Physical rehabilitation for lung transplant candidates and recipients: An evidence-informed clinical approach

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Abstract

Physical rehabilitation of lung transplant candidates and recipients plays an important role in optimizing physical function prior to transplant and facilitating recovery of function post-transplant. As medical and surgical interventions in lung transplantation have evolved over time, there has been a demographic shift of individuals undergoing lung transplantation including older individuals, those with multiple co-morbidities, and...
candidates with respiratory failure requiring bridging to transplantation. These changes have an impact on the rehabilitation needs of lung transplant candidates and recipients. This review provides a practical approach to rehabilitation based on research and clinical practice at our transplant centre. It focuses on functional assessment and exercise prescription during an uncomplicated and complicated clinical course in the pre-transplant, early and late post-transplant periods. The target audience includes clinicians involved in pre- and post-transplant patient care and rehabilitation researchers.

Key words: Lung transplantation; Rehabilitation; Physical therapy; Exercise training; Physical activity

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Core tip: This expert review brings together clinical experience and research evidence on physical rehabilitation for lung transplant candidates and recipients. The evaluation of exercise capacity, muscle function, mobility, activities of daily living and physical activity is discussed. Rehabilitation training guidelines for pre-transplant, acute care, early and late post-transplant phases are provided with special attention to complicated and uncomplicated clinical courses. Special populations such as heart-lung transplant and paediatric lung transplant are also included.

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INTRODUCTION

Lung transplantation is performed for a variety of advanced lung diseases, with primary indications including interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF) and pulmonary vascular disease. Since the world’s first successful single lung transplant in Toronto, Canada, physical rehabilitation has played an integral role in facilitating their recovery.

Although pre- and post-transplant rehabilitation is recommended in the majority of lung transplant centers in Canada, there are currently no clinical practice guidelines for rehabilitation in lung transplant candidates and recipients. Several narrative reviews have been published on rehabilitation, however they have focused on guidelines for individuals with a relatively uncomplicated pre- and post-transplant course. As the selection of lung transplant candidates has evolved over time due to surgical and medical advancements, the demographics of transplant candidates has shifted from only the youngest and fittest candidates to adults of older age and those with increased co-morbidities and functional limitations. This shift in demographics may have important implications for rehabilitation approaches and functional expectations pre- and post-transplant. In addition, lung transplant candidates can present with acute respiratory decompensation, and several medical strategies are being used to “bridge” candidates to transplantation using mechanical ventilation and/or Extra Corporal Life Support (ECLS). These technologies can have a significant impact on the degree of deconditioning that these individuals experience prior to transplant, as their capacity to participate in active rehabilitation is limited. The rehabilitation needs of individuals who have high oxygen requirements, require hospitalization pre-transplant due to respiratory failure, and/or require extensive rehabilitation post-transplant due to a prolonged and complicated clinical course are not well described.

The overall purpose of this review is to provide an evidence-informed clinical approach to rehabilitation based on over 30 years of clinical rehabilitation experience at our center, integrating the research evidence for rehabilitation in lung transplantation. The specific aims of this review are to: (1) provide a practical approach to functional assessment and exercise training pre- and post-lung transplant, including the peri-operative and long-term follow-up periods; (2) describe and contrast exercise training and mobility for lung transplant candidates and recipients with an uncomplicated and complicated clinical course; and (3) discuss rehabilitative approaches for special populations within lung transplantation such as re-transplant, heart-lung transplant and pediatrics.

FUNCTIONAL ASSESSMENT OF LUNG TRANSPLANT CANDIDATES AND RECIPIENTS

The mechanisms of exercise limitation pre- and post-lung transplant are multifactorial, including alterations in lung mechanics and gas exchange, cardiovascular limitations and peripheral muscle dysfunction, and have been described in detail elsewhere. In order to evaluate exercise capacity and function in lung transplant candidates and recipients, a combination of aerobic testing, muscle function, mobility testing and assessment of physical activity is utilized. Measures that may be used in clinical practice for physical assessment in the lung transplant population have been summarized in Table 1. The Rehabilitation Measures Database provides information on the psychometric properties, normative data, instrument description and equipment, minimally clinical important difference and considerations for a number of rehabilitation...
assessment instruments included in Table 1.

Aerobic exercise capacity
Exerc.

capacity is a major predictor of waiting list survival pre-transplant across disease categories[15,16], and is also associated with post-transplant health outcomes including days on mechanical ventilation, length of hospital stay and survival[17,18]. The six-minute walk test (6MWT)[19] is the most common functional test of exercise capacity for lung transplant candidates and recipients in Canada[5], and is used widely internationally. It is a global marker of health status reflecting severity of disease and level of functional impairment, and has been found to correlate with VO2max in lung transplant candidates[20]. The six-minute walk distance (6MWD) is incorporated into several composite scores that can determine the urgency for lung transplant including the BODE and Lung Allocation Score[21,22]. A 6MWD of less than 400 m or a predicted distance of between 45%-55% is common in lung transplant candidates[4,15,24]. The 6MWD improves significantly following transplant reaching 65%-85% predicted, with the largest gains reported in the first three to four months[23-26]. Other field-based walking tests that have been used in chronic lung disease such as the incremental and endurance shuttle walk tests, (ISWT and ESWT) may also be used to quantify exercise capacity in lung transplant candidates and recipients[27].

Upper extremity exercise capacity plays an important role in many basic and instrumental activities of daily living and may provide unique information about upper extremity endurance not reflected in the field-based walking tests. In individuals with COPD, arm exercise capacity has been measured using the Unsupported Upper Limb Exercise Test (UULEX)[28]. A small group of lung transplant candidates with ILD at our center demonstrated reduced arm exercise capacity compared to controls using the UULEX[29], however this test has not been used in routine clinical evaluation.

Muscle function
Peripheral muscle function can be tested through multiple techniques, some of which are more applicable to the clinical setting due to lower costs and fewer requirements for specialized equipment, training and personnel such as manual muscle testing, hand held dynamometry, hand held dynamometry and one-repetition maximum (1-RM; Table 1). The quadriceps is the most common muscle tested in the research literature and lung transplant candidates exhibit quadriceps weakness of 49%-86% predicted[30]. An immediate drop in quadriceps strength from pre-transplant to post-transplant at the time of hospital discharge of 15%-32% has been reported with a gradual recovery to pre-transplant levels by three to four months post-transplant[23-26]. Lower extremity muscles (e.g., quadriiceps, ankle plantar flexors) show more pronounced weakness than upper extremity muscles (e.g., biceps)[29-31].

Body composition (muscle and fat mass) can be measured as part of a physical or nutritional assessment using bioelectrical impedance analysis, dual X-ray absorptiometry or skinfolds. More specific measures of muscle size (e.g., cross-sectional area and muscle layer thickness) can be obtained from ultrasound, computerized tomography, or magnetic resonance imaging, however these are not typically performed for clinical assessment. Muscle atrophy has been reported in research studies of lung transplant candidates and recipients using several measures such as low fat free mass, reduced muscle volume and cross-sectional area[29,30].

Aerobic exercise capacity

| Measured construct | Clinical tests | Clinical utility |
|--------------------|---------------|------------------|
| Exercise capacity  | Lab-based test: Cardiopulmonary exercise test on cycle or treadmill | Cause of exercise limitation |
|                    | Field-based walk tests: 6MWT, ISWT | Assess need for oxygen |
|                    | Upper extremity endurance capacity: UULEX | Outcome measure pre-post rehab and pre-post transplant |
| Muscle function    | Peripheral muscles: Manual muscle testing or hand held dynamometry | Assess muscle strength |
| (strength,        | Handgrip force | and/or muscle endurance |
| endurance)        | Respiratory muscles: 1-repetition maximum | Exercise prescription (1-RM for peripheral muscles, MIP for IMT) |
| Physical           | Gait speed (over 4 m)[11] | Assess mobility, balance |
| performance        | Sit-stand tests (e.g., 30 s to stand; 5 times to stand)[11] | Assess need for gait aid and physical function |
| and mobility       | Short Physical Performance Battery[11] | Outcome measure |
|                    | Timed Up and Go[11] | Exercise prescription |
|                    | Balance tests (e.g., Berg balance scale, BESTest)[11,14] | Discharge planning |
| Physical activity  | Physical Activity questionnaires, e.g., PASE[21], IPAQ[25], DASI[21] | Assess physical activity |
|                    | Pedometers or accelerometers | Outcome measure |
|                    | Set activity goals (e.g., target daily step count) | |

Table 1: Physical assessment of lung transplant candidates and recipients

CPET: Cardiopulmonary exercise test; 6MWT: Six-minute walk test; ISWT: Incremental shuttle walk test; UULEX: Unsupported upper limb exercise test; MMT: Manual muscle testing; 1RM: One repetition maximum; HGF: Handgrip force; HHD: Hand-held dynamometry; MIP: Maximal inspiratory pressure; MEP: Maximal expiratory pressure; IMT: Inspiratory muscle testing; SPPB: Short physical performance battery; TUG: Timed Up and Go; FIM: Functional independence measure; PASE: Physical activity scale for the elderly; IPAQ: International physical activity questionnaire; DASI: Duke activity status questionnaire.
candidates have shown reduced functional performance on the Short Physical Performance Battery (SPPB) and Timed Up and Go (TUG) compared with controls. The SPPB has recently been used as a marker for frailty pre-lung transplant and shown to be a predictor of disability, delisting and waitlist mortality.

Physical activity
Level of physical activity can be evaluated using questionnaires, however there is no specifically validated scale for lung transplant candidates or recipients. Commercially available pedometers or accelerometers may also be used to obtain daily step counts and activity level. Measurement of physical activity can be an important adjunct to exercise capacity testing, since it is reduced pre- and post-transplant and can be used for physical activity counseling and setting targets for daily activity.

Low levels of physical activity with a reported mean of 1400-3200 daily steps, reduced time spent in moderate intensity activity, walking, standing, and greater time in sedentary activities has been reported in lung transplant candidates. A research study conducted in our center demonstrated that lung transplant candidates with ILD had increased physical activity levels on days they participated in pulmonary rehabilitation, and the 90 min rehabilitation session accounted for 58% of the total daily steps. Levels of daily physical activity improve following lung transplant however remain below predicted levels in terms of daily steps, walking time and movement intensity compared to healthy controls; and show great variability.

GENERAL PRINCIPLES OF EXERCISE TRAINING
Exercise prescription should be individualized, include both aerobic and resistance training, and follow general exercise training principles of specificity, overload and progression. Based on our clinical experience, respiratory and cardiovascular reserve, stability and clinical course of lung disease, muscle strength and muscle endurance can have a significant impact on the frequency, intensity, type and duration of exercise that is prescribed and the rate of progression. Figure 1 outlines general rehabilitation guidelines used at our center during the pre- and post-transplant phases.

Pre-transplant rehabilitation
Pre-transplant exercise training is recommended in Canadian lung transplant centers for a specified duration or during the entire waiting period prior to transplant to optimize fitness and prevent the cycle of inactivity and deconditioning that can occur with advanced lung disease. There are few randomized controlled trials that examine the effect of exercise training pre-transplant, however retrospective and pre-post studies of exercise training in lung transplant candidates have shown that 6MWD can be maintained or even increased in spite of progressive lung disease. Predictors of rehabilitation success pre-transplant (e.g., improved 6MWD) have not been identified in lung transplant candidates.

Pulmonary rehabilitation guidelines for exercise training can be applied to lung transplant candidates with modifications to account for increased severity of lung disease and multiple underlying disease states. If disease progression and functional deterioration occurs during the waiting period, physical function needs to be reassessed on an ongoing basis and exercise prescription modified as needed. Alternative modes of training including high intensity interval training and Nordic pole walking have been described in lung transplant candidates. Inspiratory muscle training has been utilized in chronic lung disease, primarily COPD, to improve inspiratory muscle strength and endurance; however studies have not been specific to lung transplant candidates. Although supervised outpatient pulmonary rehabilitation in a hospital or community setting are common, alternative modes of delivery such as tele-rehabilitation may be an important alternative for individuals living far from a transplant center, however pre-transplant tele-rehabilitation has not yet been studied in lung transplant candidates.

Guidelines for pre-transplant exercise prescription have been summarized in Table 2 from protocols used in research studies and our current clinical guidelines. Exercise intensity and duration are prescribed and progressed according to exertional oxygen saturation, heart rate and symptoms of dyspnea and leg fatigue using the modified 0-10 Borg scale. A percentage of the 6MWT speed can be used for lung transplant candidates to prescribe walking speed on the treadmill.

Special considerations for pre-transplant rehabilitation
Supplemental oxygen for exercise training: As lung transplant candidates often require supplemental oxygen for rest and/or exertion, oxygen titration is an important component of exercise training. Guidelines for oxygen supplementation for exercise are not clearly defined, so oxygen titration orders, institutional policies and delegation practices may vary between facilities. At our center, all lung transplant candidates have a prescribed oxygen titration range provided by a physician, which is often to maintain an oxygen saturation (% SpO2) of at least 88% with exercise, however, oxygen prescription may be modified based on patient diagnosis, medical co-morbidities, arterial blood gases, functional capacity and symptoms. Lung transplant candidates are supported with sufficient oxygen to maintain the prescribed oxygen saturation in an attempt to increase aerobic exercise intensity and duration to obtain a greater physiological benefit with training. In our clinical experience, oxygen requirements for exertion may increase during the waiting.
period pre-transplant with some individuals (such as those with ILD) requiring very high levels of oxygen supplementation, high flow oxygen delivery devices and/or non-invasive ventilation. There is a lack of literature on the safety guidelines and hazards of high flow oxygen for exercise training, and our clinical practice is to communicate closely with the medical team regarding arterial blood gases and/or other medical concerns.

Exercise training in pulmonary hypertension: Historically, individuals with pulmonary arterial hypertension (PH) were excluded from exercise training, however alongside changes in medical management, a number of studies over the past decade have shown efficacy and safety of carefully prescribed exercise in stable, medically optimized individuals with PH. For individuals with moderate to significant primary or secondary PH who are not symptomatic at rest, our clinical practice is to avoid of exertional hypoxemia, symptoms of chest pain, dizziness, pre-syncopé, nausea and visual changes during exercise training. We prescribe exercise intensity and duration as guided by lower dyspnea scores (e.g., Borg score 2–3 or slight to moderate). High intensity aerobic and resistance training and Valsalva maneuvers are avoided. Changes in weight, abdominal circumference, lower leg edema and other evidence of worsening right heart failure are monitored with close communication with the medical team, and care is taken to avoid interruption of continual intravenous vasodilators (e.g., prostaglandins).

Infection control: Infection control procedures are essential for preventing spread of certain infections such as methicillin-resistant staphylococcus aureus, mycobacterium abscessus or CF-related infections during group exercise programs. At our center, individuals with CF are physically separated by three meters during group exercise training and individuals with Burkholderia cepacia exercise separately at the end of the day. Guidelines on cleaning equipment, hand-washing, gown and mask use and isolation practices may vary at different institutions.

Team approach to rehabilitation: Education is an important component of rehabilitation, specifically on issues related to safe and effective exercise, exertional oxygen use, home exercise, assistive devices and energy conservation techniques. Psychosocial support to address stress and expectations during the waiting period and concerns regarding surgery is also beneficial. Collaboration with the registered dietitian to ensure that nutritional needs are being met and balancing exercise participation with nutritional needs.
Table 2: Guidelines for pre-transplant exercise prescription in stable outpatients

| Type | Aerobic | Resistance | Flexibility |
|------|---------|------------|-------------|
| Walking (treadmill, corridor, Nordic poles) | Major muscle groups of upper and lower body (quadriceps, hamstrings, plantar flexors, gluteals, biceps, triceps, pectorals, latissimus dorsi) | Major muscle groups of upper and lower body | Hold up to 10-30 s |
| Cycling (leg and/or arm ergometer) | Training modalities: Free weights/ dumbbells Elastic bands Pulleys Gym equipment Body weight (stairs, squads, wall push-ups) | | |
| Time/ | Continuous: 15-30 min | Hold up 1-2 sets x 8-15 reps | 2-3 d/wk |
| Volume | Intermittent: 5-10 min x 2-3 bouts | each, repeat | 2-5 d/wk |
| Progression | Interval: 30 s x 3 rest (12-36 min) | Body weight increases: Can hold stretches | Hold up to 10-30 s |
| | Progression time up to 20-30 min continuous | based on tolerance; (approximately 0.5 kg or 1 lb. per week, as tolerated) | to point of slight discomfort |
| | Perform regular 6MWTs and adjust speed accordingly for treadmill training; and increase Watts on cycle Higher level patients may tolerate a treadmill incline of 1%-4% | | |

1 Intermittent training is regular or irregular intervals of the same low to moderate intensity vs interval training, which involves pre-set, alternating, short intervals of high intensity to intervals of rest or lower intensity; 2 There are several different interval training protocols described in chronic lung disease; 3 SpO2: Oxygen saturation measured by pulse oximetry; HRR: Heart rate reserve; 6MWT: Six-minute walk test; ISWT: Incremental shuttle walk test; HR: Heart rate; BP: Blood pressure; RR: Respiratory rate; ESWT: Endurance shuttle walk test; reps: Repetitions; RM: Repetition maximum.

Considerations for a complicated pre-transplant clinical course: In cases of a prolonged waiting period prior to transplant, we find that exercise intensity and duration may not be progressed if there is significant disease progression, respiratory exacerbations and infections, medical instability and hospital admission for respiratory failure. Maintenance of physical function or slowing the rate of physical deterioration can become important functional goals. Increased dyspnea, decreased function or acute worsening of gas exchange should be investigated as they can indicate underlying infection, respiratory exacerbation or pulmonary embolism. Some lung transplant candidates experience profound respiratory deterioration and need to await lung transplantation on the hospital ward or in the intensive care unit (ICU). Although there is no research evidence on inpatient rehabilitation for lung transplant candidates hospitalized with respiratory deterioration and failure, we provide a modified exercise program based on patient tolerance to help offset functional decline. Corridor ambulation and bedside cycling are encouraged as tolerated, but may not be tolerable by some individuals due to severe gas exchange abnormalities that are not corrected with high levels of supplemental oxygen. Resistance exercises, which do not confer the same degree of exertional desaturation should be continued as tolerated, with a focus on maintaining proximal muscle strength (e.g., shoulder and hip) and lower limb strength in anticipation of early ambulation and return to self-care activities post-transplant. Neuromuscular electrical stimulation (NMES) has been shown to enhance muscle mass and function in individuals with severe COPD and incapacitating dyspnea, and may be a useful adjunct for individuals unable to participate in a traditional outpatient pulmonary rehabilitation program.

Selected lung transplant candidates require bridging to transplant due to respiratory failure. Mechanical ventilation and ECLS can be associated with significant deconditioning due to increased sedation time limiting mobility and active participation in rehabilitation, and in some cases, irreversible muscle damage from persistent critical illness polyneuropathy and myopathy. Facilities with an experienced critical care mobility team can mobilize individuals on mechanical ventilation and/or ECLS who are medically stable and cognitively capable; although guidelines for mobility prescription with close monitoring of weight are performed at our center. Some individuals are required to lose weight pre-transplant and may benefit from nutritional counseling in addition to aerobic exercise training. A palliative care referral for opioid administration may be beneficial to assist with symptom control of dyspnea, cough and other symptoms that may impact on exercise ability and quality of life. A study at our center observed a trend towards increased caloric expenditure during exercise training in 64 lung transplant candidates referred to palliative care post opioid initiation.
transplant are to increase general mobility, functional capacity, muscle strength and endurance, and facilitate discharge from hospital. Reduced ICU length of stay has been associated with increased quadriceps muscle strength at hospital discharge in lung transplant recipients\textsuperscript{26}. One study identified factors that contribute to an extended hospital stay which included high urgency listing status, bridging to transplant with mechanical ventilation and/or ECLS, diagnosis of pulmonary hypertension, prolonged intubation post-transplant and colonization with multidrug resistant pathogens\textsuperscript{63}. The functional consequences of a prolonged ICU stay can be profound and long-term\textsuperscript{64}.

Physical rehabilitation should begin as early as possible post-operatively and should prioritize upright positioning (e.g., sitting) and mobilization (e.g., out of the bed)\textsuperscript{66,65}. Early mobilization in the ICU has not yet been studied specifically in lung transplant patients, but the same treatment approaches reported for other critically ill patients are likely applicable. Table 3 Muscle wasting related to critical illness is early and impactful\textsuperscript{67,68} highlighting the need for rapid and effective interventions to protect the muscle from atrophy and weakness. To date, several systematic reviews support safety, feasibility and beneficial impact of early physical therapy and mobilization in mechanically ventilated patients\textsuperscript{69–76}. There is evidence that early physical therapy and mobility training can result in improved quality of life\textsuperscript{71}, physical function\textsuperscript{71,72}, muscle strength\textsuperscript{71,73} and functional outcomes\textsuperscript{69}. Further research is needed to determine whether these improvements translate into decreased hospital and ICU length of stay\textsuperscript{77,78} and better long-term physical function\textsuperscript{60}.

Rehabilitation in the ICU should take into consideration pre-transplant function, cardiorespiratory function, muscle strength, range of motion (ROM), balance, cognitive impairments, pain control and medical stability. Early active muscle training and cardiopulmonary conditioning should begin as soon as feasible within the hospital setting (e.g., turning in bed, sitting at the edge of bed, sitting in a chair, standing, and walking). In addition, self-care and activities of daily living should be encouraged as soon as possible\textsuperscript{79}. Low levels of exercise (e.g., with elastic therapy bands or unloaded pedaling on the bicycle) with subsequent increases in the duration and workload can be made as the patient progresses\textsuperscript{79,80}. In critically ill patients, even passive or active exercise training sessions for 20 min/d using a bedside ergometer is able to increase short-term functional recovery\textsuperscript{80}.

The emerging literature using NMES has shown that it may be a safe, low cost treatment for early intervention in critically ill patients who may not be able to participate in active exercise\textsuperscript{79,81} since it can passively activate the muscles\textsuperscript{75,81,82}. However, studies to date have included a general, mixed population of ICU patients and the evidence is not specific to lung transplant recipients. Furthermore, the ability to deliver NMES effectively in the context of underlying ICU

### Table 3 Exercise and mobility for hospitalized lung transplant candidates and recipients

| Setting                  | Interventions/prescription                        | Considerations for a complicated hospital course |
|-------------------------|--------------------------------------------------|--------------------------------------------------|
| Intensive care unit     | Upright positioning                              | PROM, A/AROM for those who are sedated/not actively moving |
|                         | AROM for upper extremities                       | Trunk control and sitting balance prior to standing and walking |
|                         | Acupuncture for incisional pain                  | Specialized equipment to facilitate mobility, such as: |
|                         | Progressive mobility program, consisting of:     | - Standing frames, sit-stand |
|                         | Bed mobility > dangling > transfer to chair > standing | - standing and walking slings, portable treadmills, portable ventilators for ambulation in ICU (with appropriate settings to facilitate exercise), |
|                         | > marching on spot > ambulation with HWW up to 100 m with or without MV | - manual resuscitation bag with PEEP valve |
|                         | In sitting or lying:                             | - Bedside cycle ergometer or treadmill for aerobic training |
|                         | Resistance training using light weights, elastic resistance bands | - Video gaming system (e.g., Nintendo Wii\textsuperscript{79}) for balance and strengthening exercises\textsuperscript{65} |
| Step-down unit/ward     | AROM upper extremities                           | Transfer training |
|                         | Progressive mobility program:                   | Gait training |
|                         | Up to chair 1-3 ×/day; supervised walking 1 ×/day building up to 100 m, progress to 4-5 ×/day for 10-15 min bouts and increase distance > 100 m | Gait aids: Progress from HWW > rollator > no gait aids, if able |
|                         | Stair climbing                                   | Specialized seating |
|                         | Resistance training: Up to 5 lbs. (1 set × 10 reps) | Referral to inpatient rehabilitation for those who are not independent for discharge home |
|                         | Education re: Lifting restrictions               | |
|                         | Postural correction/re-education                 | |
|                         | Oxygen titration: Maintain                       | |
|                         | SpO\textsubscript{2} > 88% on exertion           | |

ROM: Range of motion; HWW: High-wheeled walker; MV: Mechanical ventilation; AROM: Active range of motion; PROM: Passive range of motion; A/AROM: Active/assisted range of motion; PEEP: Positive end expiratory pressure.

in critically ill individuals are not clearly defined\textsuperscript{60}. A recent systematic review presented evidence that early mobilization and ambulation is safe even in patients awake on veno-venous Extra Corporeal Membrane Oxygenation (ECMO) support\textsuperscript{61}. Physiotherapists at our center undergo specialized training in managing ECMO circuits, and with the support of an early mobility team, close communication with the medical team and a positive ICU culture towards the safe mobilization of selectivity assessed critically ill patients\textsuperscript{62}.

### Post-transplant rehabilitation

**Immediate post-transplant rehabilitation in the ICU:** The rehabilitation goals in the early phase post-transplant are to increase general mobility, functional capacity, muscle strength and endurance, and facilitate discharge from hospital. Reduced ICU length of stay has been associated with increased quadriceps muscle strength at hospital discharge in lung transplant recipients\textsuperscript{26}. One study identified factors that contribute to an extended hospital stay which included high urgency listing status, bridging to transplant with mechanical ventilation and/or ECLS, diagnosis of pulmonary hypertension, prolonged intubation post-transplant and colonization with multidrug resistant pathogens\textsuperscript{63}. The functional consequences of a prolonged ICU stay can be profound and long-term\textsuperscript{64}.

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acquired myopathy and polyneuropathy\cite{83} has not been substantiated.

**Post-transplant rehabilitation in the hospital step-down unit and ward:** At our center functional reassessment and exercise are resumed following ICU transfer until discharged home or to inpatient rehabilitation, with oxygen titration orders to maintain oxygen saturation at least 88% on exertion. Most lung transplant recipients at our center are weaned off supplemental oxygen prior to hospital discharge, but a few may still require low flow oxygen for exertion for several weeks to months, especially single lung transplant recipients.

Rehabilitation interventions provided at our center during the hospital stay post-transplant are summarized in Table 3. Medical issues that may be encountered in this early post-transplant phase that can impact exercise include infection, acute rejection, anxiety, depression, post-surgical pain at the thoracotomy tube site and chest wall, arrhythmias, veno-thrombotic events, infections requiring isolation, postural hypotension, skin ulcers and poor wound healing. Side effects of medications include fluid retention, anemia, nausea, tremors, decreased visual acuity, hyperglycemia and hypertension\cite{65}, which need to be considered when prescribing exercise so that appropriate modifications should be made.

**Outpatient rehabilitation:** Structured outpatient rehabilitation within the first three months following lung transplant is available at Canadian transplant centers\cite{5}. Functional goals in the outpatient phase may include ambulation without gait aids, liberation from supplemental oxygen, return to pre-transplant muscle strength and 6MWD of 65%-85% predicted levels\cite{23-26,84}. Large functional gains are reported during this period of rehabilitation in individuals with a relatively uncomplicated post-operative course\cite{23-26}. Lung transplant recipients indicate that exercise training is a valuable part of their post-transplant care and essential to improve physical function\cite{85}. A greater improvement in 6MWD post-transplant is predicted by greater recovery of muscle strength and a lower pre-transplant 6MWD\cite{25,84}. Studies examining exercise training following lung transplantation show significant increases in exercise capacity, muscle strength and bone mineral density\cite{24,86-88} (Table 4).

**Considerations for a complicated post-transplant clinical course:** There are a multitude of complications that can significantly increase the length of hospital stay and impact rehabilitation including: Major bleeding, infections, prior multi-drug resistant infections and colonization, difficulty weaning with prolonged mechanical ventilation, pre- and post-transplant ECLS, diaphragmatic paralysis, severe agitation, delirium, depression, acute neurological events, critical illness polyneuropathy, hemodynamic instability, primary graft dysfunction and acute renal failure requiring hemodialysis\cite{65,66}.

An assessment of functional goals can help inform discharge planning and recommendations for inpatient transplant rehabilitation, complex continuing care or homecare services. A retrospective study from our center showed that lung transplant candidates who were older, had a lower pre-transplant 6MWD, were mechanically ventilated prior to transplant and had a longer total length of hospital stay were more likely to be discharged to an inpatient rehabilitation facility vs home\cite{89}. Compared to other inpatient rehabilitation patients (e.g., stroke, joint surgery) lung transplant recipients are more likely to require transfer back to acute care for medical management related to complications such as infection, rejection and cardiac events\cite{90,91}.

In our clinical practice, individuals who experienced a complicated post-transplant course may require a referral to a multidisciplinary inpatient rehabilitation program to regain basic mobility (e.g., independent transfers, walking, and the ability to engage in activities of daily living such as self care) prior to discharge home. Upon discharge, these individuals are encouraged to enroll in an outpatient pulmonary rehabilitation program, or be prescribed a program that can be done in the community or home setting to work on improving endurance and strength. These individuals often require a mobility aid (e.g., rollator walker or cane) and their 6MWD is well below predicted values, showing a slow improvement over 12 to 18 mo. Specific exercises to target balance and coordination impairments are sometimes needed to be included in the outpatient or home exercise program. Individuals with a complicated post-transplant clinical course may experience persisting myopathies and/or neuropathies, and not all critically ill survivors recover to the same extent as there may be significant differences in recovery of muscle function and rehabilitation potential\cite{89}. This remains an area of active research.

**Late/ongoing post-transplant maintenance**

The 6MWT is reassessed regularly post-transplant\cite{5}, to monitor changes in exercise capacity and exertional oxygen saturation, which may change over time. Although the majority of exercise training programs occur in the first three to four months following transplant, longer-term exercise training may provide additional benefits to exercise capacity and the management of long-term co-morbidities of hypertension, hyperlipidemia and diabetes are prevalent at one, three and five years post-transplant\cite{1,24}. A randomized trial found that lung transplant recipients who underwent rehabilitation in the first three months following transplant had higher physical activity levels, improved fitness and lower 24-h blood pressure one year post-transplant compared to recipients who did not participate in rehabilitation\cite{24}. Daily physical activity has been reported to be significantly reduced one year following transplantation as...
Table 4: Guidelines for early post-transplant exercise prescription in stable outpatients

| Type                  | Frequency | Intensity | Progression | Time/Volume | Resistance | Flexibility |
|-----------------------|-----------|-----------|-------------|-------------|------------|-------------|
| Walking (treadmill,   | 3-5 d/wk  | 50%-100%  | Start with sit-downs and when able to perform without arm support progress to squats with hand weights. | Continuous: 20-30 min | 2.3-4 d/wk | Hold stretches |
| or corridor           |           | HR reserve or < 85% age-predicted HRmax<sup>50</sup> | to point of upper extremity lifting/pulling/pushing | 1-3 sets × 8-15 reps | 60%-100% 1RM<sup>50,51</sup> | No upper extremity discomfort |
| Cycling (leg)         |           | 75%-100% 6MWT<sup>21,22</sup> | Progress time to 30 min, then progress speed on treadmill; increase incline after approximately 6 wk post-transplant (if tolerated) | 3wk-6mo post-transplant | 10-RM     | if sternal instability |
| Arm ergometry         |           | 50%-80% peak workload for cycling<sup>21,22,23</sup> | Increase Watts on cycle | 30-60 s running bouts interspersed with walking for 20-30 min | 60%-80% 1RM<sup>50,51</sup> | Extra restrictions |
| 3 month to allow for incision healing |           | 75%-80% 1RM<sup>50,51</sup> | Walk: Run program for some high level patients (at least 6 wk post-transplant) 30-60 s running bouts | 3 month post-transplant | 10-RM     | Hold stretches |

6MWT: Six-minute walk test; CPET: Cardiopulmonary exercise test; HR: Heart rate; HRR: Heart rate reserve; SpO<sub>2</sub>: Oxygen saturation measured by pulse oximetry; RR: Respiratory rate; BP: Blood pressure; ISWT: Incremental shuttle walk test; EISWT: Endurance shuttle walk test.

Compared to healthy controls<sup>55</sup>, physical activity levels varied in long-term recipients and have been found to be inversely associated with body weight<sup>37</sup>. Exercise training in lung transplant recipients in the long-term phase (> 6 mo) has been shown to have beneficial effects on endurance capacity and muscle strength<sup>87,88,92</sup>. Long-term adherence to exercise may be greater if individuals participate or resume activities they enjoy. Thinking beyond a traditional gym protocol and exploring individuals’ interests, access and resources can be helpful when counseling individuals about increasing and maintaining physical activity in their home community. National and World Transplant Games<sup>93,94</sup> and charity events are excellent opportunities for setting fitness and performance goals and staying active while raising awareness of lung disease and transplantation. As an example of the benefits of this training, lung and heart-lung transplant recipients (> 6 mo post-transplant) who participated in ten weeks of upper extremity training through Dragon Boat racing showed improved aerobic and anaerobic fitness<sup>95</sup>. Inexpensive pedometers, activity watches, fitness monitors and smart phone applications can be used to track daily steps and activity levels, and set targets to increase physical activity. Additional activities such as yoga, Tai Chi, dance and seasonal activities such as swimming, paddling, outdoor cycling, hiking, skating and snowshoeing can be done in a social setting with family and friends. A gradual introduction to new activities should be emphasized, and we counsel transplant recipients to avoid activities with an increased theoretical risk of injury such as contact sports, skydiving, bungee jumping and scuba diving. Episodic medical issues such as illness, infection or injury can interrupt an exercise regimen, so physical activity counseling on how to modify and resume exercise after an episode of illness is important and can be addressed at reassessment.

**SPECIAL POPULATIONS**

Heart-lung, multi-organ and re-transplantation

At our center individuals who have undergone heart-lung transplantation, multi-organ transplantation (e.g., lung-liver) and re-transplantation participate in a similar pre-and post-transplant rehabilitation program as lung transplant candidates and recipients. Individuals awaiting a heart-lung transplantation may have congenital heart disease with cardiac shunts that can lead to right heart shunting and severe hypoxemia that may not be responsive to supplemental oxygen<sup>96</sup>. This may necessitate lower training intensity<sup>97</sup> (e.g., using heart rate and/or Borg dyspnea and fatigue scores) and lower oxygen saturation guidelines for exercise training. Following heart-lung transplantation, a longer warm-up and cool down is recommended to allow for the slower changes in heart rate due to disrupted cardiac innervation<sup>98</sup>. The modified Borg scale is used to guide exercise training instead of heart rate. There is a lack of information on exercise training for individuals listed for re-transplant<sup>99</sup>, but based on clinical experience at our center, individuals often have a lower functional capacity compared to listing for their first transplant.
**Pediatrics**

Children (from birth to 18 years of age) are typically followed in specialized pediatric healthcare centers. Clinical assessment of the pediatric lung transplant candidate should include posture, ROM, muscle strength and gross motor function appropriately for the age of the child. The 6MWT has been shown to be a valid measure in children[100] and is utilized by a majority of pediatric centers in North America[101]. There are published normative values for 6MWD across various ages[102], however interpretation of the 6MWT data is sometimes difficult to differentiate from growth and development of the child, so it should be used as part of a thorough clinical assessment to identify issues amenable to rehabilitation. While pre-transplant physical functioning and its relationship to post-transplant outcomes has not been studied extensively, one study in pediatric patients found a correlation between 6MWD and short term transplant outcomes including length of ICU stay, days of mechanical ventilation and time until discharge[103].

**Pre-transplant rehabilitation:** There are no studies examining the impact of exercise training in pediatric lung transplant candidates, however clinical experience indicates that it can be of significant benefit for these children and helps to prevent deterioration in function. Due to the limitations of available programs for children, families must often commute to the transplant center. However, older teens may be referred to adult pulmonary rehabilitation programs with support from pediatric specialists. Children may also have exacerbations of their underlying condition requiring hospitalization and modification of their exercise programs. Exercise prescription with slow progression can be approached similarly as for adults including both aerobic and resistance training[103,104]. Strength training is unlikely to increase muscle bulk for pre-pubertal children, but can improve function. Exercise training for younger children should include activities encouraging gross motor skill development, such as integration of physical education activities and incorporate growth and developmental factors of the child's maturing system. Physical therapists should also encourage regular school attendance, participation in physical education curriculums (within medical restrictions) with appropriate modifications to help ensure adequate levels of physical activity. Collaboration with school professionals, teachers, and physical education instructors may be needed to ensure safe follow through of these recommendations.

**Post-transplant rehabilitation:** Exercise capacity and general fitness improves for children following lung transplant but remains reduced compared to age-predicted values[104-106]. Opportunities and access to rehabilitation post-transplant are often limited. A study examining the impact of an early semi-individualized physiotherapy prescribed exercise program early (within the first three months) after hospital discharge found similar improvements in 6MWD, strength and flexibility in children who attended the hospital three times a week compared to children who performed the exercise at home with parents[105], suggesting that home-based training may be a way to bridge the gap in accessibility. A study at our center with children who were attending the World Transplant Games showed the positive effects of home-based training, which included general exercise programs and event-specific, skill-based training done independently for three months prior to the Games. The children showed short term benefits in levels of physical activity and each subject demonstrated an increase in at least one parameter of fitness on the Fitness-GRAM™[106]. Taken together, these studies suggest that home-based intervention or exercise prescription can be of benefit for these children when provided with appropriate education regarding safe exercise. The transition of adolescents and young adults to adult care is an increasingly important area of focus since this has been recognized as a vulnerable time for adolescent transplant recipients[107]. Research on strategies to optimize successful transition highlights the importance of an inter-professional approach with involvement from both the pediatric and adult care centers.

**CONCLUSION AND FUTURE DIRECTIONS**

Medical and surgical advances continue to improve the availability of lung transplantation[108]. Exercise training provides an essential role in optimizing functional capacity and fitness pre-transplant, as well as improving outcomes and quality of life post-transplant. Physiotherapists and clinical exercise specialists working with lung transplant candidates and recipients require expertise in general exercise training principles and specialized knowledge of pre- and post-transplant complications, oxygen tiration, side effects of medications and a sound understanding of how to modify exercise programs during episodic illnesses/exacerbations and/or change in lung function pre- and post-transplant. Although studies have been conducted on exercise training in lung transplantation, there is a need for larger studies examining long-term outcomes[109]. Individuals with a complicated pre- and post-transplant course pose a particular challenge for clinicians, and further research on rehabilitation for this population is needed. The development of standardized physical function measures that can help predict post-transplant outcomes, and the investigation of alternative modes of exercise training are also warranted.

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