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# Current best practice in rehabilitation in interstitial lung disease

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***Abstract:*** Interstitial lung disease (ILD) is a group of chronic respiratory diseases characterized by dyspnoea on exertion and decline in health-related quality of life (HRQL). People with ILD experience significant exercise limitation with contributors that include ventilatory limitation, impaired gas exchange, decreased cardiac function and skeletal muscle dysfunction. Pulmonary rehabilitation (PR) is well established in patients with chronic obstructive pulmonary disease (COPD) as a means to overcome exercise limitation and improve activity-related dyspnoea. There is increasing evidence for similar effects of PR in people with ILD. This review discusses the evidence for PR in ILD, outlines the essential components of PR in this population, and highlights special considerations for exercise training in people with ILD. Possible future directions for PR research in people with ILD are explored.

***Keywords:*** education, exercise limitation, exercise training, interstitial lung disease, pulmonary rehabilitation

## Introduction

The interstitial lung diseases (ILDs) are an incapacitating group of chronic respiratory diseases that includes interstitial pulmonary fibrosis (IPF). Patients with ILD suffer from symptoms such as dyspnoea, cough, fatigue, anxiety and depression. Individuals with ILD have reduced health-related quality of life (HRQL) that tends to worsen with disease progression. Pulmonary rehabilitation (PR) could be an effective intervention to improve symptoms, HRQL and functional status in people with ILD. Whilst there is strong evidence for the benefit of PR in other chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD), the evidence for PR in ILD is still emerging. In this review article, we aim to describe current best practice in PR for ILD.

## Exercise limitation in interstitial lung disease

Reduced exercise capacity is a cardinal feature of the ILDs, and exercise limitation may be a more robust predictor of prognosis than resting lung function. The 6-minute walk distance (6MWD) has been shown to be an independent predictor of mortality in patients with IPF [Du Bois *et al.* 2014]. In a group of people with IPF ($n = 748$) participating in a randomized controlled trial (RCT), a baseline 6MWD $< 250$ m was associated with a twofold increase in mortality [hazard ratio, 2.12; 95% confidence interval (CI), 1.15–3.92]. A decline in 6MWD over 50 m between baseline and 24 weeks was associated with an almost threefold increase in mortality (hazard ratio, 2.73; 95% CI, 1.60–4.66). Oxyhaemoglobin desaturation during exercise also has prognostic significance. Patients with IPF who desaturated to $\leqslant 88\%$ during a 6-minute walk test (6MWT) had a median survival of 3.21 years, compared with 6.83 years in those who did not desaturate [Flaherty *et al.* 2006]. The strong relationship of exercise variables with important outcomes in ILD has led to increasing interest in therapies that might improve exercise performance.

Exercise limitation in ILD is multifactorial, with contributions including impairment of gas exchange and pulmonary circulation, ventilatory dysfunction and muscle dysfunction. The latter is an emerging area that might be particularly amenable to amelioration with PR.

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### Impairments to gas exchange and pulmonary circulation

Gas exchange limitation occurs due to pulmonary capillary destruction or membrane thickening, resulting in impaired diffusion capacity and ventilation–perfusion inequality. Consequently, exercise-induced oxyhaemoglobin desaturation is often profound, and hypoxaemia may be present at rest. Circulatory limitation may occur secondary to pulmonary capillary destruction, hypoxic pulmonary vasoconstriction or cardiac dysfunction [Agusti *et al.* 1991]. Evaluation of cardiopulmonary exercise test parameters (CPET), particularly ventilatory equivalent for $CO_2$ ($V'E/V'CO_2$) at anaerobic threshold can indicate the severity of circulatory impairment and predict the prognosis of IPF [Van Der Plas *et al.* 2014]. In patients with increased $V'E/V'CO_2$ (>45.0) there is an association with poorer survival (hazard ratio, 1.039; $p = 0.024$) [Van Der Plas *et al.* 2014].

Pulmonary hypertension (PH) is also a common comorbidity in ILD, especially in advanced disease. Recently, PH has also been demonstrated in those with less severe restriction [Raghu *et al.* 2015]. In patients with IPF ($n = 488$) and mild-moderate lung volume restriction, right heart catheterization revealed that 14% had WHO Group 3 PH (associated with pulmonary disease) and 5% had WHO Group 2 PH (associated with left heart disease). Participants with WHO Group 3 PH displayed a lower diffusion capacity, shorter 6MWD and decreased oxyhaemoglobin saturation on exertion compared with those without evidence of PH [Raghu *et al.* 2015].

### Ventilatory limitation

People with ILD may exhibit an abnormal respiratory pattern with decreased tidal volume and a rapid respiratory rate, particularly during exercise. However, abnormal ventilatory mechanics is not the major limitation to exercise performance. A large ventilatory reserve at the end of exercise, with the ability to increase minute ventilation in response to both oxygen and external dead space has been noted [Hansen and Wasserman, 1996; Harris-Eze *et al.* 1996]. This suggests that other factors may be more important contributors to decreased exercise performance.

### Muscle dysfunction

Inflammatory contributors to the pathogenesis of ILD may potentiate peripheral muscle dysfunction. In people with IPF, antioxidant capacity is reduced and response to excess reactive oxygen species (ROS) in the lower respiratory tract is diminished, both of which can induce oxidative stress [Beeh *et al.* 2002]. Production of ROS has also been associated with a decrease in plasma total antioxidant capacity after exercise in people with IPF [Jackson *et al.* 2014]. In addition, ILD patients may receive treatments such as glucocorticoids and immunosuppressive therapy, which are known to cause drug-induced myopathy. Daily use of corticosteroids for >1 year significantly decreases muscle function in patients with chronic respiratory disease [Levin *et al.* 2014]. Muscle dysfunction may also be related to nutrition and ageing. In people with COPD, nutritional status and age have a close relationship with muscle mass [American Thoracic Society and European Respiratory Society, 1999]. Whether this same relationship between worse nutritional status and ageing is also a risk factor for muscle dysfunction in people with ILD is not yet known.

Muscle size, strength and functional outcomes have been assessed in patients with ILD. Reduced quadricep strength and endurance was seen in patients with fibrotic idiopathic interstitial pneumonias relative to healthy controls [Mendoza *et al.* 2014]. However, there was no association between 6MWD and quadricep force [Mendoza *et al.* 2014]. Patients with advanced ILD awaiting lung transplant display smaller muscle cross-sectional area and lower strength compared with healthy controls [Mendes *et al.* 2015]. A distinctive pattern of disuse, with greater atrophy and weakness in lower limb muscles compared with the upper limbs is also apparent [Mendes *et al.* 2015]. This suggests physical inactivity may play a role in muscle dysfunction, particularly in advanced disease. People with ILD and dust-related ILD are markedly inactive compared with healthy peers [Wickerson *et al.* 2013; Dale *et al.* 2015]; however, activity levels are improved on days when participating in PR [Wickerson *et al.* 2013]. This highlights the multifactorial benefits that may be achieved through PR in this group.

Studies of muscle dysfunction in ILD, to date, demonstrate limitations. Sample sizes are small, and disease severity and phenotype are often not adequately described. Future research with direct investigation of muscle structure, using muscle biopsy and histological examination of fibre type and size, may be warranted. New evidence of the

pathophysiological cause of muscle dysfunction in ILD may influence the prescription of both exercise training and oxygen therapy in PR.

## Evidence for pulmonary rehabilitation in interstitial lung disease

There is accumulating evidence to support short-term benefits of PR for ILD. A Cochrane review analysed nine RCTs of PR in ILD, of which three were published in abstract form only [Dowman *et al.* 2014]. Most studies included participants with several types of ILD; however, four studies examined predominantly individuals with IPF, and one, individuals with sarcoidosis. One study was of home-based PR. These studies had differing lengths of PR programme, from 5 to 12 weeks. Three studies performed aerobic training and four studies included both aerobic and resistance training. Other interventions such as educational lectures, nutritional and psychosocial support, were provided in most studies. No adverse effects of PR were reported. Meaningful improvements in exercise capacity were seen following PR, with a weighted mean difference (WMD) for change in 6MWD of 44.34 m and 1.24 ml/kg/minute in peak oxygen consumption ($VO_2$). These improvements were confirmed in the subgroup with IPF (WMD 35.63 m and 1.46 ml/kg/min, respectively). Dyspnoea was reduced and HRQL improved, with a similar magnitude of benefit seen in the subgroup with IPF compared with other participants. Most studies were short term, so no data on survival could be presented. The two studies that evaluated effects at 3–6 months following programme completion did not find evidence of sustained benefit for exercise capacity and HRQL.

## Guideline recommendations for pulmonary rehabilitation in interstitial lung disease

Recommendations for PR currently vary across international guidelines and statements. The American Thoracic Society/European Respiratory Society Statement on PR suggests meaningful short-term benefits should be gained from PR in ILD [Spruit *et al.* 2013]. The international statement on the management of IPF makes a weak positive recommendation for PR [Raghu *et al.* 2011]. The National Institute of Health and Care Exellence (NICE) guideline suggests PR is likely to be cost effective in IPF when offered every 6–12 months [NICE, 2013]. Conversely, British guidelines for PR do not make any specific recommendation, citing the wide variation in patient presentation, lack of comprehensive PR studies (as opposed to exercise only) and the likelihood of rapid deterioration in some patients that potentially makes PR futile [Bolton *et al.* 2013]. The differences in recommendations between major international guidelines emphasize the challenges in application of PR to this diverse patient group, particularly with regard to patient selection, programme components and duration of benefits. Current knowledge of these important issues is discussed in the following sections.

## Patient selection and timing of pulmonary rehabilitation in interstitial lung disease

The ILDs display differing severity of clinical features and natural history, making prognosis difficult to predict [Raghu *et al.* 2011] and leading to concerns that some patients with progressive diseases may not benefit [Bolton *et al.* 2013]. However the Cochrane review on this topic showed similar improvements in 6MWD following PR in IPF compared with other ILDs [Dowman *et al.* 2014]. Improvements in both groups exceeded the minimum important difference for 6MWD in ILD [Holland *et al.* 2012]. There are fewer data to guide practice in other ILDs such as nonspecific interstitial pneumonia, hypersensitivity pneumonia and connective tissue disease (CTD) ILD, despite inclusion of such patients in clinical trials of PR [Holland *et al.* 2015a]. Although robust studies of PR are difficult to conduct in the rarer ILDs, consistent evidence of benefit continues to emerge. Recently, beneficial effects of PR in patients with lymphangioleiomyomatosis (LAM) were reported [Araujo *et al.* 2016]. Forty patients with LAM performed 24-exercise training sessions over 12 weeks and received disease-specific education. Significant improvements in 6MWD, endurance time, physical activity, muscle strength, dyspnoea and HRQL were reported. Although not randomized, with participants allocated to groups based on how far they lived from the training centre, effect sizes were consistent with those seen in previous PR studies in ILD. In summary, existing studies suggest that PR is effective across the spectrum of ILD and could be offered to all patients who are symptomatic on exertion, regardless of underlying diagnosis.

Specific characteristics and features of patients with ILD may be associated with a greater response to PR (Table 1) [Kozu *et al.* 2011; Holland *et al.* 2012; Huppmann *et al.* 2013; Ryerson *et al.* 2014; Spielmanns *et al.* 2016].

**Table 1.** Predictors of pulmonary rehabilitation outcome in interstitial lung disease.

| Study | Programme type | Patients | Outcome | Predictor |
|---|---|---|---|---|
| Kozu *et al.* [2011] | Outpatient PR, 8 weeks patients with IPF | IPF, mean FVC 68.6 (16)% predicted | Increase in 6MWD | MRC dyspnoea – greater improvement in those with less dyspnoea: grade 2 *versus* grade 5, 31 m further; grade 2 *versus* grade 4, 22 m further |
| Holland *et al.* [2012] | Outpatient PR, short term, 8 weeks; long term, 6 months: patients with ILD | IPF, mean FVC 76.4 (6.8)% predicted, short | Increase in 6MWD immediately following PR | Greater improvement in those with higher FVC, less desaturation on exertion, lower right ventricular systolic pressure (IPF only) |
| | | Other ILD, mean FVC 68.1 (8.4)% predicted, short | Increase in 6MWD 6 months following PR | Less exercise-induced desaturation at baseline (IPF only) |
| | | IPF, long | | |
| | | Other IPF, long | Reduction in CRQ dyspnoea immediately following PR<br>Reduction in CRQ dyspnoea at 6 months following PR | No predictors<br>Greater baseline dyspnoea |
| Huppmann *et al.* [2013] | Inpatient PR patients with ILD | ILD, mean FVC 54 (1)% predicted, IPF (5), IIP other than IPF (15), HP (12), CTD (12) | Increase in 6MWD | Lower baseline 6MWD |
| | | ILD who did not have documented sign of PF 72% | Increase in 6MWD | No PH |
| Ryerson *et al.* [2014] | Outpatient PR patients with ILD | ILD, mean FVC 69.2 (21.2)% predicted, IPF (41), unclassifiable ILD (15), fibrotic NSIP (9) | Increase in 6MWD | Lower baseline 6MWD |
| Spielmanns *et al.* [2016] | Inpatient PR patients with ILD | ILD, mean FVC F/M 53.6 (22.8)/56.8 (31.2)% predicted | No change in 6MWD | Higher baseline 6MWD |

Data are presented as mean (SD) and percentage of ILD group (%).
6MWD, 6-minute walk distance; CRQ, Chronic Respiratory Disease Questionnaire; CTD, connective tissue disease; F, female; M, male; FVC, forced vital capacity; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; M, male; MRC, Medical Research Council; PH, pulmonary hypertension; PR, pulmonary rehabilitation; HP, hypersensitivity pneumonitis; NSIP, non-specific interstitial pneumonia.

Patients with a higher forced vital capacity, less desaturation on exertion and less disability on commencement of PR have demonstrated greater improvements in exercise capacity [Kozu *et al.* 2011; Holland *et al.* 2012]. More severe baseline breathlessness has also been associated with larger improvement in dyspnoea at 6 months after PR [Holland *et al.* 2012]. In a prospective cohort study, poorer 6MWD at baseline was an independent predictor of improvement in 6MWD on PR completion ($r = -0.49$, $p < 0.0005$) [Ryerson *et al.* 2014]. In IPF, PR delivered to patients with milder disease might be more likely to produce positive outcomes [Holland *et al.* 2012]. Although current evidence does not identify the ideal timing of PR for ILD, referral early in the disease course may confer greater benefits.

## Length of training period and duration of benefits

The ideal duration of PR for people with ILD is unclear. The British guidelines for PR recommend programmes of 6–12 weeks duration, but no recommendations specific to ILD are made [Bolton *et al.* 2013]. The RCTs of outpatient PR in ILD have had programme durations ranging from 5 to 12 weeks [Dowman *et al.* 2014]. Generally, these trials were all associated with advantageous outcomes, suggesting a standard length of PR programme might be effective for participants with ILD.

A longer PR programme may assist with maintenance of benefits. Vashelboim and colleagues randomized participants to 12 weeks of exercise training or usual care, with 11 months follow up [Vainshelboim *et al.* 2015]. Although differences between groups in 6MWD were no longer evident at 11 months following training, significant differences were maintained for 30-second chair stand and St George's Respiratory Questionnaire (SGRQ), suggesting sustained improvement in leg strength and HRQL following PR. At 30 months, the survival analysis showed no significant differences between the exercise training group and control group. Further study is required to investigate whether longer training periods can increase the duration of benefit for PR in ILD.

## Pulmonary rehabilitation: programme components

The American Thoracic Society and European Respiratory Society (ATS/ERS) definition of PR describes a comprehensive intervention of patient-tailored therapies, that may include exercise training, education, and behaviour change [Spruit *et al.* 2013]. Consistent with this definition, exercise training is an essential component of PR for ILD, including resistance and endurance training. Nonexercise components may include education, psychological support and nutritional therapy, along with training in behaviours that will assist in optimal disease management. This could include early recognition and treatment of acute exacerbations. Evaluation of outcomes is also an essential component of PR to confirm its effects. All components of PR must work smoothly together to achieve optimal outcomes for people with ILD (Figure 1).

## Exercise training

Exercise training is a critical component of PR. Principles of exercise training in chronic respiratory diseases are similar to those in healthy individuals [Spruit *et al.* 2013], including individualized exercise prescription and progression of training load. Endurance training is an essential component of exercise training for ILD, and most studies have also included resistance training (Table 2) [Holland *et al.* 2008; Nishiyama *et al.* 2008; Jackson *et al.* 2014; Vainshelboim *et al.* 2014]. People with ILD may need more careful planning and modification of their exercise prescription than healthy individuals or those with COPD, due to the severity of dyspnoea on exertion, profound exercise-induced oxyhaemoglobin saturation and rapid disease progression in some patients.

### *Endurance training*

Endurance training aims to improve aerobic capacity, increase exercise endurance, and improve daily function and physical activity with less breathlessness and fatigue. Initial endurance training intensity is usually set at 70–80% of maximum exercise capacity, such as walking speed on baseline 6MWT (for walking exercise) or peak work rate on CPET (for cycling). A minimum frequency of two supervised sessions per week is suggested. The target duration of endurance exercise in each session should be 30 minutes in participants with ILD, broken into shorter intervals if needed (e.g. 15 minutes stationary cycling and 15 minutes of walking, either on a treadmill or in a corridor). Most participants achieve this duration of exercise within 1–2 weeks of training,

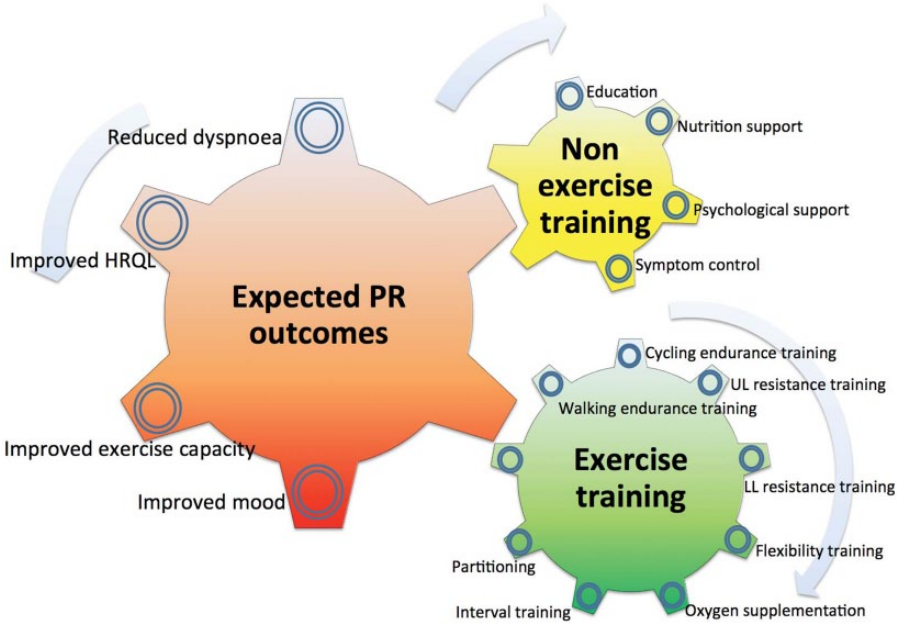


**Figure 1.** Comprehensive pulmonary rehabilitation for interstitial lung disease.
The gears with red, green and yellow colour present expected PR outcomes, exercise training and nonexercise training, respectively. The green gear is bigger than the yellow gear, because exercise training has more evidence than nonexercise training. The cogs of gears indicate their components. Comprehensive intervention in PR can be accomplished when the gears mesh together and cogs work well. Cooperation and smooth connection of all gears are vital to make PR successful. HRQL, health-related quality of life; UL, upper limb; LL, lower limb; PR, pulmonary rehabilitation.

with appropriate support from an experienced clinician. Participants should be encouraged to rate their breathlessness and fatigue regularly during exercise, aiming for moderate levels of breathlessness throughout. Intermittent monitoring of oxyhaemoglobin saturation and pulse rate *via* pulse oximetry is also recommended. Once a duration of 30 minutes is achieved, progression occurs by regular increases in the intensity of exercise (e.g. weekly increase in walking speed or cycle work rate). Participants should also be encouraged to adopt a home exercise programme, with the aim of completing 3–5 sessions of endurance exercise each week.

### *Resistance training*

Resistance training improves local muscle strength and endurance. Resistance can be generated against gravity, body weight or through the use of fixed or free weights. There are no specific guidelines for prescribing resistance training in PR, and the American College of Sports Medicine (ACSM) principles used for healthy adults or older persons are usually applied [Garber *et al.* 2011]. ACSM recommends training 2–3 days per week, with 10–15 repetitions and a single set for older persons [Garber *et al.* 2011]. For intensity, the ACSM recommends 40–50% of the 1 repetition maximum (1 RM) (very light to light intensity) to improve strength and 20–50% of the 1 RM to improve power. Modalities include resistance bands and free weights (Table 2).

Progression of resistance training may involve increasing the weight, number of repetitions per set, number of sets of each exercise or decreasing the rest period between sets [Spruit *et al.* 2013]. The best modality for limb training is not known; however, ACSM suggests emphasizing functional activities (e.g. stair climbing, sit-to-stand) as these are directly relevant to daily activities and can be easily reproduced in the home setting [Garber *et al.* 2011].

### *Flexibility training and stretching*

Flexibility training aims to increase the range of motion (ROM) of joints and muscles. There are no specific guidelines for flexibility training in ILD and its contribution to PR outcomes is unknown. The ACSM recommends flexibility

**Table 2.** Major exercise training components in four published randomized controlled trials of pulmonary rehabilitation for interstitial lung disease.

| | Training frequency | Endurance training intensity | Endurance training duration | Endurance training modality | Endurance training progression | Resistance training |
|---|---|---|---|---|---|---|
| Holland *et al.* [2008] | Twice weekly | Initial: walking, 80% of the walking speed achieved on the baseline 6MWT | 30 min per session, 8 weeks | Both stationary cycling and walking training | Progressed by an experienced physiotherapist according to a standardized protocol | Upper limb endurance training (free weights) and functional strength training for the lower limbs (e.g. sit to stand) |
| Nishiyama *et al.* [2008] | Twice a week | 80% of maximal walking speed from 6MWT, 80% of the maximum workload on cycle ergometer test | From weeks 2–9 of a 10-week programme | Treadmill | Not stated | Strength training using elastic bands; exercises included arm raising and knee extensions for 20 min |
| Vanishelboim *et al.* [2014] | Twice weekly | Interval training: in the first block, 50–60% of peak WR on CPET for cycling, 70–80% of individual average speed of 6MWT for walking; in the second block, increased up to 60–70% of peak WR in cycling and 80–90% of individual average walking speed | Two 6-week progressive blocks, 30 min; in the second block, further increased up to 20 min | Treadmill walking, leg cycling and step climbing in a continuous, sequential manner | Adding 1 min to the duration of each bout in each session, until reaching 15 min of continuous exercise; in the second block, stair climbing for 3–5 min was added to each session | One set of 12–15 repetitions with 1 min of rest between the sets for 4–6 exercises; in the second block, added two sets of 10–12 repetitions with 45 seconds of rest between the sets |
| Jackson *et al.* [2014] | Two sessions per week | Up to 80% maximum heart rate | 20/10 min | Treadmill walking/ semi-recumbent cycling | Not stated | Resistance training twice weekly, up to three sets of 15 repetitions using resistance bands |

6MWT, 6-minute walk test; CPET, cardiopulmonary exercise test parameters; WR, work rate.

exercise on at least 2–3 days per week, with 30–60-second stretches repeated two-to-four times for older people [Garber *et al.* 2011].

## Special considerations for exercise training

### *Oxygen supplementation*

Oxygen therapy is commonly delivered during exercise training for patients who exhibit significant desaturation, despite limited evidence for this practice. Management guidelines strongly recommend long-term oxygen therapy in IPF patients with resting hypoxaemia [Raghu *et al.* 2011]. The ATS/ERS statement for PR recommends supplemental oxygen during exercise training for ILD [Spruit *et al.* 2013]. Supplemental oxygen would routinely be administered to such patients during exercise training in PR, to ensure safety in the presence of profound desaturation. To date, there is no evidence to indicate that this practice results in better PR outcomes, such as greater improvements in exercise capacity or HRQL. Retrospective studies evaluating the administration of oxygen during acute bouts of exercise in ILD have reported improvements in walking distance with oxygen therapy, suggesting there may be beneficial effects on exercise performance [Visca *et al.* 2011; Frank *et al.* 2012]. However, interpretation of these findings is limited by the retrospective nature of the studies and lack of participant blinding. More evidence is needed to improve our understanding of the role of oxygen therapy during exercise training. Currently, usual practice would be to deliver oxygen therapy for any patient who desaturates to less than 85% during training, with the aim of maintaining $SpO_2$ at greater than 88%.

### *Interval training*

Interval training may provide an alternative exercise modality to endurance training in ILD. Interval training consists of periods of relative high-intensity exercise interspersed with periods of low-intensity exercise with or without rest. The aim of interval training is to allow patients to achieve the required training dose through repeated bouts rather than continuous exercise, which may reduce dyspnoea and fatigue. The ATS/ERS statement for PR suggests that interval training can be performed with fewer symptoms than continuous training [Spruit *et al.* 2013]. With regard to ILD, few published studies have included interval training, although several are currently underway. Authors of a systematic review of interval training in COPD reported a variety of interval training regimens in this group, including: two studies with 1-minute intervals of higher intensity [>90% peak power (Ppeak)], alternating with 2 minutes of low intensity (<75% Ppeak); three trials with 30-second intervals (100/45% Ppeak); one study with high (50% Ppeak) and low (10% Ppeak) intervals of 20 and 40 seconds; and one study with 2-minute intervals of high intensity (90% Ppeak) and 1 minute of low intensity (50% Ppeak) [Beauchamp *et al.* 2010]. There was no significant difference in exercise capacity and HRQL between interval training and continuous training. Further study of interval training in ILD is required.

### *Musculoskeletal disorders*

Musculoskeletal disorders are prevalent in people with ILD and may affect PR participation. For example, patients with CTD might experience joint pain and stiffness, limiting their ability to undertake PR. It is important that practitioners modify the exercise component of PR appropriately for people with musculoskeletal disorders, to avoid pain or exacerbation of chronic conditions. For instance, it might be necessary to avoid weight-bearing exercises like walking in some patients; stationary cycling may be more appropriate. Similarly, care should be taken with prescription of resistance training. In some cases, it may be necessary to seek the advice of a rheumatologist or musculoskeletal physiotherapist, to directly address underlying causes of musculoskeletal pain and dysfunction.

### *Rehabilitation after exacerbation of IPF*

The ATS/ERS definition of an acute exacerbation in IPF incorporates unexplained worsening of dyspnoea, evidence of hypoxaemia, new radiographic alveolar infiltrates, in the absence of an alternative diagnosis [Raghu *et al.* 2011]. Delivery of PR after an episode of acute exacerbation of IPF has not been described. Although PR has been recommended after an acute exacerbation of COPD, no recommendation is made for IPF [Bolton *et al.* 2013; Spruit *et al.* 2013]. Recently, a large study demonstrated negative effects of exercise rehabilitation after an exacerbation of chronic respiratory disease [Greening *et al.* 2014]. This study included 21 ILD patients (total $n = 389$).

Patients performed 6 weeks of exercise training, starting in hospital and carrying over to the outpatient setting. There were no beneficial effects on physical function or hospital readmission, and the rehabilitation group had higher mortality at 12-month follow up. Although early mobilization following an exacerbation may contribute to early hospital discharge and recovery of the ability to perform activities of daily living, a cautious approach might be required for commencement of PR in the early stages following an exacerbation for IPF. It is possible that the risks associated with exercise rehabilitation following an acute exacerbation could be higher in this subgroup of patients due to greater desaturation on exercise, greater hypoxaemia at rest and associated comorbidities.

## Nonexercise training

PR generally includes education, nutrition support and psychological support, in addition to exercise training [Spruit *et al.* 2013].

### *Education*

Disease education may provide the tools for people with ILD to understand their condition and participate in active self-management. It has been suggested that personalized education for ILD during PR should include oxygen therapy, exacerbation supervision, energy conservation, symptom control, mood disorders, medications, lung transplantation and end-of-life care [Garvey, 2010]. Holland and colleagues investigated the perspectives of patients and clinicians related to the ideal content of an educational component of PR for ILD [Holland *et al.* 2015b]. In this qualitative study, participants expressed the need for ILD-specific information and opportunity to discuss this in a group. Patients also expressed their needs for health professionals to be honest and help them prepare for the future, especially regarding prognosis. Recently, key topics for ILD education in PR have been identified: disease education, symptom management, clinical tests, autonomy, oxygen use, medications, and end-of-life counselling [Morisset *et al.* 2016]. These studies provide some guidance on the educational needs of people with ILD undertaking PR.

### *Nutrition support*

Nutritional depletion and nutritional support has seldom been investigated in ILD. Guidelines for treatment of IPF have few recommendations related to nutrition [Raghu *et al.* 2011]. A higher body mass index (BMI) is associated with better survival in IPF and low baseline BMI is associated with poor prognosis [Alakhras *et al.* 2007; Kim *et al.* 2012]. A multimodal nutritional rehabilitation programme in 122 patients with chronic respiratory failure (including 11 with restrictive diseases) encompassing education, oral nutritional supplements, exercise and oral testosterone found improved exercise tolerance in all participants and HRQL in females [Pison *et al.* 2011]. Further study of the effectiveness of nutrition support in PR for ILD is required.

### *Psychological support*

Depression and anxiety are prevalent in ILD. In one study in ILD ($n$ = 124), the prevalence of anxiety and depression were 31% and 23%, respectively [Holland *et al.* 2014b]. High levels of dyspnoea were an independent predictor of anxiety, and more dyspnoea and comorbidities were independent predictors of depression. Although the impact of PR on mood in ILD has not been studied in RCTs, uncontrolled data suggest PR might be beneficial. Ryerson and colleagues reported 6–9 weeks of PR improved depression in 52% of participants [Ryerson *et al.* 2014]. This was maintained at the 6-month follow up. The mechanism by which PR improves mood is not clear, but may be related to improved symptoms and sense of control over the disease.

### *Symptom control*

Many people with ILD have a high symptom burden including dyspnoea, cough and fatigue. PR may contribute to symptom control in patients with ILD. Specialists in symptom management, including palliative care teams, may have a key role to play in addressing the substantial unmet needs of people with ILD for symptom control and psychosocial support [Bajwah *et al.* 2012, 2015].

Chronic exertional dyspnoea is characteristic of IPF [Raghu *et al.* 2011]. The British PR guideline strongly recommends PR for all patients with Medical Research Council Dyspnoea score of 3–5 and functional limitation [Bolton *et al.* 2013]. A Cochrane review of RCTs of PR confirmed reduced dyspnoea after a PR programme in a subgroup of patients with IPF [Dowman *et al.*

2014]. A statistically significant effect for reduced dyspnoea was also seen in patients who desaturated on exertion.

Cough is prevalent in patients with ILD and for many, is their most distressing symptom. Few antitussive therapies have been investigated in ILD [Madison and Irwin, 2005]. The efficacy of PR in reducing cough is unclear. Qualitative studies have shown discussion of strategies to manage cough is a priority for patients undertaking PR [Holland *et al.* 2015b; Morisset *et al.* 2016]; however, the ideal components of such an intervention are not known.

PR may be important in ameliorating fatigue in patients with chronic respiratory disease including ILD [Spruit *et al.* 2013]. Exercise training improves subjective fatigue in people with ILD [Holland *et al.* 2008] and sarcoidosis [Strookappe *et al.* 2015]. A recent study affirmed improvement in objective muscle fatigability using intense aerobic-exercise training in patients with ILD [Keyser *et al.* 2015].

## Pulmonary rehabilitation: outcome assessment

### *Assessment of exercise capacity*

Assessment of exercise capacity is essential in PR, to establish exercise capacity, evaluate exercise-induced desaturation, prescribe appropriate exercise intensity for endurance training, and document outcomes of PR.

*The 6-minute walk test.* The 6MWT is the most commonly used test of exercise capacity in PR. A systematic review of field walking tests reports the 6MWD is a valid and reliable measure of exercise capacity [Singh *et al.* 2014]. The reproducibility of the 6MWD has been confirmed in ILD [Eaton *et al.* 2005]. However, despite excellent reliability, there is a learning effect for 6MWD in ILD, with 86% of participants increasing their 6MWD on a second test [Jenkins and Cecins, 2010]. For this reason, completion of two tests is recommended to ensure the best 6MWD is recorded, particularly on the first testing occasion [Holland *et al.* 2014c]. No serious adverse events have been reported during the 6MWT in ILD, although significant desaturation is often observed [Singh *et al.* 2014].

*Shuttle walking test.* The shuttle walking test (SWT) is an incremental test of exercise capacity, with walking speeds increasing each minute in time to an external cue [Singh *et al.* 1992]. De Boer and colleagues compared a modified SWT (allowing patients to run) with CPET in patients with sarcoidosis [De Boer *et al.* 2014]. Peak $VO_2$ on CPET had a strong correlation with SWT distance ($r = 0.87$; $p < 0.0001$). The SWT could be a useful measure of peak exercise capacity, although it has not yet been widely used in ILD.

*Cardiopulmonary exercise test.* The CPET provides detailed information about exercise responses and exercise capacity in ILD. This test is complex and may not be available in all settings; however, it has clear advantages for accurate prescription of exercise in PR, as a percentage of measured peak exercise capacity. In moderate–severe ILD, CPET and 6MWT elicit a similar $VO_2$ peak, although other cardiorespiratory measures are lower in the 6MWT [Holland *et al.* 2014a]. However, the 6MWT elicits greater desaturation than the CPET, which may be useful when planning an exercise prescription for walking.

*Other measures of exercise capacity.* Other tests of exercise capacity may have greater sensitivity to change following PR. A comparison of five exercise measurements (endurance time, peak work rate, peak oxygen consumption, 6MWD, and SWT) at the beginning and end of PR in patients with IPF found cycle endurance time was the most responsive [Arizono *et al.* 2014].

### *Health-related quality of life, dyspnoea and mood*

Measurement of HRQL is an essential component of PR. A variety of tools are available for this purpose. Many PR programmes use HRQL measures originally designed for patients with COPD (e.g. the Chronic Respiratory Disease Questionnaire [Guyatt *et al.* 1987] and the SGRQ [Jones *et al.* 1992]). Data from clinical trials of PR suggest these measures are responsive to change following PR [Dowman *et al.* 2014]. More recently, ILD-specific measures have become available, including the IPF-specific version of SGRQ [Yorke *et al.* 2010] and the King's Brief Interstitial Lung Disease Questionnaire [Patel

*et al.* 2012]. These have not been widely used in PR to date but are worthy of further study.

Dyspnoea is an important symptom, which is expected to improve following PR. The Borg Scale is often used to assess exertional breathlessness during exercise testing [Borg, 1982]. The impact of dyspnoea on daily function is often evaluated using the modified Medical Research Council scale, which grades breathlessness associated with daily activities into five levels from a scale of 0–4 [Mahler and Wells, 1988]. More comprehensive dyspnoea assessments have been used in PR for ILD, including the University of San Diego Shortness of Breath Questionnaire [Kaplan *et al.* 1994].

Mood disturbance is common in ILD and may improve following PR. Outcome tools used to measure mood in PR studies for ILD include the Hospital Anxiety and Depression Scale [Zigmond and Snaith, 1983], the Center for Epidemiologic Studies-Depression score [Radloff, 1977], the Geriatric Depression Scale [Brink *et al.* 1982] and The General Anxiety Disorder-7 scale [Spitzer *et al.* 2006].

## Possible future directions

Despite robust evidence for the benefits of PR in ILD, this field continues to evolve. Important issues still to be addressed include the ideal format and content for PR; methods to extend duration of benefit; and how PR can best be tailored to the complex needs of people with ILD. For example, the best methods to provide comprehensive PR for people with progressive or end-stage disease have not been determined. More work needs to be done to define the nonexercise components of PR that contribute to optimal outcomes, including psychosocial support, education, behavioural intervention and group therapy. An important area for future research is the effect of PR on healthcare costs. Although the clinical effectiveness of PR in ILD is increasingly understood, clarification of cost effectiveness of PR would provide impetus for commissioners and policy makers to ensure this intervention is widely available [Loveman *et al.* 2014]. The NICE clinical guideline of IPF has begun this process by modelling the cost effectiveness of PR, suggesting that it could be cost effective to deliver this intervention every 6–12 months, which could make it possible for PR to be a standard treatment in IPF [NICE, 2013].

## Conclusion

PR is an important component of comprehensive care for patients with ILD, delivering clinically important improvements in exercise capacity, symptoms and HRQL. Current studies do not suggest that PR impacts on prognosis. Exercise training is an essential component of PR for ILD and should include endurance and resistance training. Nonexercise components may include education, psychological support, symptom management and nutritional support. Given the positive impact of PR on patient-centred outcomes, efforts should be made to ensure that PR is made widely available across the spectrum of ILDs.

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## Conflict of interest statement

The authors declare that there is no conflict of interest.

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