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Lung Transplantation

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1. Introduction

1.1 History

The foundation for lung transplantation was laid in the early 1900 by Guthrie and Carrel. In recognition of his work in vascular anastomosis, Dr. Carrel received the first Nobel Prize in Medicine. Following this early work, in 1946 Demikov in Russia performed a canine lung transplant as a unit. The dog subsequently died of bronchial dehiscence. The first human lung transplant was performed by Hardy at the University of Mississippi in 1963. Patient survived a few days and succumbed to complications. Derom in Belgium was credited with the first successful human lung transplantation when he reported 10 month survival of a patient who had undergone lung transplant for end-stage pulmonary fibrosis in 1971. By 1978, 38 lung transplants had been performed worldwide but Derom's patient was the only one that had approached a beneficial outcome. Consistently noted poor outcome in the 60s and 70s led to a moratorium on clinical lung transplantation in the late 70s. Rejection and infection were the common causes of death in this early group and bronchial anastomotic healing was the barrier for transplant survival beyond 2 weeks (1).

Cyclosporine based immune suppression in kidney and liver transplantation in the early 1980s resulted in dramatic improvements in organ function and patient survival. With this experience Shumway and Reitz successfully transplanted heart-lung blocks using a cyclosporine based immune suppression on primates. Airway complications were rare in heart-lung transplantation due to the non coronary collaterals, where as this was a major drawback of isolated lung transplantation. The success of the Stanford group led to the reinstitution of clinical heart-lung transplantation in the 80s (2).

Meanwhile in Toronto, significant experimental work were done by Pearson and Cooper to solve the bronchial healing problem in animal models. The technique of omental wrap around the bronchial anastomosis was developed by Cooper et al. In 1986 the Toronto Lung Transplant Group reported successful single lung transplantation for pulmonary fibrosis in two patients (3). Technique of en-bloc double lung transplant failed due to the tracheal anastomotic complication related to ischemia. Finally bilateral sequential transplantation was developed as a method of transplanting both lungs without the heart. Currently around 147 centers perform over 2000 isolated lung transplants a year. The bronchial anastomotic technique has evolved since and bronchial wrapping is no longer considered necessary.

2. Patient selection for lung transplantation

2.1 Indications

Lung transplant is indicated for patients with chronic, end-stage lung disease for whom no effective medical therapy is available (4,5). The primary goal of lung transplantation is to provide a survival benefit. Such benefit can be conferred to patients with advanced pulmonary fibrosis, cystic fibrosis and primary pulmonary hypertension. Reports for emphysema are conflicting and for Eisenmenger's syndrome transplant did not find a survival benefit. However, as lung transplantation is a palliative treatment, improvements in quality of life in addition to survival benefit should be used to assess effectiveness of this therapy.

2.2 Contraindications

2.2.1 Major contraindications

A history of malignancy during the past two years, except for skin cancers. In general 5 year disease free survival is expected (4).
Untreatable advanced disease of another organ system, except the heart, where a heart-lung transplantation could be considered.
Untreatable extra-pulmonary infections, including chronic, active viral hepatitis and HIV infection.
Significant chest deformity.
Unreliable social support, medical non-compliance or major psychiatric or psychological disorder.
Active substance abuse or use within the past 6 months.

2.2.2 Relative contraindications

Older age; older patients have less optimal survival following lung transplantation.
Critical or unstable conditions, such as Extra Corporeal Membrane Oxygenation or mechanical ventilation.
Severely limited functional class with poor rehabilitation potential.
Colonization with highly virulent or antibiotic resistant organism.
Obesity or malnutrition (BMI>30 or BMI<17).
Mechanical Ventilation except in carefully selected patients
Severe or untreated gastroesophageal reflux disease.

2.3 Timing of referral

In general referral for transplantation evaluation is recommended when the patient's median survival (50%) is about 2 years or less or New York Heart Association class 3 or 4. Due to the natural history of underlying disease, the referral time will depend on the underlying disease. The waiting period for transplant depends on underlying disease, waiting time, blood group, height of patient and presence of pre-formed antibodies in the recipient.

3. Lung transplantation procedure

3.1 Donor selection and operation

The donor is evaluated for ABO compatibility, size, medical and social history, function, associated pathological findings on CXR or CT scan and bronchoscopic findings. Given the

improvements in clinical results and shortage of donor organs the generally accepted donor criteria are continually being challenged and expanded. Donor lung selection also depends on subjective assessment at the time of exploration in the operating room and judgment of the donor surgical team (6).

The donor pneumonectomy is approached via a midline sternotomy. The lung is inspected to evaluate its suitability for transplantation by the donor surgical team. Heparin is administered and a pulmonary plegia cannula is inserted into the main pulmonary artery ensuring both main pulmonary arteries are perfused by the cannula. A clamp is placed on the left atrial appendage and the tip of the appendage is excised for free drainage of the pulmonary effluent during the pulmonary plegic infusion. Prostaglandins and pulmonary vasodilators are administered into the main pulmonary artery followed by cold pulmonary plegia that also contains vasodilator medications. The lung is inflated to moderate amount and the trachea is stapled with lung inflated. The lung block is dissected away from the mediastinal structure with the heart or separately after the heart is excised by the 'cardiac' team. Left atrium is divided midway between the confluence of the pulmonary veins and the atrial groove ensuring that an adequate "atrial cuff" will be available with the lungs for implantation. The ligamentum arteriosum is divided toward the descending aorta avoiding injury to the left main pulmonary artery and the entire lung block is dissected away from the descending aorta and esophagus. The lungs are separated from each other at the back table by dividing the left main bronchus with the staples, pulmonary artery at the bifurcation, and left atrium between the right and left pulmonary veins. Retrograde cold flush of the preservation solution is performed through the pulmonary veins before packaging the organs in sterile fashion for transportation to the recipient operating room (8,9).

Satisfactory early and midterm outcomes had been reported with using lung donation after cardiac death expanding potential lung donors (10). Recent exciting developments on normothermic ex-vivo perfusion allowing repair of injured lung and the ability to evaluate function of the lung prior to transplantation has potential benefit of increasing the donor pool even further (11).

Age < 60
ABO Compatibility
Clear Chest Radiograph
PaO_2 > 300 on FIO_2 = 1.0 and PEEP of 5 cm H_2O
Tobacco history < 20 pack years
Absence of significant chest trauma
No evidence of sepsis or blood borne infections (Hepatitis B, C or HIV)
Prior cardiopulmonary surgery
Presence of lung pathology on CT scan
Purulent secretion on bronchoscopy or evidence of aspiration

Table 1. Established Criteria for Donor Selection

3.2 Recipient operation

3.2.1 Single lung transplant

Once a donor is verified and deemed suitable for transplant, the recipient is brought into the operating room for transplantation (12). Generally the contra-lateral lung is used to support the recipient during the transplantation procedure. Some patient will require

cardiopulmonary bypass to perform the lung transplantation safely. General anesthesia is provided via a double lumen endo-tracheal tube, a left sided tube is preferred thus avoiding the potential complication of obstructing the right upper lobe orifice. Following placement of arterial and venous access lines as well as a Trans-esophageal Echo (TEE) probe, the patient is placed in a lateral decubitus position, with groin exposed on the same side to allow canulation of femoral vessels, if needed. A variety of incisions may be used to enter the thorax including a posterolateral incision, anterior submammary incision, or a lateral incision that either spares or partially divides the muscle.

Hilar dissection is performed exposing the pulmonary vessels while preserving the phrenic nerve. Vagus neurovascular bundles are carefully preserved particularly on the left side where the recurrent laryngeal nerve emerges and encircles the ligamentum arteriosus. The recurrent laryngeal nerve may be injured during the dissection of the left main pulmonary artery and a heightened awareness of this will help to avoid injury. Dissection around main bronchus is kept to minimum to preserve its blood supply. The pericardium is opened around the pulmonary veins to release the left atrium for placement of vascular clamp. When the donor lung is in the room the recipient is given heparin intravenously and the pulmonary veins and artery are divided as distal as possible. We use a linear cutting vascular stapler. The main bronchus is divided at the lobar branch level initially and then divided with a sharp knife about 2-3 cartilage rings from the carina.

At the back table, final dissections are made to the donor lung. This includes removal of excess mediastinal tissue, mobilization of the main pulmonary artery and the left atrial and venous structures from pericardial attachments. We perform a repeat cold retrograde flushing of the pulmonary vascular bed with the preservation solution prior to implantation to evacuate any residual debris from the pulmonary vascular bed and improve preservation (9). The main bronchus of the donor is opened and microbiological specimens are collected. The bronchus is then divided with a knife leaving two rings of cartilage from the origin of the upper lobe bronchus. The donor lung is then brought to the operative field. We perform the bronchial anastomosis as to “frame” the lung in position first. The membranous portion of the bronchus is anastamosed using a running 4-0 absorbable monofilament suture while the cartilaginous portion is secured with interrupted figure-of-eight suture of the same type. Single-running suture techniques have also been described in the literature and appear to be equally effective. Next, attention is turned to the venous anastomosis. A vascular clamp is placed along a portion of the left atrium and the recipient left pulmonary vein orifices are connected by dividing the bridge of atrial tissue in-between to create a single oval “atrial cuff”. The donor atrial cuff is then anastamosed to the recipient atrial cuff in an end-to-end fashion using a single, double-armed running 4-0 polypropylene suture. Finally the pulmonary artery is prepared for the final anastomosis. Excess length of pulmonary artery is removed after appropriately sizing the vessel. This is particularly important on the right side, as there is a long length available on the donor. The donor pulmonary artery is anastomosed to the recipient in an end-to-end fashion with a single, double-armed running 5-0 polypropylene suture. Occasionally, a size mismatch exists where the recipient pulmonary artery is larger than the donor pulmonary artery. In this case, the larger inferior pulmonary trunk arising from the main pulmonary artery is anastomosed end-to-end with the donor main pulmonary artery. In this situation the upper branch is divided flush with the main artery to prevent any clots forming in the ‘blind-end’. Attention is paid to keep the donor lung cold during the entire period using ice slush and cold sponges, until reperfusion. Bolus of solumedrol is given intravenously (we give 500 mg) prior to reperfusion of the graft. In preparation for reperfusion, the patient is placed in the Trendelenberg position, air

and debris are vented through the pulmonary artery anastomosis first. Then pulmonary plegia solution is allowed to vent from the left atrial cuff anastomosis by releasing the arterial clamp to allow a slow flush. While the left atrium is observed by TEE for air bubbles the left atrial clamp is removed and the anastomosis is secured. The reperfusion is controlled by slow release of the arterial clamp and any hypotension is treated promptly by alpha-agonists. The lung is inflated while monitoring the left atrium on TEE. A leak test may be performed at this time by carefully ventilating the new lung with the bronchus submerged in warm normal saline and inspecting for air bubbles. After placement of chest tube, with satisfactory hemostasis, hemodynamics and oxygenation the chest is closed in layers with absorbable sutures. With the patient in the supine position the double-lumen endotracheal tube is changed to a single lumen tube and a fiber-optic bronchoscopy is performed to inspect the bronchial anastomosis and remove any clots or secretions present in the bronchial tree.

3.2.2 Bilateral sequential lung transplant

A bilateral anterolateral thoracotomy is a preferable incision for bilateral sequential lung transplant as it preserves the structural integrity of the sternum and prevents significant incision-related morbidity (13). In a patient with small chest cavity or when there is potential need for cardiopulmonary bypass, a clamp-shell incision is made dividing the sternum across for the transplantation. The dissection of the lung and the donor lung preparation is performed as described above. The lung with the lesser physiologic contribution is transplanted first as the other lung support single-lung ventilation.

The single lung transplants are performed sequentially while the patient is supported by the contra-lateral lung. If the operation is being performed without cardiopulmonary bypass (CPB), it is important to stabilize the patient after the first lung implantation before proceeding with the next. Following implantation of the second lung and patient stable, chest tubes are placed and sternum approximate using metal plates or sternal wires. Then the wound is closed in layers with absorbable sutures.

4. Post-operative management

Patient undergoing lung transplantation requires a team of caregivers who are committed, familiar with the protocols and able to ensure ongoing communication between members of the team. The team members include, transplant coordinators, transplant pulmonologist, transplant surgeon, anesthesiologist, pain management team, critical care specialist, ICU nurses, Infectious disease specialist, pharmacologist, physical and occupational therapist, nutritionist and social worker. Clinical pathways are developed addressing complete patient care with incorporation of immunosuppressive and infection prophylaxis protocols (14). Despite clinical pathways, regular team meeting discussing daily care of patient facilitate efficient and timely interventions and improve post-operative care.

5. Respiratory management

Despite advances in the donor management and preservation of lung, primary graft dysfunction is not uncommon following lung transplantation (15). In the majority however the degree of dysfunction is minor to moderate and reversible, therefore does not progress to graft failure. The incidence of primary graft dysfunction has been reported between 11-57

% (16). When there is primary graft failure, extra corporeal membrane oxygenation (ECMO) may be required. Early institution of ECMO had been shown to be more successful than late (17-19). When the graft dysfunction is mild to moderate, management strategies are employed as used in patients with significant lung injury.

The ventilatory management would be influenced, if the patient received a single or bilateral lung transplant. In patients with bilateral lung transplant it would be aimed at minimizing barotraumas by using low inflation volumes and moderate levels of positive end expiratory pressure (PEEP, less than 10 cm water). In patients with single lung transplant the patho-physiology of the remaining native lung will influence ventilatory strategy. Significant air trapping and auto PEEP is not uncommon in patients with emphysema. Low ventilatory volumes, adequate expiratory time and avoidance of excessive PEEP will help to prevent air trapping and significant hemodynamic instability in these patients. Positioning patients with the allograft side up and bronchodilator therapy are useful strategies in patients with single lung transplant. Very rarely isolated lung ventilation with double lumen tube is necessary to effectively ventilate when there is significant graft dysfunction.

Inhaled Nitric Oxide (NO) through the ventilator has been shown to reduce reperfusion injury in experimental models and clinical transplantation, when used as prophylaxis. It's usefulness in established graft dysfunction is controversial. Selective use of inhaled NO in peri-operative period in patients with pre-existing pulmonary hypertension is not an uncommon practice. The aim of the inhaled NO use is to reduce pulmonary artery pressures during the operation and immediately afterwards thereby assisting the right ventricular function.

As a rule aggressive weaning off the ventilator is practiced following lung transplantation to prevent nosocomial infection and promote early rehabilitation. Sedation should be carefully monitored and sparingly used. It is advisable to use short acting agents while patient is intubated. Majority of the patients are extubated within the first 24 hours after transplantation. After extubation we advocate use of epidural analgesia and avoidance of narcotics and benzodiazepines. Aggressive bronchial hygiene is mandatory to prevent collapse and development of pneumonia. While patients are intubated using soft suction catheters to clear secretion should be performed routinely. Once the patient is extubated incentive spirometry, chest physiotherapy and ambulation are necessary to promote clearance of bronchial secretions. In patients who are debilitated and have retention of secretion we have employed 'mini-tracheostomy' to facilitate removal of the secretion with a soft tip 10 french catheter. Alternatively patients will require repeat bronchoscopic suction of secretions. When a patient fails trial extubation, early tracheostomy facilitates rapid weaning of ventilation, assist in effective management of secretions and promote early physical rehabilitation.

6. Hemodynamic management

Patients selected for lung transplant undergo a detailed cardiac evaluation. Isolated single vessel coronary artery disease alone is not a contra-indication for lung transplantation. These patients would be candidates for pre-transplantation, percutaneous revascularization or would be candidates for simultaneous surgical re-vascularization (19,20). Correctable cardiac lesions such as ASD or simple VSD they are repaired during lung transplantation. Patients with primary or secondary pulmonary hypertension will have varying degrees of right ventricular dysfunction but this improves with successful lung transplantation. Peri-

operative use of inhaled NO or other pulmonary vasodilator pharmacotherapy is not uncommon and certainly useful to reduce post-operative pulmonary hypertension and the fluctuations in pressures and reduce the hemodynamic instability.

The most common hemodynamic disturbance following lung transplantation is hypotension and supra-ventricular tachyarrhythmia. The principle of keeping these patients in a relative hypovolemic status, make them susceptible to hypotension, if there is any degree of vasodilation. It is important to maintain adequate intravascular volume to maintain adequate cardiac output as well as urine output. The fluid therapy is aimed at maintaining low or low normal cardiac filling pressures. It is however not necessary to monitor pulmonary artery wedge pressures in all patients and monitoring of right atrial filling pressures are most often adequate. The fact that the lymphatic drainage is interrupted from the lung allograft following transplantation, any capillary leak in to the lung parenchyma will be cleared less efficiently. It had been shown that fluid restriction in patients with lung injury promotes early recovery (21). This may be an important factor to consider during the post operative period, due to the fact that majority of the lung grafts suffer some degree of reperfusion injury. Systemic vasodilation whether it is produced by medications or sympathetic blockade due to epidural or release of cytokines, best treated with vasoconstriction using intravenous short acting alpha-blockers than by volume. Neosynephrine is the drug of choice in the treatment of systemic vasodilation in these patients. Vasopressin is an effective systemic vasoconstricor but also appears to cause profound bronchial vasoconstriction and may cause bronchial ischemia in these patients and may affect bronchial anastomotic healing, therefore its use is avoided.

The incidence of supraventricular arrhythmias are not uncommon following lung transplantation (22). The commonest arrhythmias are supraventricular tachycardia and atrial fibrillation. Many programs take preventive measures for atrial fibrillation in the post-operative period which can reduce the incidence of this complication but unlikely to prevent it completely. The effects and complication due to atrial fibrillation are systemic hypotension and systemic embolization, perhaps made worse by fresh suture line on the left atrium. Although amiodarone is generally avoided due to its effects on the lung, we have used amidarone in patients who are resistant or unsuitable for treatment with calcium channel blockers or beta blockers. Anticoagulation will be necessary as in other patients with atrial fibrillation and the biopsy schedules needed to be considered and preferentially treated with short acting agents in the post operative period. It will be prudent to check clotting studies prior to transbronchial biopsy or endobronchial intervention as uncontrollable bronchial hemorrhage is invariably fatal.

7. Diagnosis and management of early surgical complication

The major surgical complications are bleeding, anastomotic complications and mal-rotation of the graft (24). The latter two are rare with current understanding and experience. Bleeding is less common and is due to refinement in surgical techniques, judicious use of pharmacological agents and blood products. The patients at high risk are the ones with extensive pleural adhesions, large and extensive mediastinal collateral vessels and patients with connective tissue disorders with secondary pulmonary hypertension. Patients with right heart failure and congested liver or patients on chronic anticoagulation or anti-platelet therapy are particularly susceptible and correction of coagulation defect is mandatory in these patients. If a patient persists with significant blood loss (>100 cc/hr), for 4-6 hours, the

patient needs to return to the operating room unless there is evidence of significant coagulation abnormalities.

The dreaded complication of complete bronchial anastomotic dehiscence is rarely seen now but stenosis at the anastomotic site is not that uncommon, being reported between 5-25% of the anastomoses. This complication is usually delayed for several weeks following transplantation (25). In the presence of anatamotic site infection or significant donor bronchial ischemia minor bronchial dehiscence may present as early as 1-2 weeks.

Vascular anastomotic complications are infrequently reported, and their real incidence may be higher than that reported in the literature. The venous complication if severe enough can present few hours following transplantation as acute graft dysfunction. This presents as rapidly progressing pulmonary edema, with diffuse, dense infiltrate of the affected lung or lobe. This is a potentially lethal condition and diagnosis require high index of suspicion. TEE is helpful to confirm diagnosis. Surgical correction is required if this is due to anatomotic narrowing due to surgical technique. Thrombus formation at the anastomotic site can also cause venous obstruction and this is insidious in origin and progressive. Thrombolytic agents had been successfully used in these circumstances. Arterial anastomotic stenosis presents as hypoxemia, usually associated with exercise. This should be suspected if there is no other reason for hypoxemia. Pulmonary angiogram is diagnostic and catheter based intervention including stent placement has been successfully employed.

Mal-rotation of Lobar or lung on its axis is a rare complication and if not corrected immediately will result in necrosis of the lobe or lung. Complete opacification of the lobe or lung is noted in chest radiograph. Bronchoscopic examination is confirmatory of the bronchial torsion.

8. Pain management

Patients undergoing thoracic surgery require effective pain relief to allow deep breathing, coughing and facilitate early ambulation. In lung transplant patients this becomes crucial as they are chronically debilitated and have difficulty clearing secretions. While providing effective pain relief it is necessary to prevent sedation to promote early ambulation and therefore avoidance of narcotics is preferred. Thoracic epidural analgesia is effective in providing pain relief without causing sedation. We advocate placement of the thoracic epidural pre-operatively or place it soon after patient is extubated. NSAID are avoided because of the potential interactions with other nephrotoxic agents particularly the calcineurin inhibitors. Transitioning to oral pain medication is monitored carefully prior to discharge from the hospital.

9. Immunosuppression

Immunosuppression after lung transplantation includes three major categories of immunosuppressive agents; calcineurin inhibitors (tacrolimus, cyclosporine A), antimetabolites (azathioprine, mycophenolate mofetil) and corticosteroids. In addition, approximately 45% of lung transplant patients receive induction therapy after lung transplantation. The calcineurin inhibitors are administered within hours after transplantation and may be given either intravenously or sublingually. In general, tacrolimus is dosed at 0.05-0.1 mg/ kg over 24 hours by continuous infusion and may also

be given sublingually at a dose of 0.03 mg/kg twice daily. Target tacrolimus trough levels range between 10-20 ng/ml in the first six months after transplantation, followed by levels around 10ng/ml thereafter. Cyclosporine is administered at a rate of 3 mg/kg over 24 hours with target trough levels between 350-450 ng/ ml in the first month, between 300-350 ng/ml during the first year and between 200-300 ng/ml thereafter. Both of these medications are available in oral formulation and should be given orally after extubation. Although current data have not shown a superiority of one of the calcineurin inhibitors, there has been an increasing use of tacrolimus in the lung transplant population due to reports of improved pulmonary function and possibly a reduction in the incidence of bronchiolitis obliterans syndrome (26,27).

Antimetabolites (either azathioprine or mycophenolate mofetil) are the second immunosuppressive medication that are used in the treatment of lung transplant recipients. The first dose may be initially administered prior to implantation of the lung allograft. Azathioprine is dosed at 2mg/kg daily and can be administered either intravenously or orally. Mycophenolate mofetil is dosed orally at 2-3 gram in daily divided doses. In general, antimetabolites may be associated with myelosuppression and gastrointestinal distress and doses may be adjusted based on these side effects. Two randomized multicenter studies that have not shown any difference in acute rejection, or survival between these two agents (28,29).

Corticosteroids have been the mainstay of immunosuppression since the advent of successful lung transplantation in the 1980s. First dose of methylprednisolone (between 500 to 1000 mg intravenously) is usually given prior to reperfusion of the graft in the operating room. Subsequent doses of corticosteroids range between 0.5-1 mg/kg during the first few weeks after transplantation. In general, corticosteroids are tapered to the equivalent of 5-10 mg of prednisone daily by three to six months after transplantation.

The role of induction therapy in lung transplantation has yet to be defined. There are several different types of induction therapy that are currently being used in lung transplantation including the interleukin- 2 receptor antagonists (daclizumab, basiliximab), the polyclonal agents(ATGAM, thymoglobulin) and the monoclonal antibody (OKT3). Several reports have suggested that induction therapies may reduce the incidence of acute rejection during the first six months after lung transplantation. However, longer term outcomes including prevention of chronic rejection or improving survival have not been associated with the use of induction therapy after lung transplantation (30-32).

10. Infection prophylaxis

Infections remain a major source of morbidity and mortality after lung transplantation. Prophylaxis against bacterial, viral and fungal organisms usually starts immediately postoperatively in the recipients. Initial antibiotic prophylaxis should be directed towards adequate anaerobic coverage and tailored towards any positive donor or recipient culture detected prior to transplantation. These antibiotics are usually continued between three to fourteen days post transplant depending upon the individual transplant center's protocol. Lung transplant recipients with septic lung disease (cystic fibrosis, bronchiectasis) who may be colonized with resistant organisms often receive two synergistic antibiotics based on prior sensitivities during this time period.

Viral prophylaxis is most commonly targeted against cytomegalovirus (CMV). Aggressive prophylactic therapy is directed towards this organism because of its high virulence and association with mortality in the lung transplant population. Lung transplant recipients with either donor or recipient serology that is positive for CMV usually receive prophylactic therapy with valganciclovir anywhere between three months to lifelong therapy. CMV negative lung transplant recipients who received a CMV positive donor lung may also receive CMV immunoglobulin in addition to their current valganciclovir therapy. Unfortunately, while valganciclovir prophylaxis decreases the incidence of CMV infection during the time of administration, prophylaxis does not completely prevent the development of CMV infection especially after prophylaxis therapy is discontinued. The optimal duration and type of therapy are still a matter of debate. Acyclovir and its derivatives are given to CMV negative lung transplant recipients who receive CMV negative donors in order to prevent the development of Herpes infections.

Fungal prophylaxis varies among the different transplant centers depending upon prior colonization, mechanical airway complications and environmental factors. In general some centers provide general fungal prophylaxis while others consider preemptive therapy depending upon surveillance bronchoscopy findings. Lung transplant recipients are at increased risk for developing *Aspergillus spp.* colonization of the airways leading to anastomotic infections and ulcerative tracheobronchitis. Itraconazole (or other azole substitutes) and inhaled amphotericin are the most common fungal prophylactic agents that are currently used. The azoles will increase the levels of the calcineurin inhibitors (cyclosporine and tacrolimus) so that the doses of these immunosuppressive medications should be decreased by at least 1/3 of their original dose. Calcineurin levels should be checked approximately one week after starting an azole. Of note, voriconazole and sirolimus should not be used together due to the significant rise in sirolimus levels.

11. Transplant outcomes

Significant improvements have been achieved in the past two decades with organ preservation, surgical techniques, critical care and immunosuppression. At present over 80% of patients receiving a lung transplant for end-stage lung disease are alive at 1 year and half of them are at 5 years (33). There are differences in the survival for different etiology for the underlying end-stage lung disease (Figure 1). Primary graft dysfunction is an important cause of post-operative mortality (33). The major cause of early and late mortality is infectious complications and bronchiolitis obliterans, a condition of progressive airflow obstruction associated with chronic airway fibrosis a pathologic finding known as bronchiolitis obliterans (BO). Majority of the late mortality is directly or indirectly due to the development of bronchiolitis obliterans syndrome or OB (Table 2) (34,35). Although the pathological mechanism that lead to BO is not well understood there have been many associations reported. A significant predictor of OB is prior acute rejection. Other conditions are primary graft dysfunction, gastroesophageal reflux or infections (36). Currently there are few well established therapies available for prevention or treatment of OB. Ongoing research continues to advance our understanding of the pathogenesis which may lead to effective treatment strategies in the future.

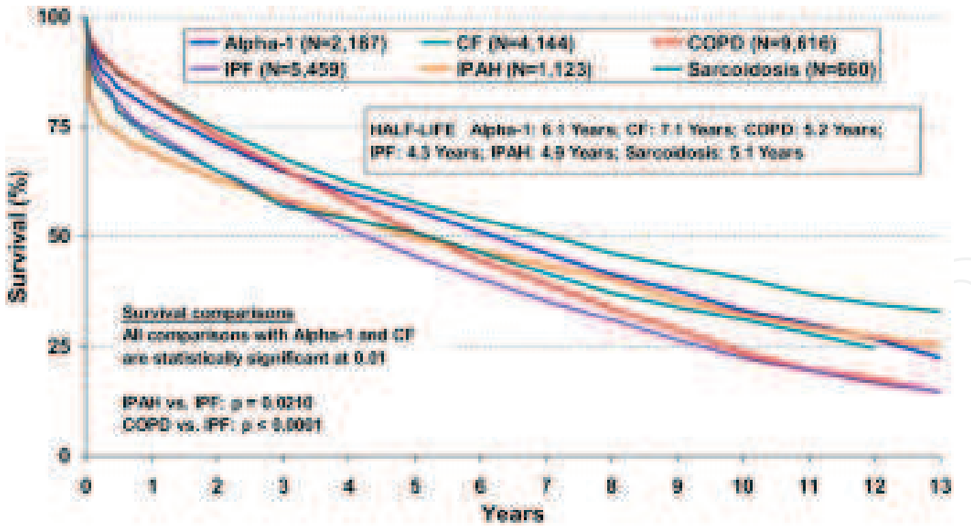

Fig. 1. Kaplan-Meier survival by diagnosis for adult lung transplants performed between January 1990 and June 2008. AT Def, α1-antitrypsin deficiency emphysema; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis.
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	0–30 days	**31 days–1 year**	**>1–3 years**	**>3–5 years**	**>5–10 years**	**>10 years**
	(*n* = 1,966)	**(*n* = 3,387)**	**(*n* = 3,073)**	**(*n* = 1,737)**	**(*n* = 2,014)**	**(*n* = 483)**
Cause of death	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Bronchiolitis	6 (0.3)	159 (4.7)	781 (25.4)	508 (29.2)	507 (25.2)	95 (19.7)
Acute rejection	74 (3.8)	61 (1.8)	48 (1.6)	10 (0.6)	15 (0.7)	1 (0.2)
Lymphoma	1 (0.1)	86 (2.5)	63 (2.1)	28 (1.6)	46 (2.3)	23 (4.8)
Other malignancy	4 (0.2)	100 (3.0)	202 (6.6)	151 (8.7)	219 (10.9)	47 (9.7)
Infection						
CMV	0	96 (2.8)	29 (0.9)	5 (0.3)	4 (0.2)	0
Non-CMV	396 (20.1)	1,205 (35.6)	710 (23.1)	329 (18.9)	363 (18.0)	81 (16.8)
Graft failure	557 (28.3)	589 (17.4)	591 (19.2)	327 (18.8)	379 (18.8)	87 (18.0)
Cardiovascular	213 (10.8)	144 (4.3)	118 (3.8)	82 (4.7)	99 (4.9)	36 (7.5)
Technical	162 (8.2)	76 (2.2)	18 (0.6)	8 (0.5)	12 (0.6)	6 (1.2)
Other	553 (28.1)	871 (25.7)	513 (16.7)	289 (16.6)	370 (18.4)	107 (22.2)

Table 2. Causes of Death Following Lung Transplantation in Adult Recipients.
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13. Conclusion

Lung transplant remains an effective treatment for selected patients with end-stage lung disease. The major rate limiting step for lung transplantation at present is the available donor organs. Chronic allograft dysfunction remains a major source of morbidity and mortality after lung transplantation. Investigations into improving donor lung availability, preventive and therapeutic approaches for OB and alternative for transplantation for end-

stage lung disease are subjects currently under intense investigation aimed at improving short and long term result of therapy for end-stage lung disease.

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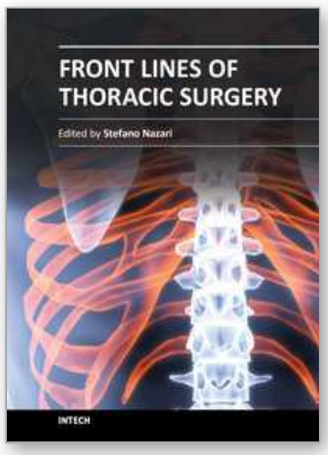

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Front Lines of Thoracic Surgery collects up-to-date contributions on some of the most debated topics in today's clinical practice of cardiac, aortic, and general thoracic surgery,and anesthesia as viewed by authors personally involved in their evolution. The strong and genuine enthusiasm of the authors was clearly perceptible in all their contributions and I'm sure that will further stimulate the reader to understand their messages. Moreover, the strict adhesion of the authors' original observations and findings to the evidence base proves that facts are the best guarantee of scientific value. This is not a standard textbook where the whole discipline is organically presented, but authors' contributions are simply listed in their pertaining subclasses of Thoracic Surgery. I'm sure that this original and very promising editorial format which has and free availability at its core further increases this book's value and it will be of interest to healthcare professionals and scientists dedicated to this field.

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