Management of the Patient Undergoing Lung Transplantation
An Intensive Care Perspective

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The postoperative management of a patient undergoing lung transplantation involves many components of care. These components include ventilatory and hemodynamic management, immunosuppression, wound care, rehabilitation, infection control and treatment, and early detection of rejection. Key words: intensive care, lung transplantation

The CARE and management of a patient undergoing lung transplantation begin far in advance of the actual transplantation procedure itself. Appropriate patient selection, optimization of pulmonary and muscular function, and complete education and counseling are components of this preoperative process. The postoperative management from a critical care perspective plays an essential role in the management of each patient. Previous articles have addressed various aspects of the postoperative management of the patient.1-3 Limited randomized controlled evidence exists given the nature of transplantation medicine. This update will review the postoperative management of patients undergoing lung transplantation with recent evidence from an intensive care perspective.

PROCEDURE

Various types of procedures can be used for lung transplantation. Single-lung, double-lung, or combined heart-lung transplantation are the types of procedures being used. The choice of procedure depends on many factors including age and comorbidities of the recipient, organ availability, and institutional preferences. Single-lung transplantation is performed for patients with interstitial fibrosis, emphysema, or pulmonary hypertension; double-lung transplantation is performed for patients with cystic fibrosis; and combined heart-lung transplantation is performed for patients with end-stage cardiac and pulmonary disease (eg, Eisenmenger’s syndrome).

As a rule, all recipients have standard monitoring devices placed during surgical procedure. These include Swan-Ganz catheter, radial and femoral arterial lines, Foley catheter, and a transesophageal echocardiography probe. A double-lumen endotracheal tube is also placed routinely. Cardiopulmonary bypass is rarely necessary; however, there are some indications (eg, severe pulmonary hypertension, pediatric lung transplantation) in which it is used to help facilitate the surgical procedure.4

Single-lung transplantation is often performed through a posterolateral thoracotomy, although in some instances, an anterior axillary thoracotomy is performed. A pneumonectomy is then performed with care taken to avoid injury to the phrenic and vagal nerves. The donor lung is placed within the chest cavity, and the anastomoses

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are then performed with the approximation of peribronchial tissues over the anastomoses. The use of a telescoping anastomosis, with the cartilaginous portions of the donor and recipient bronchi intussuscepted is favored. Double-lung transplantation is performed either through bilateral anterior thoracotomies or a transsternal bilateral thoracotomy (“clamshell” incision). First, the least functional lung, as determined by preoperative quantitative ventilation and perfusion imaging, is removed and transplanted, and then 1-lung ventilation is used on the contralateral lung. In most instances, cardiopulmonary bypass can be avoided. After completion of the anastomoses, 2 chest tubes are placed into each pleural space, and the chest is closed. The airway is inspected by bronchoscopy.

Heart-lung transplantation is performed through either a median sternotomy or an anterotranssternal thoracotomy. Cardiopulmonary bypass is used during this procedure. The donor heart lung is then placed into the chest cavity, and the tracheal anastomosis is performed followed by the right atrial and aortic anastomoses. Bilateral pleural chest tubes are placed at the time of surgical procedure.

**POSTOPERATIVE MANAGEMENT**

The management of the patient in the immediate and early postoperative period occurs within the intensive care unit setting. Ventilatory support, hemodynamic management, immunosuppression, prevention and detection of infection, and detection of early rejection are a focus of the management regimen during this time.

The recipient remains intubated and is transported to the intensive care unit. Following hemodynamic stabilization, the patient is weaned from mechanical ventilatory assistance using standard protocols (eg, pressure support weaning). Many patients require an increased FiO₂ on completion of the surgical operation, and most can be weaned to an FiO₂ less than 50% within 24 hours. In the patient with a single-lung transplant for emphysema, minimal (or zero) positive end-expiratory pressure (PEEP) as well as allowance for an adequate expiratory time phase so as to prevent air trapping is used. For other patients following single- or double-lung transplantation, low-level PEEP is a standard of care.

Weaning of ventilatory assistance can begin once the FiO₂ can be decreased. Most patients can be weaned and extubated within the first several days following transplantation. For patients with pulmonary hypertension, variable responses can occur with episodes of pulmonary hypertension and oxyhemoglobin desaturation occurring with minimal provocation. In these instances, weaning is usually not undertaken for 24 to 48 hours following surgical procedure. During this time, adequate sedation and analgesia with maintenance of ventilatory support is undertaken. Weaning is then started once the hemodynamic and oxygenation status are stable. In some instances, a quantitative lung scan can be used to assess for adequate patency and graft blood flow. If a lobar or greater defect is noted, further investigation (eg, cardiac catheterization, exploration operatively) may need to be performed.

Appropriate fluid management is essential in the early postoperative period. A negative fluid balance is often attempted during the first 24 to 48 hours to try to prevent the occurrence of pulmonary edema. Monitoring of urine output in combination with monitoring of the pulmonary artery pressure and left ventricular end diastolic pressure is helpful in the ongoing fluid management. Pulmonary capillary wedge pressure should be kept as low as feasible with the use of not only diuretic therapy but also vasopressor and inotropic support. Renal insufficiency from aggressive diuresis should be avoided. In a retrospective study involving 118 patients undergoing transplantation, central venous pressure measurements of greater than 7 mm Hg was associated with a higher intensive care unit stay and higher hospital mortality rate.

Postoperative hypotension may occur, and the usual causes for persistent hypotension should be entertained. Intravascular volume
depletion, acute blood loss, and myocardial dysfunction can be easily determined with the use of routine laboratory, electrocardiographic, and echocardiographic testing. Intrathoracic processes must also be considered. Tension pneumothorax may occur, and as the pericardium was entered during the surgical procedure, tension pneumopericardium or pericardial effusion can also occur.9

Bronchoscopy is performed prior to extubation to assess the bronchial anastomoses and also clear any secretions that may be present. Supplemental oxygen is then administered by either an air face mask or a nasal cannula with maintenance of oxyhemoglobin saturations above 90%. The apical chest tubes are removed when no air leaks are present. The basilar chest tubes are removed several days later when the chest tube drainage has decreased to less than 150 mL per 24 hours.

PULMONARY TOILET

A vital component of the postoperative care is the prevention of lower respiratory tract infection. Vigorous chest physiotherapy and postural drainage should be routinely performed. Adequate use of inhaled bronchodilator (beta-agonist, anticholinergic, or combination) therapy must be maintained. Early ambulation to move the patient into a chair and begin walking should be performed as soon as feasible. In many instances, a stationary bicycle or treadmill is moved to the patient’s room in the intensive care unit to facilitate such exercise in a controlled environment. Adequate pain control is necessary to help facilitate secretion clearance. Epidural administration of analgesia is an effective means to provide adequate pain control. Oral administration of narcotics may also be necessary for some patients following the discontinuation of the epidural or intravenous infusions.

Incisions, intravenous catheters, and chest tubes

The incision should be inspected daily noting any skin changes, swelling, or drainage. Similar inspection of the chest tube insertion sites should also be carried out on a daily basis. Activities that will pull or strain the incision should be avoided. No ointments or creams should be used on the incision. Instructions on the timing of removal of the incisional bandages should be coordinated with the surgeon.

Following surgical procedure, the patient will likely have several indwelling catheters, including central venous lines, arterial catheters, Foley catheter, and chest tubes. Standard maintenance of all catheters should be performed with frequent inspection of the insertion site. Any fever that develops should prompt immediate contact with the physician staff. Chest tube drainage should be noted, and in most instances, there should be little or no drainage noted following transplantation surgery. Daily inspection of the chest tube for air egress should be noted, and in general, air egress should diminish on successive days, with no air egress noted by the fourth day. Following complete expansion of the lung and no evidence of air egress, the chest tube can be removed. Even though all indwelling catheters should have been placed under sterile conditions, removal of all catheters should be done as soon as that catheter is no longer needed.

PREVENTIVE EFFORTS

Care to prevent transmission of infection must be a primary concern for all caregivers. Handwashing must be performed by each caregiver prior to and following patient-caregiver interaction. Handwashing should also be performed by those who are visiting the patient. Each caregiver and visitor should wear a mask during the initial 48 hours following transplantation, and the caregivers or visitors who have any type of respiratory tract infection should be prevented from providing care or from visiting the individual. Children younger than 8 years should not be permitted to visit the patient during his or her hospitalization. Anyone who has received a live vaccine (eg, measles-mumps-rubella [MMR],
varicella, influenza) should not be permitted to visit with the patient for up to 6 weeks.

PHYSICAL REHABILITATION

Fortunately, most patients undergoing transplantation are not hospitalized prior to surgical procedure. They thus have an adequate time to participate in pulmonary rehabilitation. Preoperatively, the goals for therapy should include maximization of function, improvement in muscle strength and flexibility, decrease in dyspnea, and improvement in activity endurance. These goals need to be maintained postoperatively. Rehabilitation is an essential component in the management of the postoperative patient and should begin as early as feasible following surgical procedure. This will require the early institution of rehabilitation during the intensive care unit stay. Following hemodynamic stabilization and extubation of the patient, such rehabilitative efforts can begin the following day. Aggressive pulmonary hygiene including postural drainage should begin immediately. Below the suture line, the lung is denervated, and the patient thus may not be able to sense secretions that have moved cephalad. Normal breathing patterns with retraining of the diaphragm muscle should be instituted. Directed cough techniques should also be taught. Maintenance of joint range of motion and muscle strength must be encouraged. The patient will be experiencing pain and be reluctant to move; however, efforts to maintain range of motion should be encouraged.

Although the patient will have many intravenous catheters and chest tubes in place, encouragement of self-care and activities of daily living (eg, mobility within the bed, sitting to standing activities, bathing) should be instituted. Cardiopulmonary conditioning should begin as soon as feasible within the intensive care setting. Ambulation within the room or hallway can be performed with appropriate care of the chest tubes and intravenous catheters. Supplemental oxygen to maintain oxyhemoglobin saturations above 90% should be administered. A stationary bicycle should be moved into the patient’s room to facilitate cardiopulmonary exercise. Low levels of exercise (eg, unloaded pedaling on the bicycle) with subsequent increases in the duration and workload level can be made as the patient progresses.

The patient should not lift more than 5 lb with the upper extremities for up to 6 weeks following the surgical procedure. Other activities that should be avoided include trunk bending, abdominal curl ups, trunk twisting, and arm ergometry. These rehabilitative strategies should be carried out following transfer from the intensive care unit to the regular nursing floor and subsequently to the home environment.

SUPPLEMENTAL OXYGEN THERAPY

In the immediate postoperative period, supplemental oxygen will be necessary for most patients. The evaluation of the need for supplemental oxygen can be made easily through the monitoring of arterial oxygen tension (through arterial blood gas analysis) or of oxyhemoglobin saturation (through pulse oximetry). Maintenance of oxyhemoglobin saturation above 90% (or arterial oxygen tension above 60 torr) should be afforded during both rest and exercise conditions. A fall in oxyhemoglobin saturation should prompt an increase in the inspired oxygen concentration as well as prompt investigation into the cause of the decrease. Pneumonia, fluid overload, pneumothorax, or reperfusion-ischemia injury are potential causes for such a decrease in oxyhemoglobin desaturation.

MEDICATIONS

A variety of immunosuppression protocols are used throughout transplantation centers.10 Familiarity with the protocol used within an individual center is important. Lung transplantation carries one of the poorest survival rates among all solid-organ transplantations, with mortality rates approaching 15%.11 The majority of deaths within the first year are due to infectious complications, thus making
Management of the Patient Undergoing Lung Transplantation

53

A recent study, antithymocyte globulin was shown to be superior to daclizumab in reducing the incidence and severity of acute cellular response following lung transplantation.15 Although relatively free from adverse effects, monoclonal antibodies have been associated with the development of fever and/or chills. The use of muromonab-CD3 has been associated with a cytokine release syndrome that may cause cardiopulmonary instability after its first dose.

Following the initial phase of immunosuppression, all patients begin medication combinations to prevent acute rejection. A 3-drug combination is usually used in transplant centers in the United States.16 This combination includes a glucocorticoid, a calcineurin inhibitor, and a cell cycle inhibitor. These medications are often started when the patient is in the intensive care unit. Adverse effects from such medications are often not manifest until later—following transfer of the patient to the general nursing floor or following discharge.

Corticosteroids are the most commonly used glucocorticoids. These drugs prevent the production of various cytokines and also inhibit T-cell growth factor thus reducing the potential for acute rejection.17 High doses are started and then tapered rapidly. Adverse effects occur following prolonged use and include impaired glucose tolerance, psychosis, salt and fluid retention, and skin cosmetic changes.

Calcineurin inhibitors (eg, cyclosporine, tacrolimus) are an essential component of maintenance immunosuppression and have changed the face of transplantation medicine. T-cell activation and proliferation are blocked through the prevention of cytokine gene translocation.18 Tacrolimus is up to 1000 times more potent than cyclosporine. Both have similar adverse effect profiles including nephrotoxicity, neurotoxicity, and hypertension. Both also have a significant number of drug interactions, and precipitous drops in calcineurin levels can occur from drug interactions leading to rejection. Such interactions are noted in Table 1.
Table 1. Drug interactions with calcineurin drugs

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<th>Drugs causing increased levels</th>
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<tbody>
<tr>
<td>Allopurinol</td>
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<td>Amiodarone</td>
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<td>Antibiotics (macrolides)</td>
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<td>Antifungals (azoles)</td>
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<td>Bosentan</td>
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<td>Calcium channel blockers</td>
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<td>Colchicine</td>
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<td>Systemic corticosteroids</td>
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<td>Isoniazid</td>
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<td>Propofol</td>
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<tr>
<td>Metaclopromide</td>
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<td>Methotrexate</td>
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<tr>
<th>Drugs causing decreased levels</th>
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<tbody>
<tr>
<td>Nafcillin</td>
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<tr>
<td>Rifampicin</td>
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<td>Phenytoin</td>
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<td>Phenobarbital</td>
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*Adapted from Mankidy et al.10

Cell cycle inhibitors (eg, mycophenolic acid, azathioprine) are the third class of drugs used in the maintenance of immunosuppression. Mycophenolic acid decreases lymphocyte proliferation through its effects on the formation of DNA, RNA, and proteins within the lymphocyte. Azathioprine causes chromosomal breaks in both DNA and RNA syntheses. Similar rates of acute rejection and broncholitis obliterans syndrome and survival rate at 6 months were found comparing the use of each drug with the other.19,20 Adverse effects including myelosuppression and gastrointestinal effects have been noted with both drugs.

COMPLICATIONS FOLLOWING LUNG TRANSPLANTATION

Various types of complications can occur in the patient who has undergone lung transplantation. Some of these will result in prolonged stay in the intensive care unit following surgical procedure or readmission to the intensive care unit later during the patient’s hospital stay. Ischemia-reperfusion injury is probably the most worrisome complication to occur early in the postoperative course. It is characterized by progressive lung injury over the first few postoperative hours and involved noncardiogenic pulmonary edema. The injury is mild and the edema is transient in most cases. A variety of factors have been considered in the development of reperfusion injury including poor preservation of the graft, prolonged ischemic time, or unsuspected aspiration in the donor lung. In some instances, the acute lung injury progresses to diffuse alveolar damage and is the primary cause for acute graft failure. Clinically, the moderate to severe forms of ischemia-reperfusion injury are associated with impaired oxygenation, hypotension, elevated pulmonary artery pressures, and pulmonary infiltrates on chest radiograph.21 The diagnosis is established by excluding other causes of graft dysfunction (eg, acute rejection, pneumonia, volume overload, or pulmonary venous anastomosis thrombosis). Risk factors for the development of primary graft dysfunction include advanced age of the donor, smoking history of greater than 10 pack years, and elevated pulmonary artery pressure of the recipient.22

Various strategies to attempt to prevent the development of this complication including better strategies for lung preservation, avoidance of lung hyperinflation during harvest and storage of the donor lungs, and controlled reperfusion in combination with leukocyte depletion have been used. Treatment includes maintenance of mechanical ventilatory support and diuresis. The technique of minimizing inhaled tidal volume and decreased PEEP with the acceptance of higher partial pressure of carbon dioxide levels is helpful in this regimen. The use of inhaled nitric oxide has been shown to improve hemodynamics and ventilation perfusion matching in patients with severe ischemic-reperfusion injury,23 although other studies have not found clinical benefit in this setting.24 Routine administration of inhaled nitric oxide following lung transplantation does not prevent or reduce ischemia-reperfusion injury.25 Inhaled epoprostenol
Management of the Patient Undergoing Lung Transplantation

(prostacyclin), extracorporeal membrane oxygenation, or independent lung ventilation have also been attempted with variable success.

During the initial attempts at lung transplantation, anastomotic complications occurred relatively frequently. These are much less common today. Bronchial dehiscence and necrosis is often managed conservatively with airway debridement. A high incidence of bronchial airway dehiscence with subsequent death has been reported following the early use of sirolimus, and the use of this drug in the early posttransplant period should be avoided.

Acute rejection is another cause of potential morbidity and mortality in the postoperative period. Lung transplantation carries the highest rate of acute rejection among all solid-organ transplants and can develop in up to 50% of patients within the first month following surgical procedure. Although the risk factors for its development are not yet well defined, the lack of prospective human leukocyte antigen matching or constant exposure to an external environment filled with microbes and organic and inorganic agents may help precipitate an inflammatory response that then results in acute rejection. Acute rejection may present with cough, oxyhemoglobin desaturation, low-grade temperature, or decrease in airflows. The chest radiography may show a pattern consistent with pulmonary edema or may even be normal. Diagnosis is made by transbronchial biopsy via bronchoscopy and is based on the presence of perivascular and interstitial mononuclear cell infiltrates. Treatment for acute rejection includes intravenous pulse dose steroids (consisting of 3 to 5 doses of methylprednisolone at 15 mg/kg/day followed by an oral prednisone taper) along with optimization of the cyclosporine and azathioprine doses.

Recipients of lung transplantation are at increased risk for a variety of infectious complications. Infections are responsible for the leading cause of early postoperative deaths. Infections can result in prolonged mechanical ventilation or sepsis and predispose to acute allograft rejection. Bacterial infections are most common in the early posttransplant period. Both gram-positive (Staphylococcus aureus) and gram-negative organisms (Pseudomonas spp, Klebsiella, and Haemophilus influenzae) are responsible for pneumonia during this period. The use of broad-spectrum antimicrobial prophylaxis (eg, vancomycin, cefepime) for 7 days postoperatively is often used. The antibiotic regimen should be based on the recipient and donor sputum culture results prior to transplantation as well as the individual hospital antimicrobial susceptibility patterns.

Viral infections can also be commonly seen, particularly CMV infection. The recipients who are CMV seronegative and receive CMV-positive donor lungs are at the highest risk for developing severe life-threatening disease. Although the optimal approach to the treatment of posttransplant CMV infection is unknown, most centers use a 12-week regimen of intravenous ganciclovir in high-risk mismatch patients. Actual infection with CMV is documented by the presence of cytomegalic cells on tissue biopsy or the isolation of CMV from a tissue specimen. Fever, dyspnea, and pulmonary infiltrates can be seen with acute infection. Other viral infections (eg, community-acquired respiratory viral infections such as respiratory syncytial virus, adenovirus, parainfluenza) should also be considered. Cough, wheeze, dyspnea, fever, and gastrointestinal symptoms can occur. For the patients who have community-acquired viral infection associated with radiographic abnormalities, a poorer prognosis can be expected. Care for these types of infections is often supportive, although in some instances, aerosolized ribavirin can be administered, particularly in the patients with an abnormal radiograph.

Fungal infections can also occur in the early posttransplant period. Both Aspergillus and Candida can be found. Mortality of up to 60% has been noted following invasive infection with aspergillus pneumonia. The bronchial anastomosis is a particularly vulnerable site for the development of these infections, and
careful attention to these areas must be given during all bronchoscopic evaluations. If extensive pseudomembranes are noted at the anastomotic site, sampling of this area by either bronchial brush or biopsy should be carried out. Treatment with a combination of systemic and inhaled antifungal agents along with debridement of the site has been shown to be successful. Various preventive strategies are being used (eg, oral voriconazole or inhaled abelcet, although the use of systemic antifungals is limited by the lack of in vitro activity against some infections, treatment-limiting toxicities, and interactions with the various types of immunosuppressive agents.

SUMMARY

Dramatic changes have occurred over the last decade with regard to the management of patients undergoing lung transplantation. The early intensive care postoperative management is particularly important. This management requires a thorough knowledge of the type of surgical procedure that was performed. Routine hemodynamic monitoring is essential for all patients following transplantation with particular attention to be paid to the ventilatory and fluid management of the patient. Daily wound inspection and care, removal of all indwelling catheters as soon as possible, and early mobilization and ambulation of the patient are essential to ensure reduced postoperative complications. Knowledge of the immunosuppressive medication regimens is essential for all caregivers. Vigilance to look for the associated risk factors and early signs/symptoms of ischemia-reperfusion/primary graft failure, anastomotic complications, and infection will help reduce overall morbidity and mortality and ensure an improved patient outcome.

REFERENCES


