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ICS–NCCP-ILD Consensus Statement

Management of Interstitial Lung Diseases: A Consensus Statement of the Indian Chest Society and National College of Chest Physicians (India)

[This document has been endorsed by the American Thoracic Society on May 12, 2020 and by the Asian Pacific Society of Respirology on June 25 2020]

Sheetu Singh[1], Bharat Bhushan Sharma[2], Mohan Bairwa[3], Dipti Gothi[4], Unnati Desai[5], Jyotsna M. Joshi[5], Deepak Talwar[6], Abhijeet Singh[6], Raja Dhar[7], Ambika Sharma[1], Bineet Ahluwalia[1], Daya K. Mangal[8], Nirmal K. Jain[9], Khushboo Pilania[10], Vijay Hadda[11], Parvaiz Koul[12], Shanti Kumar Luhadia[13], Rajesh Swarnkar[14], Shailender Nath Gaur[15], Aloke G. Ghoshal[16], Amita Nene[17], Arpita Jindal[18], Bhavin Jankharia[19], Chetambath Ravindran[20], Dhruv Choudhary[21], Digambar Behera[22], D.J. Christopher[23], Gopi Chand Khilnani[24], Jai Kumar Samaria[25], Harpreet Singh[26], Krishna Bihari Gupta[27], Manju Pilania[28], Manohar L. Gupta[29], Narayan Misra[30], Nishtha Singh[31], Prahlad R. Gupta[32], Prashant N. Chhajed[33], Raj Kumar[34], Rajesh Chawla[35], Rajendra K. Jenaw[1], Rakesh K. Chawla[36], Randeep Guleria[11], Ritesh Agarwal[22], R. Narsimhan[37], Sandeep Katiyar[38], Sanjeev Mehta[39], Sahajal Dhooria[22], Sushmita R.Chowdhury[40], Surinder K. Jindal[41], Subodh K. Katiyar[42], Sudhir Chaudhri[43], Neeraj Gupta[44], Sunita Singh[45], Surya Kant[46], Zarir F. Udwadia[47], Virendra Singh[31], and Ganesh Raghu[48]

[1] Department of Respiratory Medicine, SMS Medical College, Jaipur (Rajasthan)

[2] Department of Medicine, SMS Medical College, Jaipur (Rajasthan)

[3] Centre for Community Medicine, All India Institute of Medical Sciences, New Delhi

[4] Department of Pulmonary, Sleep and Critical Care Medicine, ESI-PGIMSR, Delhi

[5] Department of Pulmonary Medicine, TN Medical College and BYL Nair Hospital, Mumbai (Maharashtra)

[6] Division of Pulmonary and Critical Care Medicine, Metro Centre for Respiratory Diseases, Metro Multi Speciality Hospital, Noida (Uttar Pradesh)

[7] Department of Pulmonology, Fortis Hospital, Kolkata (West Bengal)

[8] Department of Public Health and Epidemiology, IIHMR University, Jaipur (Rajasthan)

[9] Jain Chest Care Center, Jaipur (Rajasthan)

[10] Department of Radio-diagnosis, Max Super Specialty Hospital, Noida (Uttar Pradesh)

[11] Department of Pulmonary, Critical Care and Sleep Medicine, AIIMS, New Delhi

[12] Department of Internal and Pulmonary Medicine, Sher-e-Kashmir Institute of Medical Sciences, Srinagar (Jammu and Kashmir)

[13] Department of Respiratory Medicine, Geetanjali Medical College and Hospital, Udaipur (Rajasthan)

[14] Department of Respiratory, Critical Care, Sleep and Interventional Pulmonology, Getwell Hospital and Research Institute, Nagpur (Maharashtra)

[15] Department of Respiratory Medicine, School of Medical Science and Research, Sharda University, Greater Noida ((Uttar Pradesh)

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Co-chairs of this Task Force: Virendra Singh and Ganesh Raghu

Corresponding author:: Dr Virendra Singh, Asthma Bhawan, Vidyadhar Nagar, Jaipur-302023 (Rajasthan), India; E-mail: drvirendrasingh93@gmail.com

[16] Department of Respiratory Medicine, National Allergy Asthma Bronchitis Institute, Kolkata (West Bengal)

[17] Department of Respiratory Medicine, Bombay Hospital and Medical Research Center, Mumbai (Maharshtra)

[18] Department of Pathology, SMS Medical College, Jaipur (Rajasthan)

[19] Department of Radio-diagnosis, Jankharia Imaging, Mumbai (Maharashtra)

[20] Department of Pulmonary Medicine, DM Wayanad Institute of Medical Sciences, Wayanad, Kerala

[21] Department of Pulmonary and Critical Care Medicine, PGIMS, Rohtak (Haryana)

[22] Department of Pulmonary Medicine, PGIMER, Chandigarh

[23] Department of Pulmonary Medicine, Christian Medical College, Vellore (Tamil Nadu)

[24] Department of Pulmonary Medicine, PSRI Institute of Pulmonary, Critical Care and Sleep Medicine, New Delhi

[25] Department of Chest Diseases, Institute of Medical Sciences, BHU, Varanasi (Uttar Pradesh)

[26] Department of Medicine, PGIMS, Rohtak (Haryana)

[27] Department of Respiratory Medicine, PGIMS, Rohtak (Haryana)

[28] Department of Community Medicine, RUHS College of Medical Sciences, Jaipur (Rajasthan)

[29] Department of Pulmonary and Sleep Medicine, Santokbha Durlabhji Memorial Hospital, Jaipur (Rajasthan)

[30] Department of Pulmonary Medicine, MKCG Medical College and Hospital, Behramapur (Odisha)

[31] Department of Pulmonary Medicine, Asthma Bhawan, Jaipur (Rajasthan)

[32] Department of Pulmonary Medicine, NIMS University, Jaipur (Rajasthan)

[33] Lung Care and Sleep Center, Institute of Pulmonology Medical Research and Development, Mumbai (Maharashtra)

[34] Department of Respiratory Medicine, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi

[35] Department of Respiratory Medicine, Critical Care and Sleep Disorders, Indraprastha Apollo Hospitals, New Delhi

[36] Department of Respiratory Medicine, Critical Care and Sleep Disorders, Jaipur Golden Hospital and Saroj Super Speciality Hospital, Delhi

[37] Department of Respiratory Medicine, Apollo Hospitals, Chennai (Tamil Nadu)

[38] Department of Pulmonary Medicine, Apollo Spectra Hospital, Kanpur (Uttar Pradesh)

[39] Department of Pulmonology, The Chest and Allergy Center, Mumbai (Maharashtra)

[40] Department of Pulmonary Medicine, Apollo Gleneagles Hospital, Kolkata (West Bengal)

[41] Jindal Chest Clinic, Chandigarh

[42] Chest Care Center, Kanpur (Uttar Pradesh)

[43] Department of Respiratory Medicine, GSVM Medical College and Hospital, Kanpur (Uttar Pradesh)

[44] Department of Respiratory Medicine, JLN Medical College and Hospital, Ajmer (Rajasthan)

[45] Department of Pathology, PGIMS, Rohtak (Haryana)

[46] Department of Respiratory Medicine, KG Medical University, Lucknow (Uttar Pradesh)

[47] Department of Pulmonary Medicine, Hinduja Hospital, Mumbai (Maharashtra)

[48] Department of Medicine, University of Washington, Seattle, USA

Summary of ILD Consensus Statements

Interstitial lung diseases (ILDs) are a broad and complex heterogeneous group of lung diseases. While clinical practice guidelines (CPG) have been developed for the diagnosis and management of idiopathic pulmonary fibrosis (IPF), CPG for the diagnosis and management of patients with other ILDs are lacking. There is an unmet need for the development of evidence-based CPGs for all major subtypes of ILDs. These consensus statements were developed by an ILD working-group with the collaboration of Indian Chest Society (ICS) and National College of Chest Physicians (India) (NCCP [I]), after the systematic review of the existing evidence. This statement is aimed to provide the physicians working in diverse health-care systems with a better understanding to diagnose and manage patients with non-IPF ILD in India and beyond. It is also hoped that this document will be useful to the physicians confronted with patients who are not willing, wanting and/or able to be subjected to invasive diagnostic interventions.

A working-group of multi-disciplinary clinicians familiar with the clinical management of the ILDs (pulmonologists, radiologists, pathologists, rheumatologist) and epidemiologists selected by the leaderships of ICS and NCCP(I) posed 29 search questions to address the clinically relevant situations. A systematic search was performed on the PubMed, Embase databases, and the Cochrane library. Data related to each question were reviewed in face-to-face discussions among the group members. Statements framed reflect the consensus opinion of the working-group. A modified GRADE approach was used to grade the evidence.

Outcome

The following statements were the consensus of the working-group for the patients diagnosed with ILD:

- Baseline spirometry should be obtained in all the patients with suspected ILD.
- Volume scans on multi-detector computed tomography (MDCT) [16 slice or higher] are preferable at the initial assessment.
- Bronchoalveolar lavage (BAL) may be used to diagnose certain rare ILDs. When performed, infection must be ruled out (especially, *Mycobacterium tuberculosis*) by special stains, molecular techniques and cultures of the BAL specimen, if suspected by the clinician.
- Transbronchial lung biopsy (TBLB) may be considered in those patients likely to have ILDs, particularly if the disease has a tendency for bronchocentric involvement.
- In patients not-at-high risk for surgical complications, the conditional recommendations for the surgical lung biopsy (SLB) made in the 2018 CPG was endorsed.
- Transbronchial lung cryobiopsy (TBLC) may be considered for obtaining biopsy in carefully selected patients with ILD at centers with expertise in the procedure.
- Endorsement of the conditional recommendations for the multidisciplinary discussion (MDD) made by the international experts for the diagnosis of ILD.
- Most common comorbidities encountered in ILD are gastro-esophageal reflux disease (GERD), pulmonary hypertension (PH), lung cancer, obstructive sleep apnoea (OSA) and venous thromboembolism (VTE).
- Every effort should be made to identify and treat the comorbid conditions influencing cough in ILD.
- Pulmonary rehabilitation is suggested in dyspneic patients with ILD.
- Endorsement of the recommendations for the annual influenza vaccination and pneumococcal vaccination by ACIP (Advisory Committee on Immunization Practices) to all patients with ILD.
- Treatment indicated for underlying lung disease as the mainstay of therapy and supplemental oxygen for patients with hypoxemia.
- Consideration of non-invasive ventilation (NIV) as early as possible in patients who require high flow supplemental oxygen at rest.
- The consideration of mechanical ventilation (MV) in patients with acute exacerbation of ILD (AE-ILD) with respiratory failure should be made only after proper counselling.
- Lung transplantation is the only treatment with clearly proven survival benefit in advanced ILD.
- Palliative care for all patients with advanced ILDs.
- Monitoring of disease with spirometry is advised at 4-6 months intervals.
- Oral corticosteroids for 4-12 weeks are an appropriate treatment option for patients with acute/subacute HP.
- Anti-nuclear antibody (ANA) testing (by indirect immunofluorescence method), rheumatoid factor (RF) and antibody to cyclic citrullinated peptide (anti-CCP) testing at baseline for all patients with ILD.
- Corticosteroids may be given to treat rheumatoid arthritis-ILD (RA-ILD).

- Low dose oral corticosteroids may be used for the treatment of systemic sclerosis-ILD (SSC-ILD) and high dose should be avoided in scleroderma as it is associated with risk of renal crisis.
- Cyclophosphamide or Mycophenolate mofetil treatment in SSC-ILD is appropriate for the patients with progressive disease.
- Avoidance of continued exposure to silica and direct inhalation of tobacco products is strongly urged.
- The updated recommendations published by the American Thoracic Society (ATS) for the diagnosis and treatment of IPF are endorsed; including treatment with antifibrotic agents, pirfenidone or nintedanib.

Consensus Statements

Abstract

Background. Interstitial lung diseases (ILDs) are a complex and heterogeneous group of acute and chronic lung diseases of several known and unknown causes. While clinical practice guidelines (CPG) for idiopathic pulmonary fibrosis (IPF) has been recently updated, CPG for ILD other than IPF are needed.

Methods. A working-group of multidisciplinary clinicians familiar with the clinical management of the ILD (pulmonologists, radiologists, pathologists, rheumatologists) and three epidemiologists selected by the leaderships of Indian Chest Society (ICS) and National College of Chest Physicians (India) (NCCP[I]), posed questions to address the clinically relevant situation. A systematic search was done on PubMed, Embase and Cochrane databases. Modified GRADE approach was used to grade the evidence. The working-group discussed the evidence and reached a consensus of opinions for each question following face-to-face discussions.

Results. Statements have been made for each specific question and the grade of evidence has been provided after performing a systematic review of the literature. For most of the questions addressed, the available evidence was insufficient and of low to very low quality. The consensus of the opinions of the working-group has been presented as statements for the questions and not as an evidence based CPG for the management of ILDs.

Conclusions. This document provides the statements made by the consensus of opinions among the experts following discussion of systematic review of evidence pertaining to the specific questions for the management of ILDs other than IPF. It is hoped that this document will help the clinicians understand the accumulated evidence and help better management of idiopathic and non-idiopathic interstitial pneumonias.

Introduction

Interstitial lung diseases (ILDs) are a broad and heterogeneous group of lung diseases with overlapping clinical, radiological and histopathological features. While clinical practice guidelines (CPGs) have been developed by the international experts for idiopathic pulmonary fibrosis (IPF), the need for CPGs to guide the clinicians to diagnose and treat patients with other ILDs is evident. The Indian Chest Society (ICS) and National College of Chest Physicians (India) (NCCP[I]), took an initiative for a task-force to frame the consensus statements for management of ILDs. The target audience are the clinicians who care for adults with ILD. Given the lack of evidence based CPG for general ILDs and specific ILDs other than IPF, the object of this task-force was to develop a document to help the clinicians within and beyond India to have a better understanding of the most appropriate diagnostic and therapeutic interventions available.

We believe that this document will be useful for the clinicians in making accurate diagnosis and appropriate therapeutic interventions for the patients with ILDs other than IPF.

Methodology

A working-group of multidisciplinary expert clinicians familiar with clinical management of ILD (45 pulmonologists, 2 radiologists, 2 pathologists, 1 rheumatologist, 3 epidemiologists) selected by the leadership of the ICS and NCCP, India with co-chairs Virendra Singh and Ganesh Raghu, posed 29 search questions to address the management of ILDs. A systematic search was done on the PubMed and Embase databases and the Cochrane library. A modified GRADE approach was used to grade the evidence (Table 1). The working-group discussed the evidence and reached a consensus of opinions for each question following face-to-face discussions. A consensus was sought for all the questions — it was unanimous in cases with high quality evidence. Greater than 80% agreement was used as threshold to determine consensus for those with a lesser quality of evidence. The CPGs developed by the international experts for the diagnosis and management of IPF were reviewed and endorsed by the group. The specific questions addressed in this document are pertinent to the adult patient suspected to have ILD as defined:

Unexplained respiratory symptoms with chest radiograph or computed tomography (CT) evidence of 'ILD'– these include bilateral lung involvement with parenchymal densities including bilateral nodules and/or airspace densities and/or fibrotic patterns (Figure 1).

Q 1. Should spirometry, DLCO and six minute walk test (6MWT) be performed in the initial evaluation?

Key Statements

- The American Thoracic Society (ATS) guidelines on lung function testing and six minute walk test (6MWT) for the clinical practice were endorsed as a standard of care to ensure quality.[1,2]
- Baseline spirometry should be obtained in all patients with suspected ILD. [2A]
- Plethysmographic lung volumes should be done wherever feasible. [3A]
- Initial evaluation should include diffusion capacity of the lung for carbon monoxide (DLCO) corrected to hemoglobin (DLCO corr Hb) wherever feasible. [3A]
- 6MWT should be assessed at baseline. [2A]

Discussion

Desirable Effects

Spirometry, DLCO and 6MWT are routine lung function tests to assess the functional impairment at rest and with activity of the patient in an objective manner at diagnosis as well as to prognosticate the disease rather than a diagnostic tool to characterise the sub-type of ILD.[3,4] These are also useful to assess the disease progression and the response to treatment.[5,6] In this regard, the rate of forced vital capacity (FVC) decline has been used as primary endpoint in most if not all clinical trials including IPF and scleroderma.[7,8]

During 6MWT patients appreciate their symptoms of shortness of breath by correlating their symptoms to distance walked and fall in oxygen saturation, and thereby, appreciate the need to use supplemental oxygen. Baseline lung functions are advisable for all the patients, useful for monitoring the progress of the disease and the treatment response (Figure 2).

Table 1. The modified grade system including grades and each statement was graded as per the strengths

Grade of Evidence	Criterion
Level 1 evidence	Evidence from ≥1 good quality and well conducted randomised control trial(s) or meta-analysis of RCTs
Level 2 evidence	Evidence from at least 1 RCT of moderate quality, or well-designed clinical trial without randomisation; or from cohort or case-controlled studies.
Level 3 evidence	Evidence from descriptive studies
Usual practice point (UPP)	Not backed by sufficient evidence; however, a consensus reached by the working-group, based on clinical experience and expertise
Additionally the evidence is given strengths depending on risk and benefits	
Strength A	Strong recommendation to do (or not to do) where the benefits clearly outweigh the risk (or vice versa) for most, if not all patients. *e.g.* 1A, 2A
Strength B	Weak recommendation, where benefits and risk are more closely balanced or are more uncertain. *e.g.* 1B, 2B, 3B

Definition of abbreviation: RCT=Randomised controlled trial

Undesirable Effects

There were no identified harms associated with patients performing the tests other than the requirement of learning the technique of correctly performing the test and out-of-pocket cost involved.

Q 2. Should CT scan chest be performed in diagnosis of ILD?

Key Statements

- The 2018 ATS-ERS-JRS-ALAT (European Respiratory Society-Japanese Respiratory Society-

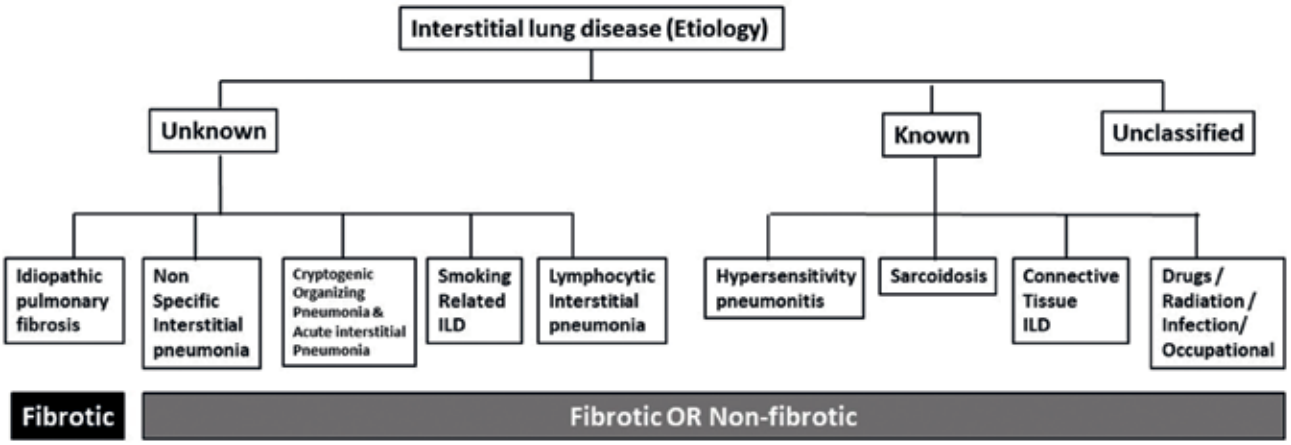

Figure 1. Classification of interstitial lung diseases on the basis of known or unknown etiology.

Spirometry	Lung volumes	Diffusion study	Six minute walk test variable	Arterial blood gas analysis
• Restrictive defect • Obstructive defect in HP, sarcoidosis and COP	• Reduced - tidal volume, vital capacity and total lung capacity	• Reduced single breath DLCO corrected for haemoglobin • May be normal in early disease • Disproportional reduction in pulmonary artery hypertension	• Measures functional impairment • Desaturation >4% and reduced distance • Useful for prognosis • Useful for follow-up monitoring	• Indicated in patients with resting hypoxia (resting SPO2<90%)

Figure 2. The role of lung function tests in the evaluation of patients with interstitial lung disease.

Latin American Thoracic Society) guidelines were endorsed and stated that high resolution computed tomography (HRCT) of the chest with proper technique is needed to recognise patterns and distribution of the abnormalities that may be diagnostic of some specific ILD on the first instance. [1A]

- Volume scans on multidetector computed tomography (MDCT) [16 slice or higher] are preferable at initial assessment. [1A]
- Follow-up CT should be obtained for clinical relevant reasons and/or during follow up when clinically indicated, with the similar acquisition protocol. [UPP]

Discussion

Desirable Effects

Obtaining HRCT scans of the chest has become quite essential component of diagnostic evaluation in ILD and is in essence a motherhood statement. The disease-specific patterns have diagnostic and prognostic significance (Figure 3).

Undesirable Effects

The major concern with the volumetric technique is the radiation dose exposure.[9] However, recent technological advances allow significant reduction of the radiation exposure without a compromise in quality.[10-15]

Quality of HRCT would be another concern, table 2 provides the recommended protocol for obtaining a good quality HRCT.[16] Interacting with the radiologist and communicating the requirements would be a step towards multi-disciplinary discussion.

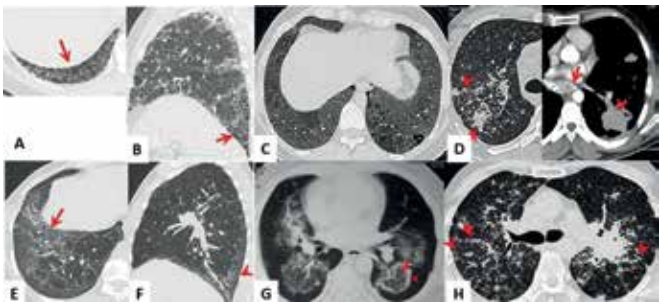

Figure 3. The axial image on high resolution computed tomography (HRCT) of chest (A) shows honeycombing with sub-pleural lower lobe predominance; sagittal image; (B) shows the sub-pleural distribution better. This is suggestive of the usual interstitial pneumonia (UIP) pattern and in the absence of an etiology, would be suggestive of idiopathic pulmonary fibrosis (IPF); (C) *Hypersensitivity pneumonitis*. Axial image shows diffuse ill-defined bronchocentric nodules (arrow) that are characteristic of this condition. These nodules coalesce to form areas of ground-glass attenuation; (D) *Silicosis*. Axial CT scan shows nodules of varying sizes (arrow) with egg-shell sub-carinal node calcification and a confluent soft tissue mass of progressive massive fibrosis; (E and F) *Scleroderma ILD-NSIP pattern [34-year-old lady with scleroderma]*. Axial supine (E) and sagittal (F) images show reticular opacities (arrow in E) with sub-pleural sparing (arrowhead in F) that are typical of an NSIP pattern; (G) *Cryptogenic organising pneumonia*. Axial CT scan shows areas of ground-glass attenuation in the centre (arrow) with peripheral consolidation (arrowhead) ---this is the typical reverse halo or atoll sign; and (H) *Sarcoidosis*. Axial CT scan shows peri-vascular (arrow), sub-pleural (arrowhead) and fissures (short arrow on the left) nodules typical of the disease.

Table 2. Recommended HRCT scanning protocol for patient's being evaluated for ILD[17]

S. No.	Protcol Recommended
1.	Non-contrast examination
2.	Volumetric acquisition with selection of: • Sub-millimetric collimation • Shortest rotation time • Highest pitch • Tube potential and tube current appropriate to patient size: ◦ Typically 120 kVp and ≤240 mAs ◦ Lower tube potentials (*e.g.*, 100 kVp) with adjustment of tube current encouraged for thin patients • Use of techniques available to avoid unnecessary radiation exposure (*e.g.*, tube current modulation)
3.	Reconstruction of thin-section CT images (91.5 mm): • Contiguous or overlapping • Using a high-spatial-frequency algorithm • Iterative reconstruction algorithm if validated on the CT unit (if not, filtered back projection)
4.	Number of acquisitions: • Supine: inspiratory (volumetric) • Supine: expiratory (can be volumetric or sequential)* • Prone: only inspiratory scans (can be sequential or volumetric)** • Inspiratory scans obtained at full inspiration
5.	Recommended radiation dose for the inspiratory volumetric acquisition: • 1–3 mSv (*i.e.*, "reduced" dose) • Strong recommendation to avoid "ultralow-dose CT" (<1 mSv)

* Though the ATS/ERS 2018 guidelines give a choice between volumetric or sequential scans for the expiratory acquisition, we suggest volumetric scan at expiration as well, for the benefits described in the text.

**Prone scans should be done in patients with minimal or absent symptoms.

Definition of abbreviations: HRCT=High-resolution computed tomography; ILD=Interstitial lung disease; CT=Computed tomography; ATS=American Thoracic Society; ERS=European Respiratory Society

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Q 3. Should following procedure(s) be performed in diagnosis?

A. Bronchoalveolar lavage (BAL)

B. Transbronchial lung biopsy (TBLB)

C. Transbronchial cryobiopsy (TBLC)

D. Video-assisted thoracoscopic (VATS) lung biopsy

Key Statements

- BAL may be used to diagnose certain rare ILDs, such as pulmonary alveolar proteinosis (PAP), pulmonary Langerhans cell histiocytosis (PLCH) and eosinophilic pneumonia. [3B]
- When performed, infection must be ruled out (especially, *Mycobacterium tuberculosis*) by special stains, molecular techniques and cultures of the BAL specimen, if suspected by the clinician. [UPP]
- Non-invasive tests, such as sputum for microbiologic and molecular testing should precede a flexible bronchoscopy; a positive result obviates the need of a BAL.
- Conventional TBLB should not be done in patients with UIP pattern on HRCT. [2A]
- TBLB may be considered in those patients likely to have ILDs, particularly if the disease has a tendency for bronchocentric involvement, such as sarcoidosis and HP. [3B]
- The site of biopsy should be guided by HRCT. [UPP]
- TBLC may be considered for obtaining biopsy in carefully selected patients with ILD at centers with expertise in the procedure. [2A]
- In patients not-at-high risk for surgical complications, the conditional recommendation for the surgical lung biopsy (SLB) made in the 2018 CPG was endorsed by this group, and should be considered for diagnosis of ILD based on availability of local surgical expertise if the HRCT does not show a characteristic pattern of a specific ILD sub-type. [1A]
- VATS lung biopsy should be preferred over open lung biopsy. [1A]
- Patients with FVC ≥55% and diffusion capacity (DLCOcorr to Hb) ≥35%; and either absent or only mild PH, are at minimal risk of complications. [2B]
- SLB should not be performed in patients with respiratory failure/those on mechanical ventilation as it is associated with risk of high mortality. [1A]

Discussion

A. Bronchoalveolar Lavage

Desirable Effects

A properly performed BAL (Table 3) helps ascertain the cellularity by differential count, rules out infections, especially, mycobacterial, fungal and viral, thereby narrows the differential diagnoses of ILD.[18] In appropriate clinical settings, BAL specimens are useful to diagnose alveolar proteinosis and alveolar hemorrhage. In resource-limited setting a properly performed and analysed BAL, may be of particular benefit in non-IPF ILDs.[19] BAL and lung biopsy of any kind are not indicated in patients with known connective tissue disorder (CTD) manifesting ILD for the purpose of the specific histopathology diagnosis.

Undesirable Effects

Although BAL is a relatively safe procedure, the risks associated with the procedure and conscious sedation are relative. Rarely, BAL may precipitate an episode of acute exacerbation of underlying ILD. Patients may experience discomfort and/or cough during the procedure. Appropriate standardisation of the process and interpretation of BAL results needs to be ensured to minimise variability.[18]

Table 3. Procedure, handling of specimen and cellular analysis to be done on BAL fluid as per the American Thoracic Society guidelines 2012[17]

S. No.	Protcol Recommended
1.	Site for taking a BAL is decided by the part of lung most affected
2.	Minimum 100mL and maximum 300mL normal saline is instilled after wedging the bronchoscope in the distal most segment
3.	Saline is instilled in 3-5 sequential aliquots and then sucked out with suction pressures less than 100mmHg
4.	Minimum 30% of instilled saline should be retrieved to label it adequate sample
5.	BAL fluid is transferred to laboratory situated in same hospital as the procedure may be transferred as such
6.	If transfer requires more than 30 minutes, it should transported on ice
7.	BAL differential count should be performed including: neutrophils, eosinophils, lymphocytes, macrophages

Definition of abbreviation: BAL=Bronchoalveolar lavage

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B. Transbronchial Lung Biopsy

Desirable Effects

The diagnostic yield of a TBLB specimen is high in ILD with a peribronchovascular or centrilobular pattern of distribution, such as sarcoidosis, hypersensitivity pneunmonitis (HP), PAP, lymphangitis carcinomatosis and alveolar microlithiasis.[20] Recent reports suggest the utility of TBLB for molecular diagnosis of UIP.[21,22]

Undesirable Effects

With the exception of sarcoidosis, TBLB has limitations with diagnostic yield because of the small size of the biopsy specimen, high probability of crush artefacts, sampling errors, inability to penetrate beyond the peri-bronchial region and disintegration of the friable tissue. Further, patients with IPF may have non-specific interstitial pneumonia (NSIP) pattern in some areas of their lungs, and thus, small sized TBLBs may mis-classifyusual interstitial pneumonia (UIP) as NSIP.[23] Bleeding (1–4%), pneumothorax (1–6%) and mortality (<0.05%) constitute the main complications.[16,20]

C. Transbronchial Lung Cryobiopsy(TBLC)

Desirable Effects

TBLC has advantages over TBLB by providing larger lung specimens with little crush artefact.[24] The larger size of the specimen increases the probability of sampling the tissue of interest. Previous data has shown that a relatively lower proportion of patients with ILD undergo lung biopsies reflecting the reluctance on part of physician or patient or due to lack of facilities for SLB.[25,26] Performing a cryobiopsy would bridge the gap of providing larger tissue with good yield without the cost, risk and surgical expertise required for SLB.

Undesirable Effects

The technique is relatively new with varying levels of expertise and lack of standardised and/or validated technique. The rate of complications are variable; pneumothorax (3-33%), moderate to severe bleeding (0-78%), acute exacerbation and death (0.04 - 4.3%).[16,26-40] Due to the risk of complications, the technique should be performed by experts trained and familiar with the technique in carefully selected patients (FVC ≥1.5L and 50% of predicted, forced expiratory volume in first second (FEV_1) ≥0.8 L, DLCO ≥ 30% of predicted, partial pressure of arterial oxygen (PaO_2) ≥60 mmHg, absence of extensive fibrotic changes on CT scan, no or mild pulmonary hypertension, no coagulopathy) in only specialized centers.[26,35,41-44] It is further suggested that the procedure be performed safely under general

anesthesia with an artificial airway (rigid bronchoscope, endotracheal tube and laryngeal mask airway) in place along with the use of fluoroscopy and prophylactic occlusion balloon/ Fogarty balloon catheter/ bronchial blocker and with stand by surgeon.[43-45]

D. Video-assisted Thoracic Surgery Lung Biopsy

Desirable Effects

VATS associated lung biopsy provides specimen with large size, from multiple lobes and with preserved architecture. This is currently considered as the gold standard for sample collection for histopathological diagnosis by obtaining adequate samples from 2-3 lobes increasing the diagnostic yield.

Undesirable Effects

This requires general anesthesia and has associated risks. Post-operative pneumonia, pleural effusion, chronic chest pain, prolonged air leak, acute exacerbation of ILD (AE-ILD), requirement of mechanical ventilation (MV), delayed wound healing, neuropathic pain, prolonged hospital stay, re-admission to hospital within one month of discharge and death are the complications of SLB.[16,46-50] Acute exacerbation requires special mention as it is associated with high mortality rates. Complications are more frequently encountered in patients with IPF (compared to other ILDs), FVC <55% or DLCO <35% and those undergoing non-elective SLB.[46,48]

Q 4. Should integrated multidisciplinary team guided discussion (MDD) be performed?

Key Statements

- The conditional recommendations for the MDD made by the international experts for the diagnosis of ILD were endorsed and the need for the MDD was emphasised whenever there are inconsistencies between clinical, radiological or pathological features. [1A]
- MDD should include clinician or pulmonary physician, radiologist, and pathologist. [2A]
- Pathologist is not needed for MDD if diagnosis of ILD is established without surgical biopsy and rheumatologist may be part of MDD on case-to-case basis. [UPP].

Discussion

Desirable Effects

Multi-disciplinary interaction is vital for improving the initial diagnosis and reducing the number of patients with undifferentiated ILD (Figure 4). The usefulness of MDD, especially in cases with atypical findings, and its clinical utility or better management has been well documented.[16,51-55] Telephone, conference calling, communication by texting via smartphones, other current and/or evolving digital/electronic means and emails are appropriate means of communication among experts, provided they allow a thorough two-way interaction.

Undesirable Effects

While there are no undesirable effects from the patients perspective, face-to-face MDD may not be feasible for all the patients with ILD. It is unclear if all the patients with ILD need a MDD by the experienced experts for accurate diagnosis. The need for MDD in difficult cases, especially for the ones that are atypical, unclassifiable or newly diagnosed is evident.[56-58] Largely, the decision will depend on the experience of the MDD team.

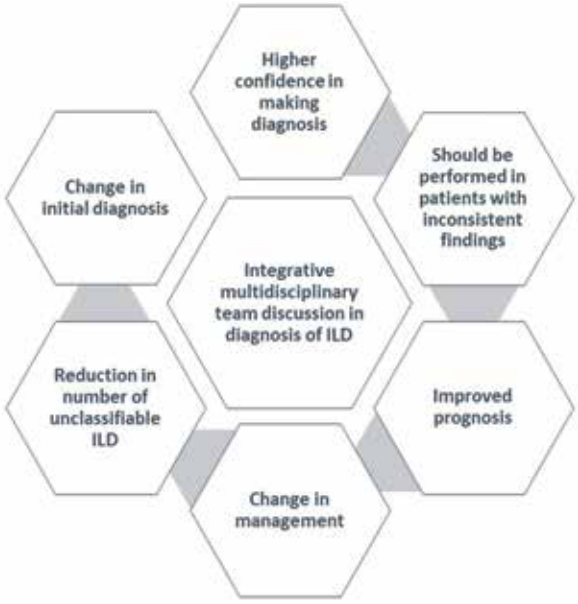

Figure 4. Advantages of multidisciplinary discussion in diagnosis of interstitial lung disease.

Q 5. What are the essential diagnostic 'evaluation' needed for patients with severe ILD presenting with respiratory failure at the initial visit (and are not in acute exacerbation)?

Key Statements

- The panel endorsed the following standard of care for all patients with interstitial lung disease with respiratory failure at initial evaluation .
  - Detailed history
  - Complete blood count
  - A comprehensive metabolic panel including, liver and kidney function tests and serum

- Electrolytes
- Chest radiograph and HRCT chest
- Electrocardiogram
- Pulse oximetry
- Arterial blood gases (if SpO_2 <90%)
- Additional tests to be considered at the initial visit include connective tissue disease markers (rheumatoid factor, anti-nuclear antibody [ANA]), myositis panel, anti-cyclic citrullinated peptide).

- Following tests may be considered in selected patients with severe ILD
  - Transthoracic echocardiogram, cardiac enzymes (clinical suggestion, acute worsening)
  - CT pulmonary angiography (only if acute worsening)
  - BAL cellular analysis or any biopsy procedure should be avoided
  - BAL can be considered to rule out infection only if clinically indicated and indispensable for decision-making

Discussion

There was no evidence pertaining to this question. A typical scenario was presented to the working group. The panel advocated detailed history and tests for the diagnosis of ILD and also tests to rule out concomitant cardiac or pulmonary vascular disorders.

Desirable Effects

The investigations of the clinical scenario would provide clues to the specific sub-type of ILD, in addition these may help in identifying diagnosing comorbid conditions that might possibly leading to deterioration of the patient.

Undesirable Effects

Other than the costs involved in conducting the investigations, the working group did not find any untoward side effect of the investigations.

Q 6. Should the following tests be done to monitor progress of ILD?

A. Forced vital capacity (FVC)
B. Diffusion capacity
C. 6MWT
D. HRCT

Key Statements

- Disease monitoring in IPF is advised at 4-6-month interval with FVC [2A], diffusion capacity of the lung for carbon monoxide (DLCOcorr to Hb) [3A], 6-MWT: for distance and SpO_2 measurements [2A] and Medical Research Council dyspnoea score (MRCDS).
- HRCT chest determined/guided by clinical needs/ indicated. [UPP]
- In other ILD's, the panel suggested FVC at 6-month interval till clinical stability is achieved, thereafter every 12 months [3A]. DLCOcorr to Hb may be repeated yearly. The role of 6MWT in CTD associated ILDs is limited due to the presence of various confounding factors. [UPP]

Discussion

The working group endorses the use of pulmonary function tests (PFTs) in prognosticating ILD. A marginal decline of 5% to 10% in FVC has also been proposed as an indicator of significant disease progression and mortality in some studies.[59] Patients who are too sick to perform the tests may be evaluated with MRCDS (Figure 5).[60,61]

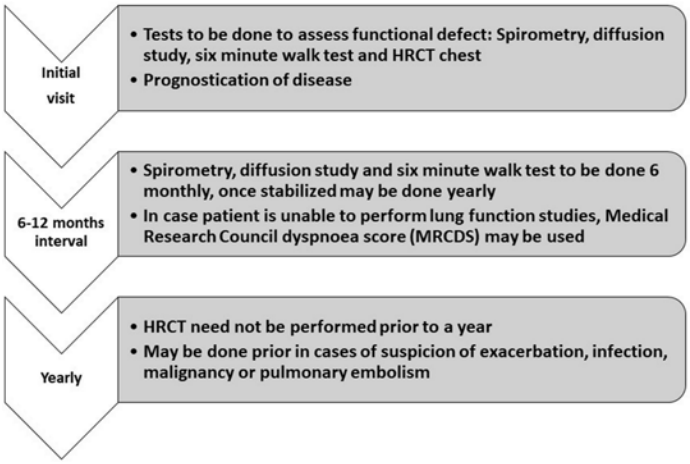

Figure 5. Investigations conducted during follow-up of patient with ILD.

Desirable Effects

Lung function tests and 6MWT test provide objective tools to judge treatment response and disease progression. Deterioration of patient can be assessed by these tests to diagnose whether deterioration is due to worsening of the disease or co-morbid illness.

Undesirable Effects

Other than the cost and the effort to perform the tests which some patient may find uncomfortable, there are no untoward effects of the investigations. The standard 6MWT that utilises finger oximetry for assessing oxygenation may give false reading in some patients with Raynaud'sphenomenon, sclerodactyly, dysrhythmia and, methemogobinemia.

Q 7. What are the common comorbidities in ILD and how to screen for them?

Key Statements

- Most common comorbidities encountered in ILD are gastro-oesophageal reflux disease (GERD), pulmonary hypertension (PH), lung cancer, obstructive sleep apnoea (OSA) and venous thromboembolism (VTE).
- Screening tools for monitoring comorbidities in ILD patients are:
  1. *GERD*: A validated GERD questionnaire. [3A]
  2. *PH*: Echocardiography as a screening tool for PH/PAH (pulmonary arterial hypertension) in ILD patients though right heart catheterization remains the gold standard for documenting the diagnosis. [3A]
  3. *CT for lung cancer:* a significant smoking history [2A], chest pain [3A], hemoptysis [3A], and areas of emphysema on HRCT [2A] act as warning signs for lung cancer and should trigger a search for the same.
  4. *OSA:* ILD patients with high body mass index (BMI) [3A] and a positive sleep apnoea screening questionnaire [3A] may be evaluated by polysomnography.
  5. *VTE:* Sudden onset and/or rapid worsening of dyspnea, palpitations, lower extremity oedema with positive Wells or Revised Geneva score may act as trigger to search for VTE. [3A]

Discussion

Desirable Effects

Diagnosis and treatment of comorbid conditions associated with ILD would likely improve the outcome and the quality-of-life of the patients.[24,62-70]

Undesirable Effects

Other than the associated costs, there are no untoward effects of the investigations.

The cost-effectiveness of CT screening for lung cancer is unknown in low-resource and tuberculosis-endemic settings.

Q 8. Should following therapies be used for management of cough in ILD?

A. Prednisolone
B. Gabapentin
C. Thalidomide

Key Statements

- A short trial of oral prednisolone in distressing cough associated with IPF is an appropriate consideration. [3B]
- Gabapentin may be tried for intractable cough. [3B]
- Thalidomide may be tried for intractable/distressing cough associated with IPF. [2B]
- Every effort should be made to identify and treat the comorbid conditions influencing cough in ILD. [UPP]

Discussion

Desirable Effects

Evaluation and treatment for comorbid conditions that might explain other reasons of cough may lead to targeted treatment and reduction in cough frequency in some patients. Empirical trial of a short course of prednisolone, gabapentin or thalidomide may be worthwhile for the potential desirable effect of suppressing intractable cough (Figure 6).

Undesirable Effects

Drug adverse effects are the undesirable consequences of the use of such agents for cough control. Weighing the risk benefit ratio, a short course may be attempted in cases of debilitating cough.

Q 9. Should following therapies be used for management of dyspnoea in progressive ILD?

1. Pulmonary rehabilitation
2. Supplemental oxygen
3. Nebulised opioid therapy

Key Statements

The working-group suggests

- Pulmonary rehabilitation in dyspnoeic patients with ILD. [2A]

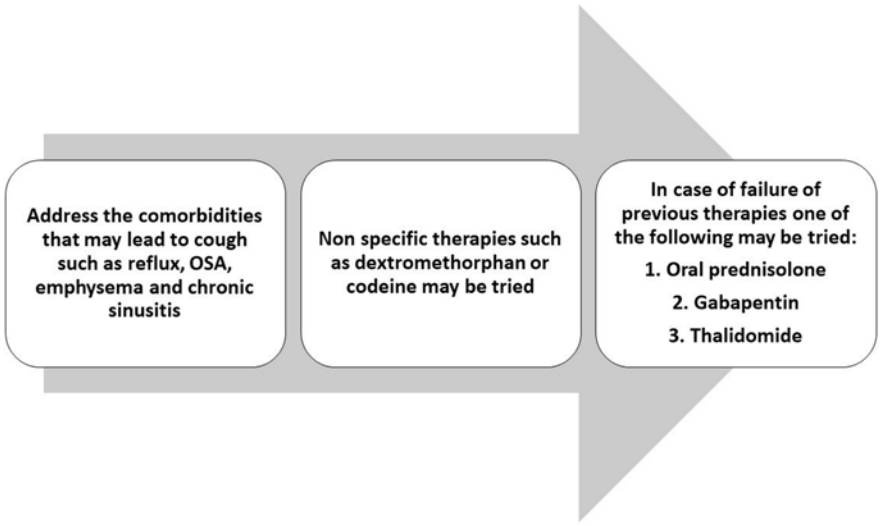

Figure 6. Flow chart describing the steps of non-specific and specific therapies in the treatment of cough associated with interstitial lung disease.

- Supplemental oxygen in patients with documented resting hypoxemia and/or exercise-induced hypoxemia, and desaturation while sleeping. [2B]
- Long term oxygen therapy (LTOT) for patients with ILD who have persistent resting hypoxemia. [3A]
- Nebulised opioid therapy is not beneficial to relieve dyspnoea in all ILD patients and may be used only for patients receiving comfort and palliative care. [2A]

Discussion

Desirable Effects

Pulmonary rehabilitation is useful for patients to cope with dysponea, inactivity and reduced quality-of-life. The beneficial effects in symptoms, physical activity, six minute walk distance and quality-of-life have been documented.[71,72]

Oxygen therapy alleviates symptoms of dyspnoea, improves activity, dyspnea scores and walk distance. Opioid therapy does not relieve dyspnea in all ILD patients[73] and may be helpful in small groups with end-stage lung disease, primarily for palliative care.

Undesirable Effects

Pulmonary rehabilitation has no beneficial effects on survival. The effects last as long as programme is continued. The lack of facilities in reasonable proximity to patients' home and cost of travelling to such facilities pose additional logistic challenges.

Cost of oxygen therapy, emotional willingness and behavioural changes to accept the dependency upon supplemental oxygen for daily activities either continuously or as needed at home and in public places, fire hazards associated with inadvertent oxygen use are some of the undesirable consequences that patients will need to be aware of.

Concomitant respiratory depression, addiction, altered mental status, lethargy, excessive sleep, and side-effects such as constipation are undesirable consequences of the therapy.

Q 10. Should patients with ILD receive vaccination against influenza and pneumococci?

Key Statement

- The working-group endorsed the recommendation by ACIP (Advisory Committee on Immunization Practices) for vaccinations (influenza and pneumococci) for all the patients with ILD. [UPP]

Discussion

Desirable Effects

Influenza and pneumococcal vaccinations have been associated with decreased infection and fewer exacerbations, hospital visits, admissions and death in patients with chronic lung disease.[74-77]

Undesirable Effects

Minimal chances of allergic reactions and cost are the undesirable consequences.

Q 11. Should pulmonary hypertension associated with ILD be treated with medications indicated for PH?

Key Statements

- The group endorses the guidelines for the management of chronic PH-specific therapy for

patients with PH [1A] and the treatment of the underlying lung disease as the mainstay of therapy and supplemental oxygen in cases of hypoxemia.[78,79]

- Ambrisentan is contraindicated in patients with PH related to IPF. The therapeutic benefits of other PH-specific therapy in ILD-related PH remains unknown. [2A]

Discussion

Desirable Effects

The group acknowledged the ambiguous results of the studies evaluating role of various drugs in PH associated with ILD.[80-83] Potential therapeutic benefits with use of sildenafil in patients with severe lung function impairment in improving gas exchange status and quality of life might be considered for the well informed patient particularly with right ventricular dysfunction.[81,84]

Undesirable Effects

Ambrisentan has been associated with disease progression and increased hospitalisation in IPF, and is thus, contraindicated in the same.[85] Side effects associated with other medications use for management of PH include systemic hypotension, liver toxicity and require monitoring for known side effects.

Q 12. Should non-invasive ventilation (NIV) and mechanical ventilation (MV) be used in patients with ILD?

Key Statements

- Consideration of NIV as early as possible in patients who require high flow supplemental oxygen at rest – especially in patients manifesting AE-ILD with respiratory failure as it has been associated with better short term outcomes. [2A]
- The consideration of MV in patients with AE-ILD with respiratory failure should be made only after proper counselling. [2A]

Discussion

Desirable Effects

NIV has been shown to improve dyspnea and respiratory failure in a subset of patients.[86,87] MV may help tide over short term respiratory failure due to reversible causes.[87]

Undesirable Effects

Apart from the cost of NIV, asynchrony with ventilator, the inability to communicate, eat and drink are hindrances to its use.

MV is associated with increased mortality and worse outcomes in patients with acute exacerbation of ILD.[88] Thus, it should be applied after weighing risk benefit ratio on case to case basis.

Q 13. Should lung transplantation be advised to patients with ILD?

Key statements

- Lung transplantation is the only treatment with clearly proven survival benefit in advanced ILD, especially IPF and should be considered in carefully selected patients. [2A]

Discussion

Desirable Effects

Lung transplant is a viable option with proven survival benefits in selected patients with end stage fibrotic lung disease.[89]

Undesirable Effects

Post-transplant survival is variable in lung transplant programmes. While the 5-year survival in most experienced lung transplant programmes is about 70%, less experienced programmes have lesser survival rates. Patients and their care-givers may need to relocate to places away from their homes to be close to lung transplant programmes. Psychosocial stress, financial restrains/burden, side effects of the procedure and medications are all significant limitations.

Q 14. Should palliative care be advised to patients with ILD?

Key Statements

- The working-group suggests that all the patients with advanced ILDs receive palliative care to improve quality-of-life. [1A]
- Multidisciplinary collaborative care for the potential of reduced rates of respiratory related hospitalisations and death. [2A]

Discussion

Desirable Effects

The most prominent symptoms in a terminally ill ILD patient are dyspnoea, cough, depression and heart burn. Palliative care aims at addressing these symptoms with the aim to provide a better quality of life through pulmonary rehabilitation,[71,72] morphine,[90] oxygen therapy,[91] NIV,[92] and anti-reflux therapy for gastro-esophageal reflux[93] (Figure 7).

Undesirable Effects

The side effects of the medications used to alleviate the symptoms to comfort the patient may limit the optimum benefits for the patient; there are no survival benefits.

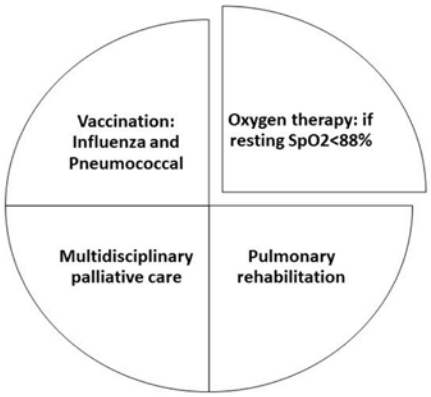

Figure 7. Components of palliative care to be administered to patients with interstitial lung disease.

Questions, Statements and Remarks Summarised for a Few Specific ILDs

Q 15. Should serum precipitins be done to evaluate for HP?

Key Statement

- Based on lack of standardisation and lack of validated testing antigens, the working-group opined against obtaining serum for precipitins routinely for patients with ILD. [2A]

Desirable Effects

A raised serum precipitin in conjugation with appropriate clinical presentation, radiology and biopsy may prompt further diagnostic evaluation that might lead towards a diagnosis of HP.

Undesirable Effects

However, these have variable diagnostic accuracies with positive results in exposed healthy individuals and negative results in patients with HP.[94,95] While the positive test merely indicates the exposure, the test is insensitive, and thus, the awareness of the presence or absence of the specific immunoglobulin-G (IgG) may not be helpful for all patients.

16. Should following drugs be used in the treatment of HP?

A. Oral corticosteroids
B. Azathioprine
C. Mycophenolate mofetil (MMF)

Key Statements

- Oral corticosteroids for 4-12 weeks are an appropriate treatment option for the patients with acute/sub-acute HP with monitoring of lung function parameters and side effects. [1A]
- Prolonged use of oral steroids [2A], azathioprine and MMF [3A] should be based on clinical response and tolerance.

Discussion

Desirable Effects

In patients with acute HP there is improvement in symptoms and lung functions with oral corticosteroids. However, this benefit is not sustained over long term. Limited retrospective data is available on role of immunosuppressants in chronic HP with studies claiming improvement in lung functions, diffusion and steroid sparing effects.

Undesirable Effects

Side effects of specific therapy (Table 4) in addition to the costs incurred are the undesirable side effects. Continued immunosuppression may have impact on survival. In countries with high prevalence of tuberculosis; monitoring for new or recurrent tubercular infection should be done. Short-term use of oral corticosteroids in HP have been advised by the group based on a randomised controlled trial (RCT) conducted over 25 years ago.[96] There is lack of evidence pertaining to the duration and dose of the corticosteroids for long-term therapy in HP. Prolonged use of corticosteroids and other immunosuppressants should be prescribed after weighing benefit of individual response and side effects associated with the drugs (Table 4).

Inability to identify the inciting antigen is associated with worse survival[97]; thereby, every effort should be made to identify the inciting antigen. The antigen may be unique to the area of residence depending on occupation, environment and local customs; thus enquiry should be directed to determining the exposure in a detailed manner.[98]

Q 17. Should pirfenidone and nintedanibbe used in treatment of IPF?

Key Statements

- All symptomatic IPF patients with FVC of >50% predicted should be initiated on pirfenidone. [1B]
- The patients on pirfenidone developing ≥10% subsequent decline in FVC in any 6-12 month period should be given a choice of continuation of therapy or switch to an alternative therapy depending on case to case basis. [UPP]
- All symptomatic IPF patients with FVC of >50% predicted should be initiated on nintedanib. [1B]
- The patients on nintedanib developing ≥10% subsequent decline in FVC in any 6-12 month period should be given a choice of continuation of therapy or switch to an alternative therapy on case to case basis. [UPP]

Table 4. Doses, side effects and management of side effects of commonly used drugs the in treatment of ILD.

S. No.	Drug	Dose	Side Effects	How to Manage Side Effects
1	Pirfenidone	1800-2400mg/day in divided doses 200mg 3 tablets thrice a day	Nausea, vomiting	Reduce or stop the drug, PPI
			Photosensitivity, rash	Cover exposed skin, sunscreen
			Elevated liver enzymes	Monitor LFT monthly for 6 months, thereafter 3 monthly
2	Nintedanib	150mg twice a day	Diarrhoea	Reduce or stop drug, Imodium
			Nausea, vomiting	Reduce or stop drug, PPI
			Elevated liver enzymes	Monitor LFT monthly for 3 months, thereafter 3 monthly
3	N-acetylcysteine	600mg thrice a day	Nausea, vomiting, diarrhoea	Self-limiting, reduce of stop the drug
4	Prednisolone	1mg/kg body weight (BW) tapered to 0.25mg/kg BW*	Hyperglycemia	Bring to lowest dose possible, sugar avoidance, oral hypo-glycemics (if patient develops diabetes mellitus), exercise
			Hypertension	Salt avoidance, exercise
			Swelling face	Salt avoidance
			Osteoporosis	Calcium, bisphosphonates, exercise
			Reduced immunity	Bring to lowest dose possible, PCP prophylaxis, Influenza vaccine (once steroid dose is <7.5mg/day), avoid crowded places
			Weight gain	Dietary modification, exercise, bring to lowest dose
5	Azathioprine	50mg twice a day	Cytopenias	Reduce or stop drug, monitor CBC monthly till 6 months thereafter 3 monthly
			Infections	Reduce dose, avoid crowded places, PCP prophylaxis
			Nausea, vomiting	Reduce or stop the drug, PPI
6	Methotrexate**	10mg/week may be increased to 20mg/week and brought down to 5mg/week	Hemtological neutropenia, Thrombocytopenias	Reduce or stop the dose Folic acid is added once a week
			Gastrointestinal	Give with food PPI Split the dose Stop or reduce the dose
			Hepatic	Monitor LFT Stop the drug
			Pulmonary toxicity	Stop the drug
			Teratogenicity	Birth control till 6 months after stopping the drug
7	Mycophenolate mofetil (MMF)	1.5-3g/day	Leucopenia	Reduce or stop drug
			Diarrhoea	Reduce dose, hydration

- Cont-

- Cont-

S. No.	Drug	Dose	Side Effects	How to Manage Side Effects
8	Cyclophosphamide	500-1000mg IV per 4 week or 1-2mg/kg/day orally	Haemorrhagic cystitis	Mesna Hydration Less with intermittent dosing
			Neutropenia	Monitoring CBC
			Infertility	Leuprorelin
9	Infliximab	3mg/kg at 0,2,6,12,18, 24 weeks	Allergic reactions	Slow infusion, anti-allergics, paracetamol corticosteroid loading
			Infections	Rule of pulmonary tuberculosis prior to initiation, PCP prophylaxis, monitoring
10	Rituximab	1000mg IV repeat at 2 weeks	Allergic reactions	Stop infusion Anti-allergic medications, paracetamol corticosteroid loading
			Cytopenias	CBC monitoring
			Infections	PCP prophylaxis, monitoring

*In scleroderma ILD the dose of prednisolone should be kept <10mg/day

**Patients on methotrexate should be followed up with monthly CBC, LFT and RFT for 6 months followed by 3 monthly testing

Definition of abbreviations: ILD=Interstitial lung disease; PPI=Proton pump inhibitors; LFT=Liver function tests; PCP=*Pneumocystis carinii* pneumonia; CBC=Complete blood count; IV=Intravenous; RFT= Renal function test.

- Either pirfenidone or nintedanib may be chosen for patients with IPF based on patient preference and tolerability. [UPP]

Discussion

Desirable Effects

Pirfenidonehave been associated with slowing of the absolute decline in FVC, increase progression free survival and reduce mortality.[99] Nintedanib has been associated with reduction in decline in predicted FVC, acute exacerbation and risk of all cause, respiratory related and on treatment mortality.[100,101]

Undesirable Effects

Side effects of the drugs (Table 4) in addition to their cost are the undesirable effects. Duration of treatment is life-long.

Q 18. Should N-acetylcysteine (NAC) be used in treatment of IPF?

Key Statement

- NAC is currently not recommended for routine treatment of IPF and may be considered in certain subgroups on a case to case basis. [UPP]

Discussion

Desirable Effects

NAC has not shown any beneficial effects on lung functions, adverse outcomes and death.[102] A genotype analysis of single nucleotide polymorphism (SNPs) of patients with IPF found that TOLLIP polymorph rs3750920 TT was associated with favourable response to NAC while CC polymorph was associated with increased mortality.[103]

Undesirable Effects

Side effects such as nausea and vomiting and cost are other issues.

Q 19. Should combination therapy be used for IPF?

Key Statement

- More evidence is needed to recommend the use of pirfenidone in combination with nintedanib or NAC and the dose of individual drugs to be used in such therapy in patients with IPF.

Desirable Effects

Large randomised controlled trials are needed to compare combination therapy with placebo before advocating the same.[104]

Undesirable Effects

The side effects and cost of therapy are more in case of combination therapy.

Q 20. Should anti-acid therapy be used in the treatment of IPF?

Key Statement

- The committee suggests that anti-acid treatment may be initiated in patients with IPF at the time of diagnosis. [3B]

Desirable Effects

There have been conflicting studies on the efficacy of anti-acid treatment in patients with IPF with some reporting lesser mortality whereas others have not found significant improvement.[105-107] Anti-reflux surgery has shown to have non-significant improvement in FVC, acute exacerbations and mortality.[108]

Undesirable Effects

Side effects are minimal for medical management of reflux disease. Surgical complications are associated with laparoscopic reflux surgery.

Q 21. Should anti-nuclear antibody (ANA) testing be performed in patients with ILD?

Key Statements

- All patients with ILD should undergo ANA testing (by indirect immunofluorescence method), rheumatoid factor (RF) and anti CCP testing at baseline. [3A]
- Additional serologic testing should be advised in patients with a high pre-test probability for CTD-ILD. [3A]
- Repeat serological testing is indicated in presence of signs and symptoms of CTD (if previously negative). [3A]
- Repeat serological testing is not indicated in previously screened serology positive CTD-ILD patients. [3B].

Discussion

Desirable Effects

ANA testing is vital to rule out CTD-ILD, since many a times ILD may be the only manifestation of autoimmune disease.

Undesirable Effects

Not all autoimmune ILDs have a positive ANA panel. Cost effectiveness has not been ascertained despite it being recommended as a screening test in 2011 and 2018 guidelines. The group endorsed and reinstated the recommendation made in the 2018 guidelines even in context of resource limited settings.[16] The diagnosis of ILD requires meticulous evaluation for an underlying CTD, with major implications for prognosis and management.[7]

Q 22. Rheumatoid arthritis associated ILD

A. Should steroids be used to treat patients of RA-ILD?

B. Should following drugs like cyclophosphamide, MMF and rituximabbe used in the treatment of RA-ILD?

C. Should drugs like methotrexate, leflunomide, anti-tumor necrosis factor (TNF) to be continued for the treatment of RA who develops ILD?

Key Statements

- Corticosteroids may be used in treatment of RA-ILD. [3B]
- Cyclophosphamide [2B], MMF [2B] and rituximab [3B] may be used in the treatment of RA-ILD in case of no response to corticosteroids
- Role of other drugs in RA patients who develop ILD:
  1. Methotrexate should be discontinued in patients of RA diagnosed with ILD. [2B]
  2. Leflunomide can be continued in patients diagnosed with RA-ILD. [1B]
  3. Other TNF agents may be used cautiously. [3B]

Discussion

The treatment of RA-ILD with anti inflammatory agents is complex as the evidence is very low. Considerable debate and discussion amongst the working-group was held. Many of drugs used in the treatment of RA are associated with causing ILD; thereby there were no consensus reached—section is divided into the drugs used in the treatment of RA-ILD and whether some of the drugs should be continued in RA patients who develop ILD.

Desirable Effects

Corticosteroids are anti-inflammatory drugs which help suppress disease activity leading to improvement insymptoms and lung functions.[109-111] Additional immunosuppressants, such as cyclophosphamide, MMF and rituximab have steroid sparing effects.[112-114]

Undesirable Effects

Immunosuppression and potential side effects associated with individual agents and infection is of significant concern and patients will need frequent

monitoring through blood counts during visits. In addition, there is propensity to cause ILD by some of the immunosuppressants, such as methotrexate.[115,116] While these risks are relative, the patient will need appropriate monitoring to detect adverse effects that may require prompt intervention.

Q 23. Scleroderma associated ILD

A. Should steroids be used to treat patients of scleroderma associated ILD (SSC-ILD)?
B. Should drugs like cyclophosphamide, MMF and azathioprine be used to treat patients of SSC-ILD?
C. Should rituximab be used to treat patients of SSC-ILD?

Key Statements

- Low dose steroids may be continued in the treatment of SSC-ILD. High dose steroids should be avoided in scleroderma as it is associated with risk of renal crisis. [2B]
- Treatment in SSC-ILD may be initiated in cases with progressive disease with either cyclophosphamide or MMF. [1A]
- MMF has better tolerability and lesser side-effects, though more expensive. [1A]
- Azathioprine is an alternate drug for maintenance therapy in SSC-ILD. [1A]
- Rituximab could be considered in patients with refractory scleroderma. It should be administered at tertiary care level after evaluating for the pros and cons of treatment. [2B]

Discussion

Desirable Effects

Corticosteroids and other drugs have been associated with improvement in dyspnea, lung functions and quality of life.

Undesirable Effects

High dose corticosteroids may precipitate renal crisis in patients with SSC-ILD.[117] Immunosuppression and secondary infection are a dreaded complication of these drugs. Effect lasts till the drugs are taken and there is no long lasting benefits. Based on scleroderma lung study I and II, the working-group endorsed the use of either cyclophosphamide, MMF or azathioprine for the treatment of SSC-ILD.[118,119] MMF is equivalent to cyclophosphamide though with better safety profile.[119]

The group acknowledged the awareness of ongoing clinical trials with antifibrotic agents – pirfenidone and nintedanib and were not aware of the data published since.[7] Nintedanib, an anti-fibrotic drug has been shown to reduce the annual decline in lung functions associated with SSC-ILD. However, there was no advantage on the other manifestations of the SSC.

Q 24. Should serum angiotensin converting enzyme (ACE) be done to evaluate for sarcoidosis?

Key Statement

The group did not consider the utility of measuring serum ACE routinely for the diagnosis of sarcoidosis. [2A]

Discussion

Poor sensitivity and specificity along with unwarranted cost have precluded ACE as test of choice for sarcoidosis.[120,121]

Q 25. Should endobronchial biopsy (EBB), transbronchial lung biopsy (TBLB) and transbronchial needle aspiration (TBNA) be performed in diagnosis of sarcoidosis?

Key Statements

- Combined EBB, TBLB and TBNA has the maximum yield for the diagnosis of pulmonary sarcoidosis. [1A]
- The choice of technique used for TBNA (conventional or endobronchial ultrasound, EBUS) is deferred to the operator when performed in conjunction with EBB and TBLB. [1A]

Discussion

Desirable Effects

The working-group reviewed the available literature and unanimously agreed that combination of procedures, such as TBNA, TBLB and endobronchial biopsies lead to higher yield in diagnosing sarcoidosis rather than either procedure alone.[122-124]

Undesirable Effects

Combining the three procedures increase the duration and cost. Combining TBLB to TBNA and EBB would increase risk of bleeding and pneumothorax; which were minimal with only former two procedures.

Q 26. Should following drugs be used in treatment of pulmonary sarcoidosis?

A. Corticosteroids
B. Methotrexate
C. Azathioprine
D. Leflunomide
E. Hydroxychloroquine
F. Infliximab

Key Statements

- Observe patients without pharmacological interventions in patients who are asymptomatic stage 0/1 pulmonary sarcoidosis. [1A]
- Treat patients with symptomatic stage 1 and all stage 2, 3 and 4 pulmonary sarcoidosis with oral corticosteroids. [1A]
- Additional immunosuppressant—methotrexate [2A], azathioprine [3A/B], leflunomide [3a], hydroxychloroquine may be tried in patients not responding to oral steroids or with associated steroid toxicity.
- Infliximab may be tried after carefully weighing the risk benefit ratio in patients with refractory pulmonary sarcoidosis. [1A]

Discussion

Desirable Effects

Corticosteroids improve dyspnea score, lung functions and radiology in sarcoidosis.[125-127] Other immunosuppressants may be given in resistant cases or those on high dose corticosteroids.[128-131] They have steroid sparing and therapeutic effects (Figure 8).

Undesirable Effects

Corticosteroids have no significant benefits for asymptomatic stage 0/1 sarcoidosis. Moreover, the effects last as long as these are used.[125] There is no long term benefits in term of lung functions. Immunosuppression is another concerning feature, not only for corticosteroids but for other immunosuppressants as well.

Q 27. Should steroids and cyclophosphamide be used in the treatment of idiopathic non-specific interstitial pneumonia (i-NSIP)?

Key Statements

- Oral corticosteroids are suggested for treatment of i-NSIP. [3B]
- Immunosuppressants, such as cyclophosphamide may be used as add-on therapy in patients not responsive to steroids. [3B]

Discussion

Desirable Effects

Corticosteroids improves symptom score and lung function with response more pronounced in cellular NSIP, concomitant consolidation, seronegative ANA and shorter disease duration.[132-134]

Undesirable Effects

Risk of immunosuppression including bacterial and mycobacterial infections is the dreaded complication and may impact survival.The current approach relies on retrospective studies; RCTs are lacking, probably due to the ambiguity with regards to the diagnosis of i-NSIP. In asymptomatic or mildly symptomatic cases close observation is often done, as the risk of treatment outweighs the benefits. In symptomatic patients oral corticosteroids are the mainstay of therapy.

Q 28. Should silica exposure and tobacco smoke inhalation be avoided in patients with silicosis?

Key Statement

- Avoidance of continued exposure to silica and direct inhalation of tobacco products is advisable. [UPP]

Discussion

Desirable Effects

Avoidance of exposure is vital to avoid harmful effects of silica on the lungs. Tobacco products need to be avoided to prevent concomitant illnesses, such as chronic obstructive lung disease and lung cancer.

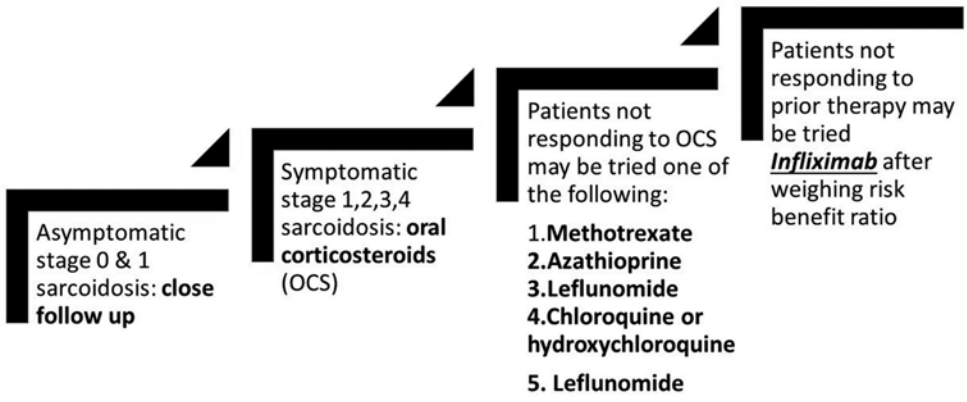

Figure 8. Step-wise treatment approach to a patient with sarcoidosis.

Undesirable Effects

Other than logistic issues of finding an alternate occupation, there are no undesirable effects. Preventive, remedial, rehabilitative measures should be implemented as silicosis is an incurable disease. Legislations and bills to promote a safe working environment are essential throughout the world.

Q 29. Should the following therapies be offered to patients with silicosis?

A. Oral corticosteroid
B. Aluminium inhalation
C. Whole lung lavage
D. Rehabilitation and exercise training

Key Statements

- No corticosteroids for routine treatment of acute or chronic silicosis as the risk benefit balance seems to disfavour their use. [3A]
- Aluminium inhalation for the treatment of silicosis is not advised. [3A]
- Whole lung lavage as potential benefits in the treatment of alveolar proteinosis due to acute silicosis/silico-proteinosis may be suggested in carefully selected patient population at specialised centers. [3B]
- Rehabilitation and exercise training of at least 4-8 weeks is advised for potential beneficial effects in terms of improvement in exercise capacity and quality-of-life in patients with chronic silicosis. [1B]

Discussion

Desirable Effects

Corticosteroids and aluminium may have improvement in symptoms of dyspnea.[135] However, risk outweighs harm.[136] In cases of acute silicosis whole lung lavage may be attempted, which may lead to improvement in lung functions.[137,138] Exercise training has the benefit of improving quality-of-life and exercise capacity.[139,140]

Undesirable Effects

The risk associated with immunosuppression caused due to corticosteroids far outweighs the benefits which are minimal. Similarly aluminium is associated with impaired cognition and dementia.[136] Experimental therapies, such as whole lung lavage, is associated with risk of it being an invasive procedure with complications such as respiratory failure and side effects of sedatives. Exercise training done under supervision has minimal side effects other than cost and logistics. Various modalities have been tried in the past for the treatment of silicosis but most lack efficacy or have potential for serious side effects. Currently pulmonary rehabilitation is the only modality that improves quality-of-life for patients with chronic silicosis.

Approach to a Patient Suspected to have ILD

A careful history of symptoms, including symptoms suggestive of CTD, environmental exposures, occupational and family history should be taken. A thorough clinical examination for signs of extra-pulmonary involvement in CTD-ILD should be taken (Figure 9). An algorithm is provided in figure 10.

Figure 9. Physical examination findings in various connective tissue diseases; (A) vasospasm induced blanching of finger tips in patient suggestive of Raynaud's phenomenon in scleroderma; (B) resorption of peripheries suggestive of sclerodactyly in scleroderma; (C) raised papules on dorsum of proximal inter-pharyngeal joints suggestive of Gottron's papules in dermatomyositis; (D) scaly lesions in the hands suggestive of mechanic's hands seen in dermatomyositis; (E) swan neck deformity due to hyperextension of the proximal interphalangeal joint and flexion of the distal interphalangeal joint in a case with rheumatoid arthritis; (F) raised papules on eyelid suggestive of heliotrope rash in dermatomyositis; and (G and H) increased skin folds around mouth and restricted mouth opening in patient of scleroderma.

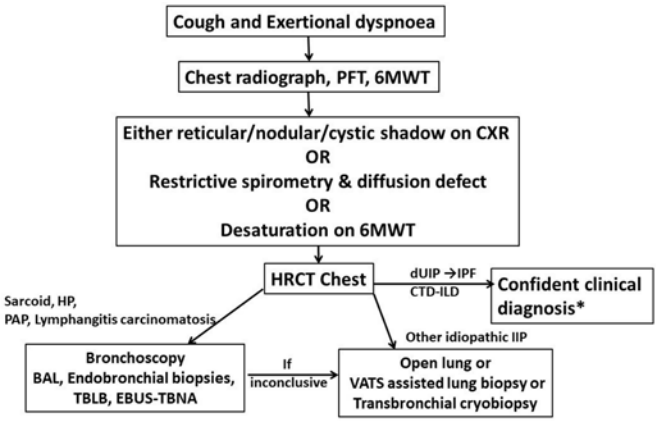

Figure 10. Algorithm providing approach to patient suspected to have ILD.

Limitations

The intent of providing this document was to guide the clinicians in the community with consensus of the opinion of experts based on their experience and systematic review of the evidences.[141] We acknowledge the limitations of the methodology used to develop this document. First, the document reflects the opinions of the selected participants including only one rheumatologist. Secondly, meta-analysis was not done and there was no methodologist involved in the project.

Acknowledging that the task force committee reached the consensus of the evidence discussed in 2018, pertinent new reports published since have not been discussed by the committee and incorporated in this document. These include the results of the INBUILD trial published in Oct 2019[142] and of subgroup analyses of the trial[143] as well as the just published guideline on diagnosis and detection of sarcoidosis[144].

Future Directions

Evidence-based clinical practice guidelines for individual ILD are needed and for this to materialise, well designed, prospective studies are warranted. These include studies to determine the diagnostic accuracy and yield of lung biopsy techniques. Molecular signatures, genomic classifiers, machine learning tools, circulating biomarkers in non-IPF fibrotic lung diseases are needed to make a diagnosis with MDD and without the requirement of SLB for the conventional histopathology features to differentiate the UIP patterns associated with ILD other than IPF. It is hoped that ongoing and future clinical trials will determine the safety and efficacy of currently available and new pharmacological as well as non-pharmacological interventions fornon-IPF fibrotic ILDs.

Conclusions

For the very first time, extensive literature search, review and discussion of available evidence was done by a working-group to formulate the consensus statements for the management of ILD in general and for a few specific ILDs, other than IPF. The consensus statement provides an understanding of the current clinical practices and a suggested framework for the practising physicians when confronted with patient presenting with ILD. The clinicians should apply the statements made in the clinical context of an individual patient, considering the patient's values and preferences, and should not consider these statements as CPG or mandates.

Summary Conflict of Interests

Ganesh Raghu[47] has received grant from NIH for IPF studies, personal fees from Roche, Boerhinger Ingelheim and Respivant for consultancy for IPF studies. He is consultant for IPF studies for BMS, Bellerophan, Fibrogen, Gilead, Nitto, Promedior, Sanofi, Veracyte, Biogen, Genentech and Avalyn.

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