Comprehensive care of interstitial lung disease

Encyclopedia of Respiratory Medicine

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ABSTRACT

Interstitial lung diseases comprise a heterogeneous group of diseases, which often have a major impact on the lives of patients. Optimal management of patients with interstitial lung disease requires a comprehensive approach to care, which encompasses disease-modifying treatment, symptom-centered management, education and self-management strategies. Especially in the more progressive and fibrotic forms of ILD, treatment should not only be aimed at prolonging life, but also at improving quality of life for patients. Symptom-centered management in ILD includes, amongst others, supplemental oxygen, pulmonary rehabilitation and palliative care. In order to optimize individually tailored treatment, patients' needs and preferences should regularly be assessed during the disease course.

Keywords

Interstitial lung disease; idiopathic pulmonary fibrosis; symptom relief; palliative care; supplemental oxygen; pulmonary rehabilitation; education; self-management; disease-modifying treatment; lung transplantation; end-of-life care

INTRODUCTION

Interstitial lung diseases (ILDs) are a diverse group of disorders affecting the interstitium of the lung. Historically, ILDs are classified in four groups: ILDs with a known cause, idiopathic interstitial pneumonias (IIPs), granulomatous disorders and rare ILDs. The disease course and prognosis significantly vary between different ILDs. Some ILDs are reversible, other ILDs have the potential for stabilization, but fibrotic ILDs are often progressive and ultimately fatal, especially idiopathic pulmonary fibrosis (IPF) (1). Therefore, pharmacological and non-pharmacological treatment strategies differ between ILDs and even within the same diagnosis, care needs may largely differ between patients. In this chapter, the comprehensive management of ILDs will be described. Different models exist to facilitate a systematic approach to comprehensive care. In this chapter the "ABCDE of ILD care" is used as a guidance to facilitate tailored care for the individual ILD patient (**Figure 1**) (2, 3).

Impact of disease

ILDs often have a major impact on the lives of patients, especially in progressive fibrotic disorders. Symptoms of cough, dyspnea, impaired exercise tolerance, fatigue, anxiety and depression, significantly impair (health-related) quality of life ((HR)QOL) (4-7). HRQOL can be defined as the influence of a medical condition on the well-being of a patient, whereas QOL is a broader concept which also encompasses factors such as personal beliefs, culture and social relationships. Dyspnea, cough and depression are assumed to be the main drivers of quality of life in IPF (4, 6, 8-10). Furthermore, fatigue, forced vital capacity (FVC), age, gender and the presence and number of comorbidities also influence quality of life in ILD (5-7, 9). HRQOL independently predicts mortality in IPF according to one study (11). The high disease burden emphasizes the importance of holistic care aimed both at prolonging survival as well as improving QOL in patients with ILD. In the end, prolonging life at an acceptable quality is what most people strive for.

ASSESS

Correct diagnosis

There is a lack of awareness about ILD in the general public and among healthcare providers such as general practitioners, radiologists, pathologists and general pulmonologists (12). Patients frequently feel misunderstood because people do not know what pulmonary fibrosis is (13). Lack of knowledge about ILDs may also lead to a delay in diagnosis and adequate treatment. Misdiagnosis and a long diagnostic trajectory can have a negative impact on QOL (14, 15). Symptom-based algorithms for general practitioners

ABCDE of ILD care

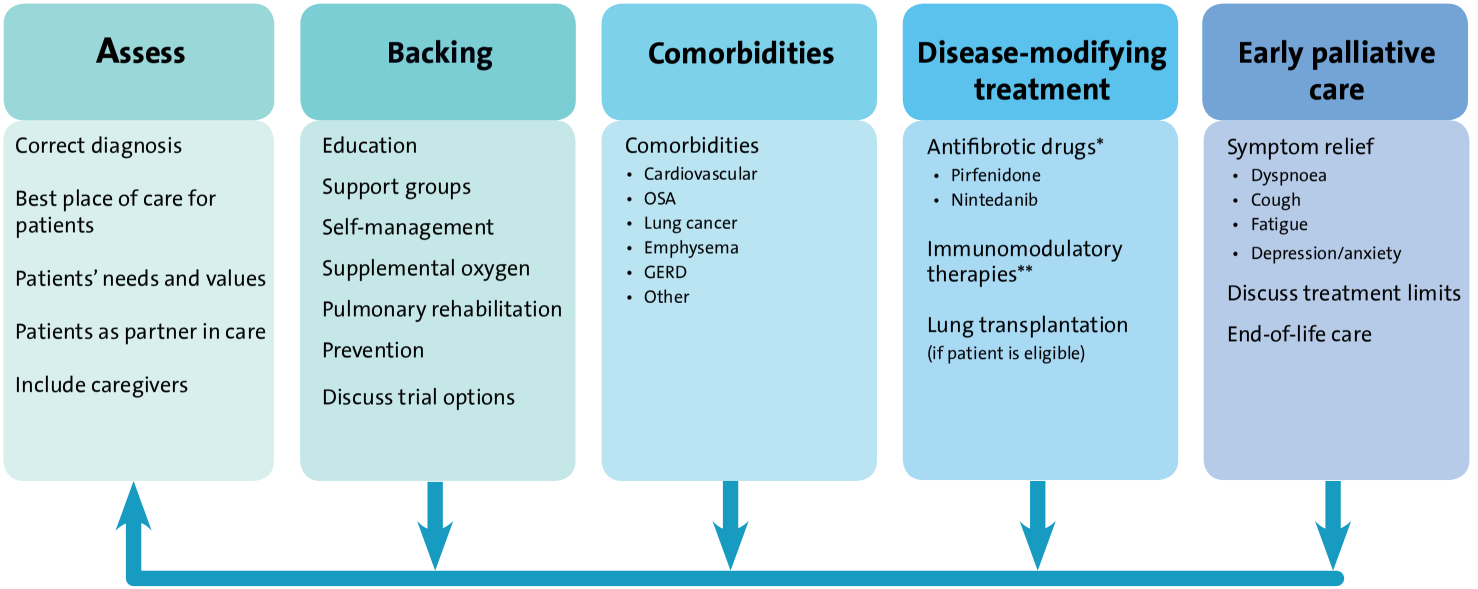

Figure 1. The ABCDE of interstitial lung disease care. The ABCDE model provides a structured approach to comprehensive care in ILD. OSA = obstructive sleep apnea, GERD = gastro-esophageal reflux disease. Adapted from Kreuter, M., Bendstrup, E., Russell, A. M., Bajwah, S., Lindell, K., Adir, Y., Brown, C. E., Calligaro, G., Cassidy, N., Corte, T. J., Geissler, K., Hassan, A. A., Johannson, K. A., Kairalla, R., Kolb, M., Kondoh, Y., Quadrelli, S., Swigris, J., Udwadia, Z., Wells, A. & Wijsenbeek, M. 2017a. Palliative care in interstitial lung disease: living well. *Lancet Respir Med,* 5**,** 968-980.

and awareness campaigns could improve knowledge of ILD and possibly enhance early diagnosis and treatment (16). Access to an ILD specialized multidisciplinary team (MDT) is essential to establish an accurate diagnosis and has shown to reduce the number of unclassifiable disease states. During multidisciplinary discussions in a specialized ILD center, the diagnosis is often changed, which regularly leads to adjustments in pharmacological and non-pharmacological management and other clinical trial options (17, 18).

Best place of care for patients

Early referral to a tertiary center seems to increase the perceived quality of care for patients (13, 19, 20). In IPF, delayed referral to a specialist center has been associated with a higher mortality, which emphasizes the need for early referral (21).

In an increasing number of countries, patients have access to ILD specialist nurses for practical and emotional support. The ILD specialist nurse often functions as the main contact for patients and can play an important role during the disease course. ILD specialist nurses provide information about the disease and medication, and help patients with the management of side-effects. Furthermore, they can direct patients to patient advocacy groups, offer practical help with supplemental oxygen and give advice about housing and employment issues, disability parking, physiotherapy and lifestyle changes (13, 14, 22-24). The availability of ILD specialist nurses can potentially improve quality of care and quality of life for patients and their partners (23, 25).

In some countries, patients have to travel long distances to visit an ILD specialist center. This can be very burdensome for patients with invalidating symptoms, impaired exercise tolerance and oftentimes high oxygen needs. When visits to the specialist center become too intrusive for patients, it could be an option to share the care between specialist center and local community center. Studies show that some patients prefer collaborative care between specialist and community centers (13, 16).

Patients' needs and values

For tailored treatment, it is essential to assess individual patients' needs, preferences and wishes. Several qualitative studies, mainly in IPF, evaluated unmet needs of patients and their partners. The most frequently reported unmet needs of patients with pulmonary fibrosis included adequate information about the disease, improved access to diagnosis, treatment and ILD specialists, psychological support, supplemental oxygen, pulmonary rehabilitation and end-of-life care, better general awareness for ILD, and more involvement of partners (12-14, 16, 20, 22, 26-35). Individual patients often have different needs, and personal circumstances, preferences, expectations and experiences may influence disease behavior and treatment success (36, 37). Furthermore, patients' needs and preferences may change during the disease course, and therefore regular reassessment of patients' needs is essential for optimal treatment (26).

Patients as a partner in care

A strong collaboration and mutual trust between the patient and healthcare provider is the foundation of comprehensive care in ILD. Patient engagement in care and self-management is essential to maintain or improve quality of life in ILD, but patients can only function as partners in care if they are well-educated about their disease and its prospects (3, 38). Effective communication and shared-decision making is important through the whole disease trajectory, from the moment of diagnosis to end-of-life.

When patients' preferences and wishes are taken into account before they start on pharmacological treatment, side-effects and non-adherence to medication may possibly be reduced (36, 38, 39). One study evaluated outcomes of a patient-centered care program in IPF. This program consisted of frequent phone calls and patient-led discussions with ILD nurses and was aimed at empowering patients and improving treatment adherence. Results indicated that patients felt more in control of their disease and highly valued the tailored information and support (23).

Inclusion of caregivers

A frequently overlooked part of comprehensive care in ILD is engaging the patient's support network in care (25). For most patients, partners and other family members are the main source of emotional and practical support during their disease trajectory. Partners can help patients adjust to a new lifestyle and cope with changes in everyday life due to their disease (26). Having a family member with ILD poses a major burden on caregivers and may lead to anxiety, frustration, limitations in daily and social activities and disturbed relationships (28, 34, 40). Caregivers of patients with ILD express the need to be more involved in care, and to receive better disease education, emotional support and practical advice (13, 26, 28, 35, 40). To improve engagement in care, partners should be more actively involved during outpatient consultations and be part of support groups and other educational activities (26, 28, 40).

BACKING

Education

The need for more accurate information and education about their disease is one of the most frequently reported unmet needs of patients and caregivers. A better understanding of the disease and its prospects could enhance self-management and help patients to cope with their disease (35). Patients with ILD are often unsatisfied with the amount and quality of available information and do not know which information sources are reliable. Online information is frequently outdated, not accurate or difficult to find for patients (22, 41, 42). Most of the online sources mainly contain information about IPF,

making it hard for patients with other ILDs to obtain specific and accurate information about their disease (41).

Patients and caregivers do not only wish to receive disease-specific information, but also individualized information about supplemental oxygen, insurance issues, alarming symptoms, prevention of infection and medication management (35). Informational needs of patients can change during their disease course. Patient's needs and wishes should be reassessed regularly by their healthcare providers, in order to provide individualized and tailored information (26). Educational patient meetings can be used to inform patients about ILD, but also to update them about new medications and clinical trials (13).

Support groups

The need for practical, emotional and psychological support is regularly reported in chronic ILD. A substantial group of patients think that psychological support is lacking in current care (12, 13, 22). Only a minority of ILD patients receive psychological care (13, 22, 41). One option to provide emotional and psychological support to patients and their caregivers is a (multidisciplinary) support program, led by a specialist nurse or psychologist. Studies showed that patients highly value these support group meetings, feel less lonely and could better place their disease in perspective. Furthermore, these programs can improve quality of life, psychological wellbeing and decrease stress for patients and/or partners (43-45). Composition and content of the program of these support groups is variable and no evidence-based directives for support groups exist to date.

Patient advocacy groups may play an important role in improving care for patients with ILD, by raising more awareness in society, providing disease-specific information, and offering practical and emotional support to patients (12). In some countries, patient advocacy organizations have established peer support groups. Meeting others with similar experiences and difficulties might be beneficial for patients, not only for emotional support but also for practical advice (14, 27). Nonetheless, it is important to keep in mind that some patients might have negative feelings towards peer support groups because it could be distressing to meet other patients with more severe disease (26).

Self-management

Self-management strategies may help patients to stay in control of their own disease, make realistic choices and prepare for the future (3). Self-management strategies are diverse and include, amongst others, self-monitoring of disease, acting on changes, medication management, oxygen use, dietary measures and exercise.

Innovative new techniques, such as eHealth solutions may be used to enhance self-management in ILD. eHealth is defined as "the use of information and communication

technologies for health". Use of eHealth has the potential to improve the quality of care by promoting self-management and by having a lower threshold to communicate with patients, using constant disease monitoring and direct feedback (46-48). In ILD, home monitoring experiences are limited, and eHealth solutions are not yet implemented in routine daily care. However, several studies have shown that home monitoring of lung function is feasible and reliable in this elderly patient population and potentially allows for earlier detection of disease deterioration or bothersome side-effects (47-50). One study evaluated a home monitoring program, including real-time wireless home spirometry and online reporting of symptoms and side-effects in IPF. Patients had access to an information library and electronic consultations, and were directly provided with feedback if their lung function significantly declined or bothersome side-effects were reported. Adherence to the program and patient satisfaction were high. Patients reported that home monitoring helped them to feel more in control, absorb information at their own pace and facilitated easier communication and interaction with healthcare providers (47, 48).

Another self-management tool for patients with ILD is to maintain a healthy diet. If needed, patients can be referred for dietary evaluation and support (25). It is not clear whether a specific diet could be beneficial for patients with ILD, since the influence of diet on disease course has never been assessed in clinical trials. However, being overweight and being underweight has been associated with worse outcomes in ILD (51, 52). Two studies showed that weight loss (>5% body mass index (BMI) decline or >5% bodyweight loss) was significantly associated with worse survival in ILD (53, 54). In these studies, BMI at baseline did not predict survival.

Supplemental oxygen

Among ILD patients, IPF patients are most likely to receive supplemental oxygen, independent of disease severity (55). The 2011 ATS/ERS/JRS/ALAT guideline for diagnosis and management of IPF provides a strong recommendation for the use of long-term supplemental oxygen in IPF patients with resting hypoxemia. This recommendation is mainly based on evidence from studies in chronic obstructive lung disease, and therefore the quality of evidence is deemed very low. According to this guideline, the timing of supplemental oxygen treatment is left up to the discretion of the treating physician. No clear peripheral oxygen saturation (SpO2) cut-off value for the use of supplemental oxygen has been advised, although most studies use a cut-off value of < 88%. The guidelines do not provide recommendations on the use of supplemental oxygen in patients with isolated exertional hypoxemia (56).

One of the aims of oxygen therapy in interstitial lung diseases is to maintain adequate SpO2 levels, and thereby prevent potential complications of chronic hypoxemia. Other

goals of supplemental oxygen are to alleviate dyspnea, increase physical activity and improve quality of life. Several studies have evaluated whether oxygen therapy could improve these parameters. Two reviews could not provide any good-quality evidence for or against the use of ambulatory oxygen in ILDs due to the low quality or retrospective nature of studies (57, 58). In the short term, oxygen therapy showed positive effects on exercise capacity, but no improvement in subjective dyspnea, although the total number of patients in these studies was low. No conclusions could be drawn regarding the impact of long-term oxygen therapy on survival in ILD (58).

Only one cross-over randomized controlled trial assessed the effect of ambulatory oxygen on HRQOL in patients with ILD who had isolated exertional hypoxemia (59). In this study, ambulatory oxygen improved short-term HRQOL and dyspnea scores. Qualitative interviews indicated that patients' quality of life improved because they felt less impaired in their daily activities. The attitude of most patients who initially had negative feelings regarding oxygen, changed because they experienced a beneficial effect from the supplemental oxygen (59). Results from other qualitative studies indicate that oxygen therapy can have a major impact on the lives of patients and their partners. Oxygen therapy is often seen as an indication of disease progression by patients and could probably be the first time that their disease becomes visible. Furthermore, oxygen therapy may also lead to practical issues and limitations in daily life (14, 26, 27, 34).

These data suggest that in ILD patients with exertional hypoxemia, the initiation of supplemental oxygen should be discussed during outpatient clinic visits and regularly reassessed during follow-up visits. The decision whether or not to start supplemental oxygen should be an individualized and shared decision between patients and their healthcare providers. SpO2 measurements at rest, oxygen desaturation during six-minute walk test, and assessment of dyspnea over time through patient-reported outcomes could help determine the need and timing for oxygen prescription (55). It should be acknowledged that guideline directions on supplemental oxygen use in ILD are lacking and access to supplemental oxygen may vary throughout the world (12).

Pulmonary rehabilitation

Pulmonary rehabilitation (PR) can be defined as a comprehensive intervention, which includes exercise training, as well as education and self-management strategies. The main goals of PR are to improve the physical condition and quality of life of patients with chronic respiratory diseases. The content of the program should be tailored to individual patients' needs and wishes, type of disease, disease severity and comorbidities (60). PR has been extensively studied in chronic obstructive pulmonary disease (COPD) and has proven to be effective in this disease. The ATS/ERS statement about pulmonary

rehabilitation suggests that PR leads to a short-term improvement in exercise capacity, quality of life and dyspnea in ILDs, but that the beneficial effects are generally smaller than in COPD (60). The 2011 ATS/ERS/JRS/ALAT guideline on IPF provides a weak recommendation for pulmonary rehabilitation in patients with IPF, based on the results of two controlled trials (56, 61, 62). The beneficial effects of PR on exercise capacity, dyspnea and quality of life in patients with ILD were also reported in two systematic reviews (63, 64) There is no current evidence regarding the optimal duration and specific content of PR programs in ILD, and the long-term effects have not completely been elucidated(61, 65, 66).

Data regarding predictors of benefit after PR are somewhat conflicting. One observational study showed that patients with IPF have more benefits from PR in early disease stages, while other studies suggest that patients with lower walking distance at baseline had more improvement in 6MWD after PR (66-69). In other ILDs, there is no evidence that disease severity predicts outcomes after PR (67). Therefore, it is advised to discuss referral to PR with ILD patients in early disease stages, but to also consider PR for patients with more severe disease. Especially in the latter group, the balance between burden and gain of PR should be carefully discussed with the patient.

There are some differences in PR in patients with ILD compared to other respiratory diseases. Patients with fibrotic ILDs have significantly more desaturation during exercise compared with matched COPD patients, when adjusted for pulmonary physiology and demographic features (70). Exercise training in ILDs should therefore take place in a facility where supplemental oxygen therapy can be provided. Extra-pulmonary manifestations of ILD and comorbidities may limit the possibilities for exercise training. For example, patients with an underlying connective tissue disease may require modifications in their training program due to musculoskeletal pain, stiffness or weakness (71). Further, the educational content of PR programs is mostly focused on COPD. Hence, part of the program content in PR is not applicable for ILD patients. Both patients and clinicians reported the need for ILD specific content in PR programs, such as management of symptoms, oxygen use and end-of-life care. Education sessions in PR programs could be an ideal opportunity to educate patients with ILD and their partners (41, 72).

Prevention

In ILD, not much emphasis has been placed on prevention strategies, although it certainly has a role in preventing morbidity and mortality. In the pathogenesis of many ILDs, external triggers are thought to play a role. Examples of such triggers include smoking, medications, work and environmental exposures, infectious causes and mechanical stress. In some diseases, removal of the trigger may result in improvement of disease, for

instance in acute hypersensitivity pneumonitis or Langerhans cell histiocytosis, whilst in other diseases the effect is limited to possibly preventing further decline (73).

In current clinical practice, patients are advised to get an influenza vaccination once yearly and pneumococcal vaccination once every five years (3). Studies in ILD patients reported no acute exacerbations after vaccination, suggesting that influenza and pneumococcal vaccination are both safe in ILD (74, 75). Further, ILD patients with and without immunosuppression had normal vaccination responses (74-76).

Smoking cessation plays an important role in primary and secondary prevention of ILDs. Some chronic ILDs mainly develop in smokers. This group includes respiratory bronchiolitis-associated ILD, desquamative interstitial pneumonia and pulmonary Langerhans cell histiocytosis, also called smoking-related ILDs. In these smoking-related ILDs smoking cessation is the initial and most important therapy. Furthermore, there is a relationship between smoking and acute eosinophilic pneumonia, pulmonary hemorrhage syndromes, IPF and rheumatoid arthritis-associated ILD, though the association is less obvious than in smoking-related ILDs. In contrast, smoking appears to be protective in sarcoidosis and hypersensitivity pneumonitis (77). Cigarette smoking leads to worse outcomes in ILD and has a negative impact on survival. Smoking also increases the likelihood of development of comorbidities such as emphysema and lung cancer, which impact survival as well (77-79). In IPF, smoking reduces treatment efficacy in patients treated with pirfenidone. Pirfenidone is primarily metabolized in the liver by the CYP1A2 enzyme; smoking incudes CYP1A2 and thereby reduces bioavailability of pirfenidone (80). Consequently, cessation of smoking is strongly advised in all patients with ILD (77).

Mechanical stress, such as in mechanical ventilation or pulmonary surgery, may increase the risk for acute exacerbations in ILD (81-83). In patients with fibrotic ILDs, the risks and benefit should always be weighed and discussed with patients, also if the reason for mechanical ventilation is non-pulmonary (56).

Discuss trial options

Evidence-based treatment options in ILD are limited and often not curative. There is a major need for better treatments across the spectrum of ILDs and many trials are ongoing (clinicaltrials.gov). The majority of ILD patients wish to participate in clinical trials, and would also like to be involved in the development of studies (13). Healthcare providers should discuss the possibility of participating in a clinical trial with patients after a diagnosis has been established (3, 16). Participation in trials may empower patients to play a more active role in their disease, gain access to potential new treatments and contribute to medical research (3). Patients who participate in a clinical trial are more hopeful than others (14). A report about IPF in the UK indicated that only a minority of patients (42%) are informed about ongoing or future clinical trials (84). These findings were also reported in a qualitative study in IPF patients and caregivers (14).

COMORBIDITIES

Comprehensive care in ILD also means looking beyond the lungs (36). Assessment and treatment of co-morbidities should not be overlooked. Comorbidities are highly prevalent in ILDs and may have an influence on quality of life and survival (85-88). In IPF, a higher number of reported comorbidities is significantly associated with poorer survival (85). Early recognition and adequate treatment of comorbidities is essential and has the potential to improve outcomes in patients with ILD (88).

DISEASE-MODIFYING TREATMENT

Pharmacological management

ILDs comprise a large and heterogeneous group of diseases, characterized by variable presence of inflammation and fibrosis, or a combination of both, depending on the underlying disease and time of assessment. Historically, all ILDs were thought to start off with inflammation and ultimately result in fibrosis of the lung parenchyma. On the basis of these ideas, all patients with ILD were initially treated with immunomodulatory therapies (89, 90). However, it has become clear that not all patients with ILD will benefit from immunosuppressive therapies and in some ILDs this may even be harmful (91). In the past decade, new insights in the pathogenesis of ILDs together with an increasing number of well-designed clinical trials, have led to the first evidence-based recommendations for the use of disease-modifying agents in some ILDs (92, 93). However, none of these new drug developments have led to curative treatment options. Furthermore, in many ILDs, therapeutic decisions are still based on case-series or expert opinion, leaving a major unmet need to find better disease-modifying treatment for ILDs.

Antifibrotic therapies

In patients with IPF, the use of high dose immunosuppression has been abandoned since the study that showed that the combination of azathioprine, high dose corticosteroids and N-acetylcysteine was not only ineffective, but also associated with an increased risk of mortality (91). Subsequently, large randomized controlled trials showed that the use of the anti-fibrotic therapies, nintedanib and pirfenidone, had a favorable effect on the decline in lung function, as measured by FVC (92, 93). Pre-specified analysis of the pooled data for the respective drugs also showed a positive effect on survival and a decrease in acute exacerbations (92, 94). The treatment guideline for IPF includes recommendations for the conditional use of nintedanib and pirfenidone (95).

Several other ILDs may also present with a progressive fibrotic phenotype, such as rheumatoid arthritis related ILD, hypersensitivity pneumonitis, systemic sclerosis ILD

(SSc-ILD) and unclassifiable ILD. The communality in disease pathogenesis and behavior with IPF suggests a potential for a common treatment (96, 97). Currently, clinical trials are underway investigating the use of antifibrotic therapies in other progressive fibrotic diseases, both as single agents or along with immunomodulatory therapies (clinicaltrials.gov).

Immunomodulatory therapies

Although immunosuppression is considered the mainstay of treatment in many ILDs, this is largely supported by findings from retrospective and observational studies (98). In SSc-ILD, there is evidence that the use of both cyclophosphamide and mycophenolate mofetil (MMF) resulted in significant short-term lung function improvement, although MMF is better tolerated (99). For many other ILDs, such as connective tissue disease-associated ILD, drug-induced ILD and hypersensitivity pneumonitis, the optimal treatment strategies have not been determined (78, 100). Details on current treatment recommendations can be found in the disease specific chapters.

Future developments

Increasing insights into the pathogenesis of different pathways involved in ILD have led to a fast expanding field of randomized controlled trials with new compounds and combinations with existing drugs (101). In current practice, patients are treated with either antifibrotics or anti-inflammatory therapy. In the future, this paradigm may shift towards more combined or targeted therapy based on the individual patient profile, in which genetic/molecular endotypes, environmental factors and behavioral aspects are likely to play a role (36, 96, 102). Collaboration between researchers, physicians, patients and pharmaceutical companies will need to guide these developments.

Lung transplantation

In progressive, non-reversible ILDs, especially IPF, lung transplantation is the only treatment option with significant survival benefit. The number of ILD patients receiving a lung transplant has steadily increased after adaptation of the lung allocation system. The lung allocation score (LAS) was introduced in the USA in 2005 and in 2011 within the Eurotransplant countries. Prior to the LAS, lung allocation was based on time on the wait list, whereas the LAS uses a complex scoring system which allocates lungs to patients with a higher urgency due to more severe disease(103, 104). Between 1995 and 2017, 37% of all lung transplantations were performed in patients with idiopathic interstitial pneumonias, according to data from the international society for heart and lung transplantation (105). Among the ILDs, IPF is the most common indication for lung transplantation, but a small percentage of lung transplants are carried out in patients with other forms of ILD. In the US, ILD is currently the most common indication for lung

transplantation (106). However, only a small minority of patients with ILD are eligible for lung transplantation due to their older age and higher likelihood of comorbidities. The upper age limit for lung transplantation has increased over time. There are some data showing that patients aged over 70 years have comparable outcomes post lung transplantation compared to patients between 60 and 69 years of age, after the implementation of the LAS system (107). If this trend continues, it is expected that more ILD patients will become eligible for lung transplantation (104).

Due to the variable disease course of different ILDs, the optimal timing for referral to lung transplantation screening is not completely elucidated. In IPF, early referral for lung transplantation screening is strongly advised because of poor survival rates and the possibility for rapid deterioration (103, 104, 108). In other ILDs, patients are generally referred for lung transplantation screening when the disease progresses despite optimal treatment (104, 109).

EARLY PALLIATIVE CARE

Palliative care is an important component of comprehensive care in progressive ILDs and is directed at symptom relief and improving quality of life. The phrase "palliative care" is often associated with end-of-life care. This hampers referral to palliative care due to negative connotations and misconceptions (110-112). Palliative care does not solely include end-of-life care, but also comprises symptom-centered pharmacological and non-pharmacological treatment (25). Palliative care can be initiated in parallel with other interventions and should not lead to discontinuation of disease-modifying treatment (25). The balance between symptom-centered and disease-centered management varies throughout the disease course. When the disease progresses, symptom-centered management becomes increasingly important(3).

According to the World Health Organization, palliative care is a holistic and multidisciplinary approach which addresses the needs of patients and their family members and helps patients to live actively for as long as possible (113). Worldwide, many cultural, social and financial barriers to palliative care exist, and only a minority of patients who need palliative care have access to it (113). Palliative care research has almost completely focused on cancer during the last decades (114). Hence, underuse of palliative care is more pronounced in ILDs and other chronic lung diseases than in oncology. Discussions regarding prognosis and treatment limitations were less frequently reported in patients with ILD and COPD than in cancer patients (115). Two retrospective studies showed that palliative care services are involved in a small minority of patients with progres-

sive fibrotic ILDs. Furthermore, referral to palliative care occurred in a very late stage of disease in ILD patients (116, 117).

One of the main barriers to palliative care in ILD is the lack of knowledge about palliative care among pulmonary physicians and the lack of (inter)national guidelines (25, 114). Moreover, there is significant variability in disease course and prognostic uncertainty, which complicates referral to palliative care and optimal timing of palliative care discussions (25, 114). Initiation of palliative care in ILD is not required in all patients, since not all ILDs have a high symptom burden or poor outcome. A disease behavior –based algorithm can be helpful in assessing whether palliative care should be considered in individual patients (**Figure 2**) (25). In all patients with inevitably progressive ILD, especially IPF, palliative care should be discussed early in the disease course. In patients with cancer, early referral to palliative care improves quality of life and prolongs survival (118-120). Further, early and integrated palliative care with a breathlessness support service improved mastery of dyspnea and survival in patients with refractory dyspnea, including those with ILD (121). In patients with fibrotic interstitial lung disease a "palliative care case conference" intervention was feasible and improved anxiety and quality of life in patients and caregivers (122).

Symptom relief

Dyspnea

Dyspnea is the most prevalent symptom in interstitial lung disease. More than 90% of ILD patients report dyspnea at diagnosis (123, 124). Dyspnea is strongly associated with QOL in ILD and is reported to be the main contributing factor to impaired QOL in this population (5, 9, 125). Increasing dyspnea may influence all aspects of daily life. Many patients with dyspnea avoid exertion, which can lead to impairment in physical activity and decline in functional capacity. Moreover, breathlessness often leads to anxiety, which in turn may worsen the dyspnea. Dyspnea has a major impact on the caregiver too, and may lead to more care dependency and social limitations (126).

Several studies have shown that dyspnea independently predicts mortality in IPF. Increasing dyspnea also predicts disease progression in non-IPF ILDs (127-129). Two studies demonstrated that dyspnea severity is independently associated with depression and frailty in patients with IPF (130, 131). Comorbidities, such as pulmonary hypertension, cardiac disease, obstructive sleep apnea, infection and psychological disorders, may also contribute to dyspnea and should be identified and optimally treated (25).

Though breathlessness is a major symptom, only a few studies in ILD have been specifically aimed at dyspnea relief. Opioids and benzodiazepines are frequently prescribed for

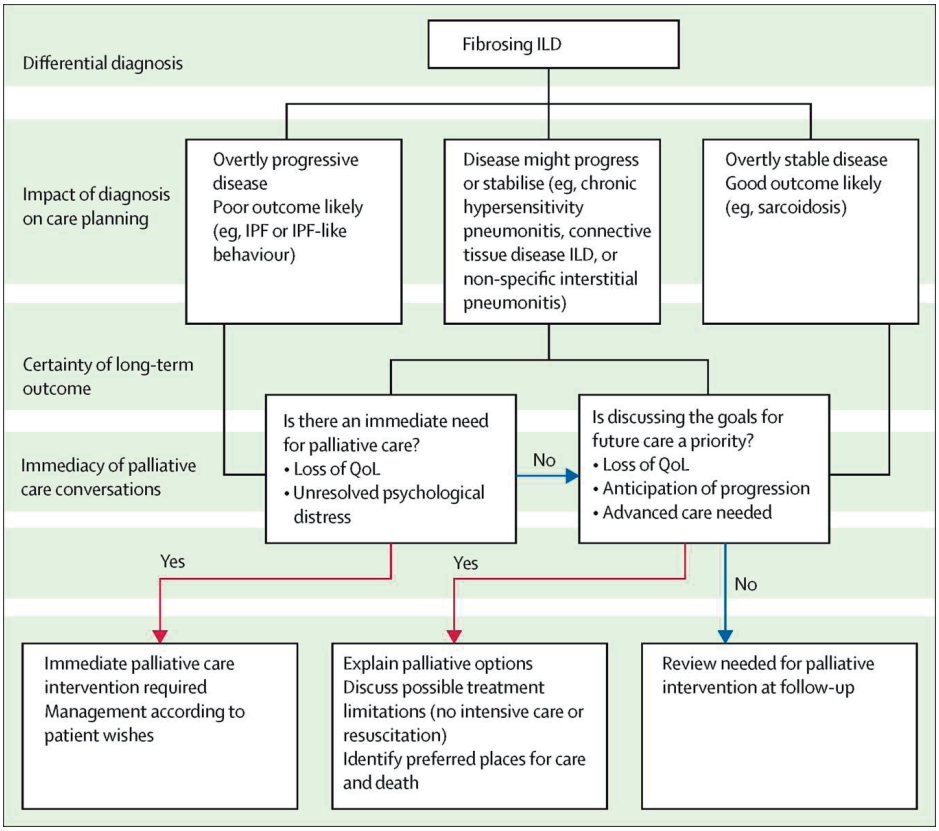

Figure 2. Disease-behavior based algorithm for referral to palliative care in ILD. ILD = interstitial lung disease, QOL = quality of life, IPF = idiopathic pulmonary fibrosis
Permission to use from Kreuter, M., Bendstrup, E., Russell, A. M., Bajwah, S., Lindell, K., Adir, Y., Brown, C. E., Calligaro, G., Cassidy, N., Corte, T. J., Geissler, K., Hassan, A. A., Johannson, K. A., Kairalla, R., Kolb, M., Kondoh, Y., Quadrelli, S., Swigris, J., Udwadia, Z., Wells, A. & Wijsenbeek, M. 2017a. Palliative care in interstitial lung disease: living well. *Lancet Respir Med,* 5**,** 968-980.

dyspnea relief in ILD according to a retrospective study about specialist palliative care (116). All patients in this study reported a benefit with benzodiazepines and opioids. Opioids may reduce the perception of dyspnea centrally in the brain (132). One review article evaluated the role of opioids to alleviate dyspnea in ILDs. Most of the included studies in this review primarily focused on COPD, and only 32 of the included patients had an ILD diagnosis. Results from these studies were inconsistent, but suggest that low-dose oral opioids may have a beneficial effect in patients with ILD. No serious adverse events, such as respiratory depression were reported, but constipation was common (132). The effect of nebulized morphine on dyspnea in ILDs has not yet been clarified (133). There are no studies in ILD assessing the role of benzodiazepines in dyspnea relief. A Cochrane review in cancer and COPD concluded that benzodiazepines may be used as

second or third-line therapy, especially if anxiety is present. A consensus statement on palliative care in ILD included opioids and benzodiazepines as potential symptom-based therapies in ILD (25). In IPF, anti-fibrotic drugs have not shown to alleviate dyspnea, and the combination of nintedanib with sildenafil in IPF also demonstrated no beneficial effect on dyspnea (92, 93, 134).

Use of a hand-held air fan can reduce dyspnea in patients with chronic breathlessness. Since the costs of this intervention are very limited and there are no known side-effects, the use of a hand-held fan may be advised to ILD patients with refractory breathlessness (135-137). The favorable effect of supplemental oxygen and pulmonary rehabilitation on dyspnea is discussed in separate paragraphs.

Cough

Cough is one of the most common and bothersome symptoms in ILD and is reported to be present in up to 87% of patients (138-141). The prevalence of cough is assumed to be highest in IPF, but cough is also highly prevalent in other fibrotic ILDs such as chronic hypersensitivity pneumonitis (up to 83% of patients) and scleroderma related ILD (up to 68% of patients) (140). Cough often leads to a major impairment of quality of life and may limit social activities (4, 6, 140).

Studies regarding the predictive role of cough in ILDs show contradictory results. One study in IPF stated that cough independently predicts mortality (141). A study in scleroderma related ILD showed a correlation between cough and ILD severity, as well as a correlation between lung function improvement and reduction of cough (142). Two other studies suggested that there was no association between cough and disease severity or progression in fibrotic ILDs (139, 140).

The pathogenesis of cough in ILDs remains incompletely understood. Furthermore, it is unclear whether distinct mechanisms play a role in cough pathogenesis in different (fibrotic) ILDs (139, 143). Co-morbidities such as gastro-esophageal reflux disease, obstructive sleep apnea, emphysema or lung cancer, may cause or worsen cough in ILDs. Other possible causes such as ACE inhibitor use, sinusitis and postnasal drip, should be recognized and adequately treated (25, 138, 144).

Cough in ILD is difficult to treat and is often refractory to regular antitussive treatment (138, 140). Consequently, effective therapeutic options for chronic cough in ILDs are lacking. One single-center randomized trial in 20 IPF patients showed that low-dose thalidomide improved patient reported cough and cough-related quality of life (145). Seventy-seven percent of patients in the treatment arm experienced adverse events,

compared to 22% in the placebo arm. Further research is needed to assess benefits and risks related to thalidomide (138, 143, 145). A phase 2 trial showed that sodium cromoglicate (PA101) reduced cough frequency by 31% after 14 days in patient with IPF and was generally well tolerated (146). PA101 had no significant beneficial effects in a group of patients with chronic idiopathic cough (146). Results from an observational study in IPF suggested that pirfenidone reduced cough and improved cough-related quality of life in patients with IPF (147). An older study in a limited number of patients with IPF, showed an effect of high dose corticosteroids on cough (148). However, with the current knowledge on the detrimental effects of high-dose immunosuppression in IPF, this practice is discouraged. The effect of anti-acid therapy on gastro esophageal reflux-related cough in ILD remains a matter of debate. One observational study showed that cough frequency did not change after high-dose acid suppression therapy, although the number of acid reflex events significantly declined, non-acid reflux paradoxically increased (149). A study with laparoscopic anti-reflux surgery showed no effect on cough (150). In scleroderma-related ILD, treatment with mycophenolate mofetil and oral cyclophosphamide decreased the reported prevalence of frequent cough, but had no influence on cough-related quality of life (142). The beneficial effect on cough in this study might possibly be due to the improvement in ILD rather than the immunosuppressive therapy itself. So currently, there is a lack of good therapies for cough in ILD. Whether results from studies on chronic cough can be extrapolated to ILD remains unclear, which underlines the necessity for more research into cough relief in ILD.

Fatigue

Fatigue is one of the major symptoms of ILD and has a significant influence on HRQOL (5, 7, 8)). Furthermore, fatigue predicts reduced physical activity in patients with IPF, independent of disease severity (151). Poor sleep quality has regularly been reported in ILDs and may be one of the contributing factors to fatigue (152). Medications and co-morbidities may also influence fatigue and factors such as sleep apnea, anemia, thromboembolism, and hypothyroidism, should be identified and treated (25). Although fatigue can be very burdensome, limited research has been done into the etiology and treatment of fatigue in ILD. A small study suggested a potential benefit of pulmonary rehabilitation on fatigue (153). No effective pharmacological treatment options are currently available.

Depression and anxiety

Depression and anxiety are common symptoms among ILD patients and can negatively impact HRQOL (6, 10). The reported prevalence of depressive symptoms in ILD is up to 49% (9, 130, 154, 155). Mild to severe anxiety symptoms may occur in up to 58% of patients, and clinically significant anxiety has been reported in about 12% of patients

(44, 130). One study showed that the presence of anxiety and depression was not related to disease severity and type of ILD. Dyspnea and comorbidities may be the main contributing factors to anxiety and depression in ILD (130, 156); the authors suggested that optimal management of these coexisting conditions may reduce anxiety and depressive symptoms.

No studies have specifically assessed the effect of pharmacological treatment on anxiety and depression in ILD. Therefore, standard treatment for anxiety and depression (i.e. anxiolytics and antidepressants) is currently advised in patients with ILD (25). Disease support programs and pulmonary rehabilitation may reduce anxiety and depression in ILD patients (43, 66, 71). Cognitive behavioral therapy has also been suggested as treatment option, but the effects on anxiety and depressive symptoms in ILD have not been studied (44). It is advised to discuss referrals for professional psychological counseling and support with all ILD patients presenting with anxiety and/or depressive symptoms.

Treatment limitations and end-of-life care

While the prognosis in ILD may vary, most patients with progressive fibrotic diseases will ultimately die from these diseases. Palliative care not only aims to improve quality of life for patients and families, but also quality of dying (25). To facilitate a dignified end-of-life path, patients' preferences should be known in order to anticipate needs. Many patients with progressive ILDs prefer talking about end-of-life early in the disease course. Some patients prefer to receive more gradual information about prognosis and end-of-life care, which emphasizes the need for regular assessments of individual patients' preferences during the disease trajectory (12, 13, 26, 28, 32).

A cross-sectional study in patients with cancer, cardiac diseases and chronic lung diseases (including ILD), showed that most patients preferred to die at home (157). Nonetheless, the majority of patients with IPF worldwide died in a hospital and a substantial number of patients died in the Intensive Care Unit (ICU)(117, 158, 159). The mortality rate for IPF patients in the ICU is high and prognosis after an ICU admission is poor (159-161). The percentage of patients dying in the ICU is highly variable across different countries, suggesting cultural differences regarding end-of-life discussions and the preferred place of death (158). Several retrospective studies showed that only a minority of ILD patients were referred to palliative care before their ICU admission (117, 161). Other studies showed that in ILD patients, end-of-life decisions were often not made (115), and that most end-of-life decisions were reported in the last days of life (159). Moreover, the majority of patients received life prolonging therapy and diagnostic procedures during the last days of their lives (159). Patients with oxygen-dependent ILD had less access to end-of-life care compared to patients with lung cancer in the last week of life, although their symptom burden was higher (162). One of the reasons for the poor access to

end-of-life care might be that in ILD patients, death was more frequently reported as "unexpected" than in lung cancer (162). Due to the unpredictable disease course, risk of acute exacerbations and rapid deterioration, it is strongly advised to initiate end-of-life discussions early in the disease course. During end-of-life conversations, issues such as treatment limitations (regarding intensive care, intubation and resuscitation) and the preferred place of dying, should be discussed with patients and caregivers (20, 25).

A decision aid tool facilitated communication and improved documentation of end-of-life decisions in ILD. Furthermore, it had the ability to identify patients in need of palliative care and led to earlier palliative care referrals (163). A multidisciplinary care program in IPF, which aimed at advanced care planning, reduced emergency room visits and hospitalizations in the last year of life. Patients who participated in the program died significantly more often at home (164). Although this was a retrospective study, the results are promising and may be used to improve end-of-life care in progressive ILDs. Though little structured research has been done in ILD about practical measures of symptom control in the dying phase, in practice many doctors will use similar approaches as for other respiratory diseases.

CONCLUSION

ILDs comprise a heterogeneous group of diseases, which often have a major impact on the lives of patients. Optimal management of patients with interstitial lung disease requires a comprehensive approach to care, which encompasses disease-modifying treatment, symptom-centered management, education and self-management strategies. Especially in the more progressive and fibrotic forms of ILD, treatment should not only be aimed at prolonging life, but also at improving quality of life for patients. Symptom-centered management in ILD includes, amongst others, supplemental oxygen, pulmonary rehabilitation and palliative care. In order to optimize individually tailored treatment, patients' needs and preferences should regularly be assessed during the disease course.

REFERENCES

1. Travis WD, Costabel U, Hansell DM, King TE, Jr., Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188(6):733-48.
2. van Manen MJ, Geelhoed JJ, Tak NC, Wijsenbeek MS. Optimizing quality of life in patients with idiopathic pulmonary fibrosis. Ther Adv Respir Dis. 2017;11(3):157-69.
3. Lee JS, McLaughlin S, Collard HR. Comprehensive care of the patient with idiopathic pulmonary fibrosis. Curr Opin Pulm Med. 2011;17(5):348-54.
4. Swigris JJ, Stewart AL, Gould MK, Wilson SR. Patients' perspectives on how idiopathic pulmonary fibrosis affects the quality of their lives. Health Qual Life Outcomes. 2005;3:61.
5. Yount SE, Beaumont JL, Chen SY, Kaiser K, Wortman K, Van Brunt DL, et al. Health-Related Quality of Life in Patients with Idiopathic Pulmonary Fibrosis. Lung. 2016;194(2):227-34.
6. Glaspole IN, Chapman SA, Cooper WA, Ellis SJ, Goh NS, Hopkins PM, et al. Health-related quality of life in idiopathic pulmonary fibrosis: Data from the Australian IPF Registry. Respirology. 2017;22(5):950-6.
7. Lubin M, Chen H, Elicker B, Jones KD, Collard HR, Lee JS. A comparison of health-related quality of life in idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis. Chest. 2014;145(6):1333-8.
8. Swigris JJ, Gould MK, Wilson SR. Health-related quality of life among patients with idiopathic pulmonary fibrosis. Chest. 2005;127(1):284-94.
9. Kreuter M, Swigris J, Pittrow D, Geier S, Klotsche J, Prasse A, et al. Health related quality of life in patients with idiopathic pulmonary fibrosis in clinical practice: insights-IPF registry. Respir Res. 2017;18(1):139.
10. Matsuda T, Taniguchi H, Ando M, Kondoh Y, Kimura T, Kataoka K, et al. Depression Is Significantly Associated with the Health Status in Patients with Idiopathic Pulmonary Fibrosis. Intern Med. 2017;56(13):1637-44.
11. Furukawa T, Taniguchi H, Ando M, Kondoh Y, Kataoka K, Nishiyama O, et al. The St. George's Respiratory Questionnaire as a prognostic factor in IPF. Respir Res. 2017;18(1):18.
12. Bonella F, Wijsenbeek M, Molina-Molina M, Duck A, Mele R, Geissler K, et al. European IPF Patient Charter: unmet needs and a call to action for healthcare policymakers. Eur Respir J. 2016;47(2):597-606.
13. van Manen MJ, Kreuter M, van den Blink B, Oltmanns U, Palmowski K, Brunnemer E, et al. What patients with pulmonary fibrosis and their partners think: a live, educative survey in the Netherlands and Germany. ERJ Open Res. 2017;3(1).
14. Duck A, Spencer LG, Bailey S, Leonard C, Ormes J, Caress AL. Perceptions, experiences and needs of patients with idiopathic pulmonary fibrosis. J Adv Nurs. 2015;71(5):1055-65.
15. Cosgrove GP, Bianchi P, Danese S, Lederer DJ. Barriers to timely diagnosis of interstitial lung disease in the real world: the INTENSITY survey. BMC Pulm Med. 2018;18(1):9.
16. Thickett DR, Kendall C, Spencer LG, Screaton N, Wallace WA, Pinnock H, et al. Improving care for patients with idiopathic pulmonary fibrosis (IPF) in the UK: a round table discussion. Thorax. 2014;69(12):1136-40.
17. Jo HE, Glaspole IN, Levin KC, McCormack SR, Mahar AM, Cooper WA, et al. Clinical impact of the interstitial lung disease multidisciplinary service. Respirology. 2016;21(8):1438-44.

18. Flaherty KR, Andrei AC, King TE, Jr., Raghu G, Colby TV, Wells A, et al. Idiopathic interstitial pneumonia: do community and academic physicians agree on diagnosis? Am J Respir Crit Care Med. 2007;175(10):1054-60.
19. Cottin V, Bourdin A, Crestani B, Prevot G, Guerin M, Bouquillon B. Healthcare pathway and patients' expectations in pulmonary fibrosis. ERJ Open Res. 2017;3(2).
20. Lindell KO, Kavalieratos D, Gibson KF, Tycon L, Rosenzweig M. The palliative care needs of patients with idiopathic pulmonary fibrosis: A qualitative study of patients and family caregivers. Heart Lung. 2017;46(1):24-9.
21. Lamas DJ, Kawut SM, Bagiella E, Philip N, Arcasoy SM, Lederer DJ. Delayed access and survival in idiopathic pulmonary fibrosis: a cohort study. Am J Respir Crit Care Med. 2011;184(7):842-7.
22. Russell AM, Ripamonti E, Vancheri C. Qualitative European survey of patients with idiopathic pulmonary fibrosis: patients' perspectives of the disease and treatment. BMC Pulm Med. 2016;16:10.
23. Duck A, Pigram L, Errhalt P, Ahmed D, Chaudhuri N. IPF Care: a support program for patients with idiopathic pulmonary fibrosis treated with pirfenidone in Europe. Adv Ther. 2015;32(2):87-107.
24. Shaw J, Marshall T, Morris H, Hayton C, Chaudhuri N. Idiopathic pulmonary fibrosis: a holistic approach to disease management in the antifibrotic age. J Thorac Dis. 2017;9(11):4700-7.
25. Kreuter M, Bendstrup E, Russell AM, Bajwah S, Lindell K, Adir Y, et al. Palliative care in interstitial lung disease: living well. Lancet Respir Med. 2017;5(12):968-80.
26. Sampson C, Gill BH, Harrison NK, Nelson A, Byrne A. The care needs of patients with idiopathic pulmonary fibrosis and their carers (CaNoPy): results of a qualitative study. BMC Pulm Med. 2015;15:155.
27. Schoenheit G, Becattelli I, Cohen AH. Living with idiopathic pulmonary fibrosis: an in-depth qualitative survey of European patients. Chron Respir Dis. 2011;8(4):225-31.
28. Overgaard D, Kaldan G, Marsaa K, Nielsen TL, Shaker SB, Egerod I. The lived experience with idiopathic pulmonary fibrosis: a qualitative study. Eur Respir J. 2016;47(5):1472-80.
29. Bajwah S, Higginson IJ, Ross JR, Wells AU, Birring SS, Riley J, et al. The palliative care needs for fibrotic interstitial lung disease: a qualitative study of patients, informal caregivers and health professionals. Palliat Med. 2013;27(9):869-76.
30. Bajwah S, Koffman J, Higginson IJ, Ross JR, Wells AU, Birring SS, et al. 'I wish I knew more ...' the end-of-life planning and information needs for end-stage fibrotic interstitial lung disease: views of patients, carers and health professionals. BMJ Support Palliat Care. 2013;3(1):84-90.
31. Collard HR, Tino G, Noble PW, Shreve MA, Michaels M, Carlson B, et al. Patient experiences with pulmonary fibrosis. Respir Med. 2007;101(6):1350-4.
32. Bridges JF, Paly VF, Barker E, Kervitsky D. Identifying the benefits and risks of emerging treatments for idiopathic pulmonary fibrosis: a qualitative study. Patient. 2015;8(1):85-92.
33. 2015 FVotp. The Voice of the Patient; A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative. 2015, march.
34. Belkin A, Albright K, Swigris JJ. A qualitative study of informal caregivers' perspectives on the effects of idiopathic pulmonary fibrosis. BMJ Open Respir Res. 2014;1(1):e000007.
35. Ramadurai D, Corder S, Churney T, Graney B, Harshman A, Meadows S, et al. Understanding the informational needs of patients with IPF and their caregivers: 'You get diagnosed, and you ask this question right away, what does this mean?'. BMJ Open Qual. 2018;7(1):e000207.
36. Moor CC, Heukels P, Kool M, Wijsenbeek MS. Integrating Patient Perspectives into Personalized Medicine in Idiopathic Pulmonary Fibrosis. Front Med (Lausanne). 2017;4:226.
37. Ziegelstein RC. Personomics. JAMA Intern Med. 2015;175(6):888-9.

38. Wuyts WA, Peccatori FA, Russell AM. Patient-centred management in idiopathic pulmonary fibrosis: similar themes in three communication models. Eur Respir Rev. 2014;23(132):231-8.
39. Britten N, Pope C, Halford S, Richeldi L. What if we made stratified medicine work for patients? Lancet Respir Med. 2016;4(1):8-10.
40. Shah RJ, Collard HR, Morisset J. Burden, resilience and coping in caregivers of patients with interstitial lung disease. Heart Lung. 2018;47(3):264-8.
41. Morisset J, Dube BP, Garvey C, Bourbeau J, Collard HR, Swigris JJ, et al. The Unmet Educational Needs of Patients with Interstitial Lung Disease. Setting the Stage for Tailored Pulmonary Rehabilitation. Ann Am Thorac Soc. 2016;13(7):1026-33.
42. Fisher JH, O'Connor D, Flexman AM, Shapera S, Ryerson CJ. Accuracy and Reliability of Internet Resources for Information on Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2016;194(2):218-25.
43. van Manen MJG, van 't Spijker A, Tak NC, Baars CT, Jongenotter SM, van Roon LR, et al. Patient and partner empowerment programme for idiopathic pulmonary fibrosis. Eur Respir J. 2017;49(4).
44. Lindell KO, Olshansky E, Song MK, Zullo TG, Gibson KF, Kaminski N, et al. Impact of a disease-management program on symptom burden and health-related quality of life in patients with idiopathic pulmonary fibrosis and their care partners. Heart Lung. 2010;39(4):304-13.
45. Magnani D, Lenoci G, Balduzzi S, Artioli G, Ferri P. Effectiveness of support groups to improve the quality of life of people with idiopathic pulmonary fibrosis a pre-post test pilot study. Acta Biomed. 2017;88(5-S):5-12.
46. Wicks P, Stamford J, Grootenhuis MA, Haverman L, Ahmed S. Innovations in e-health. Qual Life Res. 2014;23(1):195-203.
47. Moor CC, Wapenaar M, Miedema JR, Geelhoed JJM, Chandoesing PP, Wijsenbeek MS. A home monitoring program including real-time wireless home spirometry in idiopathic pulmonary fibrosis: a pilot study on experiences and barriers. Respir Res. 2018;19(1):105.
48. Moor CC, van Manen MJG, Tak NC, van Noort E, Wijsenbeek MS. Development and feasibility of an eHealth tool for idiopathic pulmonary fibrosis. Eur Respir J. 2018;51(3).
49. Russell AM, Adamali H, Molyneaux PL, Lukey PT, Marshall RP, Renzoni EA, et al. Daily Home Spirometry: An Effective Tool for Detecting Progression in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2016;194(8):989-97.
50. Johannson KA, Vittinghoff E, Morisset J, Lee JS, Balmes JR, Collard HR. Home monitoring improves endpoint efficiency in idiopathic pulmonary fibrosis. Eur Respir J. 2017;50(1).
51. Kondoh Y, Taniguchi H, Katsuta T, Kataoka K, Kimura T, Nishiyama O, et al. Risk factors of acute exacerbation of idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2010;27(2):103-10.
52. Alakhras M, Decker PA, Nadrous HF, Collazo-Clavell M, Ryu JH. Body mass index and mortality in patients with idiopathic pulmonary fibrosis. Chest. 2007;131(5):1448-53.
53. Pugashetti J, Graham J, Boctor N, Mendez C, Foster E, Juarez M, et al. Weight loss as a predictor of mortality in patients with interstitial lung disease. Eur Respir J. 2018;52(3).
54. Nakatsuka Y, Handa T, Kokosi M, Tanizawa K, Puglisi S, Jacob J, et al. The Clinical Significance of Body Weight Loss in Idiopathic Pulmonary Fibrosis Patients. Respiration. 2018;96(4):338-47.
55. Olson AL, Graney B, Baird S, Churney T, Fier K, Korn M, et al. Tracking dyspnea up to supplemental oxygen prescription among patients with pulmonary fibrosis. BMC Pulm Med. 2017;17(1):152.
56. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788-824.

57. Sharp C, Adamali H, Millar AB. Ambulatory and short-burst oxygen for interstitial lung disease. Cochrane Database Syst Rev. 2016;7:CD011716.
58. Bell EC, Cox NS, Goh N, Glaspole I, Westall GP, Watson A, et al. Oxygen therapy for interstitial lung disease: a systematic review. Eur Respir Rev. 2017;26(143).
59. Visca D, Mori L, Tsipouri V, Fleming S, Firouzi A, Bonini M, et al. Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial. Lancet Respir Med. 2018.
60. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188(8):e13-64.
61. Holland A, Hill C. Physical training for interstitial lung disease. Cochrane Database Syst Rev. 2008(4):CD006322.
62. Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, et al. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology. 2008;13(3):394-9.
63. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. Cochrane Database Syst Rev. 2014(10):CD006322.
64. Gomes-Neto M, Silva CM, Ezequiel D, Conceicao CS, Saquetto M, Machado AS. Impact of Pulmonary Rehabilitation on Exercise Tolerance and Quality of Life in Patients With Idiopathic Pulmonary Fibrosis: A SYSTEMATIC REVIEW AND META-ANALYSIS. J Cardiopulm Rehabil Prev. 2018;38(5):273-8.
65. Vainshelboim B, Oliveira J, Fox BD, Soreck Y, Fruchter O, Kramer MR. Long-term effects of a 12-week exercise training program on clinical outcomes in idiopathic pulmonary fibrosis. Lung. 2015;193(3):345-54.
66. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG, et al. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. Respir Med. 2014;108(1):203-10.
67. Holland AE, Hill CJ, Glaspole I, Goh N, McDonald CF. Predictors of benefit following pulmonary rehabilitation for interstitial lung disease. Respir Med. 2012;106(3):429-35.
68. Huppmann P, Sczepanski B, Boensch M, Winterkamp S, Schonheit-Kenn U, Neurohr C, et al. Effects of inpatient pulmonary rehabilitation in patients with interstitial lung disease. Eur Respir J. 2013;42(2):444-53.
69. Dowman LM, McDonald CF, Bozinovski S, Vlahos R, Gillies R, Pouniotis D, et al. Greater endurance capacity and improved dyspnoea with acute oxygen supplementation in idiopathic pulmonary fibrosis patients without resting hypoxaemia. Respirology. 2017;22(5):957-64.
70. Du Plessis JP, Fernandes S, Jamal R, Camp P, Johannson K, Schaeffer M, et al. Exertional hypoxemia is more severe in fibrotic interstitial lung disease than in COPD. Respirology. 2018;23(4):392-8.
71. Holland AE, Dowman LM, Hill CJ. Principles of rehabilitation and reactivation: interstitial lung disease, sarcoidosis and rheumatoid disease with respiratory involvement. Respiration. 2015;89(2):89-99.
72. Holland AE, Fiore JF, Jr., Goh N, Symons K, Dowman L, Westall G, et al. Be honest and help me prepare for the future: What people with interstitial lung disease want from education in pulmonary rehabilitation. Chron Respir Dis. 2015;12(2):93-101.
73. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax. 2008;63 Suppl 5:v1-58.

74. Litinsky I, Balbir A, Zisman D, Mandelboim M, Mendelson E, Feld J, et al. Vaccination against influenza in patients with systemic sclerosis. Clin Exp Rheumatol. 2012;30(2 Suppl 71):S7-11.
75. Kuronuma K, Honda H, Mikami T, Saito A, Ikeda K, Otsuka M, et al. Response to pneumococcal vaccine in interstitial lung disease patients: Influence of systemic immunosuppressive treatment. Vaccine. 2018;36(33):4968-72.
76. Mercado U, Acosta H, Diaz-Molina R. Antibody response to pneumococcal polysaccharide vaccine in systemic sclerosis. J Rheumatol. 2009;36(7):1549-50.
77. Margaritopoulos GA, Vasarmidi E, Jacob J, Wells AU, Antoniou KM. Smoking and interstitial lung diseases. Eur Respir Rev. 2015;24(137):428-35.
78. Lee JS, Fischer A. Current and emerging treatment options for interstitial lung disease in patients with rheumatic disease. Expert Rev Clin Immunol. 2016;12(5):509-20.
79. Hudson M, Lo E, Lu Y, Hercz D, Baron M, Steele R, et al. Cigarette smoking in patients with systemic sclerosis. Arthritis Rheum. 2011;63(1):230-8.
80. Meyer KC, Decker CA. Role of pirfenidone in the management of pulmonary fibrosis. Ther Clin Risk Manag. 2017;13:427-37.
81. Fernandez-Perez ER, Yilmaz M, Jenad H, Daniels CE, Ryu JH, Hubmayr RD, et al. Ventilator settings and outcome of respiratory failure in chronic interstitial lung disease. Chest. 2008;133(5):1113-9.
82. Bando M, Ohno S, Hosono T, Yanase K, Sato Y, Sohara Y, et al. Risk of Acute Exacerbation After Video-assisted Thoracoscopic Lung Biopsy for Interstitial Lung Disease. J Bronchology Interv Pulmonol. 2009;16(4):229-35.
83. Miyajima M, Watanabe A, Sato T, Teramukai S, Ebina M, Kishi K, et al. What factors determine the survival of patients with an acute exacerbation of interstitial lung disease after lung cancer resection? Surg Today. 2018;48(4):404-15.
84. British Lung Foundation. IPF report 2015 - Lost in the system: British Lung Foundation; 2015 [updated 2018. Available from: https://www.blf.org.uk/sites/default/files/BLF-IPF-Report-2015---Lost-in-the-System---250215.pdf.
85. Kreuter M, Ehlers-Tenenbaum S, Palmowski K, Bruhwyler J, Oltmanns U, Muley T, et al. Impact of Comorbidities on Mortality in Patients with Idiopathic Pulmonary Fibrosis. PLoS One. 2016;11(3):e0151425.
86. Margaritopoulos GA, Antoniou KM, Wells AU. Comorbidities in interstitial lung diseases. Eur Respir Rev. 2017;26(143).
87. Hyldgaard C, Hilberg O, Bendstrup E. How does comorbidity influence survival in idiopathic pulmonary fibrosis? Respir Med. 2014;108(4):647-53.
88. Suzuki A, Kondoh Y. The clinical impact of major comorbidities on idiopathic pulmonary fibrosis. Respir Investig. 2017;55(2):94-103.
89. Costabel U, King TE. International consensus statement on idiopathic pulmonary fibrosis. Eur Respir J. 2001;17(2):163-7.
90. Luppi F, Cerri S, Beghe B, Fabbri LM, Richeldi L. Corticosteroid and immunomodulatory agents in idiopathic pulmonary fibrosis. Respir Med. 2004;98(11):1035-44.
91. Idiopathic Pulmonary Fibrosis Clinical Research N, Raghu G, Anstrom KJ, King TE, Jr., Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;366(21):1968-77.
92. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071-82.

93. King TE, Jr., Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083-92.
94. Nathan SD, Albera C, Bradford WZ, Costabel U, Glaspole I, Glassberg MK, et al. Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis. Lancet Respir Med. 2017;5(1):33-41.
95. Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med. 2015;192(2):e3-19.
96. Juge PA, Lee JS, Ebstein E, Furukawa H, Dobrinskikh E, Gazal S, et al. MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease. N Engl J Med. 2018.
97. Hyldgaard C, Hilberg O, Pedersen AB, Ulrichsen SP, Lokke A, Bendstrup E, et al. A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis. 2017;76(10):1700-6.
98. Denton CP, Wells AU, Coghlan JG. Major lung complications of systemic sclerosis. Nat Rev Rheumatol. 2018;14(9):511-27.
99. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4(9):708-19.
100. Ohshimo S, Bonella F, Guzman J, Costabel U. Hypersensitivity pneumonitis. Immunol Allergy Clin North Am. 2012;32(4):537-56.
101. Lederer DJ, Martinez FJ. Idiopathic Pulmonary Fibrosis. N Engl J Med. 2018;378(19):1811-23.
102. Brownell R, Kaminski N, Woodruff PG, Bradford WZ, Richeldi L, Martinez FJ, et al. Precision Medicine: The New Frontier in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2016;193(11):1213-8.
103. Kumar A, Kapnadak SG, Girgis RE, Raghu G. Lung transplantation in idiopathic pulmonary fibrosis. Expert Rev Respir Med. 2018;12(5):375-85.
104. Brown AW, Kaya H, Nathan SD. Lung transplantation in IIP: A review. Respirology. 2016;21(7):1173-84.
105. ISHLT. ISHLT registries overview: The international society for heart and lung transplantation; 2018 [Available from: https://www.ishlt.org/registries/overview.
106. Valapour M, Lehr CJ, Skeans MA, Smith JM, Carrico R, Uccellini K, et al. OPTN/SRTR 2016 Annual Data Report: Lung. Am J Transplant. 2018;18 Suppl 1:363-433.
107. Kilic A, Merlo CA, Conte JV, Shah AS. Lung transplantation in patients 70 years old or older: have outcomes changed after implementation of the lung allocation score? J Thorac Cardiovasc Surg. 2012;144(5):1133-8.
108. Weill D. Lung transplantation: indications and contraindications. J Thorac Dis. 2018;10(7):4574-87.
109. Jablonski R, Dematte J, Bhorade S. Lung transplantation in scleroderma: recent advances and lessons. Curr Opin Rheumatol. 2018;30(6):562-9.
110. Fadul N, Elsayem A, Palmer JL, Del Fabbro E, Swint K, Li Z, et al. Supportive versus palliative care: what's in a name?: a survey of medical oncologists and midlevel providers at a comprehensive cancer center. Cancer. 2009;115(9):2013-21.
111. LeBlanc TW, O'Donnell JD, Crowley-Matoka M, Rabow MW, Smith CB, White DB, et al. Perceptions of palliative care among hematologic malignancy specialists: a mixed-methods study. J Oncol Pract. 2015;11(2):e230-8.

112. Zimmermann C, Swami N, Krzyzanowska M, Leighl N, Rydall A, Rodin G, et al. Perceptions of palliative care among patients with advanced cancer and their caregivers. Cmaj. 2016;188(10):E217-27.
113. WHO. www.who.int: World Health Organization; 2018 [updated 2018. Available from: www.who.int.
114. Brown CE, Jecker NS, Curtis JR. Inadequate Palliative Care in Chronic Lung Disease. An Issue of Health Care Inequality. Ann Am Thorac Soc. 2016;13(3):311-6.
115. Brown CE, Engelberg RA, Nielsen EL, Curtis JR. Palliative Care for Patients Dying in the Intensive Care Unit with Chronic Lung Disease Compared with Metastatic Cancer. Ann Am Thorac Soc. 2016;13(5):684-9.
116. Bajwah S, Higginson IJ, Ross JR, Wells AU, Birring SS, Patel A, et al. Specialist palliative care is more than drugs: a retrospective study of ILD patients. Lung. 2012;190(2):215-20.
117. Lindell KO, Liang Z, Hoffman LA, Rosenzweig MQ, Saul MI, Pilewski JM, et al. Palliative care and location of death in decedents with idiopathic pulmonary fibrosis. Chest. 2015;147(2):423-9.
118. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010;363(8):733-42.
119. Bakitas MA, Tosteson TD, Li Z, Lyons KD, Hull JG, Li Z, et al. Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial. J Clin Oncol. 2015;33(13):1438-45.
120. Dionne-Odom JN, Azuero A, Lyons KD, Hull JG, Tosteson T, Li Z, et al. Benefits of Early Versus Delayed Palliative Care to Informal Family Caregivers of Patients With Advanced Cancer: Outcomes From the ENABLE III Randomized Controlled Trial. J Clin Oncol. 2015;33(13):1446-52.
121. Higginson IJ, Bausewein C, Reilly CC, Gao W, Gysels M, Dzingina M, et al. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. Lancet Respir Med. 2014;2(12):979-87.
122. Bajwah S, Ross JR, Wells AU, Mohammed K, Oyebode C, Birring SS, et al. Palliative care for patients with advanced fibrotic lung disease: a randomised controlled phase II and feasibility trial of a community case conference intervention. Thorax. 2015;70(9):830-9.
123. Ryerson CJ, Donesky D, Pantilat SZ, Collard HR. Dyspnea in idiopathic pulmonary fibrosis: a systematic review. J Pain Symptom Manage. 2012;43(4):771-82.
124. Ryerson CJ, Collard HR, Pantilat SZ. Management of dyspnea in interstitial lung disease. Curr Opin Support Palliat Care. 2010;4(2):69-75.
125. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Ogawa T, Watanabe F, et al. Health-related quality of life in patients with idiopathic pulmonary fibrosis. What is the main contributing factor? Respir Med. 2005;99(4):408-14.
126. Janssen DJ, Wouters EF, Spruit MA. Psychosocial consequences of living with breathlessness due to advanced disease. Curr Opin Support Palliat Care. 2015;9(3):232-7.
127. Manali ED, Stathopoulos GT, Kollintza A, Kalomenidis I, Emili JM, Sotiropoulou C, et al. The Medical Research Council chronic dyspnea score predicts the survival of patients with idiopathic pulmonary fibrosis. Respir Med. 2008;102(4):586-92.
128. Khadawardi H, Mura M. A simple dyspnoea scale as part of the assessment to predict outcome across chronic interstitial lung disease. Respirology. 2017;22(3):501-7.
129. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Kato K, Kataoka K, et al. A simple assessment of dyspnoea as a prognostic indicator in idiopathic pulmonary fibrosis. Eur Respir J. 2010;36(5):1067-72.
130. Holland AE, Fiore JF, Jr., Bell EC, Goh N, Westall G, Symons K, et al. Dyspnoea and comorbidity contribute to anxiety and depression in interstitial lung disease. Respirology. 2014;19(8):1215-21.

131. Milne KM, Kwan JM, Guler S, Winstone TA, Le A, Khalil N, et al. Frailty is common and strongly associated with dyspnoea severity in fibrotic interstitial lung disease. Respirology. 2017;22(4):728-34.
132. Kohberg C, Andersen CU, Bendstrup E. Opioids: an unexplored option for treatment of dyspnea in IPF. Eur Clin Respir J. 2016;3:30629.
133. Boyden JY, Connor SR, Otolorin L, Nathan SD, Fine PG, Davis MS, et al. Nebulized medications for the treatment of dyspnea: a literature review. J Aerosol Med Pulm Drug Deliv. 2015;28(1):1-19.
134. Kolb M, Raghu G, Wells AU, Behr J, Richeldi L, Schinzel B, et al. Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis. N Engl J Med. 2018;379(18):1722-31.
135. Galbraith S, Fagan P, Perkins P, Lynch A, Booth S. Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial. J Pain Symptom Manage. 2010;39(5):831-8.
136. Booth S, Galbraith S, Ryan R, Parker RA, Johnson M. The importance of the feasibility study: Lessons from a study of the hand-held fan used to relieve dyspnea in people who are breathless at rest. Palliat Med. 2016;30(5):504-9.
137. Luckett T, Phillips J, Johnson MJ, Farquhar M, Swan F, Assen T, et al. Contributions of a hand-held fan to self-management of chronic breathlessness. Eur Respir J. 2017;50(2).
138. van Manen MJ, Birring SS, Vancheri C, Cottin V, Renzoni EA, Russell AM, et al. Cough in idiopathic pulmonary fibrosis. Eur Respir Rev. 2016;25(141):278-86.
139. Saunders P, Maher TM. Cough in fibrotic lung disease: An unresolved challenge. Respirology. 2017;22(8):1491-2.
140. Cheng JZ, Wilcox PG, Glaspole I, Corte TJ, Murphy D, Hague CJ, et al. Cough is less common and less severe in systemic sclerosis-associated interstitial lung disease compared to other fibrotic interstitial lung diseases. Respirology. 2017;22(8):1592-7.
141. Ryerson CJ, Abbritti M, Ley B, Elicker BM, Jones KD, Collard HR. Cough predicts prognosis in idiopathic pulmonary fibrosis. Respirology. 2011;16(6):969-75.
142. Tashkin DP, Volkmann ER, Tseng CH, Roth MD, Khanna D, Furst DE, et al. Improved Cough and Cough-Specific Quality of Life in Patients Treated for Scleroderma-Related Interstitial Lung Disease: Results of Scleroderma Lung Study II. Chest. 2017;151(4):813-20.
143. Garner J, George PM, Renzoni E. Cough in interstitial lung disease. Pulm Pharmacol Ther. 2015;35:122-8.
144. Madison JM, Irwin RS. Chronic cough in adults with interstitial lung disease. Curr Opin Pulm Med. 2005;11(5):412-6.
145. Horton MR, Santopietro V, Mathew L, Horton KM, Polito AJ, Liu MC, et al. Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis: a randomized trial. Ann Intern Med. 2012;157(6):398-406.
146. Birring SS, Wijsenbeek MS, Agrawal S, van den Berg JWK, Stone H, Maher TM, et al. A novel formulation of inhaled sodium cromoglicate (PA101) in idiopathic pulmonary fibrosis and chronic cough: a randomised, double-blind, proof-of-concept, phase 2 trial. Lancet Respir Med. 2017;5(10):806-15.
147. van Manen MJG, Birring SS, Vancheri C, Vindigni V, Renzoni E, Russell AM, et al. Effect of pirfenidone on cough in patients with idiopathic pulmonary fibrosis. Eur Respir J. 2017;50(4).
148. Hope-Gill BD, Hilldrup S, Davies C, Newton RP, Harrison NK. A study of the cough reflex in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2003;168(8):995-1002.
149. Kilduff CE, Counter MJ, Thomas GA, Harrison NK, Hope-Gill BD. Effect of acid suppression therapy on gastroesophageal reflux and cough in idiopathic pulmonary fibrosis: an intervention study. Cough. 2014;10:4.

150. Raghu G, Pellegrini CA, Yow E, Flaherty KR, Meyer K, Noth I, et al. Laparoscopic anti-reflux surgery for the treatment of idiopathic pulmonary fibrosis (WRAP-IPF): a multicentre, randomised, controlled phase 2 trial. Lancet Respir Med. 2018;6(9):707-14.
151. Bahmer T, Kirsten AM, Waschki B, Rabe KF, Magnussen H, Kirsten D, et al. Clinical Correlates of Reduced Physical Activity in Idiopathic Pulmonary Fibrosis. Respiration. 2016;91(6):497-502.
152. Milioli G, Bosi M, Poletti V, Tomassetti S, Grassi A, Riccardi S, et al. Sleep and respiratory sleep disorders in idiopathic pulmonary fibrosis. Sleep Med Rev. 2016;26:57-63.
153. Swigris JJ, Fairclough DL, Morrison M, Make B, Kozora E, Brown KK, et al. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis. Respir Care. 2011;56(6):783-9.
154. Akhtar AA, Ali MA, Smith RP. Depression in patients with idiopathic pulmonary fibrosis. Chron Respir Dis. 2013;10(3):127-33.
155. Ryerson CJ, Arean PA, Berkeley J, Carrieri-Kohlman VL, Pantilat SZ, Landefeld CS, et al. Depression is a common and chronic comorbidity in patients with interstitial lung disease. Respirology. 2012;17(3):525-32.
156. Ryerson CJ, Berkeley J, Carrieri-Kohlman VL, Pantilat SZ, Landefeld CS, Collard HR. Depression and functional status are strongly associated with dyspnea in interstitial lung disease. Chest. 2011;139(3):609-16.
157. Skorstengaard MH, Neergaard MA, Andreassen P, Brogaard T, Bendstrup E, Lokke A, et al. Preferred Place of Care and Death in Terminally Ill Patients with Lung and Heart Disease Compared to Cancer Patients. J Palliat Med. 2017.
158. Wijsenbeek M, Bendstrup E, Ross J, Wells A. Cultural Differences in Palliative Care in Patients With Idiopathic Pulmonary Fibrosis. Chest. 2015;148(2):e56.
159. Rajala K, Lehto JT, Saarinen M, Sutinen E, Saarto T, Myllarniemi M. End-of-life care of patients with idiopathic pulmonary fibrosis. BMC Palliat Care. 2016;15(1):85.
160. Mallick S. Outcome of patients with idiopathic pulmonary fibrosis (IPF) ventilated in intensive care unit. Respir Med. 2008;102(10):1355-9.
161. Liang Z, Hoffman LA, Nouraie M, Kass DJ, Donahoe MP, Gibson KF, et al. Referral to Palliative Care Infrequent in Patients with Idiopathic Pulmonary Fibrosis Admitted to an Intensive Care Unit. J Palliat Med. 2017;20(2):134-40.
162. Ahmadi Z, Wysham NG, Lundstrom S, Janson C, Currow DC, Ekstrom M. End-of-life care in oxygen-dependent ILD compared with lung cancer: a national population-based study. Thorax. 2016;71(6):510-6.
163. Sharp C, Lamb H, Jordan N, Edwards A, Gunary R, Meek P, et al. Development of tools to facilitate palliative and supportive care referral for patients with idiopathic pulmonary fibrosis. BMJ Support Palliat Care. 2017.
164. Kalluri M, Claveria F, Ainsley E, Haggag M, Armijo-Olivo S, Richman-Eisenstat J. Beyond Idiopathic Pulmonary Fibrosis Diagnosis: Multidisciplinary Care With an Early Integrated Palliative Approach Is Associated With a Decrease in Acute Care Utilization and Hospital Deaths. J Pain Symptom Manage. 2018;55(2):420-6.