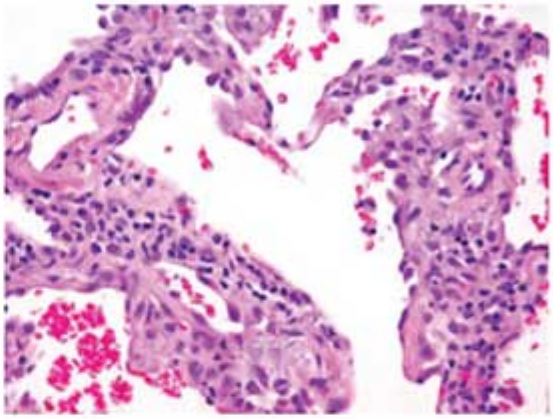

Figure 6. Cellular NSIP. On higher power the septal widening is due toa mild to moderate infiltrate of lymphocytes with scattered plasma cells, with minimal associated fibrosis.

2. **Fibrotic Non Specific Interstitial Pneumonia**

More common, interstitial thickening is more due to uniform dense or loose fibrosis and mild chronic inflammation, despite fibrotic changes lung structures still preserved

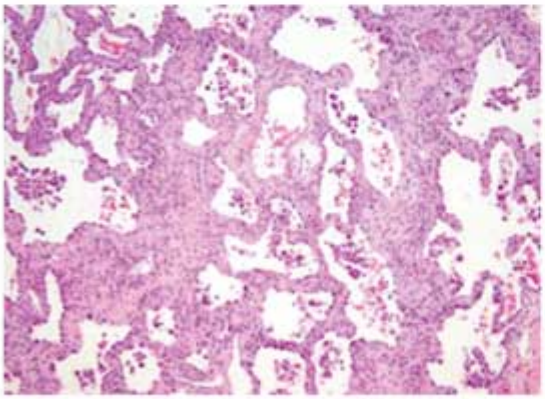

Figure 7. Fibrotic NSIP Interstitial fibrosis uniformly involving the lobule

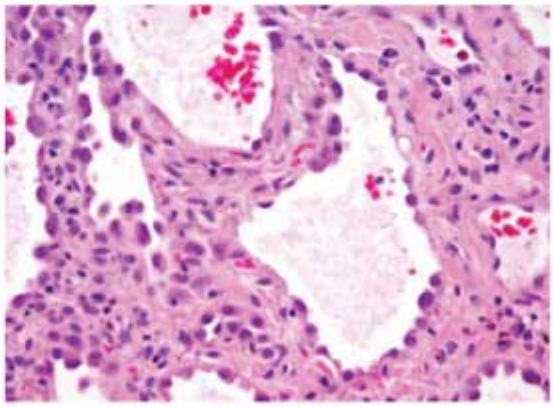

Figure 8. Fibrotic NSIP. On higher power, the alveolar septa are thickened by dense collagen fibrosis with scattered chronic inflammatory cells.

Subtype of NSIP	Key Features	Pertinent Negative factors
Cellular	• Mild to moderate chronic interstitial inflammation • Type II pneumocyte hyperplasia • Lung architecture is preserved	• Absence of dense interstitial fibrosis • Absence of diffuse severe alveolar septal inflammation. Organizing pneumonia involves <20% of the biopsy specimen • Absence of the following features: hyaline membranes and other findings of acute lung injury, granulomas, organisms or viral inclusions, dominant airways disease. Eosinophils are inconspicuous or absent
Fibrotic	• Dense or loose interstitial fibrosis with a uniform appearance • Mild to moderate chronic interstitial inflamma tion • Lung architecture is frequently preserved (enlarged fibrotic airspaces may be present)	• Fibroblastic foci with dense fibrosis are inconspicuous or absent • Absence of a temporally heterogeneous pattern Honeycombing is inconspicuous or absent • Absence of the following features: hyaline membranes and other findings of acute lung injury, granulomas, organisms or viral inclusions, dominant airways disease. Eosinophils are inconspicuous or absent

Table 2. Histologic criteria for diagnosis of i NSIP[25]

B-XII. **DIFFERENTIAL DIAGNOSIS**

The main differential diagnosis is with IPF. Historically IPF is chronic , usually >1 year at the time of diagnosis while NSIP is subacute or chronic with a history of months or years. Radiology is an important criterion in differentiating between NSIP and UIP.
Other conditions to be considered in differential diagnosis of NSIP are:
Acute lung injury including Diffuse Alveolar Damage (DAD) and Organizing Pneumonia (OP), Lymphocytic Interstitial Pneumonia (LIP), Hypersensitivity Pneumonia (HP), Desquamative Interstitial Pnemonia (DIP).

	IPF	NSIP
Duration	Chronic (>12 months)	Subacute to chronic (months to years)
Frequency	47-64%	14-36%
Age	Older	Younger
Gender	Male predominance	Female predom inance
Smoking Hx	Yes	Not established
Clubbing	60-90%	10-40%
Chest X Ray	Bilateral reticular lower zones; volume loss; ± honeycombing	Bilateral hazy reticular opacity
HRCT	• Peripheral, basal, subpleural , • Reticular • Honeycombing • Traction bronchiectas is • Focal ground-glass	• Peripheral, basal, symmetrical • Ground-glass predominance • Consolidation • Lower lobe volume loss
Histo-pathology	• UIP pattern • Dense fibrosis causing remodeling of lung architecture • Fibroblastic foci typically scattered at the edges of dense scars • Patchy lung involvement • Frequent subpleural/ paraseptal distribution	• NSIP pattern Cellular pattern • Mild to moderate interstitial chronic inflammation • Type II pneumocyte hyperplasia. Fibrosing pattern • Dense or loose interstitial fibrosis lacking the temporal heterogeneity pattern of UIP
BAL	Neutrophilia	Lymphocytosis
Treatment	Poor response to any treatment	Corticosteroid responsiveness
Prognosis	Poor	Good
Survival	50-70% mortality in 5 years	Unclear; <15% mortality in 5 years

Table 3. Distinguishing clinical/ radiographic/ pathological features of IPF and NSIP

B-XIII. **TREATMENT**

- There are no randomized trials to determine definite efficacy of any treatment protocol. Immunosuppression is reported to help in symptomatic and functional improvement.

- Mild or asymptomatic disease may be observed by serially monitoring for progression of dyspnea and deterioration of PFTs.

- Treatment should be implemented only if disease progression is confirmed thus avoiding exposure to unnecessary therapy related complication.

Corticosteroids(CS) are the treatment of choice in iNSIP
Prednisolone 0.5 – 1.0 mg/kg/d or 40-60mg/d as an initial dosage to be continued for one month before tapering to 30 mg/day for an additional two months26,27.. While the optimal treatment duration is unknown, we aim to reach 5 to 10 mg daily or on alternate days, by the end of six to nine months, with attempted cessation after at least one year of therapy. Average recommended length of treatment is 17.4 +/- 12.1 months[26, 27].

Cytotoxic Agents
No consensus is present whether a cytotoxic drug should be started at the beginning or added upon disease progression or steroid dependence.
Drugs that may be used are Azathioprine(AZA), Cyclophosphamide(CYC), Cyclosporine, Mycophenolate mofetil(MMF).

Monitoring Treatment Response
The response to therapy should be assessed at one month, and then at three to six month intervals, or sooner, if the patient reports worsening symptoms. Assessment usually includes symptoms (eg, dyspnea, exercise tolerance, cough), physical examination, spirometry, lung volumes, diffusing capacity for carbon monoxide (DLCO), and six-minute walk testing with oximetry. Interval HRCT should be performed depending on changes in the clinical assessment and pulmonary function tests.

Reinstitution Of Treatment may be needed in case of relapse which occurs mostly due to initial low dose or early cessation of prednisolone.

Prophylaxis Against Pneumocystis Jiroveci Pneumonia(PCP)
PCP prophylaxis is suggested for any patient with NSIP receiving moderate to high dose glucocorticoid (≥20 mg per day) and a second immunosuppressive agent. Some experts also administer PCP prophylaxis to patients on monotherapy with moderate to high dose glucocorti coids.

Trimethoprim/Sulfamethoxazole 80-160 mg PO q day or 160 mg 3 times/week on consecutive or alternate days.

Antifibrotic Treatment with agents such as pirfenidone is currently being considered in treating the fibrotic NSIP.

Rarely, patients will develop advanced lung disease despite immunosuppressive therapy and are potential candidates for lung transplantation.

B-XIV. **PROGNOSIS/ SURVIVAL**

- NSIP carries a much more favorable prognosis than a UIP type pattern.
- Cellular NSIP shows even better response to corticosteroids and carries a substantially better prognosis than the fibrotic type.
- NSIP has 90% 5 years survival rate for cellular; and 45-90% 5 years survival in fibrotic subtype[28,29].
- Correct and early diagnosis has significant impact on patients' outcome.

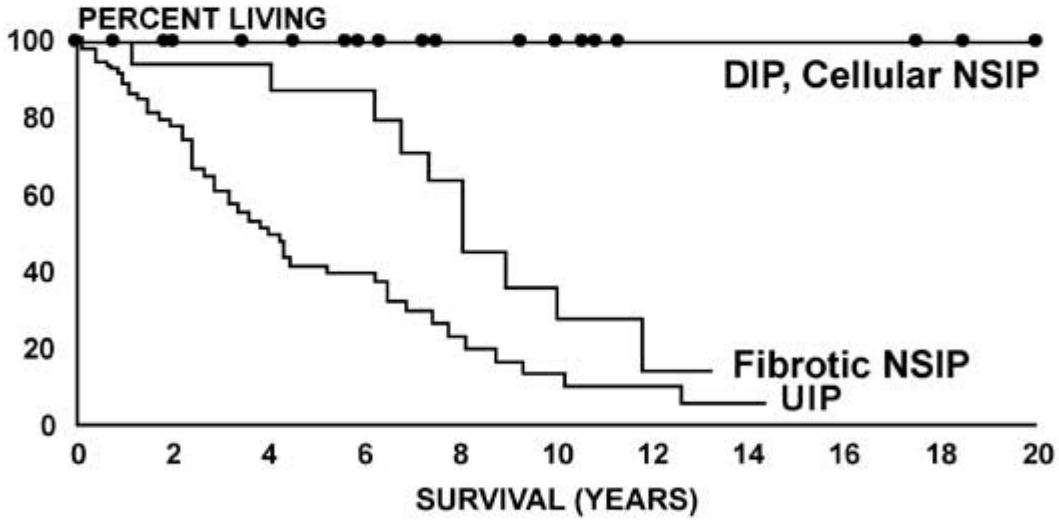

Figure 9. Kaplan-Meier survival curves in patients with cellular NSIP, fibrotic NSIP, and UIP

Part C ILD ASSOCIATED WITH CTD

C-I. DEFINITION

Connective Tissue Disease (CTD) also known as Collagen Vascular Disease (CVD) refers to disorders characterized by auto-immune mediated damage associated with circulating auto-antibodies that target various body organs[30].
Pathological mechanisms associated with interstitial changes in the lung connective tissue show similar histological, radiological and clinical characteristics as Idiopathic Interstitial Pneumonia (IIP)[31].

C-II. CLASSIFICATION OF ILD IN THE SETTING OF CTD

a. ILD in Established CTD

The most straight forward scenario is when there is an established CTD with characteristic manifestations fulfilling international criteria of one of the CTDs and subsequently ILD develops in this context. However, it is necessary to rule out drug induced ILD and infection as a complication of treatment of the primary disease.

b. CTD Presenting as ILD

ILD as the initial presenting manifestation of a Connective Tissue Disease, features of which may not have yet been identified. Diagnosing the CTD may be challenging as the attention of pulmonologists may be focused on lung manifestations while systemic symptoms may be subtle at this point.

c. ILD with Autoimmunity Features

Interstitial Pneumonia with Auto-immune Features (IPAF) is where ILD is the dominant manifestation of disease which although considered idiopathic may have some clinical, autoimmune, pathological and/or radiological features of connective tissue disease, corresponding to an incomplete or undifferentiated form of CTD and not meeting criteria for definite CTD.

Rheumatoid arthritis
Systemic lupus erythematosus
Systemic sclerosis (scleroderma)
Primary Sjogren's syndrome
Polymyositis/Dermatomyositis
Mixed connective tissue disease

Table 4. CTDs associated with lung disease

C-III. **PREVALENCE AND INCIDENCE**

The incidence of CTD associated ILD increased from 4.46 per 100,000 person-years between 1995-2000 to 12.32 per 100,000 person-years between 2001-2005[32].

ILD can be identified in all types of CTD and is particularly common in Rheumatoid Arthritis (RA), Systemic Sclerosis(SSc), and Polymyositis/Dermatomyositis (PM/DM)[33].

The overall incidence of CTD-ILD is estimated at 15%[34].

Local data is available on the relative frequencies of ILD in Pakistan [8,9]. This shows that the frequency of ILD due to CTD is 10-17%.

C-IV. **CLINICAL PRESENTATION**

A thorough history is vital. Pulmonologists should have a high suspicion and pay attention to extra thoracic features of an underlying CTD. See Table 5.

Extra Pulmonary Clinical Features

Organ	Main Manifestations
Peripheral circulation	• Raynaud's phenomenon
Skin	• Sclerodactaly, Digital ulcerations or scars, Telangiectasia • Violaceous erythematous rash over the interphalangeal joints, knuckles, elbows and knees (Gottron's sign) • Lilaceous rash of the eyelids / Heliotrope rash on the neck, upper chest and shoulders.
Joints	• Arthralgias, Arthritis and Morning stiffness lasting for more than 60 min
Muscle	• Muscle pain and weakness
Mouth and eyes	• Dry mouth and eyes (sicca syndrome)

Table 5. Key extra-pulmonary clinical features in CTD-ILD[30]

Pulmonary Features

Among the pulmonary physical findings, bibasilar end inspiratory crackles, signs of pulmonary hypertension, signs of pleuritis often with effusion can be found in RA, SSc, Systemic Lupus Erythomatosus (SLE) and Sjogren's syndrome.

Diaphragmatic weakness and respiratory muscle failure is may be seen in PM, DM and at some point in SLE.

	SSc	RA	Sjogren's	MCTD	PM/DM	SLE
Airways	-	++	++	+	-	+
ILD	+++	++	++	++	+++	+
Pleural	-	++	+	+	-	+++
Vascular	+++	-	+	++	+	+
DAH	-	-	-	-	-	++

Table 6. Most common CTD Associated Pulmonary Manifestations[35]

*SSc- Systemic Sclerosis, RA- Rheumatoid Arthritis, MCTD- Mixed Connective Tissue Disease, Pm- Polymyositis, DM- Dermatomyositis, SLE- Systemic Lupus Erythematosus, ILD- Interstitial Lung Disease, DAH- Diffuse Alveolar Hemorrhage

C-V. **DIAGNOSIS**

After a sound clinical assessment, the clinician is recommended to order a set of investigations to formulate the diagnosis.

a. RADIOLOGY : HRCT[36]

- HRCT has proved to be more sensitive than Chest radiography and conventional CT in the detection and characterization of various histopathologically confirmed ILD in patients with CTDs.
- There is evidence that the pattern of abnormality at HRCT reflects the relative proportions of fibrosis and inflammation. A reticular pattern with traction bronchiectasis at HRCT is associated with a predominantly fibrotic process, whereas ground-glass attenuation without a reticular pattern or traction bronchiectasis is associated with an inflammatory process.

Various CTD-ILD Features on HRCT

NSIP is the prevalent lung pattern in systemic sclerosis and PM/DM (more than 90%), but also may occur in RA, SLE, Sjogren's and Mixed Connective Tissue Disease (MCTD). In the images below you can appreciate the spectrum of findings seen in CTD-ILD.

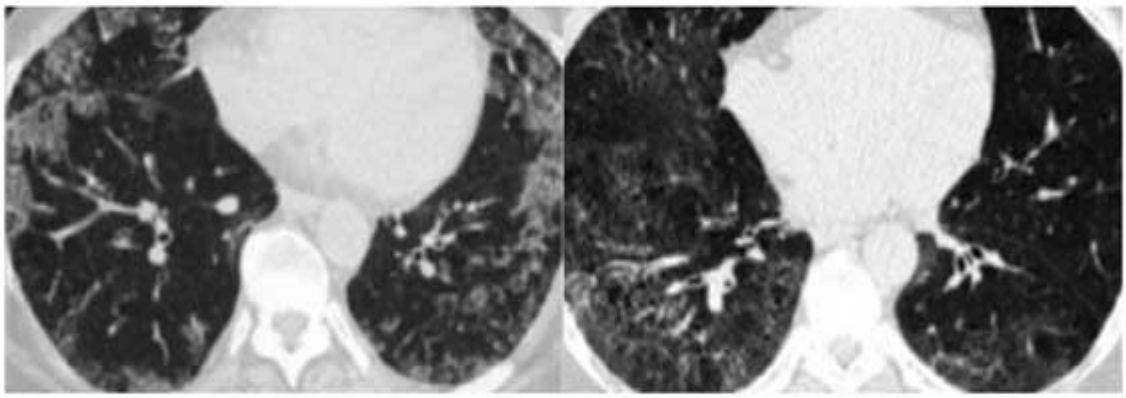

Figure. 10.CTD-ILD showing NSIP pattern on HRCT. Both pictures are from biopsy proven connective tissue disease and show obvious ground glass opacities with superimposed fine reticular densities as a result of thickening of the intralobular septa. Notice the lack of honeycombing excluding UIP as diagnosis.

Systemic Lupus Erythomatosus

- Ground-glass attenuation and consolidation reflect the presence of interstitial pneumonia, acute lupus pneumonia, hemorrhage, or occasionally bronchiolitis obliterans organizing pneumonia (BOOP).

- Reticular pattern of interstitial fibrosis involving lower zones, is seen in about 3% of patients while interlobular septal thickening and irregular linear hyperattenuating areas may be seen in 30% of the cases.

- Such abnormalities are usually mild and focal; diffuse disease occurs in only 4% and honey combing is uncommon.

Rheumatoid Arthritis (RA)

- In the early stage, the radiographic appearance consists of irregular linear hyperattenuating areas in a fine reticular pattern. The abnormality usually involves mainly the lower lung zones.

- With the progression of disease, the reticular pattern becomes more coarse and diffuse, and honeycombing may be seen.

- Interstitial lung changes are frequent and independent of disease duration. These are more frequent and severe in rheumatoid factor–positive patients and in patients with more severe joint involvement.

- Pleuropulmonary complications are common and include interstitial pneumonitis and fibrosis, rheumatoid (necrobiotic) nodules, BOOP, obliterative bronchiolitis, follicular bronchiolitis, bronchiectasis and pleural effusion or thickening.

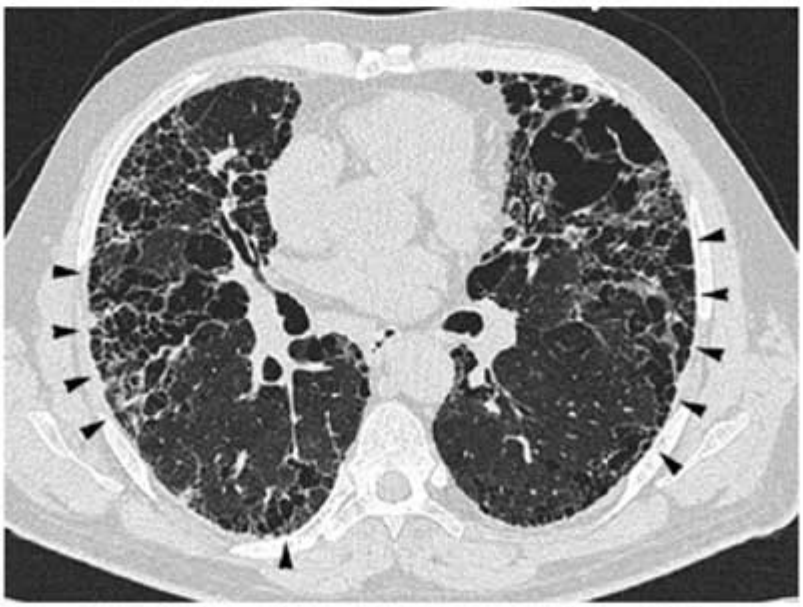

Figure 11. HRCT in a patient with RA demonstrating marked Honeycombing (arrows) with features of UIP

Systemic Sclerosis (SSc)

- Pulmonary involvement is more common and more severe in systemic sclerosis than in other types of collagen vascular disease. The most common pulmonary manifestation is interstitial fibrosis, which occurs in approximately 80% of patients .

- The abnormalities involve mainly the lower lobes and have a predominantly peripheral and posterior distribution. The overall extent of disease and the degrees of honeycombing and ground-glass attenuation progressively increases in follow-up CT scans.

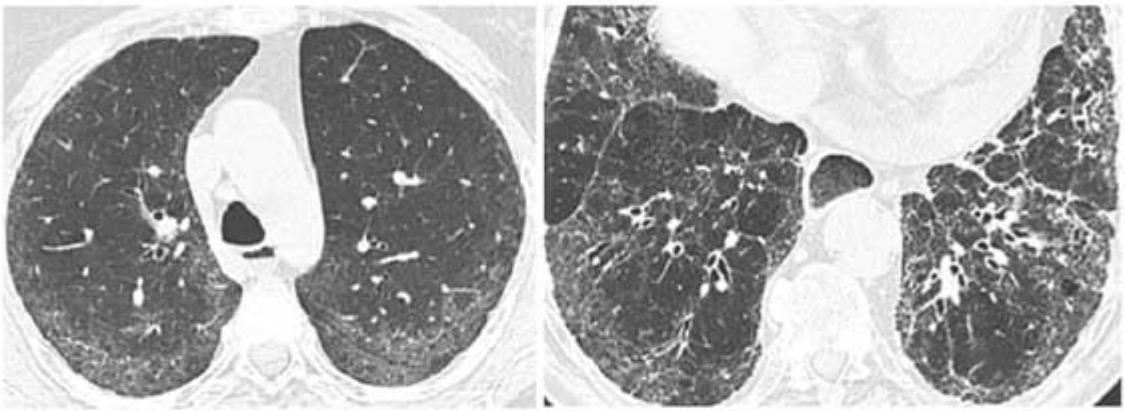

Figure 12. HRCT in a Systemic Sclerosis patient shows reticular and ground glass abnormalities predominantly at the lung bases.

Polymyositis (PM) and Dermatomyositis (DM)

- The frequency of radiographic parenchymal abnormalities is low (about 5%).
- The most common is a symmetric, predominantly basal reticular pattern that may become diffuse over time and progress to honeycombing .
- Initial findings are prominent interlobular septa, ground-glass attenuation, patchy consolidation, parenchymal bands, irregular peribronchovascular thickening, and subpleural lines.
- In advanced disease, these changes may progress to some honeycombing .

Sjogren's Syndrome

- HRCT may reflect the characteristic pattern of extensive areas of ground-glass attenuation with scattered thin-walled peribronchovascular and subpleural cysts seen in approximately 50% of patients with LIP . There may be a diffuse mid to lower lobe predominance, thickened bronchovascular bundles, interstitial thickening along lymph channels, variable size pulmonary nodules and ground glass changes.

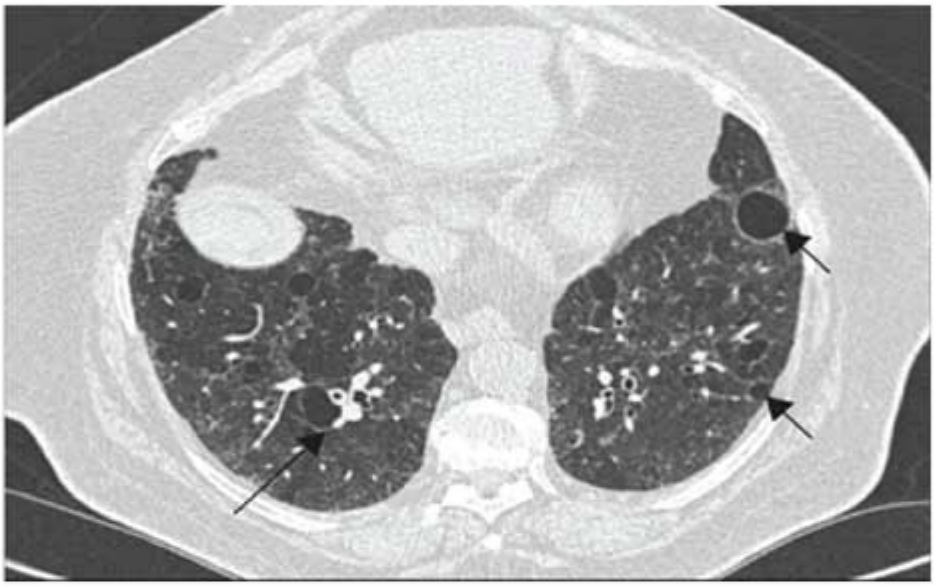

Figure 13. LIP in primary Sjogren's syndrome.HRCT shows well-defined, round, thin-walled air cysts in the peri-bronchovascular regions (arrows) with areas of ground glass and reticular attenuation.

Mixed Connective Tissue Disease

- Respiratory involvement has been described in 20%–80% of patients.
- Common pulmonary abnormalities include interstitial pneumonia and fibrosis, pulmonary hypertension, and pleural effusion.
- The abnormalities consist of irregular linear hyperattenuating areas with a reticular pattern and involving mainly the lung bases. With the progression of disease, the fibrosis gradually extends superiorly; in the late stage, honeycombing may be identified. HRCT shows a predominant subpleural distribution of fibrosis. Other radiologic abnormalities include areas of parenchymal consolidation that may be related to BOOP.

b. PULMONARY FUNCTION TESTS (PFTS)

- PFTs should ideally be obtained in all patients to assess the pattern, severity, and progression of respiratory impairment associated with ILD.
- Abnormalities associated with ILD include reductions in lung volumes and diffusing capacity for carbon monoxide (D_{LCO}), oxygen desaturation during exercise, and resting hypoxemia [Arterial, Blood Gases (ABGs), oximetry] in advanced disease.
- Most CTDs cause a restrictive lung disease pattern with a decrease in total lung capacity (TLC), residual volume (RV), functional residual capacity (FRC), and D_{LCO}.
- Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) (ie, the FEV_1/FVCratio) may be normal or increased. However, bronchiolitis obliterans may cause an obstructive ventilatory defect (reduced FEV_1/FVC ratio and FEV1, increased RV and RV/TLC ratio).
- A reduced DL_{CO} in the presence of normal lung volumes is consistent with early ILD, but may alternatively be suggestive of pulmonary vascular disease associated with a CTD[37,38].
- ABG analysis may reveal hypoxemia at rest. A 6-minute walk test with pulse oximetry provides a measure of oxygen desaturation and helps to detect disease progression.
- When assessing changes over time, changes that are considered clinically important include a decrease in FVC of ≥ 10 percent or a decrease in D_{LCO} of ≥ 15 percent[37].

c. SEROLOGY

The role of autoimmunity in ILD associated with CTDs such as SSc, SLE and RA is well established.

Laboratory studies that are helpful in the setting of ILD-CTDs include:

- **Complete blood count** including differentials to check for evidence of anemia, polycythemia, leukocytosis, or eosinophilia.
- **Anemia of chronic disease** can be found in RA, whereas SLE can cause mild anemia, leukopenia, lymphopenia, and/or thrombocytopenia.
- **Erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) levels** may be high in patients with SLE, PM and DM.
- **Complement levels** and a high ESR may be present in SLE patients who present with an acute lupus flare.
- **Deranged renal function tests and urinary abnormalities** like proteinuria and hematuria, pyuria, and/or cellular casts may be seen in renal involvement of patients with CTDs like SLE or vasculitides. Urine myoglobin levels are elevated in PM/DM.
- **Creatine kinase (CK)** if elevated may reflect myositis, which may suggest PM, DM or a MCTD, and uncommonly in patients with SLE
- **ANA, Anti Cyclic Citrullinated Antibody (Anti-CCP) and Rheumatoid Factor (RF) can be done** as initial screening test for a suspected underlying CTD.
  ANA is positive in virtually all patients with SLE at some time during the course of the disease.
  If ANA is positive, testing for other specific antibodies **Anti dsDNA, ENA profile (Jo-1, SS-A, SS-B, Scl-70) should be considered**

d. BRONCHOALVEOLAR LAVAGE (BAL)

BAL findings are typically nonspecific, being consistent with or suggestive of a given condition, rather than pathognomonic[39]. However, BAL may be valuable in clarifying other pulmonary issues which may arise in this setting, including drug-induced lung toxicity (lymphocytic/eosinophilic), opportunistic infections, alveolar hemorrhage (hemorrhagic), alveolar proteinosis (milky appearance), and malignancy (malignant cells)[39,40].

In CTD-NSIP, BAL is typically lymphocyte predominant while in CTD-OP it is of mixed cellularity (lymphocyte, neutrophils, monocytes and eosinophils) and in CTD-UIP it may be eosinophilic[41]. The typical BAL findings in CTD-ILDs are given in table 7.

Connective Tissue Disease	BAL Pattern
Progressive systemic sclerosis	Neutrophils, eosinophils
Rheumatoid arthritis	Neutrophils, lymphocytes
Primary Sj ögren's syndrome	Neutrophils, lymphocytes (CD8+)
Systemic lupus erythematosus	Neutrophils, lymphocytes
Dermatopolymyositis	Neutrophils
Mixed connective tissue disease	Neutrophils
Secondary Sjögren's syndrome	Neutrophils, lymphocytes (CD8+)

Table 7: Bronchoalveolar lavage cytology in CTD-ILDs[42].

e. LUNG BIOPSY/ HISTOPATHOLOGY

- The decision about whether a lung biopsy should be performed,needs to be taken on a case-by-case basis, taking into account the patient's clinical condition and the impact of the results on the patient's management.

- Lung tissue can be obtained via transbronchial biopsy (TBLB) or transbronchial cryobiopsy (cryo-TBB) but because of inadequate yield, video-assisted thoracoscopic surgery (VATS) or open thoracotomy may need to be performed[43].

- Rheumatoid granulomatous inflammation is considered the only histopathological feature specific of CTD[30].

- Some features that may suggest the possibility of CTD include fewer fibroblastic foci, less severe honeycombing, more prominent lymphoid hyperplasia with germinal centres and more extensive plasmatic infiltration[44,45].

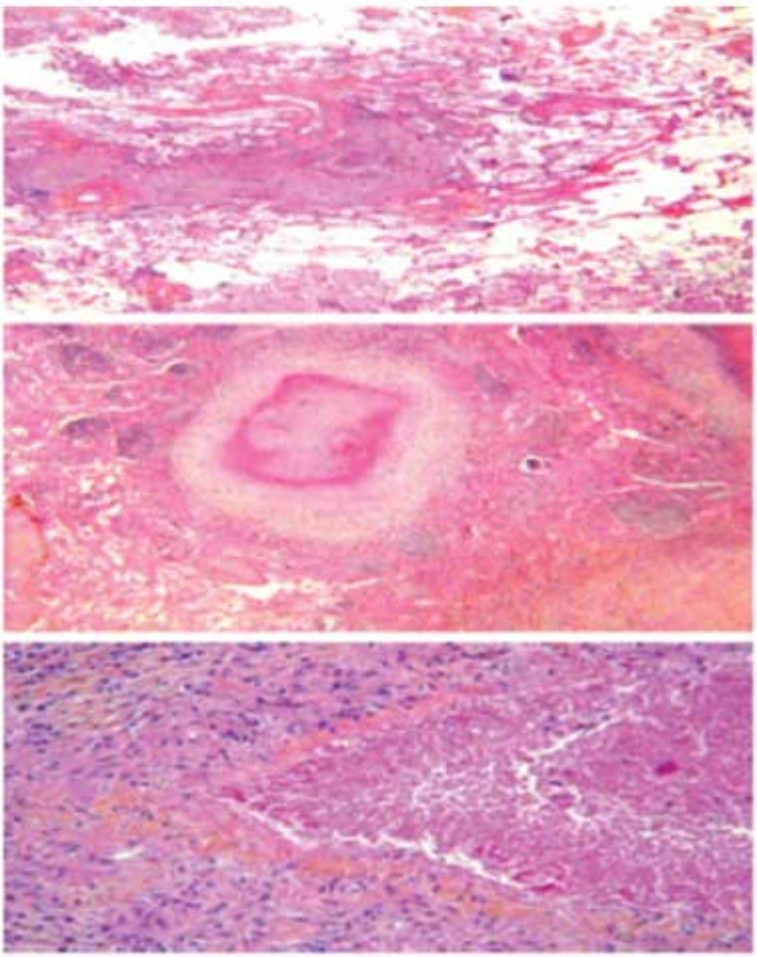

Figure 14. Rheumatoid nodule of the lung. The nodule is surrounded by interstitial pneumonia with inflammatory cells

C-VI. **TREATMENT RECOMMENDATIONS**

- A large percentage of patients with CTD ILD has limited and stable disease not requiring treatment.
- However, for those with severe or progressive disease, prompt initiation of treatment is necessary.
- Treatment strategies vary according to clinical situation for e.g. treatment of a patient with newly diagnosed CTD-ILD differs from that of someone with an acute exacerbation of the disease.
- Immunosuppression with corticosteroids and cytotoxic medications are the mainstay of therapy although data from Randomised Control Trials to support specific treatments are lacking, except in cases of ILD associated systemic sclerosis.

When to Treat?

- Although there is no consensus for optimal timing of CTD- ILD, clinically significant disease should be treated.
- A higher disease extent (reticular changes in HRCT >20%) or lower FVC (FVC <70%) are indications to commence treatment[46].

Systemic Sclerosis

First Line[47]:

- **Oral Cyclophosphamide:** 1-2 mg/kg/d for 12 months. Further benefits of cyclophosphamide are not seen at 24 months

OR

- **Mycophenolate Mofetil:** 1-1.5 g bid for 24 months

Other Treatments:

- **Anti reflux** medications (including high dose Proton Pump Inhibitors and prokinetic agents).
- **Rituximab** for patients with cyclophosphamide refractory SSc-ILD[48].
- In **SSc-ILD** patients, high dose corticosteroids (>10mg/d) should be avoided if at all possible because of risk of renal crisis. If required, low dose (<10mg/d) oral corticosteroids to be used.
- Disease monitoring is done by noting the improvement in FVC.

Rheumatoid Arthritis

- High dose prednisolone used as a first-line treatment option in RA-ILD patients. However, there is insufficient evidence to support its efficacy and safety[49,50].

- **MMF or Rituximab** may be used in RA-ILD patients to stabilize or improve lung volumes. However, data from available studies is limited.

- Drug induced pneumonitis is an important consideration in the differential diagnosis in patients suspected with RA-ILD. Methotrexate and leflunomide should be avoided in patients with RA and established ILD.

Dermatomyositis/Polymyositis

- Not every patient with ILD due to PM or DM requires treatment of the ILD as most patients follow a chronic, slowly-progressive course
- For other patients with more clinically significant disease, Corticosteroids (0.75-1mg/kg/d) have been the mainstay of treatment.
- Some patients may require combination therapy.
- Cyclophosphamide (monthly IV pulse therapy) is reserved for severe or refractory cases given its serious side effects.

Sjogren's Syndrome

- Evidence to guide treatment strategies remains limited. Only a few case series available.
- Prednisolone alone, or in combination with Hydroxychloroquine or Azathioprine is recommended.
- Limited data for use of rituximab in SS-ILD patients
- Treatment response is monitored by improvement in FVC and DLCO

Mixed Connective Tissue Disease

- Corticosteroid therapy is seen to be beneficial in such patients. It may be used in combination with steroid sparing agents.

Systemic Lupus Erythematosus

- The treatment for SLE-ILD typically includes CS along with steroid-sparing agents,
- For severe disease, high dose CS and CYC are initial treatment options
- For mild to moderate disease, CS with either AZA or MMF may be used.

	Systemic Sclerosis	RA	Sjogrens Syndrome	MCTD	PM/DM	SLE
First line treatment choice for limited CTD	Digital vasculopathy: nifedipine/ ilioprost	DMARD	Stimulation of salivary secretions (ss ica) Antimalarial agents (extragland - ular)	Corticosteroid	Corticosteroid +AZA/MMF	Hydroxy - chloroquine or chloroquine
First choice for clinical CTD - ILD	Cyclophospha mide 2mg/kg/day or MMF upto 3000mg	High dose Prednisone MMF	Glucocorticoid, antimala rial agent AZ A + prednisone	Corticosteroids + cytotoxic drug (Cyclophospha - mide)	Cyclophosph - amide AZA MMF	Corticosteroid + AZA/MMF
Follow up interval with PFT/ D_{LCO} / CXR or HRCT	Check PFT/ D_{LCO} every 6-12 month After progression; every 3 -4 months	Initiation of MTX: check chest x ray within 1 year. RA ILD: PFT/ D_{LCO} with HRCT 3 -6 months	-	-	Check PFT Stable disease: every 6 month Progression: Every 3 -4 months	-
Refractory CTD - ILD	Add Rituximab (375mg/m²) at 4- week interval for 24 weeks	Ritu ximab	-	-	High dose prednisolone + Cyclophosph - amide	High dose steroid + steroid sparing agent (C yclophospha - mide)
Rescue therapy	Lung transplantation	Lung transplantation '	-	-	-	-

Table 8. Treatment strategies according to the type of CTD

*AZA= Azathioprine, Connective tissue Disease, CXR= Chest X Ray, DLCO= Diffusion capacity of the lung for carbon monoxide, DM, Dermatomyositis, DMARD= Disease Modifying Anti Rheumatic Drug, HRCT= High Resolution Computed Tomography,ILD= Interstitial Lung Disease, MCTD= Mixed connective Tissue Disease, MMF= Mycophenolate mofetil, MTX= Methotrexate, PFT= Pulmonary Function Test, PM= Polymyositis, RA= Rheumatoid Arthritis, SLE= Systemic Lupus Erythematosust

Antifibrotic Agents

Use of Pirfenidone in Scleroderma-ILD patients has shown improvements in FVC of patients. However, current data is limited and further studies are planned to test the safety of Nintedanib and Pirfenidone in such patients.

Lung Transplantation

Lung transplantation is considered the final option in the management especially in SSc-ILD patients.

C-VII. **PROGNOSIS**

- NSIP pattern has a better prognosis than UIP, in CTD-ILD patients.
- IPF is a progressively worsening ILD and its characteristic histological pattern is UIP. Interestingly, a UIP pattern is associated with a significantly better survival in CTD related disease compared to the idiopathic variety.

REFERENCES

1. 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

2. 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

3. Baughman RP, Du Bois RM, Lynch JP, Wells AU. Diffuse Lung Disease- A practical approach. Great Britain: Arnold; 2004.

4. Katzenstein A, Fiorelli RF. Nonspecific interstitial pneumonia/fibrosis- Histologic features and clinical significance. Am J Surg Path01 1994; 18: 136-147.

5. American Thoracic Society/European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2002;165:277–304.

6. Kim DS, Collard HR, King TE Jr. Classification and natural history of idiopathic interstitial pneumonias. Proc Am Thorac Soc 2006;3(4):285–292.

7. Duchemann B, Annesi-Maesano I, Jacob de Naurois C, Sanyal S, Brillet PY et al. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. Eur Respir J 2017; 50(2):1-12.

8. Ansarie M. A national guideline and ILD PAK Registry Report: Recent landmarks in the understanding of interstitial lung diseases in Pakistan. J Pak Med Assoc. 2016;66:1050-3.

9. Zubairi A, Hassan M, Shahzad T, Sarwar S, Abbas A et al. Spectrum of interstitial lung disease from a tertiary care hospital in Karachi .J Pak Med Assoc. 2017 Jul;67(7):1065-1069.

10. Belloli EA, Beckford R, Hadley R, Flaherty KR. Idiopathic non-specific interstitial pneumonia. Respirology. 2016 Feb;21(2):259-268.

11. Cottin V, Donsbeck AV, Revel D, et al. Nonspecific interstitial pneumonia. Individualization of a clinicopathologic entity in a series of 12 patients. Am J Respir Crit Care Med 1998; 158:1286.

12. Fujita J, Yamadori I, Suemitsu I, et al. Clinical features of non-specific interstitial pneumonia. Respir Med 1999; 93:113.

13. Flaherty KR, Martinez FJ, Travis W, Lynch JP 3rd. Nonspecific interstitial pneumonia (NSIP). Semin Respir Crit Care Med 2001; 22:423.

14. Elliot TL, Lynch DA, Newell JD Jr, et al. High-resolution computed tomography features of nonspecific interstitial pneumonia and usual interstitial pneumonia. J Comput Assist Tomogr 2005;29:339–345.

15. MacDonald SL, Rubens MB, Hansell DM, et al. Nonspecific interstitial pneumonia and usual interstitial pneumonia: comparative appearances at and diagnostic accuracy of thin-section CT. Radiology 2001;221:600–605.

16. Sumikawa H, Johkoh T, Ichikado K, et al. Usual interstitial pneumonia and chronic idiopathic interstitial pneumonia: analysis of CT appearance in 92 patients. Radiology 2006;241:258–266.

17. Johkoh T, Muller NL, Colby TV, et al. Nonspecific interstitial pneumonia: correlation between thin section CT findings and pathologic subgroups in 55 patients. Radiology 2002;225:199–204.

18. Nishiyama O, Kondoh Y, Taniguchi H, et al. Serial high resolution CT findings in nonspecific interstitial pneumonia/fibrosis. J Comput Assist Tomogr 2000; 24:41–46.

19. Tsubamoto M, Muller NL, Johkoh T, et al. Pathologic subgroups of nonspecific interstitial pneumonia: differential diagnosis from other idiopathic interstitial pneumonias on high-resolution computed tomography. J Comput Assist Tomogr 2005;29:793–800

20. Jeong YJ, Lee KS, Muller NL, et al. Usual interstitial pneumonia and non-specific interstitial pneumonia: serial thin-section CT findings correlated with pulmonary function. Korean J Radiol 2005;6:143–152.

21. Hartman TE, Swensen SJ, Hansell DM, et al. Nonspecific interstitial pneumonia: variable appearance at high-resolution chest CT. Radiology 2000; 217:701–705.

22. Nagai S, Kitaichi M, Itoh H, Nishimura K, Izumi T et al. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. Eur Respir J 1998; 12: 1010–1019.

23. Veeraraghavan S, Latsi PI, Wells AU, Pantelidis P, Nicholson AG et al. BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia. Eur Respir J 2003; 22: 239–244.

24. Romagnoli M, Ravaglia C, Tomassetti S, Gurioli C, Gurioli C et al. BAL findings in idiopathic NSIP and IPF. European Respiratory Society. Annual Congress 2012. Abstract Number: 4798

25. Kligerman SJ, Groshong S, Brown KK, Lynch DA. Nonspecific Interstitial Pneumonia: Radiologic, Clinical, and Pathologic Considerations. RadioGraphics 2009; 29:73–87.

26. Flaherty KR, Toews GB, Travis WD, Colby TV, Kazerooni EA et al. Clinical significance of histological classification of idiopathic interstitial pneumonia. Eur. Respir. J. 2002; 19: 275–83.

27. Park IN, Jegal Y, KimDS, Do KH, Yoo B et al. Clinical course and lung function change of idiopathic nonspecific interstitial pneumonia. Eur. Respir. J.2009; 33: 68–76.

28. Nicholson AG, Colby TV, du Bois RM, Hansell DM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 2000;162:2213–2217.

29. Travis WD, Matsui K, Moss J, Ferrans VJ. Idiopathic nonspecific interstitial pneumonia: prognostic significance of cellular and fibrosing patterns survival comparison with usual interstitial pneumonia and desquamative interstitial pneumonia. Am J Surg Pathol 2000;24:19–33.

30. Cottin V. Idiopathic interstitial pneumonias with connective tissue diseases features: a review. Respirology 2016;21:245-258.

31. Koo, S.-M., Uh S-T. Treatment of connective tissue disease associated interstitial lung disease: the pulmonologist's point of view. The Korean Journal of Internal Medicine, (2017); 32(4): 600–610.

32. Kornum JB, Christensen S, Grijota M, et al. The incidence of interstitial lung disease 1995-2005: a Danish nationwide population-based study. BMC Pulm Med 2008;8:24.

33. Solomon JJ, Fischer A. Connective tissue disease associated interstitial lung disease: a focused review. J Intensive Care Med 2015;30:392-400.

34. Antoniou KM, Margaritopoulos G, Economidou F, Si¬afakas NM. Pivotal clinical dilemmas in collagen vascular diseases associated with interstitial lung involvement. Eur Respir J 2009;33:882-896.

35. Olson A, Brown K, Fischer A. Connective tissue disease associated lung disease. Immunol Allergy Clin North Am. 2012;32:513–536.

36. Radiology Assistant. [internet] [cited 2018 March 5]. Available from: http://www.radiologyassistant.nl/en/p46b480a6e4bdc/lung-hrct-common-diseases.html

37. Gabbay E, Tarala R, Will R, et al. Interstitial lung disease in recent onset rheumatoid arthritis. Am J Respir Crit Care Med 1997; 156:528.

38. Bradley B, Branley HM, Egan JJ, et al. 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(5):v1.

39. Lee W, Chung WS, Hong KS, Huh J. Clinical usefulness of bronchoalveolar lavage cellular analysis and lymphocyte subsets in diffuse interstitial lung diseases. Ann Lab Med 2015; 35:220.

40. Mahmud T. Out of the Fire and into the Fire Again- Advanced Interstitial Lung Disease due to Disseminated Adenocarcinoma Lung. Proceeding S.Z.P.G.M.I. 2015: 29 (2): 117-121.

41. Efared B, Ebang-Atsame G, Rabiou S, Diarra AS, Tahiri L et al. The diagnostic value of the bronchoalveolar lavage in interstitial lung diseases. J Negat Results Biomed. 2017: 1;16(1):4.

42. Wallaert B, Rossi GA, Sibille Y. Clinical guidelines and indications for bronchoalveolar lavage (BAL): collagen-vascular diseases. Eur Respir J 1990; 3:942.

43. Assayag D, Elicker BM, Urbania TH, et al. Rheumatoid arthritis-associated interstitial lung disease: radiologic identification of usual interstitial pneumonia pattern. Radiology 2014; 270:583.

44. Song JW, Do K-H, Kim M-Y, Jang SJ, Colby TV, Kim DS. Pathologic and radiologic differences between idiopathic and collagen vascular disease-related usual interstitial pneumonia. Chest 2009; 136: 23–30.

45. Fischer A, West SG, Swigris JJ, Brown KK, du Bois RM. Connective tissue disease-associated interstitial lung disease: a call for clarification.Chest 2010; 138: 251–256.

46. Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 2008;177:1248-1254.

47. Clements PJ, Tashkin D, Roth M, et al. The scleroderma lung study II (SLS II) shows that both oral cyclophospha¬mide (CYC) and mycophenolate mofitil (MMF) are effi¬cacious in treating progressive interstitial lung disease (ILD) in patients with systemic sclerosis (SSc). Arthritis Rheumatol 2015;67(10):abstr1075.

48. Daoussis D, Liossis SN, Tsamandas AC, et al. Experi¬ence with rituximab in scleroderma: results from a 1-year, proof-of-principle study. Rheumatology (Oxford) 2010;49:271-280.

49. Assayag D, Lee JS, King TE Jr. Rheumatoid arthritis as¬sociated interstitial lung disease: a review. Medicina (B Aires) 2014;74:158-165.

50. Marigliano B, Soriano A, Margiotta D, Vadacca M, Afeltra A. Lung involvement in connective tissue diseases: a com¬prehensive review and a focus on rheumatoid arthritis. Autoimmun Rev 2013;12:1076-1084.

ABBREVIATIONS

ABG - Arterial Blood Gas

ANA - Anti Nuclear Antibody

Anti-CCP - Anti Cyclic Citrullinated Antibody

ATS - American Thoracic Society

AZA - Azathioprine

BAL - Broncho Alveolar Lavage

BOOP - Bronchiolitis Obliterans Organizing Pneumonia

CK - Creatinine Kinase

CRP - C Reactive Protein

cryo TBB - Transbronchial cryobiopsy

CS - Corticosteroids

CT - Computed Tomography

CTD - Connective Tissue Disease

CVD - Collagen Vascular Disease

CYC - Cyclophosphamide

DAD - Diffuse Alveolar Damage

DIP - Desquamative Interstitial Pneumonia

D_{LCO} - Diffusing Capacity of the Lung for carbon monoxide

DM - Dermatomyositis

DPLD - Diffuse Parenchymal Lung Disease

ds DNA - double stranded Deoxyribo Nucleic Acid

ENA - Extractable Nuclear Antigen Antibodies

ERS - European Respiratory Society

ESR - Erythrocyte Sedimentation Rate

FEV1 - Forced Expiratory Volume in 1 second

FRC - Functional Residual Capacity

FVC - Forced Vital Capacity

HIV - Human Immunodeficiency Virus

HP - Hypersensitivity Penumonia

HRCT - High Resolution Computed Tomography

IIP - Idiopathic Interstitial Pneumonia

ILD - Interstitial Lung Disease

iNSIP - Idiopathic Non Specific Interstitial Pneumonia

IPAF - Interstitial Pneumonia with Auto-immune Features

IPF - Idiopathic Pulmonary Fibrosis

LIP - Lymphocytic Interstitial Pneumonia

MCTD - Mixed Connective Tissue Disease

MMF - Mycophenolate Mofetil

NSIP - Non Specific Interstitial Pneumonia

OP - Organizing Pneumonia

PCP - Pneumocystis jirovecii Pneumonia

PCS - Pakistan Chest Society

PFT - Pulmonary Function Test

PM - Polymyositis

RA - Rheumatoid Arthritis

RF - Rheumatoid Factor

RV - Residual Volume

SLE - Systemic Lupus Erythematosus

SSc - Systemic Sclerosis

TBLB - Trans Bronchial Biopsy

TLC - Total Lung Capacity

UIP - Usual Interstitial Pneumonia

VATS - Video-Assisted Thoracoscopic Surgery

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www.ildpak.com
www.ersnet.org
www.thoracic.org
www.pulmonaryfibrosis.org