Lung transplantation

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Abstract

Lung transplantation may be the only intervention that can prolong survival and improve quality of life for those individuals with advanced lung disease who are acceptable candidates for the procedure. However, these candidates may be extremely ill and require ventilator and/or circulatory support as a bridge to transplantation, and lung transplantation recipients are at risk of numerous post-transplant complications that include surgical complications, primary graft dysfunction, acute rejection, opportunistic infection, and chronic lung allograft dysfunction (CLAD), which may be caused by chronic rejection. Many advances in pre- and post-transplant management have led to improved outcomes over the past decade. These include the creation of sound guidelines for candidate selection, improved surgical techniques, advances in donor lung preservation, an improving ability to suppress and treat allograft rejection, the development of prophylaxis protocols to decrease the incidence of opportunistic infection, more effective therapies for treating infectious complications, and the development of novel therapies to treat and manage CLAD. A major obstacle to prolonged survival beyond the early post-operative time period is the development of bronchiolitis obliterans syndrome (BOS), which is the most common form of CLAD. This manuscript discusses recent and evolving advances in the field of lung transplantation.

Introduction

Various forms of advanced lung disease often relentlessly progress to respiratory failure and death despite the use of various state-of-the-art therapies given in an attempt to arrest the disease process. Lung transplantation is the only therapy that can prolong survival and improve quality of life for such patients [1,2]. However, survival outcomes for lung transplant recipients remain significantly lower than those for recipients of other solid organs (Table 1). Caregivers and patients must carefully weigh the risks and benefits of this procedure with the understanding that it is a palliative measure that can prolong survival and improve quality of life, but a myriad of complications can arise at the time of allograft implantation and beyond that can lead to subsequent poor quality of life and/or a fatal outcome. There are several recent developments in the field that hold promise for improving allograft function: refining criteria for selecting candidates for the transplant wait-list; increasing

the donor organ pool and the quality of implanted lungs via the use of donation after cardiac death (DCD) donors and the use of *ex-vivo* lung perfusion (EVLP) techniques following organ procurement in preparation for implantation; identifying immunosuppressive regimens that optimally prevent post-transplant allograft rejection yet minimize the risk of opportunistic infection; prophylactic antimicrobial therapies to prevent opportunistic infections; and, most importantly, an improved understanding of chronic lung allograft dysfunction and rejection that will lead to advances that prevent the development of chronic lung allograft dysfunction and its subsets of BOS and restrictive allograft syndrome as well as therapies that can arrest progressive loss of allograft function should CLAD develop (see Tables 2 and 3). Lastly, appropriate palliative measures need to be incorporated into post-transplant management protocols to relieve symptoms when recipients develop refractory loss of allograft function due to the appearance of advanced and progressive CLAD.

Table 1. 1- and 3-year survival for solid organ transplantation in the United States*

Organ	1 year graft survival (1/1/2009-6/30/2011)**	3 year graft survival (7/1/2006-12/31/2008)**
Lung	83.8% (N = 4,147)	63.9% (N = 3,474)
Heart-Lung	80.0% (N = 73)	57.9% (N = 55)
Heart	89.9% (N = 4,595)	80.9% (N = 4,440)
Kidney	93.8% (N = 38,915)	85.8% (N = 38,458)
Kidney-Pancreas	Kidney – 94.8% Pancreas – 88.6% (N = 2,040)	Kidney – 86.5% Pancreas – 79.6% (N = 2,131)
Liver	86.5% (N = 13,249)	75.8% (N = 13,467)
Intestine	70.9% (N = 202)	53.1% (N = 190)

*Data for National Graft Survival from Scientific Registry of Transplant Recipients (www.srtr.org/csr/current/centers/default.aspx – released July 2012)
**Time window when transplants were performed

Table 2. Risk factors associated with bronchiolitis obliterans syndrome

Risk factors associated with bronchiolitis obliterans syndrome

- Primary graft dysfunction
- Acute cellular rejection
  - Grades 2-4 are especially concerning
  - Minimal Grade A1 is also suggested to increase risk
- Lymphocytic bronchiolitis (Grade B rejection)
- Antibody-mediated rejection
- Autoimmune sensitization to collagen V or other self-antigens
- Gastroesophageal reflux
  - Abnormal/pathologic degree of reflux
  - Acid or non-acid
- Increased bronchoalveolar lavage neutrophils on differential cell count
- Virus infection
  - Cytomegalovirus pneumonitis
  - Community-acquired respiratory virus infection
- Other infection
  - Colonization and infection of the lung by *Pseudomonas aeruginosa*
  - Aspergillus colonization or fungal pneumonitis
- Exposure to excessive air pollution
- Ischemic change due to disruption of the bronchial circulation

Recent advances

Implementation of the lung allocation scoring system in the United States

The lung allocation scoring (LAS) system [3,4] was adopted in the United States in 2005 in preference to the previous time-based system (time on the lung transplant waitlist) to a need-based ranking system for lung allocation. Priority scores for transplantation are now computed and assigned on the basis of urgency (risk of death without

transplant) and the degree to which transplant can extend survival. More severely ill patients tend to get higher scores, and diagnosis is the most influential parameter. Consequently, patients with idiopathic pulmonary fibrosis have become the predominant group receiving transplants, and there has been a progressive increase in the percentage of transplants for patients ≥65 years of age. However, organ allocation appears to have become substantially more effective, and the total number of transplants has risen as deaths on the waitlist and waiting time have declined. However, outcomes have been shown to be worse for recipients with very high LAS scores [5-9], although outcomes for high-risk patients do appear to be improving [10,11]. Improved models to predict post-transplant outcomes are needed [12,13], and other candidate characteristics, such as frailty [14], need to be considered as potential components of the LAS system to better identify candidates at high risk of poor outcome.

Donor-recipient human leukocyte antigen matching

Newly developed Luminex® solid phase assays for human leukocyte antigen (HLA) antibody detection have recently replaced complement-dependent serological techniques [15,16]. Adoption of these assays has improved pre-transplant detection and identification of antibodies (pre-sensitization) against donor HLA and allows virtual cross-matching during the allocation and match process (to avoid transplants in patients who are presensitized to donor HLA antigens). By accurately predicting a donor cross-match result, bead-based virtual cross-matching has improved access for sensitized thoracic transplant recipients to organs outside their immediate region [17,18]. While technical and interpretive challenges remain, solid phase antibody assays have significantly improved transplant practice and outcomes [19,20], and various technical issues are gradually being resolved and optimal cutoff values determined.

Donation after cardiac death

The use of DCD donors (donors with non-beating hearts who have undergone planned and controlled withdrawal of life support) has provided an additional pool of donated organs as an alternative to the traditional brain-dead donor. Reports in the literature indicate that recipient outcomes are similar to those for lungs transplanted from brain-dead donors [21,22].

Ex-vivo lung perfusion

Ex vivo lung perfusion (EVLP) has recently emerged as a technique that can be used to evaluate and recondition lungs following explantation from a donor, such that the function of marginal/injured lungs can be improved and significant, persistent dysfunction can be identified prior to recipient implantation [23-29]. Lungs are perfused with

Table 3. Emerging phenotypes of CLAD: key features*

Entity	Classic BOS	NRAD	RAS
Time of Onset	• Late (usually 2-3 years post-transplant, but may occur earlier) • ≈80% prevalence at 10 years post-transplant	• Usually occurs early (e.g. 3-6 months post-transplant)	• Tends to occur later but may occur at any time • Accounts for approximately 1/3 of CLAD cases
Physiology	• Obstructive (FEV1 ≤80% of stable baseline value)	• Obstructive (FEV1 ≤80% of stable baseline value)	• Restrictive (e.g. FEV1 ≤80% and TLC ≤90% of stable baseline values)
HRCT Imaging	• Air trapping often present • No/minimal infiltrates • ± bronchiectasis	• Changes of bronchiolitis ("tree-in-bud", thickened airway walls, peri-bronchiolar infiltrates often present) • ± air trapping	• Parenchymal infiltrates usually present (DAD often present) • ± bronchiectasis • ± air trapping
Histopathology	• OB (difficult to diagnose via transbronchial biopsy)	• Cellular bronchiolitis	• Fibrosis (thickened septae and pleurae) • DAD often present • ± OB
Clinical course	• Typically progressive but may stabilize • Recipients may have coexistent chronic bacterial infection	• High likelihood of significant response to azithromycin (may no longer meet criteria for persistent BOS if recipient is an azithromycin responder)	• Tends to be relentlessly progressive • Significantly worse prognosis than BOS
Other	• Usually responds poorly to pharmacologic therapies • Can have outcome similar to primary transplant following lung retransplantation	• BAL neutrophilia (e.g. ≥15% on differential cell count) correlates with response to azithromycin therapy	• Increased risk of RAS if new onset DAD detected >90 days post-transplant

*Infection, other pathologies (e.g. acute cellular rejection, lymphocytic bronchiolitis, antibody-mediated rejection), and/or other causes of allograft dysfunction (e.g. significant gastroesophageal reflux, pleural disorders, anastomotic dysfunction, obesity, thromboembolic disease, recurrent primary lung disease, etc.), must be ruled out.

Abbreviations: BAL = bronchoalveolar lavage; BOS = bronchiolitis obliterans syndrome; CLAD = chronic lung allograft dysfunction; DAD = diffuse alveolar damage; NRAD = neutrophilic reversible allograft dysfunction; OB = obliterative bronchiolitis; RAS = restrictive allograft syndrome

a hyperoncotic, acellular serum that dehydrates edematous lungs by drawing fluid from extravascular compartments such that gas exchange can be improved and lungs initially judged to be unsuitable for transplant can be rendered usable [30-32]. Additionally, anti-inflammatory cytokines can be infused into the lungs to promote injury repair, and vector-mediated transfer of interleukin (IL)-10 has been shown to decrease proinflammatory cytokine production, promote recovery of intercellular alveolar epithelial tight junctions, improve oxygenation, and decrease vascular resistance [33-35]. Antibiotics can also be infused to suppress/eliminate infection.

Bridging to lung transplantation
Transplantation of patients receiving life support in the intensive care unit and the use of extracorporeal membrane oxygenation (ECMO) to support patients with severe respiratory failure has gradually increased, but outcomes for patients on either mechanical ventilation or ECMO have been reported to be significantly lower than those who do not require such support [10,36-38]. Nonetheless, ECMO may provide the only means of keeping a patient alive for transplantation and can also be used to support recipients through the transplant procedure [39-44]. Newer approaches and devices for ECMO are being developed that can allow patients to be ambulatory while they await organ offers and transplantation [45-49]. Additionally, an external artificial lung (NovaLung system) has recently become available for patient use [50-53], and this paracorporeal system, which is typically not flow-assisted, can be connected to an external pump for circulatory assistance if needed.

Infection prophylaxis
Infections remain a constant threat to lung transplant recipients. However, prophylactic regimens can protect recipients from certain infections, and the advent of cytomegalovirus (CMV) prophylaxis has greatly reduced the impact of CMV disease on recipient survival [54,55]. A recent, well-conducted, randomized controlled trial of prophylaxis with valganciclovir for at-risk patients (donor or recipient CMV seropositive) showed a marked reduction in CMV disease incidence for a 12-month course of valganciclovir versus a 3-month course [56]. Additional investigations need to be undertaken to refine this and other approaches to infection prophylaxis.

Detection and management of chronic lung allograft dysfunction
The predominant cause of chronic lung allograft dysfunction (CLAD) is recognized to be BOS, which is perceived to be caused by obliterative bronchiolitis as a consequence of

chronic rejection and has been linked to numerous risk factors (Table 2). The transplant community now recognizes that CLAD can be caused by a variety of allograft abnormalities [57-59], and the novel entities of restrictive allograft syndrome [60-62] and neutrophilic reversible allograft dysfunction (NRAD) [63] have been recently described and distinguished from classical BOS [64], which is recognized as an obstructive pattern on spirometry without parenchymal infiltrates in the allograft (Table 3). BOS is generally poorly responsive to augmented immunosuppression or other interventions, but recent randomized clinical trials have suggested that it can be prevented and/or attenuated by administering azithromycin [65,66]. Although preliminary work with inhaled cyclosporine A suggested benefit [67], a recent, multicenter Phase III clinical trial of inhaled aerosolized cyclosporine A given prophylactically for the primary outcome of BOS-free survival (294 subjects enrolled) was completed in 2011 and appears to have shown no benefit (see www.clinicaltrials.gov; NCT00755781).

Patients with advanced lung disease and lung transplant recipients frequently have a significantly increased degree of gastroesophageal reflux, and a number of investigations suggest that anti-reflux surgery may provide benefit for lung allograft recipients [68-74]. Other approaches such as photopheresis or the administration of intravenous immune globulin and/or anti-CD20 antibodies may benefit recipients with either refractory acute cellular rejection or BOS if evidence of a humoral response to donor antigen (donor-specific antibody) is detected [75-77]. Another recent advance is the recognition that autoimmunity (immune responses directed against self-antigens such as collagen V) may play a significant role in both acute and chronic lung allograft rejection [78-82], and tolerization with oral administration of collagen V has been shown to blunt lung allograft rejection in a major histocompatibility (MHC)-mismatched animal model [83-86].

Inducing tolerance
IL-17-secreting lymphocytes (such as Th17 lymphocytes that have been associated with autoimmune disorders) have been identified as playing key roles in acute and chronic allograft rejection [78,87-96], and ongoing research has identified an expanded number of immune cell subsets that secrete IL-17 [96,97]. Regulatory lymphocyte subsets such as CD4+FoxP3+ T cells and B1 B cells can antagonize and suppress both allo- and autoimmune rejection responses [98-104]. A better understanding of regulatory cell mechanisms is evolving and may lead to novel approaches to prevent rejection by harnessing the ability of regulatory immune cells to suppress host rejection of implanted donor tissue and inflammation.

Stem cells
Donor-derived mesenchymal stem cells have been identified as potentially playing a significant role in bronchiolar fibrosis in BOS [105-107], possibly in part because they may be capable of inhibiting the function of various immune cells (T cells, B cells, natural killer (NK) cells, dendritic cells) and cytokine secretion [108-110]. Stem cells have been shown to reduce injury and inflammation in a number of animal models [111-122], and stem cell therapies may blunt acute ischemia-reperfusion injury and fibrotic responses to lung injury.

Tissue engineering
Methods have been developed to decellularize whole lungs such that an intact extracellular matrix can be isolated, and these 3-dimensional scaffolds can be subsequently recellularized [123-126]. Such bioartificial lung grafts have been successfully placed orthotopically in animal models following successful recellularization with stem or progenitor cells and provide gas exchange, but delayed onset of inflammation and consolidation eventually led to loss of function [127,128]. Research is ongoing to determine whether a bioengineered lung can be adequately recellularized with appropriate stem cells that differentiate and replace/repopulate the more than 40 different cell types in their normal anatomic compartments such that sustained function can be attained, preferably with cells obtained from the prospective recipient so that the need for intense immunosuppression and risk of opportunistic infection can be avoided.

Xenotransplantation
Lung transplantation across species (e.g. pig lung to human recipient) may provide an alternative to allogeneic lung transplantation or could serve as a bridge to allotransplantation to allow time for a human donor-recipient match to be made and the xenograft replaced [129,130]. However, exuberant inflammatory, immune, and coagulation responses must be overcome [131-133]. Extensive genetic engineering of pigs is ongoing to prevent the acute thrombotic and severe inflammatory reactions that have occurred in various xenotransplant models, such as pig to primate xenotransplantation [129,134,135].

Implications for clinical practice
The implementation of the LAS system in the US has improved organ allocation and reduced the number of deaths on the waitlist; however, organs are being increasingly allocated to older candidates with pulmonary fibrosis. Refinement of the criteria used to select lung transplant candidates is needed and may lead to improved post-transplant outcomes if the ability to predict a greater likelihood of good versus poor post-transplant survival is

improved. New HLA antibody detection techniques will allow better donor-recipient matching and prevent pre-sensitized candidates from receiving mismatched donor lungs, and these techniques should be universally implemented by all transplant centers. The increased use of DCD donors and the use of marginal donor lungs that have been reconditioned via EVLP will likely significantly expand the number of transplants that can be performed, although supply is likely to remain inadequate to satisfy increasing demand. ECMO techniques have gradually improved such that patients with profound respiratory failure due to irreversible, end-stage lung disease can be supported until a match can be found, and the use of artificial lung devices and newer ECMO devices can allow patients to remain ambulatory prior to transplant and avoid invasive mechanical ventilation.

Advances in infection prophylaxis, especially prevention of CMV disease, have had an impact on post-transplant morbidity and mortality, and our understanding of CLAD has improved considerably over the past few years and has led to new approaches of the treatment of BOS, such as administration of azithromycin. An improved understanding of IL-17-mediated rejection responses and mechanisms of immune regulation that can prevent adverse allo- and autoimmune rejection responses may lead to novel strategies that can achieve immune tolerance and diminish the need for chronic, intense pharmacologic immunosuppression, which is associated with increased risk of adverse events (infection, renal insufficiency, systemic hypertension, hyperlipidemia, diabetes) over time. The utilization of stem cell therapies holds the promise of suppressing immune responses, but considerable research is needed to determine how stem cells can be used to prevent or ameliorate allograft rejection or injury. Tissue engineering with the restoration of cellular compartments of a lung scaffold using candidate progenitor cells and xenotransplantation (e.g. pig to human) are areas of intense research, but considerable hurdles must be overcome before these approaches can become realities in clinical lung transplantation.

Abbreviations
BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; DCD, donation after cardiac death; ECMO, extra-corporeal membrane oxygenation; EVLP, ex-vivo lung perfusion; LAS, lung allocation score; MHC, major histocompatibility complex; MSC, mesenchymal stem cell; NK, natural killer; NRAD, neutrophilic reversible allograft dysfunction.

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The author declares that he has no disclosures.

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