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Advanced interstitial lung disease: Evidence-based management and clinical approach

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Abstract. *Background:* Interstitial lung disease (ILD) is a heterogeneous group of diseases characterized by clinical, physiologic, radiologic abnormalities and variable progression. Advanced ILD (sometimes referred to as end-stage interstitial lung disease) is characterized by ILD with severe physiologic and radiologic abnormalities leading to significant impact on a patient's quality of life and poor prognosis. Special considerations are required for the management of patients with these advanced ILDs, particularly those who will ultimately require lung transplantation. Though several society and expert panels provide guidance on ILD management, there are none focused specifically on the approach to patients with advanced ILD. *Objectives:* In this review, we attempt to define advanced ILD and identify the clinical considerations required for diagnosis and management of patients with advanced ILD. *Discussion:* Pathophysiologic mechanisms of ILD and complications are not completely understood but include inflammation, fibrosis, pulmonary hypertension, venous thromboembolism, recurrent infections, and aspiration. Prognostic scores such as the GAP score and GAP-ILD index predict survival in IPF patients, but prognostic scoring systems are less frequently validated in other subtypes of ILD. Management of these patients includes consideration of anti-fibrotic medications, anti-inflammatory/immunosuppressive medications and treatment of concurrent pulmonary hypertension as indicated on a case-by-case basis. Non-pharmacologic management with supplemental oxygen, pulmonary rehabilitation, and palliative care are tailored to each patient's clinical status. Finally, early referral to lung transplantation is critical, as advanced ILD can be fatal, and sometimes rapidly so. *Conclusion:* Advanced ILD is an oftentimes fatal group of heterogeneous diseases that have varying managements depending on underlying subtype. Identification of progressive disease and complications are the first steps to management of these patients to optimize lung function and quality of life and improve outcomes before lung transplantation.

Key words: interstitial lung diseases, pulmonary fibrosis, advanced lung disease, disease management, evidence-based practice

Introduction

Interstitial lung disease (ILD) is a group of heterogeneous diseases characterized by reduced pulmonary function, exercise capacity, and distinct chest computed tomography (CT) imaging findings (1, 2). It is the leading diagnosis associated with lung transplantation across the globe (2). This group of diseases, being heterogenous, has variable course and progression. Several theories of epigenetic regulation and dysregulation mechanisms exist that contribute to the development of pulmonary fibrosis (4). These include promotors or inhibitors in DNA methylation function, histone modification, alteration to non-coding RNA, and short telomere gene alterations (4). Of these diagnoses, idiopathic pulmonary fibrosis (IPF) is associated with the worst outcomes (5)

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and is the most common subtype of ILD in patients undergoing lung transplantation (3). The subtypes of ILD most likely to have a progressive, fibrosing phenotype besides IPF include idiopathic nonspecific interstitial pneumonia (iNSIP), interstitial pneumonia with autoimmune features (IPAF), hypersensitivity pneumonitis (HP), advanced pulmonary sarcoidosis (APS) (6), rheumatoid arthritis-related ILD (RA-ILD), systemic sclerosis-related (SSc) ILD, pleuroparenchymal fibroelastosis, ILD related to occupational exposures, and unclassifiable ILD (7) (Figure 1). Progressive pulmonary fibrosis (PPF) (in these non-IPF ILDs) is defined by the presence of two of the following three criteria within the last year: worsening of respiratory symptoms, physiologic evidence of disease progression (absolute decline in forced vital capacity (FVC) of at least 5% or absolute decline in DLCO of at least 10% within one year), or radiologic evidence of disease progression (increased traction bronchiectasis or bronchiolectasis, new ground glass opacities with traction bronchiectasis, new reticulation, increased extent of reticulation, new or worsening honeycombing, and increase lobar volume loss) (8).

Defining advanced ILD

The presentation of ILD can be advanced at the time of diagnosis or at follow-up after being stable over time or slowly progressive but sometimes progression is accelerated. Acute exacerbations of slowly progressive ILD can lead to a precipitous decline in lung function and can acutely worsen the underlying process (9). Currently, there is no clear and widely accepted definition of advanced ILD. Moreover, the term "end-stage" ILD is often used interchangeably with advanced ILD, and the distinction between the two terms is nebulous. We prefer the term "advanced ILD" to more accurately describe the characteristics of the disease state. We suggest that advanced ILD is that in which severe physiologic (on PFT) and radiologic abnormalities (on HRCT) (Figure 2) significantly affect quality of life (QoL) of the patient with an overall poor prognosis that might ultimately lead to death. These patients have lung destruction along with limitation in oxygenation and ventilation manifested by dyspnea affecting activities of daily living, severely limited lung function (restrictive ventilatory defect with reduced diffusion capacity), hypoxemia at rest or with exertion, and significant fibrosis on HRCT. HRCT usually shows fibrosis exceeding 10% of the lung volume which can be progressive. Evidence of worsening interstitial abnormalities, reticulation, and bronchiectasis can be present (9) (Figure 3).

Advanced ILD can be difficult to identify, predict, and manage. Advanced ILD is associated with significant debility, recurrent hospitalizations, and death. Many of these patients die while awaiting transplantation. Close, coordinated care with a multidisciplinary team is essential for improved outcomes in this population. Therefore, we propose an approach for pre-transplantation management of this subgroup of patients with advanced disease. The goal of this review is to utilize existing evidence to suggest an approach that can be used by the clinician to diagnose, prognosticate, and manage these patients in the pre-transplantation period (Figure 4). We attempt to define advanced ILD, identify clinical practice considerations (e.g. application of prognostication tools, monitoring for disease progression and/or acute exacerbations) and suggest management considerations.

We performed a limited literature review to evaluate the data specific to advanced ILD patients. While expert panels and society guidelines have attempted to define clinical, radiologic, and pathologic features of each disease (10-12), there is a paucity of data to unify the approach to advanced ILD. Pubmed/MEDLINE databases were queried for English language, full-text articles of clinical trials, meta-analyses, reviews, systematic reviews, and randomized controlled trials between January 1, 2018, and September 12, 2023 (Figure 5). We excluded case reports and small case series (fewer than 10 patients). Search terms included "end-stage interstitial lung disease," "advanced interstitial lung disease," and "advanced lung disease." A total of 145 articles were retrieved and screened and 36 were reviewed. We supplemented these references with relevant background articles from references of selected articles and from the authors' knowledge base.

Outcomes in ILD

There is a high burden on the ILD patient given the impact of disease on their quality of life along with the associated morbidities, especially when the disease is advanced. Survival varies depending on the ILD subtype with the highest mortality associated

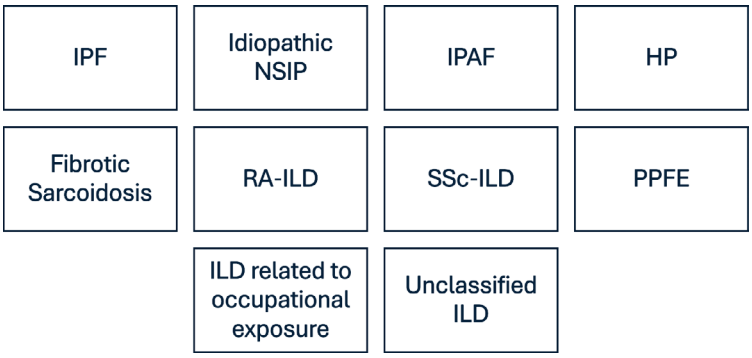

Figure 1. Subtypes of progressive ILD

Abbreviations: HP- Hypersensitivity pneumonitis; IPAF- idiopathic pneumonia with autoimmune features; IPF- idiopathic pulmonary fibrosis; ILD- interstitial lung disease NSIP- nonspecific interstitial pneumonia; PPFE- pleuropulmonary fibroelastosis RA-ILD- rheumatoid arthritis associated ILD. SSc-ILD- scleroderma-associated ILD.

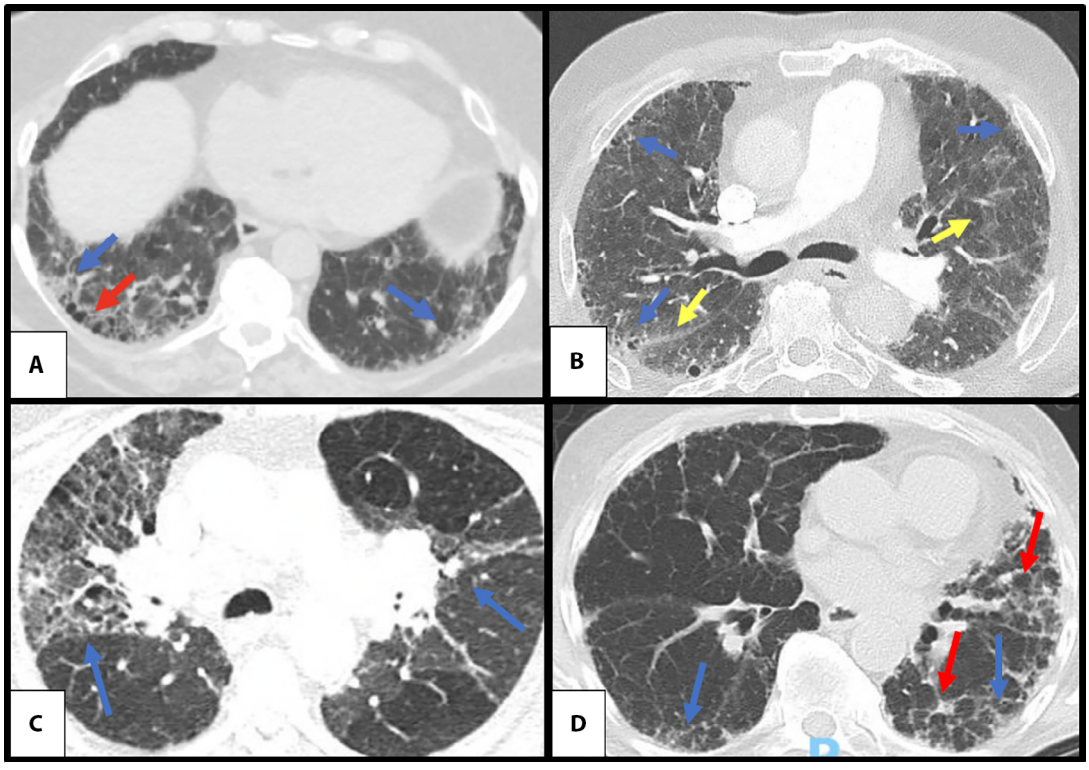

Figure 2. Examples of advanced ILD on HRCT

(A) Axial images of CT chest in a 69-year-old woman with dyspnea on exertion demonstrating peripheral reticulation (blue arrows), and bronchiolectasis (red arrows) in a patient with fibrotic HP. (B) Axial CT chest demonstrating peripheral reticulation (blue arrows) with ground glass opacities (yellow arrows) in an 80-year-old man with an acute exacerbation of underlying IPF. (C) Axial CT chest demonstrating scattered areas of architectural distortion/fibrosis (blue arrows) involving the bilateral upper lobes and lung parenchymal mosaicism in a 57-year-old woman with pulmonary sarcoidosis. (D) Axial CT of the chest demonstrating reticulation (blue arrows) and architectural distortion/fibrosis (red arrows) in a patient with CTD-ILD (Sjogren's) who had rapid clinical progression.

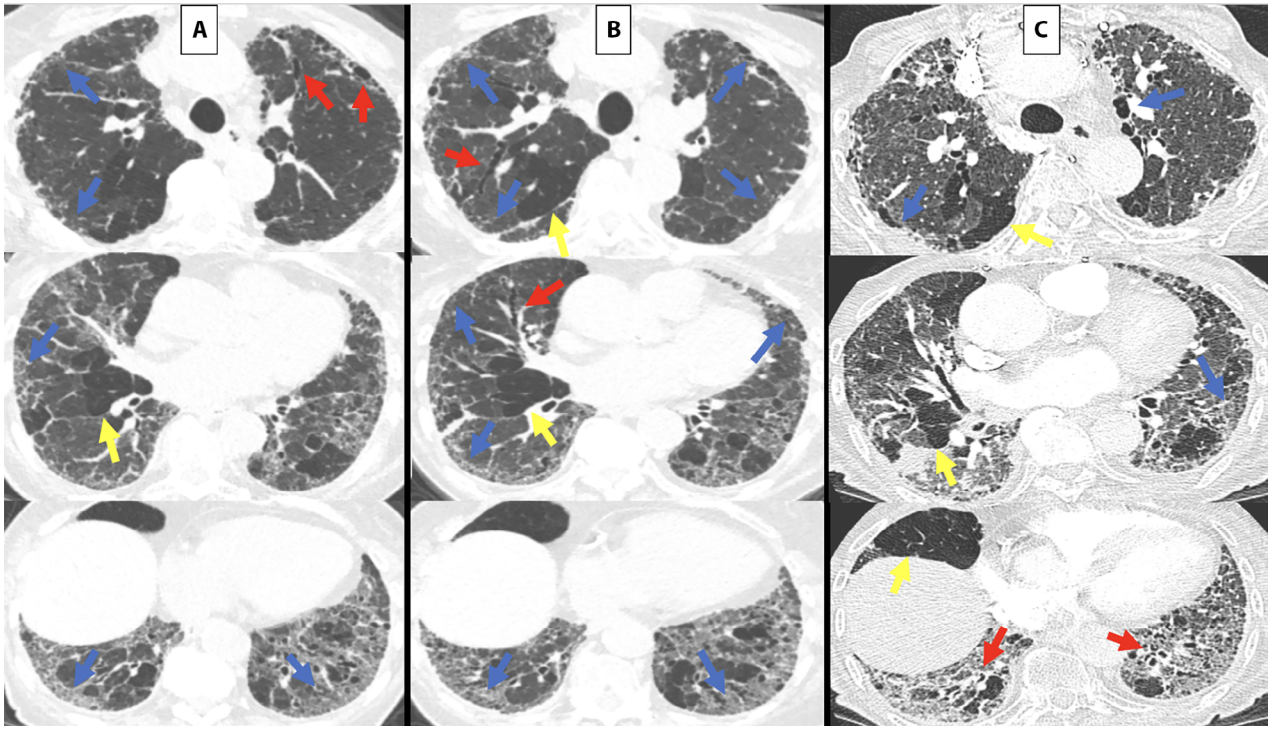

Figure 3. Progression of ILD over time

Axial CT chest without contrast in an 87-year-old woman with chronic cough and ILD demonstrating upper lobe bronchiectasis and bronchiolectasis (red arrows), peripheral reticulation (blue arrows), and mosaic attenuation (yellow arrows) three years (A) and two years (B) prior to presentation. Images at presentation (C) demonstrate progression of fibrotic changes.

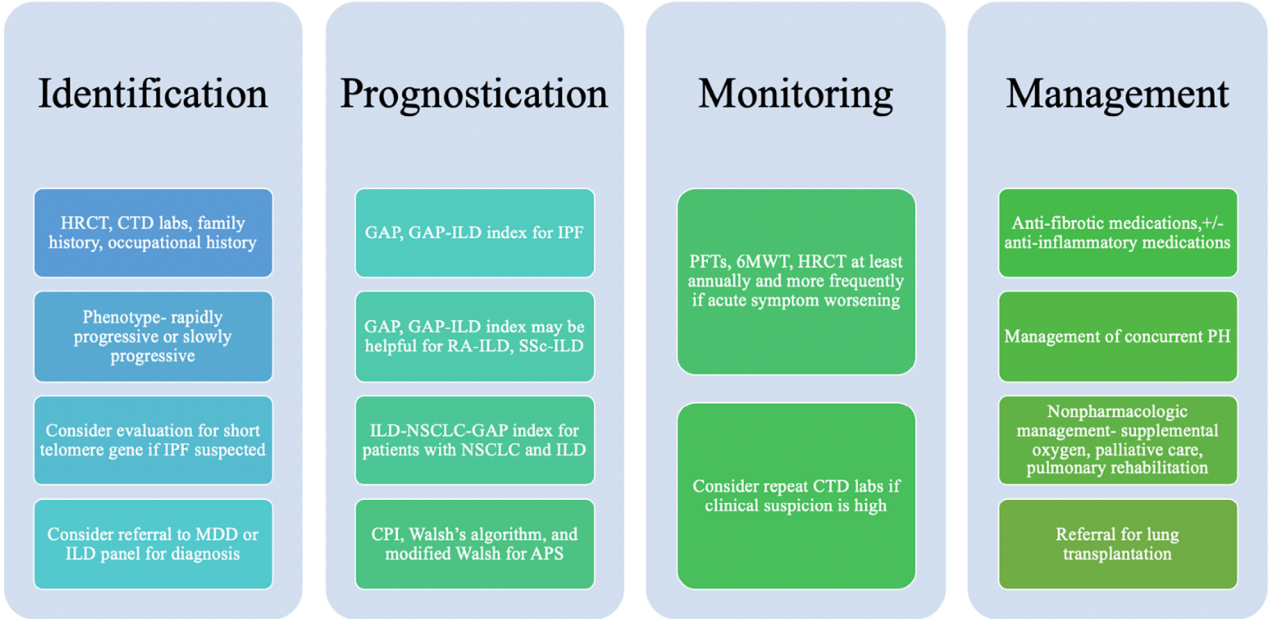

Figure 4. Approach to advanced ILD

Proposed approach to the management of advanced ILD patients consisting of identification of patients with advanced ILD, prognostication using validated indices, monitoring disease progression or evaluating for acute exacerbations, and management considerations. *Abbreviations:* HRCT- high resolution CT CTD- connective tissue disease; IPF- idiopathic pulmonary fibrosis; GAP- gender-age-physiology; ILD- interstitial lung disease; MDD- multidisciplinary discussion; NSCLC- non-small cell lung cancer; APS- advanced pulmonary sarcoidosis; PFT- pulmonary function test; 6MWT- 6-minute walk test; PH- pulmonary hypertension

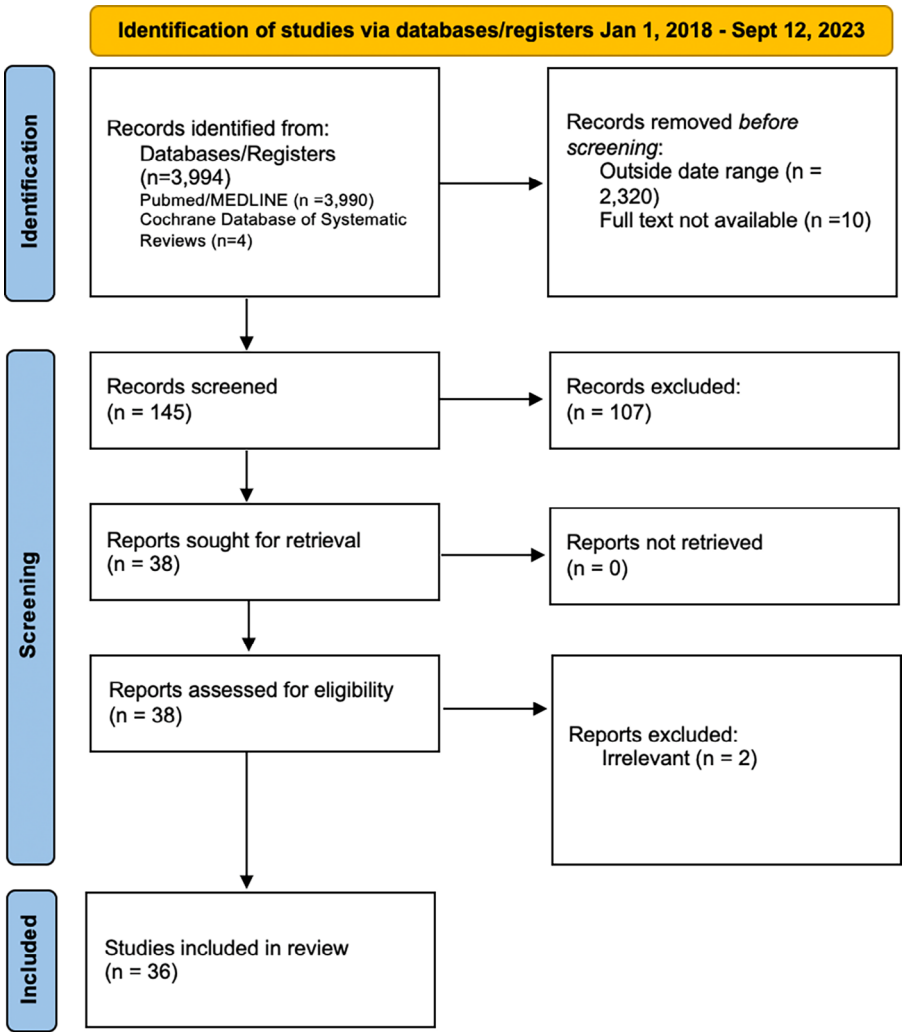

Figure 5. Methodology for Literature Review

with IPF (5). The heterogeneous nature of ILD and multisystem involvement makes it hard to predict outcomes in this patient population. IPF has a mean survival of three to five years if untreated, and is one of the most frequently occurring ILDs (13, 5). Patients with IPF have characteristically progressive but variable clinical course, and rapidly progressive IPF is associated with worse outcomes compared to the classic clinical phenotype of slowly progressive IPF (5). Predictors of clinical outcomes that confer worse prognosis include age, sex, ethnicity, smoking status, presence of dyspnea, fine inspiratory crackles on chest auscultation, and co-morbidities such as pulmonary hypertension (5). Additionally, HRCT imaging consistent with definite or probable UIP pattern confers a worse prognosis in IPF compared with indeterminate CT pattern (hazard ratio 2.42, mean survival 2.08 vs 5.76 years) and compared with definite or probable NSIP (HR 3.47, mean survival 2.08 vs 5.81 years) (14,5). Advanced pulmonary sarcoidosis (APS) occurs in 10-20% of patients with sarcoidosis and is characterized by significant risk of loss of lung function, respiratory failure, and death. Pulmonary fibrosis occurs in 10-20% of patients with pulmonary sarcoidosis, and may lead to complications of bronchiectasis, lung infections, and pulmonary hypertension (15, 6). APS has a significantly higher mortality compared to non-advanced sarcoidosis (11-21% compared with 1-5%) (6), and 75% of sarcoidosis patients die from respiratory causes (16,17).

About 15% of patients with hypersensitivity pneumonitis (HP) develop fibrotic HP (fHP), and

in these patients, identification of inciting agent portends better outcomes compared with an unidentified cause of HP (12). Patients with pulmonary fibrosis had an increased risk of death (HR 2.43) compared with those who did not have fibrosis (12). Though the term CTD-ILD (also referred to as systemic autoimmune rheumatoid diseases- SARD-ILD) refers to ILD associated with several systemic autoimmune disorders, outcomes are generally favorable compared to IPF (18). In a retrospective cohort review of 362 patients, the mean survival in patients with interstitial pneumonias associated with collagen vascular disease was 131 months compared to 80.5 months in patients with idiopathic interstitial pneumonia (18). Mean survival is also associated with imaging pattern (with worse outcomes in UIP compared with NSIP pattern) (18).

Clinical assessment of progression and prognosis of ILD

Evaluation of ILD progression requires HRCT imaging, PFT, and 6MWT and comparison with earlier studies. Use of HRCT can identify changes in fibrosis, worsening of honeycombing or traction bronchiectasis, and can identify a rapidly progressive phenotype of disease (19). Serial 6MWT can be used as an objective maker for decline in exercise tolerance. Serial PFTs can evaluate for rapid progression of decline in DLCO or FVC. However, these physiologic and radiologic parameters must be placed in the clinical context of the patient's symptoms. Serum autoimmune markers may be useful in CTD-ILD patients. For instance, the presence of anti-RNPC-3 antibodies predicts a poor prognosis in patients with SSc-ILD (20). In general, studies evaluating outcomes in ILD often utilize 6MWT, FVC and/or DLCO as the outcome measures, particularly if the treatment goal of a study is to improve functional performance (19). Of the pulmonary function tests available, FVC, TLC, and DLCO have been most consistently associated with prognosis in IPF. The composite physiology index, which was developed in 2001 and incorporates DLCO, FEV1, and FVC, correlates better with CT disease than any individual pulmonary function test. Changes in FVC and DLCO are highly predictive of outcomes in IPF and provide better prognostic data than baseline PFT characteristics. Changes in FVC greater than 10% and DLCO greater than 15% have shown association with higher mortality risk (5). The extent of honeycombing and reticulation on HRCT has been used as predictor of mortality in patients with IPF (2). Other evaluation modalities have not been well validated. A systematic review of studies evaluating the utility of cardiopulmonary exercise testing (CPET) in prognosticating outcomes in ILD found insufficient evidence to confirm the value of CPET in facilitating real-world clinical decisions (21). The gender-age-physiology (GAP) score and the ILD-GAP index have demonstrated good performance in prognosticating outcomes in ILD (22). The GAP score is a model for predicting 1-, 2-, and 3-year mortality for IPF patients. While it was initially validated in a cohort of IPF patients, it has since been validated in a broader population of patients with varying ILD subtypes and performed well across all ILD subtypes. A staging system was also created to be used with the GAP score, which assigns scores based on gender, age, percent predicted FVC, and percent predicted DLCO. For a given score, patients with IPF and unclassifiable ILD had higher mortality compared to the other ILD subtypes (23). A modified GAP model (ILD-GAP index) was created by adding a disease subtype variable to the existing GAP index to predict survival across ILD subtypes. This was developed to provide disease-specific survival estimates using a single risk prediction model (23). The ILD-GAP index performed well for all ILD subtypes (IPF, fHP, CTD-ILD, idiopathic NSIP, and unclassified ILD) in a cohort of 1,012 patients (23). The performance was maintained at all stages of disease severity (23). Further studies have attempted to validate these scores in various patient populations (24, 25, 26, 27) (Table 1). This includes addition of pulmonary physiologic components to the model in the DO-ILD index (24) and validation in IPF patients (24), SSc-ILD (26), RA-ILD (27). Several modified versions of these scores have been validated for patients with lung cancer (28). Mixed outcomes exist in patients with myositis-associated ILD (25), with one study demonstrating poor outcome prediction in this population (29). Overall, The GAP score and GAP-ILD index can be reasonably applied to subtypes of ILD other than IPF, though there is some variability in performance. In pulmonary sarcoidosis, the Composite Physiologic Index (CPI), Walsh's algorithm, and modified Walsh score are validated predictors of mortality (30).

Table 1. Validation of ILD-GAP Index (or modified version) in ILD

Study	Patients	Model	Outcome	Outcome measures
Chandel 2023 (24)	562 IPF patients	Addition of 6MWD and exertional hypoxemia to ILD-GAP index (DO-ILD model)	Improved model discrimination	C-statistics: Original gap index 0.676 (95% CI 0.635-0.717) compared with 0.752 (95% CI 0.701 – 0.802)
Cao 2020 (25)	60 patients with idiopathic inflammatory myositis in acute ILD exacerbation	ILD-GAP index	ILD-GAP index could separate the patients into two groups (survivors and non-survivors)	OR 2.292, p 0.011
Mango 2018 (26)	Systemic-sclerosis related ILD	ILD-GAP index and imaging pattern	ILD-GAP score underestimated mortality Patients with a UIP pattern had a higher mortality compared with those with a NSIP pattern	ILD-Gap model standardized mortality ratios of observed vs predicted outcomes 1.50 (95% CI 5-2.14) UIP vs NSIP HR 2.27 (95% CI 1.03-4.97)
Nurmi 2017 (27)	RA-ILD	ILD-GAP index	ILD-GAP index accurately estimated 1-year, 2-year, and 3-year mortality	p = 0.028
Brusca 2019 (29)	Myositis-associated ILD	ILD-GAP index	ILD-GAP index was a poor predictor of mortality	N/A

Management considerations

Management of advanced ILD consists of pharmacologic treatments, non-pharmacologic management, and (early) referral to lung transplantation (Figure 6). The pathophysiologic spectrum of ILD encompasses inflammatory changes and fibrotic changes, and specific ILDs can have a significant overlap of these with varying contribution, making management more nuanced. For instance, patients with IPF or typical UIP imaging pattern may respond to antifibrotics, while those with inflammatory diseases such as CTD-ILD and sarcoidosis may respond to immunosuppressive or immune-modulator therapy (31). The role of concomitant therapy in ILDs continues to evolve.

Anti-fibrotic medications

As progressive fibrosis is one of the major mechanisms of decline in patients with advanced ILD, targeting fibrosis is a cornerstone of management, especially in IPF and PPF. Nintedanib is an oral intracellular tyrosine kinase inhibitor that targets receptors such as vascular endothelial growth factor receptor (VEGF), fibroblast growth factor receptor (FGFR), and platelet derived growth factor (PDGF) (32). In the Phase 2 TOMORROW trial, the Phase 3 INPULSIS-I and INPULSIS-II trials (for IPF), SENSCIS (for SSc-ILD), and INBUILD (for progressive-fibrosing ILD), nintedanib demonstrated efficacy by reducing the decline in FVC compared with placebo (33). Pirfenidone is an oral agent which affects fibroblast proliferation and fibrosis related-proteins and cytokines and has anti-inflammatory, antifibrotic, and antioxidant properties (33). In the Phase 3 ASCEND trial, the use of pirfenidone was associated with a 47.9% reduction in proportion of patients with a greater than 10% decline in FVC or death compared with placebo (34). The CAPACITY trials suggested there was no significant reduction in decline in FVC with the use of pirfenidone at 72 weeks, though FVC decline was reduced at weeks 24 and until week 48 (32). The phase 2 RELIEF trial for non-IPF progressive fibrosing ILD showed a significantly lower decline of FVC percent predicted in the group receiving pirfenidone as compared to placebo (32). The RELIEF trial was, however, prematurely discontinued due to futility driven by slow recruitment. As such, the results must

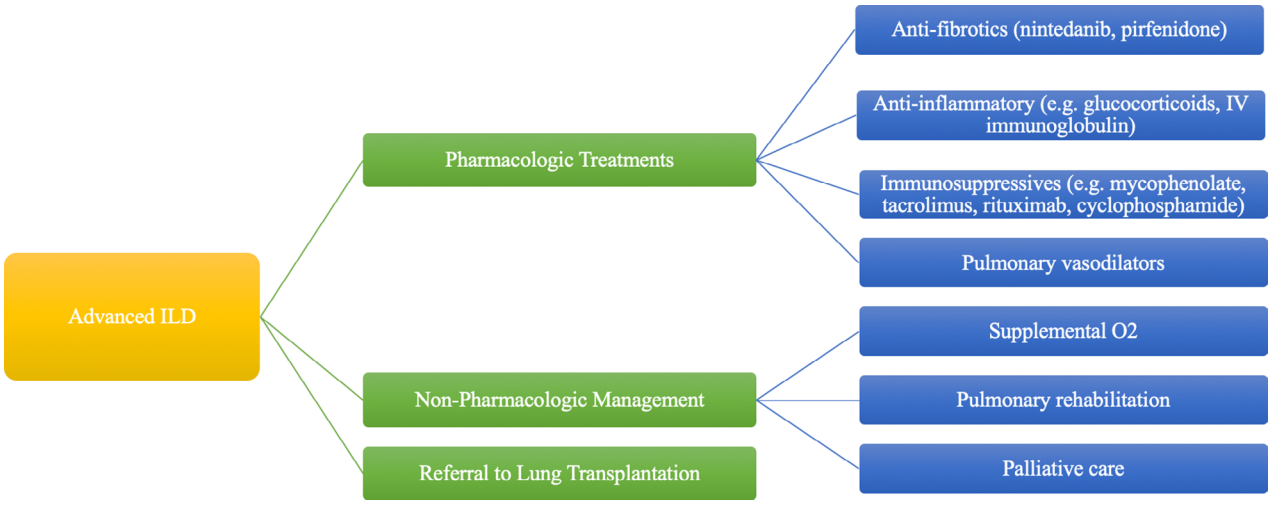

Figure 6. Management of advanced ILD
Management considerations of advanced ILD consists of pharmacologic treatments, non-pharmacologic management strategies, and early referral to lung transplantation.

be interpreted cautiously and may not reflect the true effect of the drug (33). A post hoc-exploratory analysis of pooled data from the ASCEND and CAPACITY studies suggested pirfenidone significantly reduced the incidence of multiple progression events and death after a progression event over 12 months of treatment when compared to placebo (35). The combination of nintedanib and pirfenidone was evaluated for safety in the Phase 4 INJOURNEY trial in patients with IPF, and the trial suggested no worsening of gastrointestinal symptoms with the combination compared with either alone (36). Though not powered for exploratory efficiency outcomes, INJOURNEY demonstrated an improvement in the mean absolute change from baseline in FVC in patients treated with nintedanib and add-on pirfenidone [-13.3 mL (-0.03%)] compared with patients treated with nintedanib alone [(-40.9 mL (-1.3%)] (36). Current evidence suggests continuation of these medications during the pre-transplant period, and there is no evidence that continued use is correlated with worsened outcomes. Each transplant center varies in their practice on continuation of anti-fibrotic medications in the pre-transplant period. In fact, ongoing trials are evaluating whether continued use of these medications provides positive clinical outcomes in lung transplant patients. Both medications are associated with gastrointestinal side effects of diarrhea, weight loss, and appetite loss which occur in most patients and can lead to medication discontinuation (32). In the ASCEND trial, 14.4% of patients receiving pirfenidone discontinued the medication by 52 weeks, though real-world observational studies suggest medication discontinuation in about 29% of patients over a median of 99.5 days (34). Other side effects include photosensitivity associated with pirfenidone use and increased bleeding risk associated with nintedanib (32). Medications are associated with a significant cost burden and can cost up to $10,000 every month (32).

Anti-inflammatory and immunosuppressive therapy

Anti-inflammatory/immunosuppressive medications are the mainstay of management for ILDs other than IPF that may have an inflammatory component. In general, patients with IPF do not benefit from anti-inflammatory medications, as suggested by the PANTHER trial (31, 37). In many subgroups of ILD, additional immunosuppressive therapies are required to slow progression of disease and improve overall patient outcomes. There are no guidelines that dictate when only anti-inflammatory alone or anti-inflammatory and anti-fibrotic should be initiated concurrently or sequentially with one earlier than the other. This decision is individualized for each patient

and on the clinical judgement of the clinician. The HRCT pattern, namely UIP pattern or the extent of fibrosis vs inflammatory component on imaging should be given significant weight when deciding concurrent initiation of anti-inflammatory and/or anti-fibrotic medications. In some instances of non-IPF ILD, if the presenting pattern is that of UIP then the risks of anti-inflammatory agents may outweigh the benefits. The choice of immunosuppressive medications depends on the patient and adverse effect profile of the medications. The role of immunosuppressive medication is most important in ILDs with an inflammatory component like CTD-ILD, HP, sarcoidosis, etc., and varies based on the underlying subtype of ILD. In HP, glucocorticoids are often the first line of treatment, and immunosuppressive medications have some evidence for use including mycophenolate and azathioprine (38). The American College of Rheumatology (ACR) recently summarized upcoming guideline recommendations for the treatment of SARD-ILD (39). Glucocorticoids are conditionally recommended as a first line therapy option for all SARD-ILD except for SSc-ILD, for which a strong recommendation against glucocorticoids as first line therapy is made (39). The ACR guidelines additionally recommend mycophenolate, azathioprine, and rituximab as first line treatment options for MCTD-ILD, RA-ILD, and Sjogrens-ILD. Calcineurin inhibitors (like tacrolimus) are added to the first line options for myositis-ILD. First line recommendations for SSc-ILD are mycophenolate, tocilizumab, and rituximab. In a multicenter randomized trial, rituximab and cyclophosphamide both showed efficacy and improvement of FVC at 24 months in patients with SSc-ILD, idiopathic inflammatory myopathy, and mixed connective tissue disease (40). Glucocorticoids are generally used in IPF exacerbations, although data is limited. In IPF patients with acute exacerbation, addition of cyclophosphamide pulses to glucocorticoids actually increased three-month mortality (41). In SSc-ILD, mycophenolate (42), cyclophosphamide (42), and tocilizumab (43) have data demonstrating they may preserve lung function and slow the decline in FVC. IV immunoglobulin may be used for its immunomodulatory and anti-inflammatory mechanisms (44). Glucocorticoids remain first line therapy for pulmonary sarcoidosis, but health-related quality of life is worse in patients treated with a cumulative prednisone dose of more than 500 mg per year, so decreasing the dose of prednisone to 10 mg/day and using steroid-sparing alternatives is recommended in the management of these patients (6). Methotrexate is a common second-line alternative to steroids in sarcoidosis (45) but there are many oral and injectable agents which can be used in clinical practice if needed, albeit with limited data. The European Respiratory Society (ERS) guideline for treatment of sarcoidosis recommends the addition of methotrexate to improve and/or preserve FVC and quality of life in patients with pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability who have persistent disease despite steroids or are intolerant to steroids (46). Infliximab is recommended for continued disease despite use of other immunosuppressive agents (45). Other potential anti-inflammatory options for sarcoidosis, some with ongoing trials for novel or repurposed use include, but are not limited to, CD-20 inhibitors (e.g. rituximab Clinicaltrial.gov NCT05596786), JAK-STAT inhibitors (e.g. tofacitinib NCT05246293), NRP inhibitors (e.g. Efzofitimod NCT05892614), GM-CSF inhibitor (e.g. Namilumab NCT05314517), chitotriosidase inhibitor (e.g. OATD-01 NCT06205121), newer TNF-inhibitor (e.g. XTMAB-16 NCT06169397), IL-1 inhibitors (e.g. anakinra), and CTLA-4 fusion proteins (e.g. abatacept NCT04925375) (6). The argument against rescue immunosuppressive therapy in advanced ILD stems from concern for worsened outcomes in the peri-transplantation period (discussed later), and multidisciplinary discussions including the surgical team and transplant infectious diseases team are crucial in determining the optimal management of these medications before lung transplantation. In general, these medications are not started when patients have reached the end-stage of ILD to avoid transplantation complications but can be used on a case-by-case basis to slow progression of specific ILDs.

Anti-acid medications

Concurrent acid reflux and GERD are a serious concern in patients with advanced ILD. Anti-acid medications can be considered in management of patients with chronic lung disease, as chronic microaspiration may contribute to lung disease, particularly ILD (13), and can also be associated with graft dysfunction after lung transplantation resulting in implications post-transplant as well. Data for the use

of antacids in IPF patients is mixed, and guidelines recommend against the use of antacids for treatment of IPF for the purpose of improving respiratory outcomes, though this was a conditional recommendation based on very low-quality evidence (8). The presence of symptoms is not a reliable indicator of the presence of acid-reflux and cannot reliably determine who should undergo esophageal testing during lung transplant evaluation. Many transplant centers include esophageal function testing as a part of the pre-transplant workup. A retrospective study of 226 patients undergoing lung transplant evaluation in 2015 (most commonly for ILD) found that 60% of asymptomatic patients had abnormal results on esophageal manometry or pH testing (47). These results led the authors to support high resolution esophageal manometry and 24-hour pH monitoring in all patients being evaluated for lung transplantation (47). Surgical therapy with fundoplication can control reflux and can be considered in patients awaiting lung transplantation to attempt to delay progression of IPF and reduce the risk of bronchiolitis obliterans syndrome (BOS) post-transplantation (48). Nonetheless, conflicting data in the literature exist for the contribution of GERD, acid-reflux, and microaspiration to disease burden. Lung transplant centers may evaluate patients with barium swallow study, gastric emptying study, esophageal motility studies, and/or EGD prior to transplantation based on center-specific protocols.

Management of pulmonary hypertension in patients with advanced ILD

Pulmonary hypertension related to ILDs is generally due to chronic hypoxemia and is placed under World Health Organization (WHO) group 3. However, advanced ILD can also present with concurrent PAH in patients with CTD-ILD, for instance, or WHO group 5 disease, such as patients with sarcoidosis and pulmonary Langerhans cell histiocytosis (49). Pulmonary hypertension (PH) that occurs in patients with advanced ILD can benefit from pulmonary vasodilators and/or calcium channel blockers if there is positive vasoreactivity testing (13). The diagnosis of pulmonary hypertension should be considered in any patient with underlying advanced lung disease and worsening symptoms, especially if clinical symptoms appear to be out of proportion to the PFT and CT (stability or only mild worsening of lung volumes or fibrosis respectively) (50). Estimates of PH prevalence in ILD vary. One study evaluated the mean pulmonary artery pressure in a cohort of patients with IPF and determined that 31.5% of patients met the criteria for PH, and the mean pulmonary artery pressure for the cohort was 23.4 mmHg (51). The prevalence of PH in advanced ILD is around 30-50% (52), and 60-90% in patients listed for lung transplantation (53). Right heart catheterization (RHC) is the gold standard for diagnosis, and evaluation for concurrent PH in these patients is crucial for both management and prognosis, especially when the underlying diagnosis confers increased risk of PH (in patients with CTD-ILD, for instance) (50). Patients with SSc who have PH have significantly lower survival function compared to patients without PH (54). Post-capillary PH noted on RHC is managed with standard therapy as in patients without advanced ILD. Identification of the subsets of ILD with PH is important to understand the underlying pathophysiology of disease (55). This includes CTD-ILD, IPAF-associated PH, and sarcoidosis-associated PH (SAPH). Some patients with PH-associated with CTD-ILD and sarcoidosis respond to pulmonary vasodilators if chosen carefully (46). In patients with well-defined pre-capillary PH and idiopathic interstitial pneumonia, the RISE-IIP trial was terminated early due to increased hospitalizations and death in patients treated with riociguat (56). Studies have demonstrated negative results in using bosentan and sildenafil in IPF patients with precapillary PH (56,-). Recently, inhaled medications have increasing appeal due to reduced systemic toxicity and ability to reach most ventilated areas of the lung, reducing potential VQ mismatch in patients with PH and lung disease. Inhaled treprostinil resulted in an improvement in 6MWT distance in PH-ILD patients in the INCREASE trial, and the medication has since received Food and Drug Administration (FDA) approval for that use (56). Finally, inhaled nitric oxide in PH-IPF patients has shown an improvement in moderate and vigorous physical activity levels at eight weeks compared with placebo (56). Nonetheless, patients with PH-ILD continue to have poor outcomes and should be referred to expert centers for consideration of pulmonary vasoactive therapy and lung transplantation. Use of pulmonary vasodilators in patients with advanced ILD without pulmonary hypertension has been explored. Initial studies investigating early pulmonary

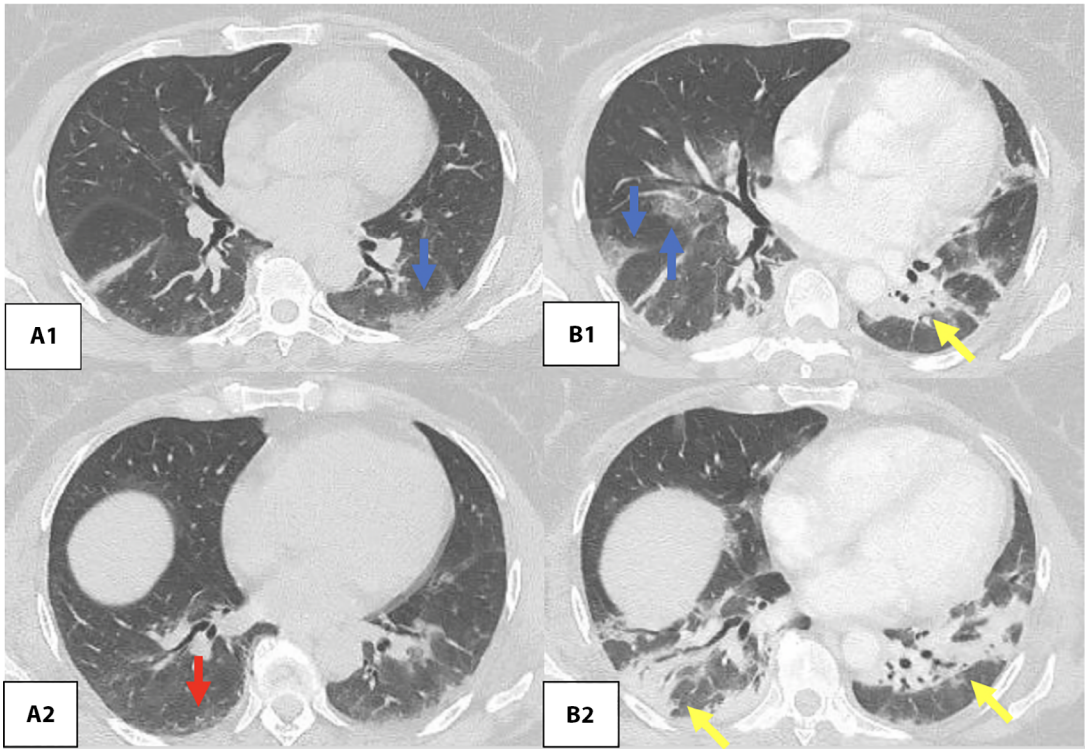

Figure 7. Example of acute exacerbation of ILD
Axial images of CT (A1-2 and one month later B1-2) chest demonstrating acute, rapid progression/exacerbation of interstitial lung disease in a 58-year-old woman with underlying rheumatoid arthritis on rituximab. Underlying subtle peripheral reticulation (red arrow) present with developing ground glass opacities (blue arrows) and consolidation (yellow arrows).

hypertension medications such as endothelin receptor antagonists and phosphodiesteriase-5 inhibitors and their anti-fibrotic properties in patients with IPF and SSc-ILD have been negative (56). These studies were performed in patients regardless of whether they had PH or not (56). Secondary endpoints from these studies (namely, STEP-IPF) suggest efficacy of sildenafil in improving 6MWT distance in a subset of patients with evidence of right ventricular systolic dysfunction on echocardiogram (56). Current trials are ongoing to evaluate the role of inhaled treprostinil in patients with IPF who do not have PH (NCT04708782).

Management of acute exacerbation of ILD

Acute exacerbations of ILD are diagnosed clinically and supported by HRCT imaging findings with superimposed ground glass opacities or worsening fibrosis compared to baseline scans (Figure 7) after exclusion of other causes of clinical worsening. Biomarkers can assist this clinical diagnosis but are not currently available for use, Krebs von den Lungen-6 (KL-6) is associated with alveolar epithelial cell dysfunction and has been suggested to have a role in evaluation of acute exacerbation of IPF (59). Increased levels of surfactant proteins and matrix metalloproteinases 7 protein may suggest acute exacerbation (59). Some biomarkers of acute exacerbation in specific CTD-ILDs have been suggested, including KL-6 in IPF, RA-ILD and HP, D-dimer and IL-6, and BAL neutrophilia and lymphopenia (59). Oftentimes, patients require hospitalization and supportive care with supplemental oxygen and intravenous steroids, though the data for the use of steroids in this setting is limited.

Supportive measures

Oxygen supplementation: Resting hypoxemia, defined as a PaO2 ≤55 mmHg or PaO2 equal to 56-59 mmHg with evidence of cor pulmonale, polycythemia, and/or pulmonary hypertension, is a marker of advanced ILD (60). Chronic long-term

oxygen is generally provided for patients with hypoxemia at rest or with nighttime desaturation for patients with IPF (13). The evidence for long-term oxygen use is sparse, and retrospective studies have shown no survival benefit (60). Ambulatory oxygen may allow patients to increase physical activity and maintain quality of life (13), and its use may not significantly improve certain parameters of perceived breathlessness in patients (60). There is no data available suggesting a role for noninvasive ventilation in patients with advanced ILD. Pulmonary rehabilitation: Pulmonary rehabilitation has long been established to improve outcomes in disease processes such as COPD (13). In patients with ILD, the evidence is less robust. Studies of ILD patients undergoing pulmonary rehabilitation generally suggest safety and improved exercise tolerance (61). Pulmonary rehabilitation improves quality of life, dyspnea, and 6MWT in patients with IPF (13). In studies of patients with APS, participation in a pulmonary rehabilitation program for two months significantly increased exercise tolerance at 6 and 12 months and decreased dyspnea scores at 6 months (61). While traditionally pulmonary rehabilitation was considered in patients with limited functional capacity, its utility even in early disease is suggested to improve quality of life and dyspnea scores (13). Palliative care referral: In pre-transplant patients, referral to palliative care occurs at a median of 32 days prior to transplant or death (62). Early palliative care involvement is associated with improved quality of life, increased patient and family satisfaction, and decreased hospitalization in some groups of patients (62). A review of studies evaluating the role of palliative care in advanced ILD suggested that palliative care involvement should be timed when patients had adjusted to their diagnosis and prognosis and advocates for an individualized approach to the timing of involvement, particularly in the event of pivotal events in the disease process (63). There is some retrospective data showing that end-of-life care costs were reduced in IPF patients treated by a multi-disciplinary care team that included an expert in palliative respiratory care (64). This is primarily driven by reduced hospitalizations and interventions, and a lower proportion of deaths taking place in the hospital (64). Palliative care involvement should be considered with every hospitalization and with progression of disease (64), though literature guiding timing of referral is limited.

Consideration for lung transplant referral

Of the adult lung transplantation performed from 1995 through June 2018, among ILDs, idiopathic interstitial pneumonias (IIP) accounted for 26.1%, ILD (not IIP) accounted for 5.7%, CTD accounted for 0.9%, and sarcoidosis accounted for 2.4% (65) (Table 2). More recently, ISHLT statistics suggest IPF accounted for 29% of all lung transplants performed between 2010-2018 (66). This difference in reporting of underlying disease (2019 and 2022 versions) of lung transplantation data makes comparison difficult. The most recent reporting in 2022 includes the following diagnosis: COPD, alpha 1 antitrypsin disease, cystic fibrosis, idiopathic PAH, IPF, retransplantation, and other. The comparison between ILD subtypes is not possible using this iteration of the society report (66).

Lung transplantation remains the last option to improve QoL and sometimes prolong survival in patients with advanced ILD irrespective of the underlying etiology (13). Patients with advanced ILD disease should be considered for lung transplantation evaluation if they have progressive disease that does not respond to other treatments or if they are

Table 2. Lung transplantation by diagnosis January 1995 through June 2018 [Data adapted from (65)]

Diagnosis	Total Lung Transplantation (%)
COPD	19,152 (30.1)
Idiopathic Interstitial Pneumonias (IIP)	16,583 (26.1)
CF	9,674 (15.2)
ILD- not IIP	3,609 (5.7)
Alpha 1 antitrypsin disease	2,969 (4.7)
Retransplant	2,556 (4.0)
Idiopathic PAH (IPAH)	1,863 (2.9)
Non-CF bronchiectasis	1,714 (2.7)
Sarcoidosis	1,540 (2.4)
Pulmonary hypertension - not IPAH	978 (1.5)
Lymphangioleiomyosis/ tuberous sclerosis	581 (0.9)
CTD	564 (0.9)
Obliterative bronchiolitis	539 (0.8)
Cancer	38 (0.1)
Other	1,170 (1.8)

diagnosed with a disease with a known reduced-short term survival (67). Lung transplantation provides a 75% reduced risk of death in patients with IPF (13).

Patients with ILD should be referred early for transplantation. The ISHLT has established guidelines on when patients should be referred for each process based on lung functions, 6MWT, presence of concurrent disease processes such as pulmonary hypertension, and worsening status including increased frequency of exacerbations (68). A diagnosis of IPF should prompt referral to a lung transplant center at the time of diagnosis (13). Transplantation can be performed successfully for other advanced ILDs including CTD-ILD (4), fibrotic HP, anti-MDA5-positive dermatomyositis-associated ILD (69) and pulmonary sarcoidosis (70). For referral for advanced ILDs other than IPF, referral is suggested when there is progressive disease despite optimal treatment or decrease in pulmonary function associated with functional limitation or dyspnea and if expected survival at 2 years is predicted to be less than 50%, though accurate prognostication in most ILD is difficult (71). In patients with CTD-ILD, specific extrapulmonary manifestations and transplant considerations should be made for each disease (4, 72, 73). In general, evidence of UIP or NSIP, an FVC less than 40% of predicted, dyspnea or functional limitation, and any oxygen requirement should prompt referral (4). Management of immunosuppressive and anti-fibrotic agents in potential lung transplant candidates is crucial. Anti-fibrotic medications can be started and continued until the moment of lung transplantation. While there is theoretical risk that the anti-fibroblast activity of the anti-fibrotic may impair wound healing and increase risk of bronchial anastomosis complications, there is no evidence of this in the current literature (74). Current practice in some institutions is to continue these medications as their benefit far outweighs risk, which includes risk of bleeding with nintedanib (74). Interestingly, though a small retrospective study has suggested that use of antifibrotics led to a reduction in lung allocation score in patients with IPF awaiting transplantation, other studies have not replicated this data (75). In single lung transplantation, there is no consensus on whether anti-fibrotic should be continued after transplantation. Moreover, studies are ongoing to evaluate the role of antifibrotics in reducing bronchiolitis obliterans syndrome after transplantation, and current INFINITx-BOS study is ongoing to evaluate the efficacy of nintedanib in reducing the rate of decline of pulmonary function in these patients (74). Immunosuppression in the pre-transplantation period should be weighed carefully with consideration of risks (76). In general, high-dose steroids should be avoided due to increased risk of graft loss in non-IPF ILD and worse CLAD-free survival and graft survival in IPF (76). Most transplant centers prefer prednisone doses of 20 mg or less at the time of transplantation. The increased infection risks and side effect profiles of other immunosuppressive medications should be considered in the peri-transplant period. Once the patient is being evaluated for transplant, decisions on anti-inflammatory and immunosuppressive regimens should be in consultation with the multidisciplinary lung transplant team.

Future directions

Clinical trials are ongoing to evaluate the role of other disease modifying medications in ILD, particularly immunosuppressive agents and novel antifibrotic agents. Recent UNOS changes to the approach to transplant listing and lung allocation scoring have potential impact on patients with ILD, though literature on outcomes has not been published to date. Other medications such as statins and alternative therapies such as with stem cell therapy, gene therapy, and laser therapy are under investigation, though no data exists for their use at this time (31, 77, 78). Multiple ongoing trials are enrolling, and patients should be presented with the option to learn more about and consider enrollment in clinical trials as part of their management plan.

Conclusion

Advanced ILD is oftentimes a fatal disease which is difficult to manage and necessitates transplantation in many cases. Pre-transplantation management includes monitoring and prognostication of disease progression and management of acute exacerbations, as well as pharmacologic and nonpharmacologic treatments to decrease the rate of decline. We suggest utilizing an algorithmic approach for ILD patients with advanced disease.

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