Consensus Statement for the Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis in Resource Constrained Settings

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Abstract

Background. Idiopathic pulmonary fibrosis (IPF) is a specific type of chronic fibrosing interstitial lung disease (ILD) that is progressive in course. Although evidence-based guidelines for IPF are available, these are difficult to interpret for the average physician and may not be suitable for use in resource-constrained settings. There was an unmet need to formulate guidelines that are pragmatic, easy to understand and suited for application in resource-limited settings.

Methods. This statement was made by a group of expert pulmonologists. Twenty-five questions regarding diagnosis and management of IPF were framed. A literature search was conducted using the PubMed and EmBase databases. The expert group discussed available evidence relevant to each question and recommendations were arrived at by consensus.

Results. A thorough clinical and laboratory evaluation should be performed in patients suspected to have ILDs and potential underlying causes should be ruled out. A high resolution computed tomography (HRCT) of the chest is essential to identify the pattern of ILD. The need for a lung biopsy should be decided based on the appearance on the HRCT. Once a diagnosis of IPF is made, anti-fibrotic drugs (pirfenidone or nintedanib) should be offered after discussing the expected benefits and potential adverse effects with the patient. Recommendations have been made on other issues in the management of IPF, such as management of cough and dyspnoea, role of supplemental oxygen, mechanical ventilation and lung transplantation.

Conclusion. This consensus statement provides practical and easy-to-use recommendations for the diagnosis and management of IPF in resource-limited settings.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a distinct type of chronic fibrosing interstitial lung disease (ILD). The disease is generally progressive in course and is associated with an incessant decline in lung function over months to years. The prevalence of IPF in the developed world is anywhere from 1.25 to 63 per 100,000 population.[1] Although IPF has been reported from the developing world for over half a century, the incidence and prevalence of ILDs or IPF are not yet known in these regions.[2] Though seen uncommonly in general practice, ILDs are frequently encountered by pulmonary physicians.[3] The proportion of patients with IPF among all patients with ILD has been variably reported between 13% and 44% in different studies from India.[4-7] Of late, there has been a renewed interest in IPF in the international pulmonary research community.[8-11]

There are important gaps in the knowledge of physicians on IPF, especially in developing countries.[12] In a recent study[12], about 30% of the physicians (general practitioners and chest specialists) believed that the terms ILD and IPF were synonymous. About half of the physicians could not correctly recollect the important features of IPF on high resolution computed tomography (HRCT) of the chest or identify pirfenidone and nintedanib as the drugs useful in the treatment of IPF. About 30% to 40% still considered glucocorticoids and azathioprine to be useful in the long-term management of IPF despite evidence to the contrary.

Several evidence-based guidelines for the diagnosis and management of IPF are available, but these do not offer a ready reckoner for the practicing physician or pulmonologist.[8-11] Further, three years have elapsed since the last guidelines.[11] During this period, some valuable knowledge has surfaced, especially regarding the evidence for the utility of two recently approved drugs, namely, pirfenidone and nintedanib. Also, there are no guidelines for practice in resource-constrained settings. Therefore, it was felt that a consensus statement that assimilates the current evidence, amalgamates expert opinion and is tailored to resource-limited settings, can be formed. While framing this statement, we have largely considered the current evidence and recommendations of the joint statement of American Thoracic Society (ATS), European Respiratory Society (ERS) and other international Societies.[8-11]

This consensus statement for the diagnosis and management of patients with IPF has been developed by an expert group of pulmonologists. An initial review of the literature was followed by a face-to-face meeting. Existing literature was reviewed by performing a search in the electronic databases (PubMed, and EmBase). The literature search was carried out under five subgroups: (a) clinical history and investigations, (b) diagnosis, (c) evidence for the use of antifibrotic agents in the treatment of IPF, (d) practical issues in the use of antifibrotic agents for the treatment of IPF, and (e) other issues in the management. Questions were framed based on discussions with special reference to resource-limited settings. The questions were circulated among all the experts before the Expert Group meeting. Group Chairs coordinated the discussions in each area while the literature review was presented and opinion of the Expert Group recorded by rapporteurs. Further discussions were held by means of telecommunication (mails and telephone). A consensus approach was followed to arrive at the final recommendations.

The grade system has been used with some modifications to classify the quality of evidence as

1, 2, 3 or usual practice point (UPP) (Table 1).[13] The strength of recommendation is graded as A or B (Table 1). Grade A denotes a strong recommendation for which the word "recommended" has been used. Grade B represents a weaker recommendation, and has been mentioned as "suggested". The issues of feasibility, cost-benefit, and practicality in resource-limited settings were taken into consideration while making a recommendation.

Table 1. Categorisation of level of evidence and grading of recommendation on the basis of the quality of evidence available

Classification of level of evidence	
Level 1	High-quality evidence supported by consistent findings from well-executed randomised controlled trials, or overwhelming evidence from well conducted observational studies with strong effects
Level 2	Moderate-quality evidence from randomised trials that suffer from inconsistency, indirectness, flaws in conduct, reporting bias, imprecise estimates, or other limitations
Level 3	Low-quality evidence from observational studies or from controlled trials with serious limitations
Useful Practice Point	Not supported by sufficient evidence; however, a consensus reached by the working group, based on clinical experience and expertise
Grading of recommendation based on the quality of evidence	
Grade 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
Grade B	Weaker recommendation where benefits and risk are more closely balanced or are more certain

Adapted from Agarwal et al[13]

Nomenclature

It is important to understand the differences between various terms used to describe ILDs and their related entities/subtypes in clinical practice.

Interstitial lung disease is defined as a group of heterogeneous diseases that are characterised by inflammation and/or fibrosis in the lung parenchyma. It is also referred to as diffuse parenchymal lung disease (DPLD). Interstitial lung disease includes a large number of idiopathic disorders as well as diseases with known aetiologies. The method of diagnosis, modality of treatment and prognosis differ between the various ILD subtypes.

Idiopathic interstitial pneumonia (IIP) are a specific group of ILDs without a known cause.[8,10] These are further classified into chronic fibrosing IIPs (IPF and idiopathic non-specific interstitial pneumonia [NSIP]), acute/subacute IIPs (acute interstitial pneumonia [AIP] and cryptogenic organising pneumonia [COP]), smoking related IIPs (respiratory bronchiolitis-ILD [RB-ILD] and desquamative interstitial pneumonia [DIP]) and rare IIPs (idiopathic lymphocytic interstitial pneumonia [LIP] and idiopathic pleuro-parenchymal fibroelastosis).[10] If the IIP subtype cannot be identified, it is termed as unclassifiable IIP.

Idiopathic pulmonary fibrosis is a specific type of a chronic fibrosing ILD of unknown aetiology that is progressive and is characterised pathologically by a usual interstitial pneumonia pattern (UIP) with or without a radiological UIP pattern.

Approach and Clinical Evaluation

Q 1. What should be the initial approach to a patient suspected to have IPF? What is the role of clinical history and examination in the diagnosis and differential diagnosis of IPF?

We recommend a three-step approach to make the diagnosis (Figure)[14]:

1. *Establish the diagnosis of ILD*: This mainly entails identifying the cause of the patient's clinical manifestations and excluding other causes, both pulmonary and non-pulmonary.
2. *Identifying the cause of the ILD*: If no cause is identified, then the possibility of IIP may be considered.
3. *Establish the type of IIP*: Subtype of the IIP is identified (IPF or non-IPF). Non-IPF IIPs are further classified according to standard recommendations.[8,10]

A focused clinical history and physical examination are the first critical steps in the evaluation of patients suspected to have ILDs. Most patients with ILDs present with dry cough and progressive dyspnoea. Physical examination usually reveals tachypnoea, clubbing and in advanced cases, cyanosis and/or signs of pulmonary hypertension. Auscultation of the chest may reveal crackles that are usually fine and end-inspiratory; wheeze may be heard in diseases that also involve the airways apart from the parenchyma, such as hypersensitivity pneumonitis (HP) and sarcoidosis. Detection of 'velcro crackles' may prompt further investigations and help in early detection of the disease.[15] Squeaks may also be heard in some patients. Diseases that may mimic ILDs include pulmonary oedema (dyspnoea, and basal crackles), chronic obstructive disease (dyspnoea, wheeze and coarse crackles),[16] bronchial asthma (dyspnoea and wheeze, especially with certain environmental exposures),[12] lung cancer (especially, lepidic predominant adenocarcinoma on radiology), lymphangiitis carcinomatosis (interstitial pattern

on radiology), bronchiectasis (cystic pattern on radiography), and occasionally tuberculosis (TB) (especially miliary TB).

Once an ILD is suspected, a detailed clinical evaluation should be done to identify the underlying cause. A history of environmental/occupational exposure (smoking, organic dusts [especially, farm dust and birds] or inorganic dusts (especially occupational dusts), intake of drugs (especially, chemotherapeutic agents and anti-metabolites, amiodarone and nitrofurantoin) and history of connective tissue disorders (CTDs) should be elicited.[10] A family history of any ILD should also be asked for. Careful examination to look for any signs of an underlying CTD is indispensable. If a definite aetiological agent cannot be identified, the ILD may be an IIP. In several instances, the cause of the ILD is identified only after investigations.

Although the subtyping of IIP is predominantly based upon the findings of a HRCT of the chest, certain clues in the history may help. For instance, the age of onset (majority with an onset after 60 years have IPF), manner of onset (insidious onset excludes AIP and COP), history of smoking (IPF, RB-ILD or DIP) and history of pneumothorax (makes a cystic ILD more likely) may point towards specific causes.

Idiopathic pulmonary fibrosis is commonly seen in males, smokers and in the older age groups; the diagnosis should be reconsidered in persons less than 50 years of age.[9] Most patients have an insidious onset of breathlessness that progresses over months. Occasionally, a patient with IPF may present directly with acute or subacute onset of breathlessness due to an acute exacerbation of a hitherto unrecognised chronic illness.[17] Apart from respiratory symptoms, a history of gastroesophageal reflux may be present in a large but variable proportion (36%-94%) of patients with IPF.[6,18-21] On examination, clubbing (25%-50%) and fine end-inspiratory 'Velcro-like' crackles (80%-94%) are more commonly encountered in IPF than other ILDs.[22,23]

Recommendation

We recommend that a thorough clinical history and physical examination be undertaken during the initial evaluation to establish the presence of an ILD, identify any underlying cause (CTDs, Drugs, Environmental/ occupational exposures, and Familial disease) and form an initial impression of the IIP subtype. (UPP)

Q 2. What investigations should be done in patients suspected to have IPF?

Investigations in patients with IPF are performed with an aim to establish the diagnosis, exclude alternate diagnoses, assess the disease severity and prognosis and identify the co-morbidities. Some basic laboratory tests are required in all patients (Table 2). In resource-constrained settings, investigations should be targeted according to the clinical evaluation. Precipitins against avian proteins and other antigens implicated in hypersensitivity pneumonitis should be tested. Among the autoantibodies, rheumatoid factor, anti-nuclear antibodies (ANAs), anti-neutrophil cytoplasmic antibodies, and anti-cyclic citrullinated peptide may be sufficient. Other autoantibodies and muscle enzymes, such as creatine kinase (for myositis-associated ILD) may be tested if there is a clinical suspicion of a specific autoimmune disorder.

Table 2. Investigations to be performed in patients suspected to have idiopathic pulmonary fibrosis

Investigations	Purpose
Establishing diagnosis	
Chest radiograph	Suspect interstitial lung disease (ILD)
High resolution computed tomography (HRCT) of the chest	Identify a definite or possible usual interstitial pneumonia (UIP) pattern
Lung biopsy (surgical lung biopsy or transbronchial lung cryobiopsy)	Establish the histological diagnosis in those without a definite UIP pattern on HRCT chest
Excluding other disorders	
Antinuclear antibodies	Identify a connective tissue disorder (CTD) associated ILD
Rheumatoid factor	Identify rheumatoid arthritis related ILD
Anti-cyclic citrullinated peptide antibodies	Identify rheumatoid arthritis related ILD
Anti-neutrophil cytoplasmic antibodies (ANCA)	Identify ANCA-associated ILD
Other specific autoantibodies (anti-Scl-70, Ro, La, Jo-1 and others) and muscle enzymes, such as creatine kinase	Identify specific CTD, such as systemic sclerosis, Sjogren's syndrome and others according to clinical suspicion
Serum precipitins for organic dusts	Suspect hypersensitivity pneumonitis
Assessment of disease severity and prognosis	
Spirometry	Assess lung function at baseline and serially
Diffusion lung capacity	Assess gas exchange capacity at baseline
Six-minute walk test	Assess exercise capacity at baseline and serially
Co-morbidities and treatment adverse effects	
Echocardiography	Assess for pulmonary hypertension and underlying coronary artery disease
Liver function tests	For monitoring treatment-related adverse effects
Complete blood counts	For monitoring treatment-related adverse effects

In this regard, it is important to recognise interstitial pneumonia with autoimmune features ([IPAF]; variously referred to as lung-dominant CTD, autoimmune-featured ILD or ILD associated with undifferentiated CTD). The term has been proposed to identify individuals with ILD with features suggesting a CTD but not meeting all the features for classifying into a definite or characterisable CTD.[24] The diagnosis of IPAF can be considered if specific features from three primary domains (clinical, serologic and intrathoracic morphologic) are present. As an example, in this classification, an ANA titre ≥1:320 (with a diffuse, speckled, homogeneous pattern, or any titre with a nucleolar or centromere pattern) is considered a serologic feature. For a detailed description of IPAF, the readers can refer to the ERS/ATS research statement.[24]

Recommendation

We recommend relevant targeted investigations to be performed after clinical evaluation to establish the diagnosis of IPF, assess disease severity, identify co-morbidities and to exclude alternative diagnoses. (UPP)

Q 3. What is the role of pulmonary function tests and exercise testing? Which pulmonary function tests must be carried out at the time of diagnosis of IPF?

Pulmonary function testing is required primarily to assess the severity of the respiratory involvement, and prognostication. It also helps in identifying any airflow obstruction that may be present due to co-existing emphysema. Spirometry is the recommended test for the routine assessment of the disease severity, as it is easy to perform and reproducible. The ratio of forced expiratory volume in one second (FEV_1) to the forced vital capacity (FVC) less than the lower limit of normal represents airflow obstruction.[25] If the ratio is normal, but the FVC is below the lower limit of normal, it may suggest a restrictive defect. The severity of restrictive defect can be further graded as mild (>70% of the predicted), moderate (50%-70% of the predicted) and severe (<50% of the predicted) depending on the FVC values. Spirometry generally shows a restrictive defect in patients with IPF. Several large studies[26-28] assessing the efficacy of various agents in IPF have utilised change in FVC as a major endpoint of treatment. Decline in FVC is also a predictor of mortality.[29,30]

Other pulmonary function tests include lung volumes, diffusion capacity of the lung for carbon monoxide (DLCO), pulse oximetry and arterial blood gas analysis. Lung volume testing is required to confirm a restrictive defect in case the clinico-radiologic picture is not congruent with the spirometry results. It may also be useful when spirometry shows an airflow obstruction and there is an ILD on imaging. In such cases, lung volume measurement helps in identifying a mixed obstructive-restrictive defect and in quantifying the restrictive defect. Diffusion capacity of carbon monoxide is a useful investigation as it helps in identifying abnormal gas exchange, especially in early disease, when spirometry may be normal.[31] It also helps in prognostication.[32] Further, combined pulmonary fibrosis and emphysema (CPFE) might present with a normal FVC but a disproportionately low DLCO. Unfortunately, the reproducibility and accuracy of DLCO estimation are low, intra individual variability may be high, and standardisation may be difficult within and across laboratories.[33-35] In resource-constrained settings, a laboratory with standardised DLCO testing may not be routinely available. Therefore, cost-benefit ratio should be considered when recommending DLCO to any patient with IPF.

Pulse oximetry is useful in identifying hypoxia in patients with advanced disease. It also helps in assessing oxygen desaturation occurring with exercise.[36] Arterial blood gas testing is required in patients who have resting hypoxia (resting pulse oximetric saturation <90%). If there is significant airflow obstruction, blood gas testing helps in identifying the presence of hypercarbia.

Exercise testing is helpful in assessing the exercise capacity of patients with IPF.[37] Although, it is affected by the presence of co-morbidities (such as obesity) and complications of the disease (such as pulmonary hypertension), it provides a more global assessment of the patient's disability than lung function testing alone.[38] A comprehensive cardio-pulmonary exercise testing is not routinely required. A six-minute walk test (6MWT) is a simple method for the assessment of the exercise capacity in patients with IPF.[39] It also helps in identification and quantification of exercise-induced desaturation.[8,40-43]

Recommendations

We recommend that spirometry be performed in all patients with IPF and forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and the ratio of FEV_1/FVC should be measured. (1A)

We recommend that lung volumes need not be routinely measured in patients with IPF. (UPP)

We suggest that DLCO may be performed in patients with IPF if a standardised testing is available. (2B)

We recommend that pulse oximetry should be performed in patients with IPF to identify hypoxia. (UPP) Arterial blood gas analysis should be performed if hypoxia is detected on pulse oximetry and in patients with airflow obstruction. (UPP)

We recommend that a 6MWT be performed in patients with IPF to assess the exercise capacity. (1A)

Diagnosis of Idiopathic Pulmonary Fibrosis

Q 4. What is the role of chest radiograph and computed tomography scanning to establish DPLD? What are the high resolution computed tomography criteria for diagnosis of IPF?

A chest radiograph shows a reticular (net-like) pattern in IPF.[23,44] Early changes appear in the lower zones; initially, only an indistinct ('fuzzy' or 'shaggy') heart border or diaphragm outline may be seen rather than a distinct reticular pattern. Chest radiograph, however, has poor sensitivity and should not be used to exclude IPF. Further, it does not allow identification of the subtype of ILD. The chest radiograph may be used to monitor progression over longer periods, such as a year, and to exclude other causes of deterioration in patients suspected to have acute exacerbation of IPF.

An HRCT of the chest is the cornerstone of diagnosis of IPF.[9] An HRCT is performed in full inspiration at thin collimation (0.5-1.5 mm) using a high-resolution reconstruction algorithm (bone algorithm). The appropriate window settings (window level and width) should be used. Volumetric acquisition with contiguous sections is preferred as it covers the entire parenchyma and is mandatory if fibrosis scoring is required.[45] However, non-contiguous thin sections at intervals of 10 mm are also sufficient for making a diagnosis of IPF. Expiratory scans are required if air trapping is suspected based on the presence of mosaic perfusion on inspiratory film. Prone scanning is required only when there are dependent subpleural ground-glass opacities rather than distinct changes of reticulation and/or honeycombing.

Idiopathic pulmonary fibrosis is characterised by usual interstitial pneumonia (UIP) pattern on HRCT chest.[9] A '**definite UIP**' pattern on HRCT of the chest is characterised by the presence of reticulation (typically intralobular septal thickening), predominantly in the basal, subpleural regions and honeycombing with or without the presence of traction bronchiectasis and the absence of any characteristics considered 'inconsistent with UIP'.[9] The presence of any of the following features makes the CT appearance 'inconsistent with UIP': predominant involvement of the upper or mid lung, abnormalities predominantly distributed in the peribronchovascular pattern, ground-glass opacities greater in extent than reticular abnormality, profuse micronodules, discrete cysts away from the regions with honeycombing, diffusely present mosaic attenuation/perfusion, and segmental/lobar consolidation. In case, a subpleural basal predominant reticular abnormality is present without honeycombing and there are no features that are 'inconsistent with UIP', the pattern is labelled as '**possible UIP**'. When a 'possible UIP' pattern is accompanied by traction bronchiectasis or bronchiolectasis, it may be termed as 'probable UIP'.[14] When there are features mostly favouring UIP with some inconspicuous feature(s) suggestive of a 'non-UIP' pattern, it is termed as a pattern 'indeterminate for UIP'. Patients with 'inconsistent with UIP' pattern may have features typical of a non-UIP ILD, such as sarcoidosis or HP. A definite UIP pattern on HRCT has classically been associated with a 90% probability of a histological UIP pattern.[46,47] Therefore, a lung biopsy is not necessary to make a diagnosis of IPF if there is a definite UIP pattern seen on HRCT chest.[9] However, if there is a pattern of 'possible UIP' or 'inconsistent with UIP', a lung biopsy is required to arrive at a diagnosis of IPF.[9]

A definite UIP pattern on HRCT is encountered in 50% of patients with IPF.[48-50] The remaining 50% may have a 'possible UIP' pattern or a pattern 'inconsistent with UIP' and may go on to be diagnosed as IPF on a surgical lung biopsy. In one study, a possible UIP pattern had a positive predictive value (PPV) of 94% in the diagnosis of biopsy confirmed IPF. However, it is notable that in their cohort derived from a clinical trial of IPF, the prevalence of IPF was very high (90%).[51] In a recent study, in subjects aged ≥ 60 years and with reticular densities occupying at least one-third of lung volume but without honeycombing, the specificity for IPF diagnosis was 96%. However, ground-glass densities were associated with significantly reduced odds (odds ratio, 0.55; 95% confidence intervals, 0.34-0.89) for a diagnosis of IPF.[50] On the contrary, in another study, a possible UIP pattern on HRCT had a PPV of only 62.5%. However, when this was combined with a traction bronchiectasis score ≥4, male gender and age ≥60 years, the PPV increased to 95%.[52]

Thus, about half of the patients suffering from IPF in a clinical setting would not have a 'definite UIP' pattern on HRCT chest. All these patients must be offered a lung biopsy. However, several factors make a surgical lung biopsy or cryobiopsy (read later sections) difficult in resource-constrained settings: the unavailability of a trained thoracic surgeon in the hospital or region, a relatively high complication rate of surgical lung biopsy, the lack of trained pulmonary pathologists, unwillingness of the patient to undergo an invasive procedure and presence of advanced disease that makes a patient unfit for the procedure.[7] Due to these practical difficulties, in resource-limited settings, subjects aged ≥60 years (especially male) with extensive reticular densities and/or extensive traction bronchiectasis on HRCT and absence of other features 'inconsistent with UIP' may be assigned a working diagnosis of IPF, if the multidisciplinary discussion team (MDT, *see Q 8*) feels that the possibility of an alternate diagnosis is low.

Recommendations

We recommend that a 'definite UIP' pattern on HRCT be considered diagnostic of IPF in the absence of a CTD and significant exposure to drugs and organic and inorganic dusts. (1A)

We recommend that a surgical lung biopsy or cryobiopsy be offered to patients who do not have a 'definite UIP' pattern on HRCT chest. (1A)

We suggest that a working diagnosis of IPF be made in the absence of a lung biopsy in a subject aged ≥60 years with extensive reticular densities and/or extensive traction bronchiectasis on HRCT and absence of features 'inconsistent with UIP', if the MDT feels that the possibility of an alternate diagnosis is low. (2B)

Q 5. Should routine bronchoscopy with procedures namely bronchoalveolar lavage and transbronchial lung biopsy be performed in patients suspected to have IPF?

Cellular analysis on bronchoalveolar lavage (BAL) fluid has been investigated in the diagnosis of IPF and its differentiation from other ILDs, such as NSIP and chronic hypersensitivity pneumonitis. A 'typical' cellular analysis of BAL in IPF shows neutrophilia, eosinophilia and lack of lymphocytosis. However, different cut-offs for BAL neutrophilia ranging from 3%-5% have been used.[9,53-56] Importantly, BAL neutrophilia is not specific to IPF and may be observed in fibrotic NSIP, fibrotic sarcoidosis, HP, CTD-ILD, diffuse alveolar damage, infections and aspiration.[56,57] A BAL eosinophil count of >2% may be observed in 40%-60% of the patients with IPF.[55,58] However, a remarkably high BAL fluid eosinophilia (20%-25%) suggests an eosinophilic lung disease.[55,59] BAL lymphocytosis has been defined at a threshold of >15% lymphocytes.[56] However, different thresholds of 20%, 25%, 30%, 40% and 50% have been observed and proposed to favour a diagnosis of sarcoidosis, HP or NSIP over IPF.[9,54,56,60] In a study, a lymphocyte differential count >30% changed the 'perception' of diagnosis of IPF to HP or NSIP in only six of 74 patients with suspected IPF of whom only two were confirmed on biopsy.[60] In another study, BAL findings failed to differentiate between idiopathic NSIP and UIP.[53]

To summarise, BAL fluid analysis does not help in confirming a diagnosis of IPF. The sensitivity and specificity of cellular analysis of BAL fluid in this regard are unknown. Further, there is no consensus on the thresholds for defining BAL neutrophilia, lymphocytosis and eosinophilia. Finally, the risk of acute exacerbation of IPF is increased after performing BAL.[61] However, BAL, may be useful in identifying infections, malignancy, alveolar haemorrhage and certain ILDs, such as pulmonary alveolar proteinosis, and pulmonary Langerhans cell histiocytosis (PLCH). If these are the diagnostic considerations in a patient with suspected IPF, BAL may be performed. BAL should be performed through standardised techniques, including adequate fluid volumes, processing and pathologic analysis.[56]

Transbronchial lung biopsy (TBLB) has been studied in the diagnosis of IPF, which is characterised by UIP on histopathological examination. The sensitivity of TBLB in identifying a UIP pattern (criteria of possible, probable or definite UIP used in different studies) varies from 0-32 percent.[62-65] Irrespective of operator expertise, TBLB is associated with a small specimen size, sampling errors, crush artefacts, a failure to penetrate beyond the peribronchial sheath, and disintegration of the friable tissue.[66] Further, patients with IPF may have NSIP pattern in some areas of their lungs (lobar histologic variability), and thus, small sized TBLBs may misclassify UIP as NSIP.[67] However, TBLB is helpful in exclusion of other diseases, such as infections, sarcoidosis and lymphangitis carcinomatosis, if these are among the differential diagnoses.

Recommendations

We recommend that BAL fluid cellular analysis should not routinely be used to make a diagnosis of IPF or to differentiate IPF from other common ILDs. (3A)

We suggest that BAL may be used to diagnose infections, malignancy, alveolar haemorrhage, and certain rare ILDs, such as PAP and PLCH. (UPP)

We do not recommend conventional forceps TBLB as a means for the diagnosis of IPF. (3A)

Q 6. When should a surgical lung biopsy be performed for the diagnosis of IPF?

Surgical lung biopsy (SLB) is required for diagnosis in about 50% of patients with IPF who do not have the classical clinical, radiological and physiological features of UIP.[46,68] The yield and safety of SLB in ILDs, in general, and IPF in particular are variable. In a prospective study involving 224 subjects with ILDs, the yield of a specific diagnosis was 87%.[69] In a recent study, the addition of SLB increased the observers' confidence levels of initial clinical-radiologic diagnosis of suspected IPF in 78% of cases.[70] A meta-analysis of studies of SLB in ILDs showed a pooled yield of 95% (range, 42%-100%).[71] IPF was finally diagnosed by SLB in 75% to 91% of suspected cases, whereas 19% to 74% of IPF cases were not initially suspected by HRCT.[72,73]

Complications of SLB include post-operative pneumonia, prolonged air leak, acute exacerbation, mechanical ventilation, prolonged hospital stay, and death.[74] These are more frequently encountered in patients with IPF as compared to other IIPs.[75] Acute exacerbation of IPF is especially an important concern with SLB.

Surgical lung biopsy can be performed by thoracotomy/mini-thoracotomy (open lung biopsy [OLB]) or with video-assisted thoracoscopic surgery (VATS). In a previous study, the 30-day mortality of a SLB in IPF was found to be 17% (OLB 16%, VATS 19%).[76] However, subjects in this study were acutely ill, with accelerated clinical courses.[68] In a randomised trial, both thoracoscopic and limited thoracotomy performed for SLB in patients with ILD yielded 100% definite histologic diagnosis and were equally safe with no short-term mortality.[77] Another randomised trial comparing VATS and OLB revealed a comparable yield as well as safety.[78] A more recent study[79] showed that VATS biopsy is safer than OLB with a 30-day mortality of 0 *versus* 5.4%. A meta-analysis has revealed a point post-operative mortality rate of 3.6% (2.9% with VATS as compared to 8.0% with OLB, although significant heterogeneity was observed in studies reporting OLB).[71]

Whether a minimum lung function is required for safely performing SLB remains unknown. In one study, patients selected for SLB were mandated to have FVC ≥50%-55% and DLCO ≥40% of predicted.[75] In a meta-analysis, lower mortality was observed in studies that excluded patients with DLCO less than 35% or FVC less than 55% compared to those not excluding them (1% *versus* 3.7%, p=0.026).[71] A study of over 3000 subjects who underwent VATS lung biopsy for a diagnosis of ILD found that pulmonary hypertension, pre-operative corticosteroid treatment, and low diffusion capacity were significant risk factors for operative mortality.[80]

The specimen obtained with SLB are much larger than those with TBLB (and cryobiopsy, *see Q 7*), and are generally, sufficient to identify the features of UIP on histopathological examination. The histopathological features of 'definite UIP' pattern include **patchy** involvement of lung parenchyma by marked fibrosis or architectural distortion, with/without **honeycombing** in a largely **subpleural**/paraseptal distribution along with the presence of **fibroblast foci** and absence of features, such as hyaline membranes (suggest diffuse alveolar damage), organising pneumonia, granulomas (suggest sarcoidosis), significant interstitial inflammation away from areas of honeycombing (suggest NSIP), inflammation or fibrosis that is airway-centered (HP), or any other feature(s) that is suggestive of an alternate diagnosis.[9] If there are other features of UIP but with the absence of either patchy involvement or fibroblastic foci, and no feature inconsistent with UIP, it is termed as 'probable UIP'.[9] If there is only patchy or diffuse lung parenchymal involvement by fibrosis, with/without interstitial inflammation in the absence of an alternate diagnosis, it is termed as 'possible UIP'.

Recommendations

We recommend that a surgical lung biopsy be performed to diagnose IPF if the HRCT does not show a 'definite UIP' pattern. (1A) *Also see recommendation under Q4.*

We recommend that a VATS lung biopsy be preferred over OLB. (1A)

We suggest that patients should preferably have a FVC ≥55% and DLCO ≥35% and the absence of pulmonary hypertension to minimise the risk of complications. (2B)

Q 7. Should a lung cryobiopsy be performed for a diagnosis of IPF?

Transbronchial lung cryobiopsy (TBLC or bronchoscopic lung cryobiopsy [BLC] or cryo-TBLB) is a technique in which a cryoprobe is introduced through the flexible bronchoscope deep into a bronchopulmonary segment.[81] The activation of the probe results in freezing of the lung parenchyma (at the level of the terminal bronchiole) around the probe which is then sheared off by withdrawing the probe along with the bronchoscope *en bloc*. It yields larger lung specimens with little crush artefact. The yield of TBLC has varied across studies.[82] In general, the pooled yield for a definitive or probable diagnosis is 86% for DPLDs.[82] In a study of 69 patients with fibrotic ILDs, the yield of TBLC was 91%.[83] A diagnosis of IPF could be made with high confidence in 36 and low confidence in three patients. In another study, it was concluded when there is uncertainty about the diagnosis of IPF on the basis of clinical and HRCT data alone, the addition of TBLC increased the diagnostic confidence level in 77% of the cases.[70] A recent multi-centre study from a developing country[84] suggested a diagnostic yield of about 78% among patients with DPLDs.

Transbronchial lung cryobiopsy is associated with complications, such as pneumothorax (3%-33%), moderate to severe bleeding (2%-79%), acute exacerbation of IPF and even death (0.74%). Due to the risk of complications, the technique should be performed in carefully selected patients (FVC ≥1.5L and 50% of predicted, FEV_1 ≥1L, no or mild pulmonary hypertension, no coagulopathy) in specialised centers. It is further suggested that the procedure be performed under general anaesthesia with an artificial airway in place along with the use of an occlusion balloon.[84,85]

Recommendation

We suggest that transbronchial lung cryobiopsy may be performed as an alternative for surgical lung biopsy for the histopathological diagnosis of IPF in selected patients at specialised centers. (2B)

Q 8. What is the role of multi-disciplinary discussion in the diagnosis and how can we implement it in the resource-limited setting?

A multi-disciplinary discussion team (MDT) is a forum that enables the integration of available clinical, radiologic and histopathological information of a patient for arriving at a diagnosis.[86] There are two important reasons for the need of a MDT in the diagnosis of ILDs (including IPF). First, there is no reference standard for the diagnosis of ILDs/IPF in several cases. Histopathological examination, considered as the benchmark, is fraught with poor inter-observer agreement. In a study of patients with ILD, the coefficient of agreement (κ) for diagnosis of first choice was 0.38.[87] Only 39% of the cases could be diagnosed with 100% confidence. In several cases, the histological features may be intermediate between two entities;[86] here, the clinical and radiologic data may contribute in deciding the more likely diagnosis. For a diagnosis of IPF, the inter-observer agreement among individual academic clinicians, radiologists and histologists is only fair to moderate (κ_w of 0.56, 0.40 and 0.30, respectively).[88,89] However, the agreement for the diagnostic likelihood of IPF between different MDTs is high (κ=0.71).[90]

The second reason for the need of a MDT is that 50% of the patients with IPF do not have a definite UIP pattern on HRCT.[48] However, only a proportion of these patients would undergo a lung biopsy. Even in the developed countries, only 28%-38% of these patients are diagnosed by SLB.[86] This number may be even lower in resource-constrained settings.[91] In such circumstances, a multi-disciplinary discussion (MDD) between the clinician and radiologist becomes obligatory.

Not all cases of ILDs or suspected IPF require a MDD.[86] For example, an elderly gentleman with a definite UIP pattern on HRCT without any significant environmental exposures can be diagnosed with IPF with high confidence without a MDD. It is preferable that members of the MDT meet face-to-face, however a discussion through telecommunication is also acceptable.[86] The presence of a pathologist is required only if a lung sampling (BAL, TBLB, TBLC, or SLB) has been performed. Occasionally, a rheumatologist may form part of the MDT if the clinician thinks that there is a difficulty in differentiating a CTD associated ILD from IPF. In that case, the rheumatologist must have interacted with the patient in person.

Recommendation

We recommend that MDD should be employed for the diagnosis of IPF in those patients who do not have a definite UIP pattern on HRCT or in whom features, such as age, serologic profile, environmental exposures or others are not consistent with a clear idiopathic nature of the disorder. (2A)

An algorithmic approach is recommended to arrive at the final diagnosis in suspected cases of ILD is shown in the figure below.

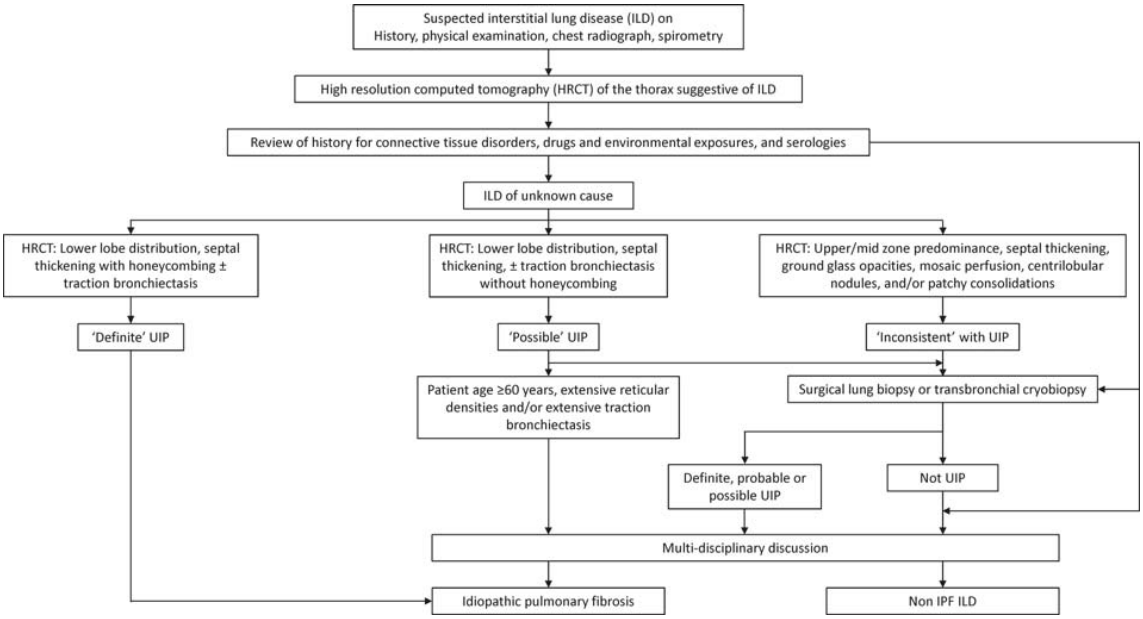

Figure. Algorithmic approach to the diagnosis of interstitial lung diseases. A 'possible UIP' pattern, when accompanied by traction bronchiectasis is termed as 'probable UIP'. An 'inconsistent with UIP' pattern may be consistent with/characteristic of a non-UIP interstitial lung disease (such as sarcoidosis or hypersensitivity pneumonitis). Alternatively, it may be closer to UIP with an inconspicuous atypical finding (for example, an area of mosaic attenuation) and then it may be termed as 'indeterminate for UIP'.[14]

Definition of abbreviations: UIP=Usual interstitial pneumonia; IPF=Idiopathic pulmonary fibrosis

Q 9. What evaluation should be performed to assess the prognosis?

Idiopathic pulmonary fibrosis is a progressive disease that is ultimately fatal in a few years' time. The median survival is three years and the average 5-year survival is only 20%. Thus, prognostication is important to convey the correct information to the patients about their disease, to plan them for lung transplantation and prepare them for end-of-life care, as required. There are several predictors of survival in IPF that may be classified into clinical, radiologic, physiologic, pathologic and biomarker-based. The factors associated with a poor prognosis in IPF are summarised in table 3.[29,30,32,92-117]

Table 3. Factors associated with poor prognosis in idiopathic pulmonary fibrosis

Clinical
Older age[92-94]
Smoking[93,94]
Degree of dyspnoea at diagnosis (Modified Medical Research Council scale)[96]
Increase in dyspnoea scores at six months[29]
Digital clubbing[92]
Low body mass index[97]
Radiologic
Fibrosis score on high resolution computed tomography scan (based on reticulation and honeycombing)[102,103]
Presence of pulmonary hypertension on right heart catheterisation and/or echocardiography[98,100]
Physiologic
Low forced vital capacity[32,92]
Low total lung capacity[32,92]
Low diffusing capacity for carbon monoxide[32,92]
10 point reduction in the percentage predicted forced vital capacity over one year or less[29,30]
15 point reduction in the percentage predicted diffusing capacity over one year or less[29,30]
Reduction of >50 meters in the six-minute walk test distance[105]
Pathologic
Organising pneumonia or profuse fibroblastic foci on lung biopsy[114-116]
Biomarker-based
Elevated B-type natriuretic peptide in serum[101]
Elevated Krebs von den Lungen-6 (KL-6) levels in bronchoalveolar lavage and/or blood[107,109,110]
Elevated surfactant proteins A and D in serum[107]
Elevated matrix metalloproteinases in bronchoalveolar lavage and/or blood[117]
Elevated CC-chemokines in bronchoalveolar lavage and/or blood[107]
Absence of mucin 5B gene polymorphism[113]

Among the physiologic parameters, FVC, total lung capacity and DLCO are predictors of survival.[32,92] A 10% change in percent predicted FVC and/or a change of 15% in percent predicted DLCO over one year are considered significant and predict survival.[29,30] Lesser reductions (5%-10%) in FVC within a period of six months are also predictive of poor survival.[29] An important caveat with smaller reductions in lung function is that these changes may represent the inherent variability in spirometric measures. Hence, minor alterations in spirometry should always be correlated with change in symptoms and/or fibrosis on HRCT chest. The 6MWT distance and its longitudinal changes also predict survival.[104] A fall of >50 meters over six months is associated with a three-fold increased risk of mortality.[105] The minimum clinically important difference, i.e. the minimum change in the distance walked that correlates with other outcome measures was about 30 meters in one study.[106]

The presence of pulmonary hypertension (PH) is associated with a reduced survival in IPF with one-year mortality of 28% *versus* 5.5% in those without PH (p=0.002).[98] The accurate assessment of PH requires right heart catheterisation (RHC). However, RHC is an invasive test and even in the event of finding PH on RHC, there is going to be little change in the management of the patient. There is a poor correlation between echocardiographic and RHC assessment of pulmonary artery pressures. However, echocardiography is non-invasive and can easily be repeated.[99] A systolic pulmonary artery pressure of >50 mmHg on echocardiography may predict a reduced survival.[100] Thus, echocardiography may be employed for the detection of PH with an intent of prognostication and identification of co-existing cardiac disease.

Apart from individual predictors, development of composite scores and clinical prediction rules has also been attempted. Composite scores and clinical prediction models have been developed for prognostication in IPF by combining several clinical, physiological and/or radiologic parameters. The clinical, radiological and physiological (CRP) score includes age, smoking history, clubbing, extent of reticular opacities and PH on a chest radiograph, total lung capacity and partial pressure of arterial oxygen (PaO_2) at maximal exercise. The score was found to predict survival;[92] however, it has not been validated. The gender-age-physiology (GAP) model is a validated multi-dimensional index and staging system that as the name suggests includes gender and physiologic parameters (FVC and DLCO) as components (Table 4).[118] The 1-year, 2-year and 3-year mortality can be predicted using this system (https://www.mdcalc.com/gap-index-idiopathic-pulmonary-fibrosis-ipf-mortality).

Among the prognostic factors discussed above, the individual clinical parameters alone do not offer accuracy while the pathologic and biomarker-based predictors do not offer practical utility. Echocardiography, the GAP index and the longitudinal changes in FVC and the 6MWT distance are objective parameters that are backed by sufficient evidence and are simple, non-invasive, and convenient to use.

Table 4. The gender age physiology (GAP) index and staging system

Predictor	Points
Gender	
Female	0
Male	1
Age, years	
Less than or equals 60	0
61-65	1
More than 65	2
Physiology	
FVC, percentage of predicted	
More than 75	0
50-75	1
Less than 50	2
DLCO, percentage of predicted	
More than 55	0
36-55	1
Less than or equals 35	2
Unable to perform	3
Staging system	**Points (1-year mortality)**
Stages	
I	0-3 (5.6%)
II	4-5 (16.2%)
III	6-8 (39.2%)

Adapted from Ley, et al[118]

Definition of abbreviations: FVC=Forced vital capacity; DLCO=Diffusion capacity of the lung for carbon monoxide

Recommendation

We recommend the presence of PH on echocardiography, 10% absolute change in percent predicted FVC over one year, change in the 6MWT distance of 50 meters and the GAP index be used as parameters for prognostication of patients with IPF. (2A)

Treatment of Idiopathic Pulmonary Fibrosis

Q 10. What are the drugs that are effective in the treatment of IPF and what is the evidence for their use?

Pirfenidone and nintedanib are disease modifying drugs found to be effective in the treatment of IPF.[28] Pirfenidone is a pyridine derivative that has anti-inflammatory, anti-oxidant and anti-fibrotic properties.[119] It acts by the regulation of transforming growth factor-β and inhibition of fibroblasts and collagen synthesis although its precise mechanism of action in IPF is not clear. The efficacy and safety of pirfenidone have been studied in several randomised controlled trials. In the phase 2 study by Azuma *et al*[120] involving 107 subjects in Japan, the decline in the vital capacity in pirfenidone-treated patients (p=0.037) was reduced (mean difference of 100 mL from placebo, at nine months). There was also a significant decline in episodes of acute exacerbations (14% in placebo *versus* none in pirfenidone, p=0.003) at nine months as compared with placebo.[120] In the phase 3 trial, performed in Japan, pirfenidone was observed to reduce mean change in vital capacity by 70 mL at 52 weeks (p=0.042), and progression-free survival time was improved (p=0.028).[121] This was followed by the CAPACITY (Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes) trials (studies 004 and 006) conducted across several countries in Europe and North America.[26] In study 004, comprising 435 subjects, pirfenidone (2400 mg/day) was found to reduce the decline in FVC with a difference of 4.4% between the study and placebo groups (p=0.001) at 72 weeks. In study 006, the difference in the change in FVC at 72 weeks between the study and placebo groups was not significant. In the pooled analysis, the mean change in FVC at 72 weeks was -11.0% in placebo *versus* -8.5% in the pirfenidone group (p=0.005). About 21% of pirfenidone treated patients had a ≥10% decline in percentage predicted FVC as compared to 31% in the placebo group (p=0.003). In the Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) study, pirfenidone resulted in a relative reduction of 47.9% in the proportion of patients, who experienced an absolute decline in percentage predicted FVC by 10 points or who died, as compared to placebo.[27] The mean decline in FVC was 235 mL in the pirfenidone *versus* 428 mL in the placebo group (p<0.001). Progression-free survival was improved by pirfenidone (p<0.001) and the decline in the 6-minute walk distance was reduced (p=0.04). In the analysis of pooled data of CAPACITY and ASCEND trials, pirfenidone was found to reduce the risk of all-cause mortality at one year by 48% (p=0.01) while the risk of death from IPF at one year was reduced by 68% as compared with placebo (p=0.006).[27] In another analysis[122], patients receiving pirfenidone were found to have a lower risk of non-elective respiratory-related hospitalisation over one year.

Nintedanib is a multiple tyrosine kinase inhibitor that causes suppression of several signalling receptors including fibroblast growth factor, vascular endothelial growth factor and platelet derived growth factor. Its efficacy in IPF has been studied in one phase 2 (To Improve Pulmonary Fibrosis with BIBF-1120 [TOMORROW]) and two phase 3 studies (INPULSIS-1 and 2).[28,123] In the TOMORROW study, nintedanib (150 mg twice daily) resulted in 68% reduction in the rate of loss of lung function (FVC), fewer acute exacerbations and a preserved health-related quality of life, as compared with placebo. The results of INPULSIS-1 and 2, two replicate 52 weeks studies, also suggested that nintedanib significantly reduced the decline in FVC as compared to placebo (-114.7 mL with nintedanib *versus* -239.9 mL with placebo [p<0.001] in INPULSIS-1 and -113.6 mL with nintedanib *versus* -207.3 mL with placebo [p<0.001] in INPULSIS-2).[28] In INPULSIS-2, there was a significant benefit in terms of the time to first exacerbation (hazard ratio, 0.38; 95% CI, 0.19 to 0.77; p=0.005), while this was not observed in INPULSIS-1. In the pooled analysis, there was no significant difference in the time to first investigator-reported acute exacerbation between the nintedanib and placebo groups. However, the time to the first adjudicated acute exacerbation (confirmed or suspected) was increased with nintedanib compared to placebo. No reduction in mortality was observed.

The comparison between the two drugs is described in table 5 while the difference in the inclusion criteria of the CAPACITY, ASCEND and INPULSIS trials is shown in table 6.[26-28] The two drugs have been shown to lead to a clinically similar benefit by reducing the decline in FVC. However, to date, the reduction in mortality has only been demonstrated with pirfenidone while nintedanib has been shown to decrease the number of acute exacerbations.

Table 5. Comparison between pirfenidone and nintedanib

	Pirfenidone	Nintedanib
Evidence for efficacy	CAPACITY 1 and 2, ASCEND trials	INPULSIS 1 and 2 trials
Major outcome affected	Slower rate of decline of forced vital capacity	Slower rate of decline of forced vital capacity
Progression free survival	Prolonged by 26%	No evidence
Mortality	Reduced (hazards ratio 0.52)	No reduction
Exacerbation frequency	Insufficient evidence	Reduced
Risk of respiratory related hospitalisations	Decreased	No evidence
Most common adverse effects	Nausea, rash, dyspepsia	Diarrhea, nausea, upper respiratory symptoms
Pill burden	12/day	2/day
Cost	<INR 6,000/month	>INR 60,000/month

Definition of abbreviations: CAPACITY=Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes; ASCEND=Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis; INR=Indian rupees

Recommendation

We recommend that treatment with antifibrotic agents (pirfenidone or nintedanib) be offered to patients with IPF with a forced vital capacity ≥50%. (1A)

Q 11. When should treatment with anti-fibrotic agents be started in patients with IPF?

It is intuitive that the maximum benefit of treatment in terms of prolonged survival and sustained benefits in maintaining the quality of life may be derived in those with preserved lung function. Post-hoc analysis of data from the CAPACITY and ASCEND trials has shown that pirfenidone leads to a similar benefit in those with preserved lung function (FVC% predicted ≥80% or GAP stage I) compared to those with more advanced disease with reduced lung function (FVC % predicted <80% or GAP stage II-III).[124] Analysis of data from INPULSIS trials also shows that the benefit of treatment with nintedanib in terms of slowing of FVC decline is similar in patients with preserved lung function (percentage predicted FVC >90%) and those with more impaired lung function (FVC % predicted ≤90%).[125] The same is also true when data were analysed at a cut-off of FVC 70% of predicted.[126] Thus, treatment should be offered to all patients with IPF. The information on the efficacy of antifibrotic agents in those with severe disease (FVC<50%) is sparse. In the analysis of initial data from an open label extension study of the INPULSIS trials (INPULSIS-ON study), it appears that patients with FVC<50% may derive similar benefits from the treatment as those with less advanced disease.[127]

Recommendation

We suggest that treatment with antifibrotic drugs may be considered in patients with IPF with FVC <50%. (UPP)

We recommend that issues related to costs, anticipated benefits, and adverse effects of antifibrotic drugs be discussed with all patients with IPF. (UPP)

Q 12. Should antifibrotic drugs be commenced as monotherapy or in combination? Which drug should be started first: pirfenidone or nintedanib?

The evidence of efficacy in IPF is for monotherapy with either pirfenidone or nintedanib. The efficacy of the combination of the two drugs has not been studied; the pharmacokinetics have been reported in a study of 50 patients.[128] The plasma concentration

Table 6. Differences between the inclusion and exclusion criteria in the CAPACITY, ASCEND and INPULSIS trials

Criteria	CAPACITY	ASCEND	INPULSIS
Inclusion criteria			
Age	40-80 years	40-80 years	≥40 years
Time of diagnosis	Within two years	Within 6-48 months	Within five years
Basis of IPF diagnosis	Definite UIP on HRCT, or UIP on lung biopsy if 'definite UIP' not present on HRCT	Definite UIP on HRCT, or UIP on lung biopsy if 'definite UIP' not present on HRCT	Definite UIP on HRCT, or Presence of reticulion and traction bronchiectasis consistent with fibrosis in predominantly basal and peripheral regions, or UIP on lung biopsy
FVC, percent predicted	≥50%	50%-90% (FEV_1/FVC>0.8)	≥50%
Diffusing capacity, percent predicted	35%-90%	30%-90%	30%—79%
Six-minute walk test distance	≥150 meters	≥150 meters	
Exclusion criteria			
	Obstructive lung disease	History of chronic obstructive lung disease/asthma	—
	Active connective tissue disease	Active connective tissue disease	Abnormal liver function tests
	On lung transplant waiting list	Expected to receive lung transplant within one year Unstable angina/recent myocardial infarction Recent/active smoking Bronchodilator response	Likely to undergo lung transplantation during the study Unstable angina/recent myocardial infarction Therapeutic anticoagulation High dose antiplatelet therapy

Definition of abbreviations: CAPACITY=Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes; ASCEND=Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis; IPF=Idiopathic pulmonary fibrosis; FVC=Forced vital capacity; UIP=Usual interstitial pneumonia; HRCT=High resolution computed tomography; FEV_1=Forced expiratory volume in one second

of nintedanib was lowered on administering it along with pirfenidone while the concentration of pirfenidone was not affected. However, in a recent study (INJOURNEY), pre-dose plasma trough concentrations of nintedanib was not affected by the administration of pirfenidone.[129] The gastrointestinal side effects were higher with simultaneous administration of the two drugs as compared to nintedanib alone (70% *versus* 52%). As data on the efficacy of the combination therapy with the two drugs are lacking, monotherapy is currently the accepted way of starting the treatment.

Pirfenidone and nintedanib have not been compared in any head-to-head study. Thus, direct evidence for one drug's superiority over the other is presently unavailable. When discussing the treatment options, the physician should clearly inform the patient about the benefit expected from either drug. The patient should clearly be explained that neither drug represents a cure for the illness. The drugs do not completely alleviate the symptoms. Both the drugs are essentially aimed at slowing down the progression of fibrosis and the resulting decline in lung function. The major differences between the drugs should be discussed (Table 5). The patient should be explained that as per the current evidence, pirfenidone has been shown to reduce mortality and hospitalisations while nintedanib has been shown to reduce the risk of exacerbations. The incidence of adverse effects with both the drugs should be elaborated upon. Finally, details including pill burden and cost differential should also be discussed. The patient should then be assisted in making an informed choice about the treatment. Every effort should be made to ensure that the decision to start treatment is a shared decision.

Recommendations

We recommend that treatment should be started with monotherapy with either pirfenidone or nintedanib. (1A)

We recommend that the patients be assisted in making an informed choice between the two drugs after discussing with them the current evidence. (UPP)

Q 13. How to assess progression in patients with IPF? When to change treatment: whether to add or switch to the other drug?

Progression in IPF has been defined as an absolute decrease in the percentage predicted FVC by 10 points in the 2011 ATS/ERS guidelines.[9] This threshold has also been used as an endpoint in trials of therapy in IPF. However, progression of the disease may not necessarily denote treatment failure. It is because the rate of decline in lung function varies across patients

and may vary in the same patient during different time periods. Further, in a post-hoc analysis, patients who had a 10% absolute decline in FVC (percent predicted) during the first three to six months of treatment had a slower decline in lung function in the next six months if they received pirfenidone as compared to those who received placebo.[130] Thus, even after progression of the disease as defined above during one time period, the patient may be expected to draw benefit if the drug is continued. However, as two effective drugs are now available, the patient should be explained the options of continuing with the same drug or switching to other treatment. If the patient has good tolerance to the current treatment and the decline in lung function is not significant, the option of continuing the same drug may be offered. However, if the tolerance is poor and/or the decline in lung function is significant and the patient is willing to take the other drug, a switch may be advisable. In case of declining lung function, a combined use of pirfenidone and nintedanib may also be tried, though it is associated with a higher incidence of adverse effects. Combination therapy should be administered as an investigational treatment and the patient data be collected and saved for entry into a clinical registry.

Recommendations

We recommend that progression of the disease be defined as an absolute change of 10 points in the percent predicted FVC. (2A)

We suggest that in patients with a decline in lung function <10% with good tolerance of the drug, the same drug may be continued. (UPP)

We suggest that the treatment may be switched to the alternative agent in case of a decline in FVC by >10% or significant adverse effects. (UPP)

Q 14. What prescribing information should be given to patients started on pirfenidone or nintedanib?

Pirfenidone: Pirfenidone should be started at a dose of 200 mg thrice a day and should be increased by 600 mg per day every 2-3 days till a dose of 2400 mg per day is reached.[120] The common adverse effects of pirfenidone include nausea (35%), a photosensitive rash (30%), dyspepsia (20%), giddiness (20%), vomiting (15%), arthralgias (10%), insomnia (10%), loss of appetite or weight (10%) and hepatitis.[26] Patients should be advised to take the drug with food in order to reduce the gastrointestinal adverse effects and should avoid or minimise exposure to sunlight to prevent photosensitive reaction. They should use sunscreens (sun protective factor 50 or higher) and wear clothing that protects from direct exposure to sunlight. Liver function tests should be performed at baseline and monitored every two weeks for the first month and then every month for the next five months and then every three months. In case of an elevation of >3 times the upper limit of normal (3 × ULN), more frequent monitoring or dose reduction/temporary cessation may be resorted to. An elevation of >3 × ULN but <5 × ULN with symptoms of liver damage or an elevation >5 × ULN should prompt discontinuation of the drug.

If a patient does not tolerate the recommended dose (2400 mg/day), it can be temporarily reduced by 600 mg per day and then slower dose escalation may be attempted. In case, the patient does not tolerate the full dose despite repeated attempts at dose escalation, a lower (maximum tolerated) dose may be instituted. In that instance, the patient should be told that such a dose may be only partially effective or ineffective, as most evidence for efficacy of pirfenidone is for the 2400 mg per day dose. The alternative anti-fibrotic drug, i.e., nintedanib should also be offered.

Nintedanib: Nintedanib should be prescribed at a dose of 150 mg twice a day to be administered with food. Diarrhoea is the most common adverse effect (60%); others include nausea (25%), cough (15%), nasopharyngitis (10%), vomiting (10%), decreased appetite and weight loss (10%). The risk of bleeding (most commonly epistaxis) or arterial thrombotic events may be increased. The monitoring of liver function tests may be performed as outlined above for pirfenidone. If there are intolerable adverse effects, the dose may be reduced to 100 mg twice a day. In case of diarrhoea, adequate hydration and anti-motility agents should be tried. If symptoms do not resolve, the drug may be stopped and a re-initiation of the treatment may be attempted after a few days.

Recommendations

We recommend that a dose of 2400 mg per day (in three divided doses) be used for pirfenidone and a dose of 150 mg twice a day be prescribed for nintedanib. (1A)

We recommend that the dose be reduced in case of intolerance, and all attempts made to increase it again to the target dose. (UPP)

Q 15. What are the treatments that have been found to be ineffective or harmful in IPF?

The following agents have been investigated and found ineffective in the treatment of IPF:

1. *N-acetylcysteine*: No significant benefit with respect to the preservation of FVC,[131] may be beneficial in those with an rs3750920 (TOLLIP) TT genotype, and might be harmful in those with a CC genotype[132]
2. *Imatinib*: No effect on survival or lung function[133]
3. *Bosentan*: No effect on time to worsening of IPF or death[134]

4. *Macitentan*: No effect on pulmonary function or time to worsening of disease or death[135]
5. *Sildenafil*: No effect on exercise capacity[136]
6. *Colchicine*: No effect on disease progression or survival[137-140]

The following agents have been found to be harmful in the treatment of patients with IPF:

1. *Warfarin*: Increased mortality with use specifically for IPF as well as when used for non-IPF medical indications[141-143]
2. *Glucocorticoid monotherapy*: Associated with significant morbidity, possible harm and without any survival advantage demonstrated to date[137,140,144-146]
3. *Combination of prednisone, azathioprine, N-acetylcysteine:* Increased risks of death and hospitalisation[147]
4. *Ambrisentan*: Increased risk for disease progression and respiratory hospitalisations[148]

There is absence of any good quality evidence for the use of following agents, sometimes employed by the physicians in clinical practice for the treatment of IPF: doxycycline and cotrimoxazole.[149]

Recommendation

We recommend that the following agents not be used for the treatment of IPF:

Imatinib, bosentan, ambrisentan, macitentan, sildenafil, warfarin, N-acetylcysteine, and combination therapy with prednisone, azathioprine, and N-acetylcysteine (1A); colchicine and glucocorticoid monotherapy. (2A)

Q 16. How frequently should the patient be followed up and what evaluation should be performed?

A patient with IPF who is started on an anti-fibrotic drug should be followed up frequently in the initial phase of the treatment, primarily for liver function test monitoring. Spirometry may be performed every three months for the first year. If the clinical condition and lung function remains stable, the frequency of spirometry can be reduced to every six months. DLCO may be performed every six months, if standardised testing is available. It is especially useful for the patients with CPFE.[150] As mentioned previously, the 6MWT distance and its longitudinal changes, and the degree of oxygen desaturation during exercise are useful for prognostication.[104] A follow-up computed tomography is not routinely required. It may be performed in case of a rapid acute decline of lung function, a suspicion of respiratory tract infection or other complications, such as pneumothorax or pulmonary embolism.

Recommendations

We suggest that patients with IPF on treatment with anti-fibrotics be followed up with liver function tests as advised. (UPP)

We recommend that spirometry be performed every three months initially and then six monthly in case of clinical and physiologic stability. (1A)

We suggest that DLCO be performed every six months, if standardised testing is available, especially in those with CPFE. (1B)

We suggest that 6MWT be performed every six months to assess longitudinal changes in the exercise capacity. (2B)

Adjunctive Therapies

Q 17. What is the role of acid suppressive drugs in the treatment of IPF?

Gastroesophageal reflux (GER) is commonly encountered in patients with IPF ranging from 0 to 94 percent across different studies.[19,20,151] The studies in which invasive pH monitoring and/or oesophageal manometry have been employed found higher prevalence of abnormal GER as compared to controls having other respiratory diseases or those derived from the general population.[152] GER in patients with IPF may not manifest with the typical oesophageal symptoms of heartburn and regurgitation.[19] Chronic cough, hoarseness of voice, throat pain, sore throat and dysphagia are the non-esophageal symptoms of GER. Due to the frequent occurrence of GER in patients with IPF, GER and the resultant micro-aspiration have been proposed to have a role in the pathogenesis of the disease.[152] Both the acid and non-acid refluxate (bile acids and pepsin) may be responsible for injury to the lung epithelium and subsequent fibrosis.[153,154] Further, micro-aspiration may be a risk factor for acute exacerbations of IPF in some patients.[155]

Gastroesophageal reflux has been mainly treated with acid suppressive therapies, such as H2 receptor antagonists and (more commonly with) proton pump inhibitors (PPIs). Whether acid suppression results in better outcomes in IPF has been addressed in three large retrospective studies of cohorts of IPF patients enrolled in randomised controlled trials of other agents. In one study, among patients assigned to the placebo arm, those taking anti-acid treatment at start of the study had a smaller reduction in FVC at week 30 as compared to those not consuming anti-acid drugs (60 mL *versus* 120 mL, p=0.05).[156] In a pooled post-hoc analysis of placebo groups of CAPACITY and ASCEND trials, antacid therapy was not found to improve outcomes and was potentially associated with a higher risk of infection in those with advanced IPF.[157] Among subjects in the treatment group, the

outcomes of patients who received pirfenidone with antacid therapy were comparable to those administered pirfenidone alone.[158]

Besides acid suppression, PPIs have been proposed to suppress pulmonary inflammation and fibrosis, which warrants further investigation.[159] However, treatment with PPIs is not without the risk of adverse effects and may be associated with pneumonia, *Clostridium difficile* infection, cardiovascular events, hip fractures, dementia and electrolyte abnormalities.[152] Several lifestyle modifications have been suggested to improve GER. Among them, only weight loss, elevation of the head-end of the bed, and to some extent, a left lateral decubitus position are effective.[160] As non-acid reflux is also potentially important in the pathobiology of IPF, surgical methods such as Nissen fundoplication are under active investigation. A small study of laparoscopic anti-reflux surgery in IPF did not demonstrate any significant lessening in lung function decline at one year.[161]

Recommendations

No definite recommendation can be made about the efficacy and safety of PPIs as a blanket treatment for all patients.

We recommend that both oesophageal and non-oesophageal symptoms of GER be actively sought for in patients with IPF. (3A)

We recommend that lifestyle measures and acid suppressive therapies including PPIs be used to manage symptomatic GER. (2A)

Q 18. How to manage cough and dyspnea?

Cough predicts disease progression in patients with IPF independent of the disease severity, and may also predict time to death or lung transplantation.[162] Moreover, chronic cough may be distressing and incapacitating, having a major bearing on the quality of life, and requires effective treatment.[163] Cough in IPF is likely multi-factorial contributed by mechanical, biochemical and neurosensory factors.[163] It is also influenced by co-morbid conditions, such as gastroesophageal reflux, obstructive sleep apnoea, emphysema, chronic sinusitis, upper respiratory infection, upper airway cough syndrome or certain drugs, such as angiotensin converting enzyme (ACE) inhibitors. Whether treatment of the underlying co-morbidity improves cough is uncertain. In a small study, acid suppression in patients with IPF having gastroesophageal reflux disease (GERD) did not reduce the cough frequency.[164]

The treatments for cough include drugs that suppress the central cough reflex (dextromethorphan, gabapentin, amitriptyline, and opioids), those that suppress sensory neurons (lidocaine, benzonatate), and drugs acting on airways to reduce inflammation, smooth muscle contraction, and mucus secretion (beta-agonists, leukotriene antagonists, macrolide antibiotics).[165] Apart from these, thalidomide has been found to improve cough and also leads to better respiratory quality of life in patients having IPF.[166,167] It is, however, associated with a high incidence (74%) of adverse effects including constipation, dizziness, and malaise.[166] In a small study[168], interferon alpha reduced cough in some patients. The role of corticosteroids in suppressing cough in IPF is equivocal and at present these cannot be recommended for this indication due to the potential for adverse effects.[169,170] In a recent phase 2 study, a novel formulation of inhaled sodium cromoglicate (PA101) has been found to reduce daytime cough frequency and warrants further investigation.[171] Pirfenidone has also been found to reduce cough apart from delaying the progression of the disease.[172]

Dyspnoea is the predominant symptom that impairs the QoL in patients with IPF, especially those with advanced disease. There is no proven treatment that may help reduce the dyspnoea in patients with IPF. Opioids such as oral morphine or subcutaneous diamorphine might be useful.[173-175] Opioid dose should be carefully titrated to avoid sedation and respiratory depression. Sildenafil may also reduce the degree of dyspnoea, however, its use needs further validation as there is a concern for worsening of the ventilation-perfusion matching with its use.[136] The role of oxygen in reducing exertional dyspnoea in patients who do not have resting hypoxaemia is controversial and needs further investigation.[176,177] Pulmonary rehabilitation (PR) has been found to diminish dyspnoea in some studies (*see Q 19*).

Recommendations

We recommend that co-morbidities be looked for, diagnosed and treated in patients with IPF having significant cough. (UPP)

We suggest that cough suppressants (opioid or non-opioid) may be used for managing cough in IPF; careful balancing of efficacy with tolerance is required. (3B) Thalidomide may be considered for refractory cases. (3B)

We suggest that opioids may be used for reducing dyspnoea with a careful titration of the dose. (3B)

Q 19. Should patients with idiopathic pulmonary fibrosis receive pulmonary rehabilitation?

Pulmonary rehabilitation has a proven role in several chronic respiratory disorders, such as chronic obstructive pulmonary disease (COPD). Its role in IPF is under investigation. The components of PR include exercise training (combining endurance and resistance training), an educational programme-specific to the disease, and special sessions of breathing retraining.[178] A more comprehensive

programme should also include nutritional interventions, address psychiatric co-morbidities and include end-of-life communication.

As compared to COPD, PR in IPF produces only modest short-term gains in dyspnoea, exercise capacity and activities of daily living, but may not improve health status.[179] In a randomised trial in patients with IPF, PR led to improvement in exercise capacity and health-related quality of life.[180] However, there were no significant effects on pulmonary function, oxygenation or dyspnoea. In other studies, improvements have been observed in 6MWT distance, physical activity levels, functional capacity, quality of life, fatigue severity scores, as well as pulmonary function and symptoms including dyspnoea.[181-185] Home-based rehabilitation is also effective in improving 6MWT distance, quality of life, and dyspnoea.[186,187]

The benefit of PR may be variable depending on the severity of the disease. In a study[188], significant improvements in 6MWT distance and health status occurred following PR only in patients with Medical Research Council (MRC) dyspnoea grade 2 or 3; patients with grade 4 or 5 on MRC dyspnoea scale showed little improvement or even deteriorated following PR. Hospitalisations were reduced following PR only in patients with MRC dyspnoea grade 2, 3 or 4.

Recommendations

We suggest that patients with IPF who have up to MRC grade 4 dyspnoea may be offered pulmonary rehabilitation aimed at aerobic conditioning, flexibility training, strength training, dietary interventions and psychological support. (2B)

We suggest that patients with IPF be encouraged to increase their daily physical activity to their best tolerated levels in order to improve/preserve their exercise capacity. (UPP)

Q 20. What immunisation should be advised to patients with IPF?

No study has evaluated the efficacy of any vaccine in patients with IPF. Whether patients with IPF are more susceptible to pneumococcal pneumonia is not known; however, if patients with a compromised lung function do develop pneumonia, the consequences could be catastrophic. The 13-valent polysaccharide conjugate vaccine (PCV13) and the 23-valent polysaccharide vaccine (PPV23) were found effective in preventing vaccine-type pneumococcal community-acquired pneumonia and invasive pneumococcal disease among adults 65 years of age or older.[189,190] One meta-analysis[191] found that adults with chronic illness (in general) did not derive benefit from pneumococcal vaccine. However, this study included any type of pneumococcal vaccine (not specifically PCV13 or PPSV23) and any type of chronic illness (not specifically lung disease). Also, the cost-effectiveness of either vaccine in patients with IPF is unknown.[192,193] However, due to the safety of these vaccines, their ease of administration and potential to prevent life-threatening illness, their benefits seem to outweigh the risks and costs. Further, pneumococcal vaccine is also recommended for patients with other chronic lung diseases, such as COPD.[16]

The PCV13 vaccine requires to be administered only once and should be given first followed by the PPV23 after 6-12 months.[194,195] If the first dose of PPV23 has been administered before the age of 65 years, a second dose should be administered after five years.[196] If a patient has already received PPV23 before the PCV13 vaccine, the PCV13 can be administered one year later.

Influenza vaccine is known to decrease exacerbations and the risk of respiratory failure in patients with COPD.[197,198] In a study in patients with chronic lung disease (including ILDs), influenza vaccination led to fewer hospitalisations and deaths.[199] The effects of influenza have not been separately studied in patients with IPF; however, respiratory viruses are known to trigger exacerbations in patients with IPF.[200] The effectiveness of influenza vaccine in patients with IPF is unknown. However, in view of the significant prevalence of influenza and the potential to prevent exacerbations in patients with IPF, influenza vaccination may be beneficial for patients with IPF.

There are two peak seasons for influenza in the tropics: the monsoon and the winter seasons.[201] Sub-regional variations may exist in the circulation of influenza viruses. As an example, in India, temperate areas north of the 30-degree latitude have a typical northern hemisphere seasonality while most of the country has a southern hemisphere seasonality.[202,203] The influenza vaccine should be administered every year in April-May and September-October for protection in the monsoon and winter seasons, respectively, according to regional seasonality.[201] The southern hemisphere vaccine is available during the former period and the northern hemisphere is available during the latter. Recently, the northern hemisphere became available as early as June.

Recommendation

We recommend that all patients with IPF be offered pneumococcal and annual influenza vaccines according to the recommended schedules. (3A)

Q 21. What is the role of supplemental oxygen therapy?

In two small studies[204,205], home oxygen therapy (about 16 hours/day) was found to attenuate cardiac dysfunction and lead to lower mean pulmonary artery pressure and pulmonary vascular resistance than no oxygen therapy. However, after adjusting for

age, gender and disease severity, oxygen therapy does not seem to affect survival.[140] Further, oxygen does not lead to any reduction in the exercise-induced increase of pulmonary artery pressure in patients with IPF.[206] The role of oxygen in reducing exertional dyspnoea in patients who do not have resting hypoxaemia is controversial and needs further investigation.[176,177] There is some evidence that exercise capacity may improve with the use of ambulatory oxygen.[177,207,208]

Patients with IPF who are hypoxaemic at rest usually progress rapidly. Although, oxygen may be useful in IPF to alleviate dyspnoea and hypoxia in patients with resting hypoxaemia; unlike COPD, it may not prolong survival significantly. Ambulatory oxygen in patients without resting hypoxaemia may have a role in increasing exercise capacity, but requires to be studied further.

Recommendations

We recommend that home oxygen therapy be prescribed to patients with resting hypoxaemia for palliation. (3A)

No recommendation can be made on the use of ambulatory oxygen in patients without resting hypoxia. However, ambulatory oxygen may be considered if it improves adherence to a rehabilitation programme. (UPP)

Q 22. How should pulmonary hypertension (PH) associated with IPF be diagnosed and treated?

Pulmonary hypertension is defined as an increase in the mean pulmonary arterial pressure (mPAP) of ≥25 mmHg at rest (severe PH if mPAP >35 mmHg) and a low pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg as measured during right heart catheterisation (RHC).[209] The prevalence of PH in patients with IPF varies from 32%-86% depending upon the timing of measurement during the disease course and the methods used for diagnosis, with a serial increase observed as the disease progresses.[98,210-213] However, significant PH may be detected even in those patients who have relatively preserved lung function.[214] There is a significant association between disease duration, declining FVC and hypoxaemia with the development of PH.[210] Patients with IPF who have PH have a higher risk of acute exacerbation and higher 1-year mortality than those who do not (28% *versus* 5%, p=0.002).[98,215,216]

Right heart catheterisation is the gold standard for the diagnosis of PH. However, it is an invasive test; moreover, detection of PH does not usually lead to any significant change in the management of the patient. It should be performed only in the following situations: (a) evaluation for lung transplantation; (b) accurate prognostic assessment for the use of off-label treatment if severe PH is found on echocardiography; and, (c) selected cases with suspected right heart dysfunction or diastolic dysfunction.[217]

Echocardiography has been used for the detection of PH in patients with IPF. The right ventricular systolic pressure estimated on echocardiography is not accurate for the detection of PH in IPF.[99] The mean difference between right ventricular systolic pressure on echocardiography and pulmonary artery systolic pressure (PASP) assessed by RHC is 8 mmHg.[218] If the PASP is >40 mmHg, PH may be suspected, but would need confirmation.[219,220] Mild, moderate and severe PH is defined at PASP cut-offs of 40, 50 and 60 mmHg, respectively. The advantage of echocardiography is that it is non-invasive and repeatable.

A finding of increased size of the main pulmonary artery that equals or exceeds the size of the aorta on a CT chest is suggestive of PH but is not accurate, however it may predict poor outcomes.[221,222]

The drugs used to treat primary PH and other forms of PH including phosphodiesterase inhibitors (sildenafil), endothelin receptor antagonists (bosentan, ambrisentan, and macitentan) and guanylate cyclase stimulator (riociguat) have been studied in patients with IPF (or ILDs). No significant clinical improvement has been observed with any of the agents (with harm noted with ambrisentan).[134,136,148,223,224] Some improvements in the secondary outcomes, such as arterial oxygenation, diffusion lung capacity, degree of dyspnoea, and quality of life were observed with sildenafil in the Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis (STEP-IPF) trial; however, participants in this study were included irrespective of presence of PH and a subgroup analysis was not presented.

Recommendations

We suggest that echocardiography may be used as a mode of detection of PH in patients with advanced IPF or those in whom exercise limitation is not fully explained by the degree of restriction. (3B)

We suggest that RHC be performed only in selected cases. (3B)

We recommend that PH in association with IPF not be treated with anti-PH drugs. (1A) If there is severe PH on echocardiography in the abscence of advanced parenchymal disease, it should be confirmed with RHC and the patient should be evaluated for an independent cause of PH at specialised centres. (UPP)

Q 23. What are the diagnostic criteria for an acute exacerbation of IPF? How should an acute exacerbation be treated?

Acute exacerbation of IPF (AE-IPF) has been defined as an acute, clinically substantial respiratory deterioration associated with new widespread alveolar abnormality.[9,225,226] The annual incidence of acute exacerbation in patients with IPF varies from 1% to 20% (pooled incidence 4.1 per 100 patient-

years).[227,228] The criteria proposed by the IPF Clinical Trials Network (IPFnet) for AE-IPF and later modified by an International Working Group[226] include: (i) diagnosis of IPF (previous or concurrent); (ii) clinical worsening (or increasing dyspnea) of less than one month's duration; (iii) the presence of new radiologic abnormalities on HRCT of the chest (ground-glass opacities in both lung fields with/without-consolidation, on a background of UIP pattern); and (iv) the condition not fully explained by heart failure or fluid overload. Besides, any obvious extra-parenchymal cause, such as pneumothorax, pleural effusion and pulmonary embolism also need to be excluded.[226,229] If an HRCT is not available, and the remaining criteria are fulfilled, the event may be termed as a 'suspected acute exacerbation'.

Acute exacerbation of IPF occurs predominantly in advanced disease and has a median survival of three months. The severity of IPF is an important risk factor for acute exacerbation. Potential triggers include respiratory infections, aspiration, drug toxicity, air pollution, BAL, lung biopsy, and pulmonary or non-pulmonary surgical procedures.[61,75,200,230-234] BAL, when performed during an AE shows neutrophilia and elevation of albumin concentrations.[17,235] Histopathological examination of lung biopsy specimen shows diffuse alveolar damage pattern (which may show some organisation) or organising pneumonia on a background of UIP.[17,235] The mortality is high (40%-96%) despite use of lung-protective ventilation and use of high dose glucocorticoids.[17,236,237] Even those who survive the illness beyond three months remain restricted in their activities.[237]

Infection has a complex relationship with acute exacerbation. While AE-IPF needs to be differentiated from an overt lower respiratory tract infection, it may also be triggered by an occult respiratory infection (for instance, a viral illness). AE-IPF may be associated with increased bacterial burden in BAL fluid even if conventional bacterial cultures are negative.[238] Although differentiating a triggered exacerbation from an idiopathic exacerbation is not required, identifying a specific infectious agent may have a bearing on the management.

The diagnosis of AE-IPF, thus mainly relies on clinical criteria and HRCT features. In most cases, a CT-pulmonary angiography (CTPA) along with an HRCT should be obtained if the patient condition permits. CTPA is performed to identify a pulmonary embolism especially in those with no increase in pulmonary parenchymal opacities. BAL is not routinely required. However, if a specific infection seems likely, for example, if a patient has a lobar consolidation (suggesting a bacterial pneumonia), centrilobular nodules or a cavity (suggesting tuberculosis) and other such manifestations, a BAL should be performed, in case sputum examination does not yield a diagnosis. Performing a lung biopsy (conventional, TBLB, cryoprobe TBLB or SLB) may be associated with a high morbidity and mortality and should not be attempted.[239]

The treatment of AE-IPF is controversial. The existing guidelines and statements do not provide clear recommendations due to the lack of randomised controlled trials.[9,11,226] The use of several agents to treat AE-IPF has been reported in observational studies with variable success and includes glucocorticoids, cyclophosphamide, cyclosporine, rituximab, plasma exchange, polymyxin-B immobilised fiber column hemoperfusion, intravenous immuno-globulin, tacrolimus, and thrombomodulin.[236,240-253] While managing patients with AE-IPF, supportive care with oxygen supplementation, management of co-morbid illnesses, stress ulcer prophylaxis and thromboprophylaxis should be instituted. If there are clinical features pointing towards an infective cause (high grade fever, high procalcitonin, positive cultures, lobar consolidation), it should be treated. A broad-spectrum antibiotic, such as amoxicillin-clavulanate, along with azithromycin should be administered.[254] If the features are favouring more of an inflammatory illness (low grade fever, normal procalcitonin, negative cultures), glucocorticoids may be administered with or without antibiotics. Either high dose oral prednisolone (1-1.5 mg/kg) or three pulse doses of intravenous methylprednisolone (0.5-1 gram each) may be administered depending on the severity. No recommendation can be made on the use of other immunosuppressive agents, plasmapheresis, or others, such as polymyxin-B immobilised fiber column hemoperfusion. The patient should be managed in a specialised centre and the expert pulmonologist must use his/her own discretion in the use of these experimental treatments.

Recommendations

We recommend that the definition suggested by the International Working Group[226] be used to define AE-IPF. (UPP)

We recommend that a thorough clinical evaluation should be made to identify an underlying cause of exacerbation. (UPP)

We recommend that an HRCT of the chest be obtained if AE-IPF is suspected. (UPP) We suggest that a BAL be performed only if infection is strongly suspected. (UPP)

We recommend that a lung biopsy not be performed for the diagnosis of AE-IPF. (3A)

We suggest that antibiotics be used in the treatment of AE-IPF. (UPP)

We suggest that glucocorticoids be used in the treatment of AE-IPF if a clear infective cause of the exacerbation is absent. (3B)

Q 24. What is the role of invasive and non-invasive ventilation (NIV) in IPF?

The use of mechanical ventilation in IPF is associated with a prolonged hospital stay, increased costs and is associated with markedly increased mortality.[255] In studies of patients with IPF who were mechanically ventilated, the in-hospital mortality has been reported to be 85%-100%.[256-258] Non-invasive ventilation may be useful for compassionate use as it provides relief from dyspnoea and helps avoiding invasive ventilation.[257,258] Failure of NIV to maintain adequate ventilation is common.[259,260] However, if management on NIV is attempted, the associated mortality is lower (55%-74%).[257,261] Nasal high flow cannula may reduce breathing rate and minute volume and may emerge as a useful alternative to NIV.[260]

Recommendations

We recommend that the use of invasive mechanical ventilation be avoided in patients with advanced IPF. (3A)

We suggest that NIV be used for artificial respiratory support in patients with IPF who present with respiratory failure. (3B)

Q 25. When should the patient be considered for lung transplantation?

Lung transplantation is the only 'curative' treatment available for patients with IPF. It is the only effective treatment in advanced IPF. The five-year survival rate for lung transplantation in IPF in high-volume centers is 47%-53%, which is lower than that for other pre-transplant diagnoses.[262] Bilateral lung transplant may offer somewhat better survival than single lung transplantation; however, due to the shortage of organs, single lung transplantation remains a viable option.[263-265] The mortality of patients with IPF while on the waiting list for transplantation is higher compared to other diagnoses.[266]

Patients with IPF must be referred for transplantation if they satisfy any of the following criteria: DLCO <40% predicted, FVC <80% predicted, presence of any dyspnoea or limitation in functional capacity that is attributable to the lung disease, or a decrease in pulse oximetry saturation below 89% at rest or during exertion.[267] Most patients with IPF satisfy one or more of these criteria at the time of diagnosis. Criteria for placing patients on transplant list include: decline in FVC ≥10% during six months of follow-up, decline in DLCO ≥15% during six months of follow-up, on 6MWT: oxygen desaturation to <88% or distance walked <250 meters or >50 meter decline in distance walked over six months, or pulmonary hypertension on RHC or transthoracic echocar-diogram, or hospitalisation because of respiratory decline, pneumothorax, or acute exacerbation.[267]

Recommendations

We recommend that lung transplantation be offered to patients with IPF as a definitive form of therapy. (2A)

We recommend that standard criteria for referral and listing for transplant be followed. (UPP)

We recommend that bilateral lung transplantation be preferred over single lung transplantation in patients with IPF. (2A)

Future Directions

In the developing world, the knowledge on IPF remains poor; physicians still believe that ILD and IPF are synonymous.[12] In our experience, we frequently come across patients with IPF treated with immuno-suppressive agents and those with other ILDs being prescribed pirfenidone.[268] Therefore, it is imperative that awareness about IPF and ILDs in general is increased among general physicians and chest physicians (*see Box*). Making guideline-recommended HRCT facilities (performance and proper interpretation) available is another challenge in resource-limited settings. If met, it could go a long way in overcoming diagnostic hurdles. A safe surgical lung biopsy, especially VATS-guided, remains a pipe-dream in many parts of the world. In this circumstance, a biomarker that could be assessed in the blood, BAL or small TBLB specimens is required, which would be sensitive and specific enough to be introduced into clinical practice. Molecular techniques, such as genomics, proteomics or ribonucleic acid-based technologies could also lead the way to futuristic IPF diagnostics. A recent study found a sensitivity and specificity of 63% and 86%, respectively, in identifying a UIP pattern in exome enriched ribonucleic acid derived from TBLBs using machine learning algorithm.[269]

Box. Problem areas in resource-constrained settings that need to be addressed and improved.

- Awareness among physicians on interstitial lung diseases and their subtypes
- Good quality high resolution computed tomography (HRCT) scans of the chest
- Facilities for the accurate interpretation of HRCT scans by trained thoracic/pulmonary radiologists
- Facilities for the safe conduct of surgical lung biopsy (especially with video-assisted thoracoscopic surgery) and transbronchial lung cryobiopsy
- Facilities for the accurate interpretation of lung biopsies by specialised pulmonary pathologists
- Promoting the employment of multidisciplinary discussion teams, wherever required
- Adherence to recommended drugs for treatment in their appropriate dosing schedules
- Costs of anti-fibrotic drugs

On the therapeutic front, randomised studies are required to clarify the role of combination *versus* sequential/switch therapy with antifibrotic drugs. Several novel therapies including STX-100 and GSK 3008348 (alpha-V-beta-6 integrin antagonists), GLPG-1690 (selective autotaxin (ATX) inhibitor), BMS 986020 (anti-lysophosphatidic acid), FG-3019 and PBI-4050 (anti-connective tissue growth factor), TD139 (anti-Galectin 3), CC-90001 (C-Jun NH2-terminal kinase inhibitor), GSK2126458 (multiple targets), KD025 (ROCK-II inhibitor), tyrosine antagonists, immunomodulators (lebrikizumab and tralokinumab), mesenchymal stem cell therapies, and others are in various phases of clinical trials and might hold promise.[270] Future phase 3 trials would need to include either pirfenidone or nintedanib as standard-of-care treatment in the control and intervention arms.

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