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Narrative Review

A Review of Lung Transplantation and Its Implications for the Acute Inpatient Rehabilitation Team

Katie Hatt, DO, Nicholas C. Kinback, MD, Anoop Shah, MD, Ernesto Cruz, MD, Eric L. Altschuler, MD, PhD

Abstract

Since the late 1980s, lung transplantation has become an option for some individuals (in 2014, 4000 lung transplantations were performed) with end-stage lung disease aimed to help these individuals restore function and improve survival and quality of life. Individuals living with end-stage lung disease already are deconditioned, with poor endurance and limited exercise capacity. There are additional post-transplantation factors that can contribute to poor endurance and decreased exercise capacity. Although pulmonary rehabilitation in the pretransplantation phase is a crucial component for positive functional outcomes after lung transplantation, the incidence of post-transplantation complications, coupled with the need for immunosuppression, often warrants close monitoring by medical professionals. The acute inpatient rehabilitation unit offers an ideal setting for such patients to receive therapies to improve functional status while allowing for monitoring and medical management with a comprehensive team approach, including both the rehabilitation and the transplantation teams. In this article, we review the medical issues, physiologic changes, common complications after lung transplantation, and potential side effects of immunosuppressant therapy, as well as address rehabilitation specific concerns, outcomes, and goals of the patient undergoing lung transplantation in the acute inpatient rehabilitation unit.

Level of Evidence: V

Introduction

According to the International Society for Heart and Lung Transplantation, more than 4000 lung transplantations (LTs) were performed in 2013 [1]. The primary indication for LT is end-stage lung disease (ESLD), which most commonly results from advanced chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, cystic fibrosis, emphysema caused by alpha-1 antitrypsin deficiency, and pulmonary arterial hypertension [1,2]. Despite optimal medical management, appropriate candidates for transplantation candidates generally (1) are symptomatic during activities of daily living (consistent with class III or IV New York Heart Association classification) and (2) have a life expectancy that is not predicted to exceed 24-36 months [2].

Survival after LT has significantly improved during the last 2 decades as the result of improvements in surgical techniques and immunosuppression. Despite these advances, the median survival of all etiologies for LT ranges from 4 to 6 years; individuals with double-lung transplants (DLTs) have a slightly better survival compared with those with single-lung transplants (SLTs) [1,3]. Long-term outcomes after LT remain the worst of the solid-organ transplants. According to the Scientific Registry of Transplant Recipients July 2015 reports, the national 1-year adult expected survival was 88%, whereas the 3-year expected survival was 68%. Chronic rejection, seen in the form of bronchiolitis obliterans syndrome (BOS), is the main impediment to positive long-term pulmonary outcomes after transplantation. Other factors influencing outcome are related to the use of high-dose immunosuppressant agents and subsequent side effects.

Quality of life (QOL) has shown to be improved after LT. Self-ratings for health-related QOL between lung recipients and a normative sample of healthy people have been shown to be comparable [1,4]. Improvement in QOL is dependent on the incidence of postoperative complications, including infections and rejections, which can lead to increased physical restrictions in addition to symptoms of depression and anxiety [4-6].

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After LT, pulmonary function is improved; however, patients continue to have significant limitations primarily as the result of general deconditioning, poor strength, and other peripheral factors, with physiological changes associated with post-transplantation medications compounding this effect [7]. Given the prolonged hospital course of LT, the complexity of care, and the need for close monitoring when complications occur, acute inpatient rehabilitation can be an ideal setting to help improve endurance and maximize independence before discharge. Not unlike spinal cord injuries and strokes, LT recipients have a unique set of medical complications and rehabilitation challenges in which physiatrists should be well versed, given this increasingly more common rehabilitation population.

History of LTs

Dr. James Hardy performed the first LT in humans in 1963 on a 58-year-old man with lung cancer [8]. The patient survived only 18 days after the transplantation, eventually succumbing to kidney failure [8,9]. LTs were continued during the next several decades, with the majority of patients meeting the same fate.

High-dose corticosteroids were helpful in preventing acute rejection in patients during this early era; nevertheless, mortality remained high, with the leading cause of death attributed to poor healing of the airway and vascular anastomoses [9]. With the advent of improved surgical techniques, additional immunosuppressive agents were required for long-term graft survival. The initial discovery of cyclosporine, followed later by the use of tacrolimus and mycophenolate mofetil, significantly reduced the need for high-dose steroids and subsequently improved post-transplantation healing. It was not until 1983 that Dr. Joel Cooper, of the Toronto Lung Transplant Group, performed an LT on a 58-year-old man with pulmonary fibrosis in which the recipient experienced long-term survival. When the group reported their experience in 1986, the recipient was alive and well [9,10].

Overall positive outcomes, defined by increased survival and QOL, have improved with advances in surgical techniques, medical therapies, and the donor/recipient selection process. Infectious complications are a leading cause of death at all time points after LT, accounting for 35% of deaths in the first year and 20% of deaths thereafter [11,12]. Primary graft dysfunction is the most common cause of death in the first 30 days, whereas chronic lung allograft dysfunction, typically manifesting as BOS, is the most common cause of mortality after the first year. Chronic rejection, accounting for 40% of post-transplantation mortality, remains the primary impediment to better long-term outcomes after LT [12].

Physiologic Changes After LT

Physiologic changes in LT occur as the result of anatomical alterations, which are influenced by the type of LT surgery performed (ie, SLT versus DLT) as well as the pathogenesis of the pretransplantation diagnosis. Respiratory immunologic defense mechanisms can be altered as a result of anatomic changes that occur pre- and post-LT, including denervation of the transplanted lung (impairing cough reflex), phrenic nerve damage (with potential for diaphragm paralysis and impaired lymphatic drainage), and weakened accessory muscles (resulting in poor cough impairing mucous clearance and reducing respirations). Damage to the vagus nerve intraoperatively can cause reduced gastroesophageal motility, thereby increasing the risk of aspiration and infection [13-15]. One retrospective study, in which the authors examined 263 LT recipients, found more than 70% of LT recipients with evidence of laryngeal penetration or tracheal aspiration, the majority of which was silent aspiration [16]. Aggressive pulmonary toilet, incentive spirometer use, and evaluation and treatment by a speech and language pathologist are encouraged and should be considered integral to the rehabilitation treatment plan [13].

Potential causes of oropharyngeal dysphagia after LT include gastroesophageal reflux disease (GERD), recurrent and superior laryngeal nerve injury, and local trauma from endotracheal intubation or intraoperative transesophageal echocardiogram [16]. GERD has been found to be associated independently with greater rates of rejection quantified as 3 times greater than those patients without GERD, due to associated risk of pneumonia and accelerated onset of BOS [16,17]. As the result of these increased risks, surgical intervention, with Nissen fundoplication for example, is a reasonable option for the treatment of recurrent or persistent symptoms of GERD. Patients undergoing LT even without overt symptoms of GERD should be considered for proton pump inhibitor therapy and lifestyle modification (ie, eating small, frequent meals and avoiding lying flat after eating) to decrease the risk of rejection.

Changes in Exercise Physiology After LT

Individuals who progress to ESLD ultimately requiring LT are likely to develop systemic effects of chronic respiratory failure, including skeletal muscle impairment, resulting in decreased exercise capacity. These changes include muscle atrophy, muscle weakness, a decrease in the proportion of type 1 muscle fibers, and an increased reliance on anaerobic metabolism, which can continue to impair exercise capacity even after LT has been performed [7,18,19]. Pre- and post-LT measures of muscle wasting may have a role in prognostication, whereby larger muscle mass measures

have shown to be protective with respect to functional outcomes [20,21].

Both pre- and post-transplantation factors play a considerable role in the overall exercise capacity of recipients undergoing LT [19-27]. The extent of cardiac and pulmonary dysfunction largely will depend on the patient's condition before transplantation. Pulmonary rehabilitation should be initiated early in the pre-transplantation period to maximize cardiopulmonary function and improve muscle strength/mass and exercise endurance before transplantation. Research suggests impaired oxidative capacity of peripheral skeletal muscle is a major contributor of the limitations of maximal oxygen consumption (VO_2 max) and exercise capacity in recipients of transplants [7,18,19,25,28]. It is imperative for the rehabilitation physician to understand the cause of LT recipients' exercise limitations as multifactorial and largely the result of skeletal muscle changes rather than solely secondary to cardiopulmonary factors.

VO_2 max, which equates to aerobic capacity, is dependent on 3 factors: (1) ventilatory capacity, (2) maximal cardiac output, and (3) O_2 consumption by the working muscles. After LT, there are significant improvements in overall pulmonary function; however, peak exercise remains reduced to 40%-60% of predicted values [7,19]. Williams et al [29] looked at maximal exercise capacity in recipients of SLT ($n = 6$) versus DLT ($n = 7$). At 3 months post-transplantation, VO_2 max was 46% of predicted values in the SLT group and 50% of predicted values in the DLT group. At 1-2 years post-transplantation, there was no improvement in VO_2 max or maximal work capacity in either group, despite improvements in lung function and return to regular activities.

In another study, Miyoshi et al [30] found that during incremental cycling to VO_2 max, minute ventilation reached 46.8% of maximum voluntary ventilation at peak exercise in recipients of SLT ($n = 6$) and 33.4% of maximum voluntary ventilation in recipients of DLT ($n = 6$). Oxygen saturation was maintained close to resting values in both groups. These studies suggest the benefits of exercise plateau well before maximal ventilation and changes in oxygen saturation are minimal indicating ventilatory factors are unlikely to contribute significantly to exercise capacity limitations in LT recipients [18,30].

Furthermore, studies comparing LT recipients with heart-lung transplantation recipients found those with heart-lung transplants had reduced heart rate and stroke volume due to cardiac denervation, whereas cardiac function after LT was found to be sufficient and did not prematurely limit maximal exercise capacity in this group [19]. These findings suggest cardiac output also is not the limiting factor in VO_2 max in the LT population. Oxygen consumption by working muscles is the major impediment to exercise capacity and VO_2 max post-transplantation. Lower extremity fatigue, as opposed to dyspnea, is a more common reason stated for ceasing exercise after LT.

Several studies have demonstrated impaired oxidative capacity of the lower extremity after LT [19,31]. Changes in muscle oxidative capacity are likely a reflection of changes in muscle that occurred in the pretransplantation condition. Reduced muscle mass, reduced type 1 muscle fibers, and decreased concentrations of oxidative enzymes in the quadriceps femoris muscle, for example, have been reported in both individuals with COPD and LT recipients, implying some degree of exercise intolerance precedes the transplantation [19].

Evans et al [32] found recipients of SLT ($n = 9$) had a lower resting pH of the quadriceps femoris muscle and an earlier decrease in pH during bilateral knee extension exercise. Furthermore, the work rate at which the pH decreased was correlated with VO_2 max, suggesting an intrinsic abnormality of skeletal muscle as the culprit for limiting exercise capacity. Another study that looked at biopsied vastus lateralis muscle of LT recipients found this population to have less muscle oxygen desaturation during peak cycling exercise compared with control patients, implying an impaired ability of the muscle to uptake and use the available oxygen [23]. These changes are associated with an increased reliance on anaerobic metabolism, early onset of lactic acidosis, and reduction in peak exercise capacity [19,31].

After LT, the use of immunosuppressant medications, particularly cyclosporine and corticosteroids, also may affect VO_2 max and exercise capacity because of the profound effects these medications have on cellular features of skeletal muscle [19,33]. Steroid-induced myopathy is a well-documented cause of muscle atrophy, with chronic corticosteroid use, particularly affecting proximal muscles and selective type II fibers in peripheral muscles [19]. Cyclosporine has been shown to inhibit skeletal muscle mitochondrial respiration in vitro and to diminish endurance exercise time in rats [22]. At therapeutic levels, cyclosporine can decrease ATP production during oxidative metabolism by blocking a calcium-dependent pore in the inner mitochondrial membrane, leading to an inability of working muscle to use oxygen and resulting in an early shift toward glycolytic metabolism, thereby limiting exercise capacity [34]. This logically also may apply to tacrolimus, which largely has replaced cyclosporine as the first-line calcineurin inhibitor.

The rehabilitation physician should acknowledge the potential pre- and post-transplantation factors contributing to generalized weakness, deconditioning, and impaired exercise capacity to help guide the most effective treatment plan. Aside from the aforementioned factors, other considerations for causes contributing to decreased exercise capacity post-LT include critical care myoneuropathy, glucocorticoid-induced myopathy, intraoperative phrenic nerve damage, and

poor nutritional status. Rehabilitation after LT has been shown to improve skeletal muscle force as well as exercise tolerance [22] and should be initiated as early as possible in the transplantation process, ideally starting with pretransplantation pulmonary rehabilitation and early mobilization in the intensive care unit with ongoing post-transplantation rehabilitation. Further research is warranted to determine an optimal exercise-training program to improve skeletal muscle function and exercise capacity in LT recipients [19,31,35].

Rehabilitation Outcomes After LT

Outcome data are limited with respect to LTs as a population; nevertheless, the increasing frequency of LT and the changing demographics of acute rehabilitation necessitate a comparison with other rehabilitation populations. Progress of LT Functional Independence Measure score gains has been found to be slower than other populations and is more in line with Functional Independence Measure gains seen in stroke patients [36,37]. Although exercise capacity and skeletal muscle function are expected to improve with exercise, therapy after transplantation studies indicate LT recipients do not reach predicted levels in maximal exercise capacity or skeletal muscle strength [35].

Patients should be advised that although recovery is expected to occur, it tends to be slow. LT recipients have reported substantial gains in their functional capacities and have shown marked improvement in scores on the physical function subscales of QOL questionnaires [38,39]. Despite improved scores in physical function after LT, however, scores remain lower than normative values [39]. Studies in which authors examine exercise training after LT are limited; however, it is proposed that physiological adaptations, such as improved skeletal muscle function, would improve physical functioning and QOL of recipients of transplants undergoing an appropriate exercise program [25,40].

One important measure of physical endurance pre and post- LT is the 6-minute walking distance test (6-MWD), which is the distance that a patient can walk in 6 minutes. This functionally may determine his or her household and even community ambulatory capabilities, predict VO_2 max, and have a correlation with survival in patients who undergo LT [27,41]. The 6-MWD certainly is improved after participation in a comprehensive pulmonary rehabilitation program. In one study, 6-MWD in meters in SLT recipients (n = 212) increased from 267 ± 134 m to 381 ± 120 m ($P < .0001$) and in DLT recipients (n = 338) increased from 284 ± 144 m to 412 ± 126 m ($P < .0001$) [24]. These improvements were seen after patients had participated in a pulmonary rehabilitation program for an average of 41 days, which conveys the importance of such programs. Increase in 6-MWD up to 365-425 m confers a survival advantage, although there is no single value that predicts outcomes [27]. Thus, there is utility in using 6-MWD as a measuring tool for survival and predicting functional QOL.

The vast majority of LT patients, cited at 88% in one single center study, return home on discharge with typically near full independence [36]; however, complications (primarily attributable to infection and rejection) may necessitate transfer back to an acute care hospital before returning home. Hospital readmission rates in patients undergoing LT have been documented as high as 19%-40% of total acute rehabilitation admissions [24,36,37]. Such findings warrant special considerations and close surveillance for LT patients, because they tend to have high complications rates [42-45], slower functional gains, and more readmissions compared with other acute rehabilitation populations [24,36,37].

Goals of Rehabilitation in LT

Pulmonary rehabilitation is a cornerstone of treatment for LT. The primary goals of pulmonary rehabilitation of individuals with chronic lung disease (CLD) are to decrease symptoms (ie, dyspnea, anxiety) and improve QOL. A partnership between the transplantation team and the rehabilitation team should begin before transplantation to maximize the benefits and limit complications. Patient and family education is crucial to prepare recipients for what to expect before, during, and after transplantation. Ideally, pulmonary rehabilitation is initiated before transplantation to maximize overall physical condition and activity tolerance, improve endurance, and decrease comorbidities [7].

Rehabilitation continues to show benefit for the LT recipient in the immediate and long-term post-LT phase with options including inpatient, outpatient, and home-based therapies [28,35,46,47]. Rehabilitation in the post-LT phase offers a structured exercise program aimed to optimize physical and emotional health, which has a positive impact on overall outcomes, including exercise tolerance, endurance, and QOL [46,47]. The greatest natural recovery in exercise capacity is seen during the first 3 months after LT, and with a structured exercise regimen patients can continue to improve more over the following year [7,28,46].

Even with appropriate pre- and perioperative pulmonary rehabilitation, LT recipients may face prolonged hospital courses secondary to various complications, as discussed previously. The physiologic changes associated with CLD (prolonged inactivity, deconditioning, and poor nutrition) coupled with effects of immunosuppressant medications, prolonged hospital/intensive care unit stays, and episodes of organ rejection can significantly affect these individuals' recovery process [28]. In such cases, the inpatient rehabilitation setting is an ideal one to address functional improvements

through a structured exercise program while continuing to provide close medical monitoring.

LT Acute Rehabilitation Admission Criteria and Disposition

LT is often followed by a long postoperative course with potential complications necessitating an interdisciplinary team approach. Involvement of rehabilitation medicine early in the treatment course is important for long-term disposition and treatment planning. LT recipients should be evaluated by physical therapy, occupational therapy, speech and language specialists, social work, and often neuropsychology and dietary specialists. After input from these sources and medical stability have been ascertained, a patient may be deemed appropriate and qualify for admission to acute inpatient rehabilitation.

Although no formal criteria exist in the literature, admission to acute inpatient rehabilitation after LT should be evaluated like other cases of general debility, cardiopulmonary deconditioning, or neurologic impairment (in the setting of neurologic complications such as stroke or encephalopathy post-LT). Similar to most other rehabilitation diagnoses, individuals who undergo LT should be considered for acute rehabilitation admissions if they meet the following criteria: (1) need for regular visits by a rehabilitation physician, (2) need for rehabilitation nursing care, and (3) need for at least 3 hours of therapy per day from at least 2 therapy modalities (physical therapy, occupational therapy, speech therapy). Patients should be medically stable before admission to acute rehabilitation.

Given the long and complex postoperative course of these patients, a thorough history and chart review must be performed when they are admitted to the inpatient rehabilitation unit, followed by a complete review of systems. Special attention should be paid to pain generators, bowel and bladder function, and signs and symptoms suggestive of cardiac, respiratory, neurologic, or gastrointestinal pathology. It is important to be mindful of patients having had months of deconditioning, even before undergoing surgery, noting premorbid and current functional status. This will help determine goals of therapy and guide patient and therapy expectations during the inpatient rehabilitation course. As well, a review of current and projected medications should be discussed with the transplantation team, because this may impact their transition to rehabilitation or the community.

A thorough physical examination, noting baseline status, is fundamental to the rehabilitation physician's admission practices and continues to apply to recipients of transplants. Careful attention should be paid to auscultation of the heart and lungs to determine baseline status, with or without arrhythmia, followed by a comprehensive neurologic examination, with the noting of baseline manual motor testing, presence of tremor, intactness of sensation, and mental status. Incision cleanliness, presence of staples, and tracheostomy status should be documented, and the individual should be checked for decubitus ulcers. Of note, staple/suture removal after LT often is delayed because of the healing limitations of chronic corticosteroids.

A rehabilitation treatment plan should be devised with involvement of a comprehensive, interdisciplinary team of physicians, therapists, nurses, wound care specialists, and social work. Recipients of transplants may require frequent weight shifts, bowel regimen, pain control regimen, tracheostomy care, frequent incentive spirometry, and Foley catheter care. It is recommended to have family involvement early in the rehabilitation course, because admission to inpatient rehabilitation is the start of bridging the patient back to their home environment. Likewise, psychosocial support is imperative because LT recipients are patients who are used to being sick, disabled, and cared for by others. They will need support for their new role in which they may now be expected to be independent, return to work, and provide support for others.

Discharge planning should begin at the time of admission to inpatient rehabilitation via a multidisciplinary approach to encourage successful reintegration into the community. At discharge from inpatient rehabilitation, close follow-up with the transplantation team and other necessary specialists should be scheduled. Because of the inevitable need for poly-pharmacy and monitoring for medication side effects after LT, medication instructions should be reviewed thoroughly by the physician, and necessary prescriptions for outpatient laboratory tests should be provided. Home equipment should be ordered where indicated and ideally a home safety evaluation should be performed. A plan should be in place for continued pulmonary rehabilitation for exercise therapies at the outpatient or home based level, and all patients should receive instructions for a home exercise program to continue maximizing functional gains.

Education is a crucial component for successful rehabilitation and favorable transplantation outcomes. Recipients of transplants, and their families/caregivers where applicable, should be educated regarding self-care and self-assessment to monitor for complications, as well as compliance with a new, rather strict medical regimen [48]. Specifically, they should be educated about possible allograft rejection symptoms such as fever, chest pain, shortness of breath, chills, and cough. Education also should focus on chronic complications to be aware of secondary to prolonged use of immunosuppression. For instance, use of immunosuppressant agents, especially steroids, has been linked to an increased risk of osteoporosis [47].

Return to work may be a goal for a number of LT recipients. Patients should be cognizant of industrial hazards and educated to take appropriate precautions. Patients with mild functional limitations may confer a benefit from return to work. The optimal time for return to work is suggested to be around 1 year after transplantation [49]. This time frame would likely coincide with maximal improvement in functional status and improved QOL.

LT recipients also should be instructed regarding the following restrictions post-transplantation: avoid smoking, avoid lifting objects greater than 10 pounds for at least 6 weeks, avoid sporting activities strenuous to the chest for at least 3 months, avoid driving for at least 1 month, avoid airplane travel until cleared by the transplantation team, wear a mask in crowded and polluted areas for at least 3 months, avoid reptiles and birds as pets and avoid cleaning up litter, avoid alcohol and grapefruit juice due to medication interaction, avoid pregnancy due to lifelong immunosuppression, avoid live vaccinations, and avoid dental procedures, uncooked vegetables, and fresh flowers for at least 6 months. These restrictions are the incentive for our practice of maintaining neutropenic-like precautions during inpatient admissions [50]

Insurance reimbursement for LT patients in the acute rehabilitation setting can vary. For instance, some insurance companies' use Clinical Risk Groups to determine payment based on a risk-adjustment tool and a clinically based classification system to measure a population's burden of illness [51], whereas other insurance companies reimburse on a per-diem basis. In the LT population, we have seen functional gains, with patients progressing from a dependent functional status to modified independence, during inpatient rehabilitation stays lasting anywhere from 1 or 2 weeks up to 2 months. It is crucial to have appropriate and sufficient reimbursement available during this time to support the necessary services when functional gains are being made.

Further research into the cost-benefit analysis of acute inpatient rehabilitation after LT will be an important topic for future studies. Currently, a number of studies have been conducted that examine the overall cost of LT, with one large center estimating total cost to be \$153,921 $\pm$ \$133,981 SD [52]. Other analyses have found with increased life expectancy, the majority of the costs are incurred after discharge [53], which would further increase with readmissions. As aforementioned, QOL is also largely dependent on complications and consequently readmissions. Therefore, any steps taken in the acute rehabilitation setting to prevent such adverse events would in theory benefit QOL, lower the cost of readmissions, and improve overall cost-benefit analysis of LT. Indeed, we believe LT (and other post-transplantation states) may merit being the 14th-approved 60% diagnosis.

Medical Management of LT Patients During Admission to Acute Rehabilitation

Immunosuppression After LT

Induction and maintenance of immunosuppression after LT is necessary to prevent acute and chronic rejection of the lung allograft. Maintenance immunosuppression is achieved with a glucocorticoid (ie, prednisone), a calcineurin inhibitor (ie, cyclosporine or tacrolimus), and a nucleotide-blocking agent (ie, mycophenolate mofetil or azathioprine) [1]. Mechanistic target of rapamycin (mTOR) inhibitors sirolimus and everolimus are newer agents that may be potential alternatives for patients who cannot tolerate calcineurin inhibitors [54].

Potential side effects of tacrolimus and cyclosporine are similar and include metabolic abnormalities (hyperkalemia and hypomagnesemia), hypertension, and nephrotoxicity [55]. The incidence of new-onset diabetes is increased in recipients of transplant who receive tacrolimus [56], and dose-dependent neurotoxicity (resulting in tremors, headache, and delirium, for example) can occur [55,57]. Immunosuppressive-associated leukoencephalopathy is a potential significant complication of cyclosporine or tacrolimus therapy, which can present, for example, with rapid decline in neurologic function, seizures, altered mental status, or visual changes. Although this condition is reversible with early detection and subsequent cessation or decreased dose of the inciting medication, it can be fatal if not identified early [26,58].

Both cyclosporine and tacrolimus have been associated with renal failure with chronic kidney disease cited as high as 68% at 5-year follow up post-transplantation [59]. In patients with mild acute kidney injury, it is recommended to keep drug levels on the lower end of the therapeutic range with close monitoring, whereas severe or persistent kidney dysfunction may warrant temporarily suspending the medication and consulting transplantation nephrology.

Mycophenolate mofetil has potential side effects of gastrointestinal symptoms (nausea, diarrhea, abdominal cramping), and bone marrow suppression with resulting cytopenias [60]. Azathioprine can cause gastrointestinal toxicity (manifesting with symptoms of nausea, vomiting, diarrhea, fever, malaise, myalgia, and liver enzyme abnormalities), as well as hepatotoxicity and blood dyscrasias (anemia and thrombocytopenia) [61]. These nucleotide-blocking agents also have been associated with new or reactivated infections with JC virus, resulting in progressive multifocal leukoencephalopathy (PML) [60,61]. Recipients of transplants should be monitored for neurologic symptoms including hemiparesis, confusion, cognitive deficiencies, and ataxia, with PML included in the differential.

Drug-induced pulmonary toxicity is a rare side effect that has been associated with medications such as mTOR inhibitors (sirolimus and everolimus) [54]. Symptoms include dry cough, progressive dyspnea, fatigue, and weakness typically developing within 6 months of initiating therapy. Toxicity is not clearly correlated with drug serum levels. Pulmonary toxicity due to mTOR inhibitors potentially is reversible if recognized early and should therefore be considered in patients presenting with the aforementioned symptoms [54,62]. Of note, mTOR inhibitors also are associated with an increased risk of venous thromboembolism (VTE), which can have a similar clinical presentation.

Patients receiving immunosuppressant and prophylactic therapy after LT should be monitored on an ongoing basis for adverse reactions, adequacy of immunosuppression, and drug levels. Typically, monitoring includes blood counts, liver function tests, blood urea nitrogen, creatinine, potassium, magnesium, glucose, and cytomegalovirus (CMV) viral load. Drug levels of tacrolimus and cyclosporine should be monitored with doses adjusted accordingly in conjunction with the transplantation team. Leukocytosis is expected in LT patients receiving high-dose steroids; however, an increase from baseline should prompt further evaluation of an infectious source. Because of the increased risk of arrhythmias [44], patients should also be monitored for electrolyte abnormalities (ie, hypokalemia, hypomagnesemia, hypocalcemia).

Noninfectious Complications After LT

Examples of noninfectious complications include allograft rejection, anastomotic complications, pleural complications (pneumothorax and pleural effusions, for example), primary graft dysfunction, recurrent primary disease, drug-induced pulmonary toxicity, and VTE [43,44,63-66]. Likewise, all chronic use of steroids predisposes this population to osteoporosis and increased risk for pathologic fractures as another late-onset complication. In the acute setting, however, the incidence of VTE in LT patients is reported up to 29%, greater than in other surgical patients, although the real incidence is unknown, because it is suspected a majority of VTE cases are silent or confounded by concomitant illness resulting in the condition being underdiagnosed [65]. Risk factors for VTE after LT are associated with abnormalities in hypercoagulability and include increased age, a history of diabetes, pneumonia, or cardiopulmonary bypass. Pulmonary artery reserve tends to be limited during the recovery phase; as a result, an embolus to the transplanted lung can have serious consequences [42,43,64].

Cardiac complications after LT are relatively common and include atrial dysrhythmias, hemodynamic instability, coronary artery disease, and constrictive pericarditis. Atrial dysrhythmias are seen in up to 25%-35% of LT recipients, with atrial fibrillation being the most common [44,67]. Onset of arrhythmias has been associated with prolonged hospital stays and increased mortality [44].

Acute kidney injury also is common (56%-69%) after LT [45]. Although less than 10% of those who develop acute kidney injury will require renal replacement therapy, the need for renal replacement therapy is associated with an increased risk for early mortality [63]. The maintenance dosages required for antirejection medications are greatest in LT patients compared with other solid-organ transplants, resulting in increased risk of complications. Renal failure, for example, is a major long-term complication associated with chronic use of tacrolimus or cyclosporine. Other risk factors for post-transplantation renal failure include a history of pulmonary hypertension or idiopathic pulmonary fibrosis, reduced glomerular filtration rate, mechanical ventilation $>$24 hours, and use of intravenous amphotericin B [63].

Neurologic complications after LT include encephalopathy (including immunosuppressant-associated leukoencephalopathy, and PML), stroke, tremors, and peripheral neuropathy. Strokes have been reported in approximately 5%-10% of LT recipients [64,68]. Development of a cardiac arrhythmia predisposes this population to stroke. Also, the left atrial anastomotic site serves as a potential nidus for thrombus formation, which can result in embolic stroke days to weeks after transplantation.

Infectious Complications After LT

LT recipients are at increased risk for infectious complications secondary to high level immunosuppression and the adverse effects that transplantation has on the innate pulmonary host defenses (ie, impaired cough reflex and reduced mucociliary clearance). LT recipients are at increased risk for bacterial infections (including *Pneumocystis jirovecii*), viral infections (such as CMV), and fungal infections (most commonly *Aspergillus* and *Candida* species). Bacterial pneumonia is the most common infection seen, followed by CMV infections [69,70].

Because of the risk of infection, prophylaxis often is warranted post-transplantation. Because the risk of *Pneumocystis jirovecii* pneumonia in LT patients is relatively high, indefinite prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) or dapsone is recommended [70]. CMV prophylaxis is achieved with valganciclovir, and treatment is continued for 6-12 months, depending on serologic status [71]. Nebulized amphotericin B is used for prophylaxis against fungal agents, including *Aspergillus* in patients without respiratory tract colonization, whereas voriconazole is used in patients with known fungal colonization. Antifungal prophylaxis generally is continued during

the course of hospitalization, including inpatient rehabilitation and on discharge until transplantation follow-up [72].

Adverse Effects From Prophylactic Treatment

Valganciclovir is a nephrotoxic and teratogenic agent. Blood dyscrasias, including severe leukopenia, neutropenia, anemia, and pancytopenia, also can occur [71,72]. TMP-SMX may cause electrolyte abnormalities (specifically hyperkalemia and hyponatremia), and blood dyscrasias (agranulocytosis, aplastic anemia or thrombocytopenia), in addition to dermatologic reactions (including Stevens-Johnson syndrome) and hepatic necrosis. Dapsone can be used as an alternative prophylactic therapy in patients who do not tolerate TMP-SMX side effects or have sulfa allergies [73].

Amphotericin B is also a nephrotoxic agent and may cause electrolyte abnormalities, specifically hypokalemia and hypomagnesemia [72,74]. Voriconazole has been associated with arrhythmias/QT prolongation, hepatotoxicity, and nephrotoxicity. Of note, this class of antifungal (azoles) may have significant interactions with other commonly used medications in patients undergoing transplantation, including tacrolimus, cyclosporine, and sirolimus [75]. For instance, voriconazole may increase the serum concentration of tacrolimus and may decrease the metabolism of cyclosporine [75]. Given the large number of potential interactions, particularly with respect to hepatic metabolism and nephrotoxicity, a strong case can be made for continued monitoring by an ongoing dialogue with the transplantation team while patients who have undergone transplantation are in acute inpatient rehabilitation. Knowledge of these complications and collaborative treatment with the transplantation team will help to minimize adverse events and decrease readmissions.

These prophylactic medications required post-transplantation can be quite expensive. Costs may vary country to country, or even regionally, reaching upwards of $5500+ per month [76,77], and those medications with a single manufacturer may be subject to sudden increases in price. Research continues to support the need for prophylaxis in LT patients [70-74,78,79]; thus, the cost of these medications should be included in the cost of transplantation.

Special Considerations in LT Recipients in the Acute Rehabilitation Setting

LT recipients are a unique population in the rehabilitation setting. The complexity of this highly technical, thoroughly modern procedure with regard to surgery and medications initially may prove intimidating, especially in centers not accustomed to high LT patient volume. Nevertheless, during the course of rehabilitation, the old adage of listening to a patient when describing symptoms can be a most useful and often very reliable guide in treatment. Attention should be paid to common medical conditions and symptoms such as infection, chest pain, dyspnea, anxiety, and bowel dysfunction, as the management of these may differ in the patient undergoing transplantation. In the rehabilitation setting, functional setbacks observed in therapy may be the first sign of impending complication and warrant a workup.

Our current practice, out of an abundance of caution, is to consider recipients of transplants with impaired immune status in the same category as neutropenic patients with regards to precautionary measures to avoid infection. For instance, masks should be worn when entering the patients' room, hand hygiene is crucial, and fresh flowers, plants, and uncooked vegetables should be discouraged. In addition, use of rectal thermometers, suppositories, and enemas should be avoided to decrease the risk of infection. Further research on the need for such precautions is warranted.

LT recipients may experience significant chest pain postoperatively and throughout their rehabilitation course. A thorough history will help decipher between a visceral, somatic, or neuropathic etiology of the chest pain, because all 3 types are highly prevalent in this population. Visceral causes of chest pain, including cardiopulmonary etiologies (ie, acute ischemia), are less common in the acute transplantation period as the result of pretransplantation cardiac work-up. In the long term, however, patients who undergo LT have increased prevalence in risk factors for coronary artery disease (ie, hypertension, diabetes, renal failure), predisposing this population to cardiac events [1]. Somatic pain due to the surgical incision needs to be managed effectively to allow for successful pulmonary toilet and mobilization of secretions. Patients with DLT may experience a greater degree of sternocostal pain because of the extended incision, although limited data currently exist on this matter. Neuropathic agents may be helpful in treatment of sternocostal pain, which is likely to have both somatic and neuropathic components. Postoperatively, patients may be started on short- and long acting narcotic medications; however, weaning narcotic medications during the rehabilitation stay is preferable, as postoperative somatic pain should subside. Concurrently, neuropathic agents such as gabapentinoids or tricyclic antidepressants should be optimized, because neuropathic pain is likely to persist on a more chronic basis. Increasing such medications should be done cautiously, and in certain situations tricyclic antidepressants may be preferred to gabapentinoids, due to the high likelihood that LT recipients progress to varying degrees of chronic renal impairment [80,81].

Anxiety is a common symptom among LT recipients. The symptoms associated with an anxiety attack closely mirror signs and symptoms of pulmonary disease, which may manifest with physiological signs of tachycardia,

sweating, and dyspnea. The first priority when assessing dyspnea has to be a thorough history, physical examination, consultation with the LT team, and medical work-up necessary to rule out pulmonary or cardiac causes of dyspnea. This having been said, a psychiatric diagnosis of anxiety or depression is common in individuals with lung disease. In fact, one of the primary reasons for individuals with pulmonary disease to undergo pulmonary rehabilitation is alleviation of anxiety. One study reported rates of depression at 37%-71%, and rates of anxiety at 50%-75% in patients with severe COPD disease [82]. Anxiety in patients with CLD is intimately linked with patients' fears of acute dyspnea attacks with a sense of suffocation and fear of death [82]. These comorbid psychological impairments have been implicated to predict increased functional impairment, disability, morbidity, lower QOL, and decreased adherence to treatment [82]. As such, it is essential for the rehabilitation team to be aware of the role anxiety and depression have played in the life of an individual with CLD and to include psychiatry and/or psychology for appropriate counseling, cognitive-behavioral therapies, and management of psychiatric medications. In our experiences, we have found patients without preexisting anxiety-related psychiatric diagnoses often have not needed pharmacologic treatment and, rather, benefit from frequent reassurance their symptoms are common, as well as frequent encouragement from team members regarding progress in goals and improvements in overall function. This is an important issue, which warrants further study.

Tremors are commonly seen in recipients who undergo LT and can have quite a debilitating effect on fine motor movements, subsequently impacting activities of daily living. Use of immunosuppressant agents after LT, including the calcineurin-inhibitors and steroids, for example, has been associated with tremors [55]. Management of tremors may include changing the inciting agent (eg, calcineurin-inhibitor) and employing functional use of adaptive equipment (such as weighted utensils to help offset the tremors). In our experiences, we have found LT patients report onset of tremors occurring even before transplantation and initiation of immunosuppression. Further research is warranted into the etiology and treatment of tremors in this population, especially compared with nontransplanted lung disease and other solid-organ transplants.

Postoperative factors such as use of opioids for pain management, decreased mobility, and use of anesthesia predisposes LT recipients to bowel dysfunction with constipation. With regard to treatment of constipation in a LT recipient, magnesium and phosphate-containing cathartics should be avoided in those with renal disease, and enemas and rectal suppositories should be avoided in all LT patients because of the risk of infection. A daily regimen with an oral stool softener (ie, Docusate) and stimulant (ie, senna) titrated for daily bowel movements can be an effective means of managing constipation.

Bowel dysfunction also may manifest as diarrhea. In the LT recipient, diarrhea may be a side effect of immunosuppressant medications and often is seen in patients requiring artificial nutrition via nasogastric tube, for example. *Clostridium difficile* infection also is common in this population, likely because of the occurrence of several risk factors, including immunosuppression, use of protein pump inhibitors for gastrointestinal prophylaxis, and the use of antibiotics for infective prophylaxis. The risk of *C. difficile* infections is nearly doubled post-LT, although no antibiotic prophylaxis is recommended at this time [83]. The rehabilitation physician should have a low threshold to test for *C. difficile* in LT patients presenting with diarrhea; however, they must also consider other infectious agents, such as ova and parasites, based on patient history (ie, history of travel or eating raw or undercooked foods) because an immunosuppressed state may allow a dormant infection to resurface.

Traditional rehabilitation team meetings should be effective in identifying some of the complications attendant to LT, including decline in neurologic function that may be seen with leukoencephalopathy, sudden change in shortness of breath, and other physiologic changes that may warrant more urgent collaboration with the transplantation team to promote a successful post-transplantation outcome. It is important for the pulmonary transplantation team also be part of the rehabilitation team, because this partnership is essential for favorable outcomes, including functional improvements and success of the transplant.

Conclusion

LT is a complex procedure that aims to improve survival and QOL in patients with ESLD. Inpatient rehabilitation can be a key transition point between acute care and discharge to home, where patients can focus on functional improvements to reintegrate into the community while allowing for close medical monitoring and intervention. Although LT may appear on the surface to be generalized deconditioning on par with a prolonged hospital stay for pneumonia, the pathophysiology stemming from significant musculoskeletal impairment, chronic immunosuppression, and impaired aerobic capacity suggests it may be a unique diagnosis requiring more specific and intensive rehabilitation. The rehabilitation physician must work closely with an interdisciplinary team to enable patient success. Close monitoring and awareness of transplant rejection symptoms, medication side effects including infections and electrolyte abnormalities, risk of neurologic and cardiopulmonary complications, and treatment of comorbidities drastically improves patient outcomes and therefore improves QOL and readmission rates.

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Disclosure

K.H. Department of Physical Medicine and Rehabilitation, Lewis Katz School of Medicine at Temple University, Philadelphia, PA
Disclosure: nothing to disclose

N.C.K. Department of Physical Medicine and Rehabilitation, Lewis Katz School of Medicine at Temple University, Philadelphia, PA
Disclosure: nothing to disclose

A.S. Department of Physical Medicine and Rehabilitation, Lewis Katz School of Medicine at Temple University, Philadelphia, PA
Disclosure: nothing to disclose

E.C. Department of Physical Medicine and Rehabilitation, Lewis Katz School of Medicine at Temple University, Philadelphia, PA
Disclosure: nothing to disclose

E.L.A. Department of Physical Medicine and Rehabilitation, Lewis Katz School of Medicine at Temple University, 3401 North Broad Street, Philadelphia, PA 19140. Address correspondence to: E.L.A.; e-mail: eric.altschuler@temple.edu
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Katie Hatt, DO, and Nicholas C. Kinback, MD, contributed equally to this article.

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