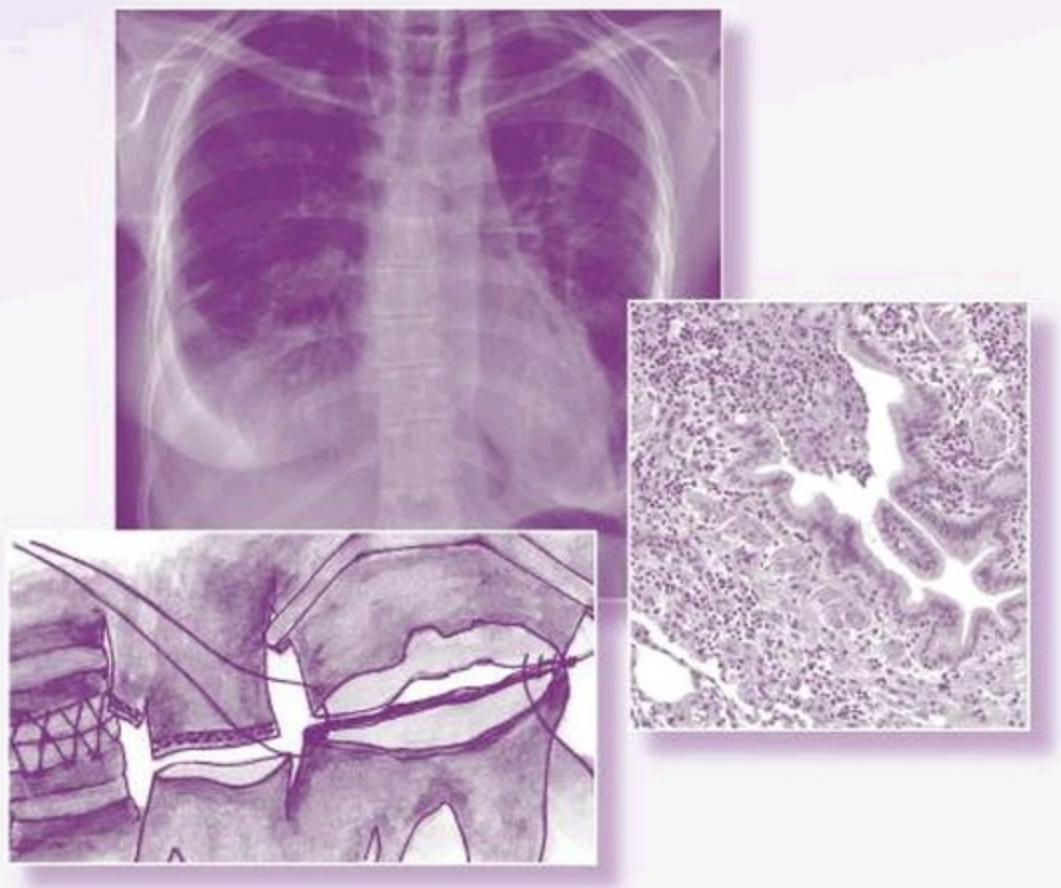
Lung Transplantation



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The opinions expressed in these volumes do not necessarily represent the views of the National Institutes of Health.

Lung Transplantation

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Preface

Almost 30 years since the first successful lung-heart transplant, lung transplantation has come of age. No longer experimental therapy, selected patients with many different end-stage lung diseases can be treated successfully with lung transplantation. The process of lung transplantation is complex and requires a multidisciplinary approach, with many specialists interacting in the selection and management of patients. Therefore, a sound understanding of all aspects of critical care and immunology, and related surgical complications is essential to success. This book provides an opportunity to keep readers abreast of advances in the field of lung transplantation remote from their own expertise.

Many recipients live long lives, seen and managed by local health care workers in their own communities. Therefore, a broad understanding of lung transplantation is required for those likely to be involved in the care of these patients, before and after transplantation. We believe that this book will provide them that knowledge.

In this book, leading experts present current evidence and personal experiences in the field of lung transplantation. This is a comprehensive account of contemporary practice of lung transplantation presented in a concise manner, for easy reading and quick reference.

The book is divided into several parts. The first part is an introduction, covering history, immunology, ethics, and organizational structure of a lung transplant program. Part II addresses specific advanced lung diseases that may necessitate lung transplantation. Parts III and IV deal with the transplantation process itself, divided into donor and recipient issues. Parts V–VII address postoperative care as well as early and late medical management. The book concludes with part VIII, speculation on the future of lung replacement therapy.

We reached out to international experts with a wealth of personal knowledge in lung transplantation, producing a state-of-the-art review of this field. We believe this book will appeal to physicians, nurses, surgeons, intensivists, immunologists, pathologists, social workers, donor, and transplant coordinators who are involved in the field. We especially feel that providers who may come in contact with lung transplant patients in community practice will

benefit from this work. This is a thorough, up-to-date source on lung transplantation, where we are now approaching 30 years of experience. We believe that the most knowledgeable caregivers will become familiar with this book as an essential aide to care giving.

Wickii T. Vigneswaran
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1
The History of Lung Transplantation

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I. Introduction

The foundation for clinical transplantation was laid at University of Chicago by Alexis Carrel (Fig. 1) (1). In recognition of his work in vascular suture and the transplantation of blood vessels and organs, he was awarded the first Nobel price in Physiology or Medicine in 1912. His pioneering work was continued by others at University of Chicago and around the world in various animal models. After subsequent fundamental advances in immunology, clinical organ transplantation became a reality.

Canine lungs were transplanted as a unit with the heart in 1946, in Russia by Demikov, who in the following year transplanted a lung alone (2,3). The dog's death from bronchial dehiscence heralded that the airway anastomosis would be the most formidable technical barrier to success. Hardy reported the first successful human lung transplant at the University of Mississippi in 1963 (4). However, consistently poor outcomes in the late1960s and early 1970s (5) led to an NIH moratorium on clinical lung transplantation in the late 1970s. A combination of the advent of cyclosporine-based immunosuppression, refinements in the criteria for the selection of recipients; improvements in lung preservation, better surgical technique and postoperative management led to the renaissance of lung transplantation in humans in Toronto in 1983 (6). Now, lung transplantation is a widely accepted treatment for certain types of end-stage lung disease.

In this remarkable success story there have been four overlapping phases: (*i*) *the demonstration of technical feasibility*; (*ii*) *the progressive improvement of operative technique*; (*iii*) *the improvement of regimens of immunosuppression*; and (iv) *the residual obstacles to further success.*

II. Technical Feasibility

In 1950, Metras reported successful whole lung transplants in dogs, including the first bronchial artery and left atrium anastomoses (7). Juvenelle is credited with the first pulmonary reimplantation, but not with the intent of lung transplantation (8). His

Figure 1 Alexis Carrel (1873–1944), University of Chicago (1904–1906).

Figure 2 William Elias Adams (1902–1973), the father of lung transplantation at the University of Chicago.

purpose was to evaluate the role of autonomic nerves in the pathogenesis and potential therapy of asthma.

Several groups studied the ability of reimplanted lungs to sustain life, using contralateral pneumonectomy. The early experiments failed, generally because of pulmonary edema and venous thrombosis (9–12). Studies of dogs had strongly suggested serious pulmonary function deficit after denervation, but Haglin showed that primates recovered nearly normal function after lung reimplantation (13).

At the University of Chicago, William Elias Adams (Fig. 2), a native of Iowa, was the father of lung transplantation. From 1934 to 1935, he had served as Professor Phemister's 5th chief resident before he and Phemister accomplished the first successful esophagogastrectomy in a single stage for the treatment of cancer. Later he became the chairman of the department of surgery. During Adams' presidential address to the American Association for Thoracic Surgery, merely nine years after the first reimplantation of the right lung of a single dog, he foresaw successful lung transplantation in humans as part of his life long interest in the preservation and restoration of pulmonary function (14). In the 1960s, Nigro et al. showed that a single reimplanted canine lung could sustain life (12,15), and Gago et al. introduced the concept of single lobe transplantation (16). Benfield et al. carried these University of Chicago studies further at the University of Wisconsin, dispelling the erroneous belief that increased pulmonary vascular resistance was a sine qua non of lung grafting (17). Angiographic and autopsy examination of animals in which only the left atrium had been divided and anastomosed showed that pulmonary hypertension directly correlated with technically related venous outflow obstruction. In the 1970s Benfield's group, by then at UCLA, proceeded to address the still vexing issue of differentiating rejection from infection in pulmonary allografts by showing that lung biopsies were to be the definitive method of differential diagnosis (18).

III. Improvement in Immunosuppression and Operative Techniques

When Hardy et al. transplanted the first human lung in 1963 (4), immunosuppression consisted of preoperative thymic radiation and postoperative azathioprine and prednisone. The patient succumbed to uremia after 18 days, but the grafted lung was grossly normal at autopsy. This showed the potential feasibility of successful human lung transplantation. Derom in Belgium was credited with the first successful human lung transplantation when he treated end-stage pulmonary fibrosis with a single-lung transplant and his patient survived 10.5 months (19). Veith's group in New York was among the most active lung transplant units in the laboratory and clinically (20). By 1978, 38 lung transplants had been performed worldwide. Derom's patient was the only one that had approached a beneficial outcome.

Rejection and infection were common causes of death in this early experience with clinical lung transplantation. Impaired healing of the bronchial anastomosis was also a leading cause of death, particularly in patients who survived more than two weeks. Lenfant, later to become the director of the National Heart and Lung Institute, invited a book chapter that summarized the evidence up to the 1970s and that contributed to the temporary suspension of lung transplantation in humans (21).

Cyclosporine-based immunosuppression in kidney and liver transplantation in the early 1980s resulted in dramatic improvements in organ function and patient survival. The Stanford group, led by Shumway and Reitz, demonstrated the benefit of cyclosporine-based immunosuppression in a primate model of heart-lung transplantation (22). This led to the reinstitution of a clinical heart-lung and lung transplantation program at Stanford. In heart-lung transplant recipients, airway complications were rare whereas they had been common in the previous lung transplant recipients. This disparity in favor of heart-lung transplants was believed to be because of relatively better preservation of blood supply from noncoronary collateral circulation in the en-bloc heart-lung operations.

In parallel with the work at Stanford, the Toronto Lung Transplant Group led by Pearson and Cooper, was among investigators who conducted experiments in animals aimed at improved airway healing. Not surprisingly, impaired tensile strength of bronchial anastomoses was related primarily to steroid therapy (23). Fortunately, cyclosporine had no apparent adverse effects on airway healing (24). In Toronto, Cooper favored wrapping bronchial anastomoses with omentum. Other groups showed that bronchial revascularization could occur without wrapping, and that there was no correlation between the extent of revascularization and the occurrence of anastomotic complications (25).

In 1986 Cooper reported successful single-lung transplantation in two patients with pulmonary fibrosis (6). For some time thereafter, many investigators considered single-lung transplantation to be inappropriate for patients with emphysema or cystic fibrosis. Theory and past experience suggested that there would be dynamic hyperinflation of the native lung after placement of an allograft and that the risk of infection in the allograft would be prohibitive in patients with cystic fibrosis. To address these concerns, en-bloc double-lung transplant with a tracheal anastomosis, using cardiopulmonary bypass, was done for six patients with obstructive lung disease by the Toronto group, three of whom suffered major airway complications (26).

In 1989, however, Mal et al. demonstrated the feasibility of single-lung transplant in patients with emphysema without significant contralateral hyperinflation (27).

Finally, bilateral sequential transplantation, through bilateral anterolateral sternothoracotomy, was devised as a method to avoid mandatory cardiopulmonary bypass and to improve healing. Airway complications using this technique were less than 10% (28).

A major contribution to the improved success of single-lung transplantation has been improved and more careful selection of recipients. Whereas early lung transplantation recipients were usually ventilator-dependent, malnourished patients or those with steroid-related myopathy and osteoporosis, in the late 1980s and early 1990s, the crucial value of preoperative pulmonary rehabilitation and improved general physical condition was recognized. Currently, most lung transplantation recipients are ambulatory (29).

A. Residual Obstacles to Greater Success and Current Efforts to Overcome These Obstacles

A shortage or donors and organs had been, and continue to be an overwhelming limitation in the field of transplantation. Institution of standardized protocols of donor management including lung protective ventilation, lung recruitment maneuvers and aggressive tracheal lavage have been shown to double organ recovery rates without detrimental effects on 30-day or 1-year survival (30).

Lung grafts must immediately function well enough to allow survival of the recipient. Because primary graft dysfunction (PGD) occurs in 10% to 25% of cases, it is the most common cause of death within 30 days after transplantation. PGD is associated with high rates of bronchiolitis obliterans syndrome (BOS), or rejection, and it correlates with decreased one- and five-year survival rates (31). The widespread clinical use within the past five years of a preservation solution specifically designed for the lung has led to more consistent quality of the donor allograft and to lower rates of PGD. Traditional preservation solutions such as Euro-Collins were designed to maintain intracellular ion balance and cell wall integrity. Low potassium dextran (LPD, Perfadex®, Vitrolife, Goteborg, Sweden) has an extracellular fluid ion balance and has been shown to have beneficial effects on endothelial cell function and pulmonary microcirculation. Five single institution reports have demonstrated significantly better initial lung function with LPD, while one study showed no difference (32).

Airway healing after lung transplantation remains a concern. A telescoped bronchial anastomosis had been universally accepted on the basis of the experience by Veith in the 1980s (33). However, several groups have demonstrated the superiority of end-to-end anastomoses. For example, Garfein et al. demonstrated a 32% incidence of severe airway stenosis after telescoped anastomoses as compared with 5% stenosis following end-to-end anastomoses in single-lung recipients for emphysema (34).

Posttransplantation immunosuppression using triple therapy with steroids, an antimetabolite and a calcineurin inhibitor has remained quite stable during the past 20 years. In a recent open-label randomized trial of 90 patients who received either cyclosporine or tacrolimus, subjects who were treated with tacrolimus experienced significantly less acute rejection. Lymphocytic bronchitis was also less frequent among patients receiving tacrolimus (35).

Finally, routine prohylaxis against bacterial pathogens, cytomegalovirus and aspergillus has been shown to decrease the incidence of infection. Pneumonia remains among the most common causes of morbidity and mortality in the first year after transplant, and the differentiation of infection and BOS (rejection) remains a challenge.

IV. Current Status

Where do we stand with human lung transplantation in the 21st century? The Registry of the International Society of Heart and Lung Transplantation recorded 24,904 lung transplants between 1985 and 2006 (36). Currently 147 centers actively offer and do lung transplants, but only 23 centers do more than 30 transplants annually. Of the 2168 lung transplants known to the International Society for Heart and Lung Transplantation in 2006, about 67% were bilateral. About 32% of patients treated with lung transplantation had emphysema that generally was associated with cigarette smoking, and about 4% had emphysema associated with α_1-antitrypsin deficiency. The ravages of pulmonary fibrosis prompted 26% of lung transplants and cystic fibrosis was the indication for transplantation in 16% of lung transplant recipients.

Overall, survival after lung transplantation has steadily improved with the passage of time. Between 1988 and 1994 median survival was 3.9 years. During 2000 to 2006, the period for which the most recent collective data are available, median survival had increased to 5.5 years, including a 1-year survival rate of 81.4%, and a 5-year survival of 53.5%. Patients who received bilateral lung transplants survived significantly longer than patients after single-lung transplantation (median survival of 6.2 years vs. 4.5 years, $p < 0.0001$).

In general, young recipients survive longer than older patients. This is consistent with the association of relative youth in patients with cystic fibrosis, and the fact that such patients nearly always received bilateral transplants to mitigate the risk of lung graft infection. Recipients treated for cystic fibrosis had the best median survival (6.4 years) of any group. Conversely, patients with pulmonary fibrosis, who are usually older, had a median survival of 4.1 years.

BOS (graft rejection) was the most common cause of death within the first year after lung transplantation, and also within five years. Associated with the death of recipients within the first year were requirements for the use of intravenous inotropes and mechanical ventilation.

It is gratifying to early lung transplantation research workers, that lung transplantation is now generally accepted by government and private health care funding agencies. It is remarkable that only about 60 years after it was a dream, and just over 20 years since the first truly successful human lung transplant, successful lung transplantation is providing good palliation for an increasing number of patients world-wide. Our hope and our expectation are that the history we have reported is but a prelude to better and more long lasting methods of treating end-stage pulmonary dysfunction.

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2
Immunology of Lung Transplantation

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I. Introduction

Lung transplantation remains the hope for many incurable pulmonary diseases, such as cystic fibrosis, pulmonary fibrosis, and chronic obstructive pulmonary disease. Remarkable progress has been made in improving outcomes, although the incidence of acute rejection remains over 50% in the first year, and the five year graft survival is still less than 50% due primarily to the development of chronic rejection and graft dysfunction (1). Many of the significant advances made in solid organ transplantation, including lung, have been the result of advances in immunology. In 1905 Alexis Carrel proclaimed that the surgical challenges of organ transplantation had been solved, but it was not until the implementation of immunosuppression that solid organ transplantation became a viable treatment option for patients with end-stage disease (2,3). In the United States, there are nearly 30,000 solid organ transplants performed yearly. Lung transplant recipients face the worst post-transplant survival statistics of the solid organs except small bowel and provide the biggest challenge for immunology to continue to improve outcomes (1). Acute rejection mediated by alloreactive T and B cells is usually treatable with immunosuppression but has been found to be an important risk factor for chronic rejection. Chronic rejection is characterized by the development of obliterative bronchiolitis (OB) in allografts and manifests as bronchiolitis obliterans syndrome (BOS) in humans with no effective treatment. Previous studies support a role for alloreactive T and B cells in the development of BOS, but recent studies highlight a role for autoimmunity in the pathogenesis of the rejection response (4–6). However, many of the specific mechanisms are unknown (reviewed in Refs. 1,7).

II. Alloimmunity

The primary basis for rejection of solid organs is host recognition of non-self donor antigens or the alloimmune response. After transplantation, the T-cell receptor (TCR) on host T cells recognizes peptide-major histocompatibility complex (MHC) [or human leukocyte antigen (HLA)] present on donor cells. In lung transplantation HLA matching is not typically done because of the difficulty of completing these studies during the limited time available for harvesting and transplanting lungs. The immune response to alloantigens is primarily initiated by a T-cell response, which may then promote a B cell response leading to alloantibody production. Why humans have evolved to have

alloreactive T cells is unknown, but may be a result of the inherent affinity of the TCR for MHC molecules (8). Humans all have allogeneic lymphocytes circulating regardless of whether they have previously been exposed to alloantigens. These mostly naive lymphocytes can be activated after transplantation when T cells are presented with their cognate antigen in the right context of MHC.

The initiation of T-cell alloreactivity has been established to occur via at least two pathways (Fig. 1). In the *direct pathway*, recipient T cells recognize intact donor MHC molecules displayed on the surface of donor cells, either traditional hematopoietic antigen-presenting cells (APCs) or other nonhematopoietic graft cells (9,10). The *indirect pathway* is defined by recipient APCs engulfing and processing damaged donor cells and presenting donor-derived MHC peptides to recipient T cells via self-MHC: donor peptide complexes (11). The direct pathway, characterized by alloreactive T cells with a high precursor frequency and a wide range of receptor specificities capable of recognizing numerous allo-MHC molecules, dominates the early post-transplant period when numerous donor APCs are present (9,10). In contrast, T cells involved in the indirect pathway are aimed at a single or a few principal donor MHC peptides displayed on the surface of recipient MHC molecules (9,10). The indirect pathway is likely to

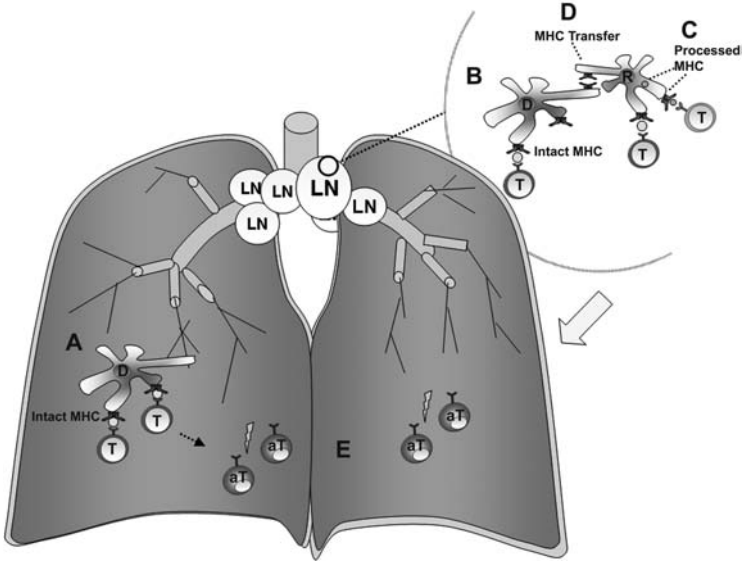

Figure 1 (*See color insert*) Mechanisms of initiating an alloimmune response—lung is a "lymph node with alveoli." After lung transplantation, allorecognition may occur via direct, indirect, or semi-direct antigen presentation to T cells. (**A**,**B**) *Direct allorecognition* occurs when donor dendritic cells (**D**, blue) displaying intact donor MHC:peptide complexes directly present antigen in the lung to naive T cells (T) infiltrating the graft from the blood early after engraftment (**A**) or when donor DCs migrate from the lung allograft to lymph nodes when the lymphatics are restored (**B**). (**C**) *Indirect alloantigen* occurs when recipient dendritic cells (R, pink) in the draining lymph nodes activate naive T cells with complexes of self-MHC and processed donor MHC peptides. (**D**) *Semi-direct pathway* may occur when intact donor MHC molecules are transferred from donor to recipient dendritic cells, and subsequently presented by recipient dendritic cells to naive T cells. (**E**) Activated $CD4^+$ and $CD8^+$ T cells (aT) then return to the lung and induce rejection of the allograft.

remain active throughout the life of the allograft because of either the infiltration of recipient APC in the allograft or the persistence of donor antigens in the lymphoid tissue (12). The indirect pathway may therefore be responsible for allorecognition later in the post-transplant period and may represent the basis of chronic allograft rejection (13).

Although indirect allorecognition may dominate chronic lung rejection, direct recognition of MHC by T cells can contribute to chronic rejection after donor APCs have been depleted (14,15). $CD8^+$ T cells recognize antigens presented by class I MHC that is present on all cells, unlike class II MHC ($CD4^+$ T cells) that is expressed primarily by specialized hematopoietic cells. In mouse models, there is evidence that $CD8^+$ T cells with direct class I MHC alloreactivity to the graft persist and contribute to the chronic destruction and subsequent obliterative airway disease of transplanted tracheal allografts (16). Further, after transplantation in a rat model, class II MHC was found to be upregulated on the epithelium and endothelium of lung allografts (17). Increased class II MHC on lung allografts has also been reported in lung transplant patients with chronic rejection (18). The expression of class II on nonhematopoietic cells in an allograft may provide a means of direct allorecognition for $CD4^+$ T cells, although proof of this in vivo is lacking. The persistence of direct allorecognition may also be explained by the newly proposed *semi-direct pathway* of alloantigen presentation (Fig. 1) (19). Semi-direct allorecognition describes the process in which recipient APC may acquire intact donor MHC:peptide complexes through either cell-cell contact or exosomes (12). This additional pathway may enable recipient APC to interact with both $CD4^+$ and $CD8^+$ T cells simultaneously. It is possible in human lung transplantation that episodes of acute rejection may injure lung epithelium and endothelium leading to cellular fragments of donor MHC that can be taken up by recipient APC and presented to alloreactive T cells. However, no direct proof of the semi-direct pathway occurring in lung transplantation has been reported.

In lung transplantation acute rejection occurs quite frequently in the first year post transplant and is characterized by the infiltration of $CD4^+$ and $CD8^+$ T cells and mononuclear cells into the perivascular and peribronchiolar regions of the lung (20). Interestingly, acute rejection can occur immediately postoperative during a time when lymphatics are not available to drain donor APCs to secondary lymph nodes, which are thought to be the site of initiating alloreactivity. In other solid organ allograft animal models the removal of lymphatics has been shown to prevent acute allograft rejection (21). Recently, Gelman et al. demonstrated in a mouse model of orthotopic lung transplantation that secondary lymphoid organs are not necessary for acute allograft rejection (22). These data suggest the lung is the primary site of activation of naive allogeneic T cells (Fig. 1) immediately after transplant and makes the lung distinct from other solid organs including intestine (21).

III. Innate Immunity: Dendritic Cells

While the adaptive immune response plays a significant role in acute and chronic rejection after lung transplantation the role of the innate immune response in shaping the adaptive immune response is critical. The normal lung has dendritic cells (DCs), macrophages, epithelium, and endothelium, which all contribute to its defense against the environment and mediate the innate immune response. The major APC type in the lung is the DC (23,24). DCs after transplantation directly induce the alloimmune response either by activating T cells in the lung or draining lymph nodes (Fig. 1). Studies have

found that depletion of DC significantly abrogate acute allograft rejection in both animal models and human kidney transplant patients (reviewed in Ref. 24). Studies in the mouse model of orthotopic lung transplantation also support an essential role for DC in acute allograft rejection (22). Since the mucosal surface of the lung is estimated to have a network of 500 to 750 DCs per square millimeter, comparable to the network of Langerhans cells found in the skin, depletion of DC would be difficult prior to transplant of human lungs (25).

The lung has several different types of DCs characterized by anatomic location, cell surface receptors, and morphology and their biology is unique to the lung (23). DCs capture antigens from the allograft, the environment, or both, and as they migrate to the draining lymph nodes their phenotype matures leading to upregulation of costimulatory markers necessary for efficient T-cell activation (23). The stimuli received by DCs and their particular biology determine the type of T-cell response. T-cell responses differ by the secretion of cytokines, which define different subsets, such as Th1 (interferon γ, lymphotoxin), Th2 (IL-4, IL-5 and IL-13), or the newly recognized Th17 (IL-17, IL-22) (26). Alternatively, DC may have a phenotype that is more tolerogenic and activate regulatory T cells (Tregs), which can suppress other T cells, or anergize T cells and make them unresponsive. Interestingly, data in small studies of patients with allograft tolerance show that DC may be involved in promoting tolerance and may be useful as tolerogenic vaccines (24). Future studies on the unique biology of lung DC may provide novel therapies for inducing tolerance to lung alloantigens.

IV. Innate Immunity: Pattern Recognition Receptors

The molecular basis for signaling between the innate immune response and environmental stimuli became much clearer with the discovery in 1997 of the Toll like receptor (TLR) subfamily (27). Since that time several families of pathogen recognition receptors (PRRs) have been identified, such as NOD-like receptors (NLRs) and the RIG-like helicases (RLHs) (28). Ligation of PRRs on DC leads to DC maturation and upregulation of cytokines and costimulatory molecules, signals required for the adaptive immune response to be initiated. Interestingly, all PRRs are not exogenous and a role for endogenous ligands in activation of the innate immune response has also been observed (29). The lung, with chronic exposure to microbes in the environment, significant I/R injury during transplantation, and risk of infection may be particularly vulnerable to activation of PRRs by endogenous and exogenous ligands after transplantation. The unique exposure to the environment may underlie the poor outcomes found in organ transplantation of lung, skin, and intestine compared to other solid organs (reviewed in Refs. 30,31). Interestingly, TLR4 polymorphisms have been linked to BOS in human lung transplant patients and a decreased sensitivity to LPS was associated with less BOS (32,33). A greater understanding of the innate immune response in the lung and its impact on promoting alloreactive T-cell responses may provide novel targets for therapeutics.

V. Innate Immunity: Macrophages and Other Innate Cells

While DCs are the likely APC responsible for initiating the alloimmune response, other innate cell types in the lung clearly modify the adaptive immune response. Macrophages, neutrophils, and NK cells have been implicated in transplantation. Macrophages play a role in lung homeostasis and pathogen defense and have been shown to be a

source of growth factors thought to mediate the fibroproliferation characteristic of OB in humans (34). Depletion of macrophages in a rat model of heterotopic tracheal transplant prevented the development of OB, suggesting macrophages play a causative role in OB lesions (35). Another role for macrophages may be related to the bridge between innate and adaptive immunity. Recent studies highlight the role of Th17 cells in the pathogenesis of OB (5), and monocytes/macrophages have been suggested to have a key role in the induction of Th17 immunity (36). In addition, Th1 immune responses were diminished in macrophage-depleted lung allografts (37).

NK cells are key components of the innate immune response. Their role in lung transplant rejection remains unclear but insights gained from transplantation studies in other solid organs and the lung suggest a role for these cells in the rejection response. For example, NK cells have been found to affect chronic graft vasculopathy in a cardiac model of transplantation and have recently been implicated in human lung transplant patients (38–40). It is known that NK cells are resistant to calcineurin inhibitor–mediated immune suppression. Therefore, MHC class I expressed on donor-derived resident NK cells could remain a strong stimulus for immune responses in the immunosuppressed transplant recipient. NK cells may be a future target for therapies to prevent OB (41).

VI. Immunology of Chronic Allograft Dysfunction

Studies in humans with BOS have consistently implicated persistent alloimmunity in the pathogenesis of OB. Humans with anti-donor HLA antibodies have been found to be more likely to develop BOS (42,43) and anti-donor specific indirect T-cell responses have also been associated with BOS in several studies (13,44,45). Data from animal models support a role for alloantibodies in promoting the pathogenesis of OB but have also found that they are not necessary to induce OB (46,47). An oligoclonal expansion of $CD4^+$ T cells in the peripheral blood was also found to be associated with the development of BOS, suggesting that specific $CD4^+$ T cells may expand and contribute to the pathogenesis of OB (48). Taken together, these studies suggest that the alloimmune response both during acute and chronic rejection involves a limited subset of T cells, as well as B cells and alloantibodies that may be exploited and targeted by future therapies.

VII. Autoimmunity and OB

Autoimmunity is emerging as one of the most significant contributors to the development of OB/BOS in human lung transplantation. Type V collagen [col(V)] is located within the lung interstitium and expressed by airway epithelial cells and its expression is enhanced by I/R injury and interstitial remodeling (49). T-cell reactivity to col(V) was also found to exacerbate acute rejection in rat allografts suggesting autoreactive T cells may promote graft failure (50). Col(V)-reactive $CD4^+$ T cells were associated with a nearly 10-fold increased risk for BOS in clinical lung transplantation, which was a greater risk than that associated with acute rejection episodes, HLA mismatch, or anti-HLA antibodies (5). Cellular immune responses to col(V) were mediated by IL-17A, TNFα, and IL-1β, but not IFNγ (5). While DCs are known to be key in initiating cellular immunity, col(V) reactivity was dependent on monocytes ($CD14^+$) (5). These data provide evidence of a new paradigm involving coordination between $CD4^+$ T cells and monocytes to produce an effector response and suggest autoreactive Th17 cells to be mediators of BOS.

Col(V) is not the only autoantigen that has been identified in lung transplant recipients. Antibodies to the epithelial specific protein, K-α1 tubulin, were found in a significant number of patients with BOS (51). Sera positive for anti-K-α1 tubulin antibodies induced pro-fibrotic growth factors from airway epithelial cell lines providing evidence that autoreactivity like alloimmunity may induce fibrosis. The same group has also found that an acute alloimmune response in the lung can promote the development of col(V) and K-α1 tubulin autoreactivity in a mouse model and the resulting airway injury and fibrosis involved IL-17 (6). The macrolide, azithromycin, an important treatment for a subset of patients with BOS, has previously been found to suppress IL-17 induced IL-8 production from human smooth muscle cells providing further support for IL-17 playing a role in BOS (52). Thus, alloimmune-mediated damage may lead to epitope spreading that results in an autoimmune response and the characteristic response may be IL-17 mediated.

VIII. Tregs and Lung Transplantation

One possible hypothesis for why autoimmunity and alloimmunity cannot be as easily suppressed once initiated is that Tregs are absent or dysfunctional after transplantation. A correlation between decreased Tregs and the incidence of BOS has been reported in lung transplantation recipients (53). Further, Bharat et al. found in 2006 that T cell lines reactive to col(V) isolated from lung transplant recipients produced IL-10 and were capable of suppressing proliferation and IFNγ secretion from autoreactive T cells (54). However, subjects who developed BOS had an associated decline in the frequency of IL-10 producing T-cell clones (54). These data suggest lung transplant recipients may dampen the autoimmune response to col(V) through either natural Tregs or adaptive Tregs. Interestingly, a recent study provided evidence that during inflammation alveolar epithelial cells may induce Tregs specific for endogenous lung antigens, suggesting lung epithelium is a major regulator of induced Tregs (55). The normal homeostasis of the lung may be undermined by immunosuppression and alloimmunity. Strategies to promote immune tolerance to col(V), alloantigens, or as yet to be identified antigens in lung transplantation hold promise to prevent the devastating complication of OB/BOS.

IX. Summary

The lung can be considered a "lymph node with alveoli" that is highly susceptible to perturbations in local immune homeostasis. The lung has immunocompetent cells within the airways, interstitium and alveoli, as well as within bronchus associated lymphoid tissue (BALT) that are sufficient to mount local immune responses even in the absence of systemic secondary lymphoid tissues (22,56). T and B cells in the lung can interact with other immunologically active components of the lung, such as extracellular matrix, and epithelial and endothelial cells, as well as cells of the innate immune system. Therefore, the lung is immunologically unique compared with other solid organ allografts such as the kidney, heart, or liver. The insults the lung encounters during transplantation, such as I/R injury, infection, and acid reflux induce chemokines, which recruit lymphoid cells to the lung and promote acute and chronic rejection, as well as the development of BALT. BALT in turn may be a site of continued antigen presentation and T and B cell proliferation, perpetuating the alloimmune response and providing an environment that may be prone to autoreactivity. The lung has distinct mechanisms of

maintaining immunity while trying to avoid impacting gas exchange, but these mechanisms may be deleterious in the face of chronic immune modulation as in lung transplantation. Substantive improvements in the survival of lung transplant recipients is likely to occur only after we are able to fully understand how the distinct interactions of immune and nonimmune cells in the lung impact the physiology of the transplanted lung.

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3
Ethics in Lung Transplantation

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I. Background

Lung transplantation is now an established therapy for end-stage pulmonary disease; survival and post-transplantation quality of life continue to improve. With slightly more than 2000 transplants performed globally in each of the last few years, there has been continued increase in the number of lung transplants performed over the last decade (1). The one-year survival rate now approaches 80%, with a 63% three-year, 51% five-year, and 28% ten-year survival rate Scientific Registry of Transplant Recipients (SRTR). The trend during this time as been for recipients to be older, especially in the United States.

Human lung transplantation began in 1963 and nearly ended then, with little clinical success until the introduction of Cyclosporine A in 1983. However, before Cyclosporine, long-term survival was rarely achieved. The development of the calcineurin inhibitors and increased understanding of transplant immunology led to increased patient survival. Currently, modern maintenance immunosuppressants combined with induction agents, such as IL-2 receptor antagonists, anti-thymocyte globulins, and the CD52 receptor antagonists, have greatly improved one- and five-year survival.

The main indications for lung transplantation have remained stable over time: chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), alpha-1 anti-trypsin deficiency, and pulmonary arterial hypertension (PAH). Over the past 15 years, there has been a decline in the percentage of transplants for COPD, with an increase in transplantation for IPF (1). During this same period, the number of transplants for PAH declined. These demographic changes are multifactorial; in the developed world, smoking rates have decreased, which will affect both COPD and IPF. In addition, there now are medical therapies for PAH, which can improve the quality of life for these patients.

At the end of 2006, there were approximately 1885 patients active on the lung transplant waiting list in the United States. In 2007, nearly 1500 lung transplants were performed, with a greater number of patients added to the waiting list. Despite all efforts, the supply of organs remains inadequate to meet the demands for transplantation, and unlike either renal or cardiac transplantation, there are limited mechanical support or replacement options that provide extended help for patients with end-stage pulmonary disease.

Transplantation raises a number of ethical concerns. Some are unique to lung transplantation. Others are common to all solid organ transplantation, and they pertain to issues such as organ scarcity, availability, allocation, and payment. In the language of medical ethics, these issues are equity, justice, and utility. In addition, what must be

considered within the field of transplantation is that there is often more than one patient. There is the recipient, but there are also other possible recipients, and sometimes a living donor, so harm and beneficence have wider ramifications.

II. Equity

Equity implies fairness, impartiality, and freedom from bias. In transplantation, this becomes an issue with not only organ allocation but, before that, with accessibility to a transplant center or to the listing process.

It stands to reason that in order to be evaluated for transplantation, a patient must have access to transplant centers. There are currently 79 centers in the United States (2) (27 states) and Canada that perform lung transplantation. Part of the limited access to transplantation is not only geographic, but also related to physician ignorance and insurance contracts that preferentially direct patients to favored centers. The lack of information about the advances in transplant medicine has been seen with other organs as the field of transplantation has grown rapidly and become a clinical success. Part of the efforts of United Network for Organ Sharing (UNOS) has been to increase both patient and physician awareness of the clinical success of lung transplantation so that patients can be referred to a transplant center earlier for consideration. There is an increased need for patient advocacy and an awareness of the issues in prelisting allocation.

Not all patients are potential transplant recipients. There are clear medical reasons that preclude transplantation, such as cancer, or severe comorbidities that in themselves limit patient survival. These medical factors are certainly less controversial reasons to deny patients transplantation. Age, however, is controversial. In lung transplantation, age sometimes has been used as a parameter to exclude the old or very old from transplantation. Is this discriminatory? Age is not unique or exclusionary; everyone will at some point be older. Exclusions of the old or very old from transplantation is common and is often justified on the basis of other comorbidities and the concept of "physiologic age." The average age of lung recipients is increasing, and in 2007 it was 49.8 years (1).

The softer criteria by which patients are evaluated for possible transplant candidacy are the economic burden, the availability of insurance, and the psychosocial, which refer not only to psychiatric diagnoses or conditions, but also to education, coping/adjustment strategies, and social factors.

III. Economics

Lung transplantation is costly. There are the costs of organ procurement, which often include ground or air transportation of an entire surgical team, and costs of the operation and postoperative hospitalization. These costs are just the beginning. As with any organ transplant, immunosuppressive medications are required to prevent graft rejection, anti-infective medications are needed to prevent opportunistic infections, and outpatient routine surveillance procedures, such as bronchoscopy, must be performed. Medications alone can cost more than $5000 monthly within the first year if there is no insurance copayment and prescription medication coverage. Few patients would be able to afford this. Medicaid/Medicare and private insurance companies do have the coverage for lung transplantation, although they may restrict access to a few "approved" or "certified" transplant centers. In the United States, patients without insurance and prescription medication coverage are often excluded from transplantation on this basis.

IV. Psychosocial

The psychosocial evaluation for transplant candidacy is important for both post-transplant quality of life and medical outcomes. Most transplant centers adopt a multidisciplinary approach that includes social workers, psychologists, and psychiatrists who are integral to the process of identifying risk factors or high-risk behaviors, which may affect these outcomes. However, there are no uniform criteria to assess the psychosocial appropriateness of a candidate. The International Society for Heart and Lung Transplantation (ISHLT) Guidelines for the Selection of Lung transplant Candidates state that "untreatable psychiatric or psychologic condition[s]. . .absence of a consistent or reliable social support system [and] substance addiction" are the only absolute contraindications (3). There are no uniform or validated standards by which to evaluate patients from a nonmedical standpoint. Most centers assess potential recipients on the following criteria: adaptive and coping mechanisms to deal with stress and medical treatment, adherence and compliance with medical recommendations, substance abuse, cognitive understanding of the transplant and its entailments, and social support. Centers in the United States are more rigorous about psychosocial evaluation than those outside the United States. (U.S. centers perform psychosocial evaluation in 92% of cases compared with 53% in non-U.S. programs (4).) On average, 4.6% of patients are excluded from transplantation on the basis of psychosocial criteria, and 2.4% are excluded even before an evaluation. The United States excludes more patients (5.6%) compared with European programs (2.5%), although this may in part be due to national health coverage systems (5). Data about lung transplant programs are scarce; however, lung and heart transplant programs have similar listing criteria, and based on the few studies that have been done, heart programs are more stringent in using psychosocial criteria to exclude candidates, with an average of 5.6% excluded after evaluation, compared with 2.8% in liver programs and 3% in renal programs (4).

An important component of the psychosocial evaluation is the determination of the likelihood of patient adherence and compliance with the post-transplant medical regimen. Adherence and compliance are crucial for successful transplantation and are different behaviors. In 2008, there was a Consensus Conference on Nonadherence in the setting of transplantation (6). The summary report distinguishes between *compliance*, which is patient behavior matching recommendations, and *adherence*, which they define as patient behavior matching an "agreed upon" recommendation. The consensus statement preferentially chose adherence as the greater issue. However, it must be noted that forces external to the patient-physician relationship also affect adherence. For example, transportation to and from clinic visits may be difficult for some because of physical limitations or cost, less compassionate employers may not understand the need for frequent office visits, and parents who are the primary caregivers for their children may not be able to juggle their schedules. Adherence implies a larger systems context that needs to be addressed by the transplant team. Compliance, on the other hand, is based on individual decision-making and choice and directly reflects the patient's engagement in their own medical care. While often the concepts of compliance and adherence are used interchangeably, in the context of transplantation, they should not be.

Nonadherence is not unique to transplantation. In studies of chronic diseases, there is a 24.8% nonadherence rate with medications, compared with 22.6% in organ transplantation (6). Earlier studies confirm this with 28% nonadherence in renal transplant recipients (7). The consequences of nonadherence are different for renal and lung transplant recipients. There is no dialysis equivalent for the loss of a lung graft.

However, in a study of heart, liver, and lung transplant recipients, lung recipients demonstrated a 15.9% nonadherence rate over two years (8). Nonadherence correlated with younger age at transplantation and a higher level of education. There was no difference on the basis of sex or marital status, and there was no difference in the depression scores of these patients compared with those of other chronically ill, non-transplant patients. In these and other studies, pretransplant nonadherence and medical treatment delinquency correlates with post-transplantation patterns of behavior and is therefore important to the candidate-screening process.

V. Psychiatric

There are well-established assessment instruments for depression, such as the Beck Depression Inventory, and for coping mechanisms for medical conditions, such as with the Medical Coping Modes Questionnaire. There are only a handful of such instruments that specifically address the transplant patient (9). The transplant process has unique stressors that span the time from identification of the need for a transplant through the evaluation period, to the listing and waiting period, when the potential recipient is by necessity waiting for the death of another individual. Post transplantation, there is not only the stress of a major operation but accompanying guilt and fear of rejection that persist. The clinical tools that have been used in the transplant setting are the Transplant Evaluation Rating Score (TERS) (10), Psychosocial Assessment of Candidates for Transplantation (PACT) (5), Heart Transplant Stressor Score (HTSS) (11), and recently for pediatric patients, the Pediatric Transplant Rating Instrument (12). One transplant center in the United States has begun to use a standardized tool across all solid organ transplants to help with psychosocial assessments, the Stanford Integrated Psychosocial Assessment Tool (personal communication). These tools have not been widely adopted or validated in their original forms but have focused attention on transplant-specific stressors in the psychosocial evaluation.

VI. Distributive Justice and Organ Allocation

The allocation of organs has historically been based on a "first come, first served" model. This model is flawed in that it does not give weight to utility arguments and is often structured to favor the worst off. One asserted benefit of such a system is that it is blinded to differences among potential recipients and therefore appears unbiased. This may not be true since this system fails to treat all as equals because of the differences in access to a transplant center, patient information, and geographic and medical biases in referral patterns. Recently, modifications in the organ allocation system were made on the basis of the patient's imminent death and projected post-transplant outcome, with priority given to the sickest patients with the best prognosis after transplantation. The problem with this approach is that it ignores one issue: transplant centers can circumvent this new rule by making patients who are "too sick" for transplantation inactive on the list. Unfortunately, there is no ideal, clinical and ethical, allocation system for lung transplantation. Nevertheless, the transplant community has begun revising standard allocation systems in efforts to help the greatest number of patients with the best projected outcomes, while simultaneously insuring maximum survival for those who are still waiting for their organs.

The first modification to lung organ allocation occurred in 1995 when patients with IPF were given an additional 90 days on the waiting list. At the time, allocation was determined solely by wait times, blood types, and region. This change was an effort to acknowledge the poorer prognosis and accelerated disease course of those with IPF,

compared to those with COPD and other pulmonary diseases. The Lung Allocation Score (LAS) (13) improved on this step and is consequently more equitable. The LAS was implemented in May 2005 in response to concerns that the previous allocation system, being the same for all diseases and patients, did not achieve the best outcomes. (Chapter 12 discusses the LAS comprehensively.) The LAS is based on the waiting list urgency measure, which is an estimate of the number of days lived without a transplant, and the post-transplant survival measure, which is an estimate of the number of days survived within one-year post transplantation. The transplant benefit is the difference between the two. The raw score is the difference between the transplant benefit and the waiting list urgency measure. One key feature of the LAS is that when it was enacted, there was a built-in review mechanism that was to occur three years after implementation, and would be repeated semiannually, so that new clinical and biometric parameters could be factored into the LAS score.

The practical implication of the LAS has been to decrease wait times, with 10% now receiving a transplant within 9 days of listing, and 25% within 31 days (14). There has also been decreased mortality on the waiting list and an increased number of transplants. Another unintended consequence has been the decreased need for living donors in the United States because of decreased wait times. The ethical implications of the LAS are less concrete but are nonetheless important. First, the LAS recognizes that there are important differences between potential recipients based on underlying physiology and pathophysiology of disease. Patients are unique and should not necessarily be treated the same. Equality does not necessarily lead to equity. The LAS also begins to address the issue of utility—who can best benefit from a given organ at a particular time. Utility in transplantation is complicated because one has to consider the question: are all saved lives equal? Is it the total number of life years or quality life years that we seek to prolong, rather than saving a particular individual's life? Utility in transplantation has focused on cumulative life-year utility because this is seemingly less affected by socioeconomic status and personal, behavioral characteristics.

One interesting consequence of the LAS system has been the reduced number of patients with COPD receiving transplants since the LAS is based on a complex physiologic scoring system. Unlike liver transplantation where there are no data to suggest that either the pretransplant or post-transplant course is affected by whether the underlying cause of liver failure is alcohol abuse (15), in lung transplantation, the obstructive diseases most linked to smoking have a better pretransplant course and therefore will have a lower LAS, and will be less likely to receive a transplant. Unwittingly, because of the natural history of COPD, there has emerged under the umbrella of pathologic considerations, an ethical acceptable "sin tax" against smoking. Simply put, former smokers who get COPD more often than IPF, are less likely to get transplanted under the LAS system.

VII. Donor Availability

The need for lungs continues to exceed the supply of organs, which places the responsibility for appropriate organ allocation in the hands of the physicians and transplant team. Allocation of these scarce resources to patients is part of transplant medicine and includes issues of evaluating potential donors, in addition to evaluating recipients, as discussed earlier. In lung transplantation there is also the further ethical question of single versus bilateral (or double) lung transplantation, which is an additional question of organ allocation.

A. Deceased Donor Organs

There is a chronic and worsening shortage of donors for all organs. This problem is especially severe for lung donors. Measures to increase the deceased donor supply in the United States and Europe have included "liberalizing" brain death standards, required request (United States), presumed consent (some European countries), use of "expanded criteria" donors, and donation after cardiac death (DCD). None of these efforts have succeeded in increasing the number of deceased donors. In the United States and Europe, deceased donors continue to provide the majority of organs, including lungs. But donor lungs are especially vulnerable to becoming "unusable" during the dying process. It is believed that only 18% of lungs from brain-dead donors were transplanted in 2006. Up to 81% were not recovered from donors (16) and 70% to 85% of lungs from organ donors may not be suitable for use (17). The reasons for this situation are many and include acute lung injury after brain death, pneumonia, and aspiration. The latter may be related to the fact that brain-dead donors are mechanically ventilated, which further increases the risk for pulmonary contamination. Reliance upon conventional deceased donors has not and will not meet the demands for lung transplantation.

DCD, or non-heart-beating donation (NHBD), is increasing for abdominal organs in the United States. While graft outcomes are less favorable for liver and kidneys compared with either living or brain-dead donors, they have cut down on the surplus of potential recipients. In lung transplantation, DCD is much less frequently used; in 2006, only 22 lungs were recovered from DCD donors according to the SRTR database. Importantly, lung preservation techniques do not require the premortem administration of heparin that has troubled some opponents of DCD donation. Additionally, with DCD, some programs re-intubate after cardiac death to aerate the lungs, which raises additional concerns about the ethics of DCD. However, the data suggest that the risk to the recipient for primary graft dysfunction is not greater than that of standard criteria (or brain dead) organ recipients (18). However, if the DCD donor was in an uncontrolled setting, meaning the donor was dead at presentation, or was unsuccessfully resuscitated, the one-year mortality was as great as 31% (17). "Controlled" DCD donation (Maastricht class III) does have good short- and medium-term survival, and therefore DCD donation may be an untapped source of alternative donors (19,20). In addition, there have been suggestions that DCD lungs may have lower levels of bacterial colonization (35% compared with 50% in brain-dead donors) because of shorter ventilation times (21). A recent study from the Netherlands suggested that up to 28% of lungs in DCD might be physiologically suitable for transplantation, whereas only 5% of lungs were procured (22). While awaiting long-term DCD data on rates of rejection, bronchiolitis obliterans, and survival, DCD should be considered as an alternative organ source for those patients who have a higher expected waiting list mortality.

B. Living Donor Organs

Since its first use in 1990 in the United States in a case involving living lung donation from a mother to a daughter, the use of living-related donors remains controversial in lung transplantation. The ethics of living donation are complex and bring to the fore issues regarding the benefit:harm ratio for the potential donor, questions of coercion or undue influence, whether informed consent is really obtainable, and the specter of organ markets. Organ procurement from a willing donor transforms a well person into a patient and has both accompanying harms and benefits for that individual. The benefits are most often psychological, from helping a loved one, but can also be financial if the loved one

is the primary wage earner of a family, for example. The harms are both physical and psychological. The estimated mortality associated with pneumonectomy is 1% to 3%. The minor complication rate for donors is 10% to 15%, and in some estimates includes morbidity of up to 50% (23). While much of these data are extrapolated from operative series of patients with lung cancer undergoing lung resection, they certainly present the range of possible risks to a donor. More recently, it has been suggested that only 20% of donors have perioperative complications (24). For most conditions, two donors are necessary, especially for those patients with CF who have better outcomes with a double lung transplant (DLT). Living donor transplants are still rarely performed. In 2007, there were only two living related lung transplants reported in the United States. In other countries, living lung donation is crucial for organ availability. Japan relies upon living donor lobar transplantation for two-thirds of their lung transplants (25). As noted, the implementation of the LAS has contributed to the decline of living donors in the United States.

The outcomes after living lung donation are varied, although the most extensive data come from a single center, the University of Southern California. Reporting on the first 123 patients receiving 128 lobes and using 253 donors, they had a 70% one-year, 54% three-year, and 45% five-year survival for the recipients, which is slightly lower than, but comparable to, the ISHLT registry (26). About 20% of their donors had at least one perioperative complication, but there were no donor deaths. The Japanese experience with living donor lobar transplantation is more successful with an 81% one-year recipient survival (25).

There has also been increasing awareness that the long-term consequences of living lung donation are not well characterized for either recipients or donors. This lack of knowledge is extensive. There are no robust donor registries comparable to the transplant registries that have provided the transplant community with a wealth of information. Donors often travel significant distances to the transplant center and are reluctant to return there for follow-up care. In addition, one of the hazards with living donation is that the recipient may die, and knowledge of this could cause psychological harm to the donor. Therefore, transplant centers may be reluctant to contact the living donor for long-term follow-up. The Ethics Statement of the Vancouver Forum on Live Lung, Liver, Pancreas, and Intestine Donor in 2006 suggested "centers should consider long-term access to health care after the procedure as a prerequisite for donation" (27). This recommendation has not been implemented widely. Prager et al. followed 20 living donors and showed that there was no significant increased rate of depression or decline in pulmonary function. However, 13/15 donors did not feel their medical follow-up was sufficient (28). Ethically, living donation is a question of a risk/benefit evaluation among two or three people. In living donation, the concept of double equipoise, including donor and recipient, has been proposed by Cronin et al. (29). It can often provide a possibility of life for those who are too ill to wait for cadaveric donation, but at what cost to donors?

VIII. Single Vs. Double Lung Transplantation

Lung transplantation with few exceptions, such as CF, can be either single (SLT) or double lung (DLT). The arguments for SLT are that it is an easier operation, associated with lesser short-term mortality. However, DLT may have benefits for long-term survival (30). Recently, studies have looked at the COPD and PF transplant populations to determine whether there is a survival benefit with DLT, but conflicting data remain with stronger data suggesting that in those with IPF there is no survival benefit with a

DLT (31–33). With the exception of recipients with CF, the increased use of SLT in place of DLT could maximize the number of transplant recipients while minimizing the number of deaths of those waiting, if both lungs are suitable and are used.

IX. Retransplantation

Retransplantation in lung transplantation represents a small number of transplants performed annually. When chronic graft dysfunction and bronchiolitis obliterans emerge, retransplantation is the only option. Survival rates are less than for primary lung transplantation, with 59% one-year and 32% five-year survival (34). Yet as the survival from lung transplantation improves, there will continue to be an increasing demand for retransplantation, which already has increased over the last decade from 2.5% to 5.9% of the total transplants (35). As with any organ retransplantation, this is a question of justice and fairness: should one person be given a second scarce resource at the expense of a second person who has not received a first organ? To whom does the medical profession and society have the most pressing duty, to the patient previously transplanted or to a new needy, potential transplant recipient? Of course, concerns about medical adherence to treatment regimens play a major role in retransplantation decisions, but is it "fair" to hold these failing transplantation patients to a higher standard of burden for transplant eligibility?

X. Heart-Lung Transplantation

The simultaneous transplantation of heart-lung has been declining, and in 2007, only 34 patients were on the waiting list in the United States. The ethical issues surrounding this type of transplantation are similar to that of other multi-organ transplantation; is there maximal utility of the organs? Is it ethical to distribute two scare resources to one person instead of two? Given the small and shrinking numbers of heart-lung transplantation, it is difficult to reliably ascertain survival and graft function measures for comparison with solitary lung transplantation. However, there are certainly suggestions that solitary heart transplantation outcomes are superior to heart-lung transplantation. For example, the one-year survival of heart-lung recipients is 71%, compared with one-year survival for heart only transplantation of 86% (1,36).

XI. Consent

Transplantation of any organ necessarily exchanges one set of health concerns for another. The problems of chronic pulmonary disease are exchanged for the possibility of immunosuppressant associated diabetes mellitus, or post-transplantation malignancies or infection. More immediately and less well characterized is the possibility of donor to recipient transmission of infectious diseases. The process of informed consent rests on the principle of respect for persons. It is designed to inform patients about the risks, benefits, and alternatives of procedures to allow them to make personal choices on the basis of their own values and preferences. What constitutes informed consent in daily practice often falls short of the mark. This is especially the case in transplantation where many nuances of both medical and psychiatric health are difficult to explain to patients and also difficult for patients to understand. The time-trade off decision in transplantation, potential downstream complications in exchange for the possibility of either improved life, or even of life itself is not as simple or straightforward as decisions made for other medical or surgical procedures.

XII. Conclusion

Lung transplantation faces several challenges. First, we must continue to strive for better outcomes for organ recipients, continuing the improvements in survival and quality of life achieved in recent decades. Second, we must increase the supply of organs for transplantation, by developing new strategies to retrieve a larger percentage of deceased donor lungs. This may mean developing organ-specific preservation solutions, or improving lung reconditioning techniques, or advancing the management of brain-dead donors to reduce potential injury to donor lungs. Finally, we must address the ethical questions that arise in lung transplantation. Is there adequate informed consent? Should there be greater formalization of the use of psychosocial criteria for transplantation? Are there ways to improve the economics of transplantation for the recipient? How can we most ethically allocate organs between new transplant candidates and those who require retransplantation?

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4
Structure and Support for Success

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I. Introduction

Lung transplantation, like many other solid organ transplantation, requires a dedicated multidisciplinary team and a wide variety of support personnel to be efficient and successful. However, there is very little information that exists regarding what structure or design a lung transplant program should have, and what type of support is required to be successful. In the United States, the United Network for Organ Sharing (UNOS) expects certain manpower and service requirements to be in place to be recognized as a lung transplant program, and programs are frequently audited for their performance (1). Similarly, to be certified by the Center for Medicare and Medicaid Services (CMS) for reimbursement, there are expectations that include minimum number of transplants performed and survival outcomes (2). Outside the United States few regulatory guidelines exist. This may be due to the structure under which health care is provided in these countries. Considering the continued growth of lung transplant programs around the world and because of the unusual and rigorous scrutiny solid organ transplantation programs are subject to, an effective design and efficient process is necessary to be successful. In this chapter, I will attempt to present the ways this could be achieved from current information available, common practices, and our personal experiences.

II. Design

Lung transplantation is the only available therapy for a variety of end-stage lung diseases that offers hope of prolonged survival and improved quality of life. In the United States, there are nearly three times more recipients waiting as available donors. A similar problem exists in other countries, perhaps to a lesser extent (3,4). Therefore, critical evaluation and management of potential lung transplant recipients is necessary. In addition, efficient utilization of the scarce donor organs in a fair and just manner is warranted, while minimizing the waiting time mortality and improving long-term outcome for the recipients.

Organizational effectiveness of any program is defined by the ability of the organization to produce the desired results in a timely, efficient, and cost-effective manner. Lung transplant patients require multispecialty expertise care across departments that can adapt readily to both internal and external changes. An organizational design that recognizes the interrelationship within and among organizational subsystems and the organization as a whole is therefore an essential requirement. There are several contemporary organizational designs available, such as a product line or service line design, matrix system design or network design, which rely on identifying strategic goals and interact across departments, albeit each to a different degree (5–8). These

types of designs provide more fluid structure, accommodate frequent changes in the internal and external environment, and maximize efficiency while achieving the identified goal. The service line design is defined as a comprehensive group of services specified by a diagnosis or procedure, ranging from prevention to rehabilitation. They tend to be decentralized with wide spans of control and employ rules through integration of departments. In the Matrix design, the identity of the departments is maintained while providing horizontal integration. The model establishes interdepartmental links with recognized lines of responsibility, facilitates communication, education, research, and training through committee structure. The network design is a hybrid model, relying on a core common knowledge base and independent expert teams that can respond autonomously to opportunities or problems. The faculty and staff maintain their appointments in their departments but create an entity (Transplant Center) that coordinates all clinical care and administrative function into one area. For patients, this offers the perception that the care is truly multidisciplinary at every level of clinical care, administration, and research. Any one of the above designs can be adopted for a lung transplantation program based largely on the local culture and climate. Also, once adopted, a particular design can evolve into another in response to internal and external forces.

III. Structure and Support

Since a lung transplant program is so complex, there is a heightened need to identify and obtain adequate contiguous space, *physical structure*, for the transplant team. The ideal program structure integrates surgeons, physicians, and the staff, physically in proximity within the hospital that brings the revenue and expenses together in one organization. The benefits of the administrative, clinical, and translational research staff to be in proximity include improved communication, added efficiency of operation, reduction in duplication of efforts, and improved synergy among team members. It is also necessary to develop a *financial model* to track and monitor revenue that transplant surgeons and physicians generate to the Hospital and the Departments of Medicine and Surgery. The relationship between the transplant physician and the hospital system is well presented in the article the "Down Stream Financial Effect of Hepatology," illustrating the importance and the necessary role of the hospital (9) supporting transplant medicine and surgery. It is also important that the Hospital and the Departments of Medicine and Surgery comprehend where their patients and source of revenue originate. Without this knowledge, it will be difficult to understand which services are actually making a positive financial contribution.

A successful program clearly defines the purpose of the effort. This means the *mission*, vision, and the goals of the program must be clearly articulated and widely understood keeping in alignment with the institution's mission, vision, and goals. There must be an understanding, alignment, and agreement among and between all key stakeholders. Trust between the leadership of the organization and the leadership of the transplant program is crucial (10,11). Job descriptions with measurable outcome indicators should be developed, and incentives for achieving these outcomes should be clearly defined. The transplant *personnel* consist of the leaders and the medical and surgical directors. They should have the time, resources, and authority to develop their program. Once the design and structure are in place, the aspect of the organizational effectiveness that separates the good from the great is the quality of its leadership. A key leadership quality lies in relationship management, which involves skills in building and

cultivating relationships across the organization. This type of activity is critical in helping the program achieve its goals and navigating through complex situations that frequently involve interactions with a wide spectrum of intense specialists.

The requirement for a successful lung transplant program is a dedicated multidisciplinary team and the ability to provide continuity of care for patients throughout. Many of these patients have a wide variety of issues peculiar to transplant in general, and a few specific to lung transplantation. The nature and urgency of these issues are very different, and the required approach and interventions are unlike a non-lung transplant patient. Basic understanding of these concepts by a well-structured support team is therefore imperative for success.

Additional faculty support for medical and surgical directors from their respective section is necessary to provide 24/7 coverage. The medical and surgical faculty should retain their academic homes, supported by physician extenders, who are essential to provide additional support in managing the various clinical issues during the workup, transplantation, in postoperative period, and follow-up. There are various types of physician extenders who can fulfill these roles. Who would best meet the requirements is mainly determined by the local culture and needs. The advanced nurse practitioners by nature are detailed in their approach. Typically clinical in nature, they are well suited to care for this complex patient population managing several parallel ongoing medical and social issues that need to be addressed and communicated. Physician assistants are by training more technical, procedure oriented, nevertheless detailed, and therefore best suited in the perioperative period, in assisting with the donor and recipient procedures, coordinating the surgery, and caring for these complex patients in the immediate postoperative period. Nurse coordinators work in conjunction with the physicians and physician extenders in providing support and facilitating patient-physician interactions. The roles can overlap and cross training is valuable to improve an individual's experience and provide necessary coverage for the program. Different support personnel for clinical services can be assigned responsibility for the pretransplant workup and post-transplant care. The surgical team generally takes responsibility for the transplant procedure and immediate transplant postoperative care. The medical team takes responsibility for the pretransplant workup and post-transplant follow-up. This division is arbitrary and a truly multidisciplinary approach is the best form for a program to be successful. The ideal staffing structure is one that achieves the goals and objectives, is efficient and cost effective, allows timely decision-making regarding operational and clinical issues, and supports the growth of the program. A comparative benchmark data is available from The UNOS in the United States from their staffing survey (Table 1) (12). This survey provides information that is helpful in developing manpower requirements in the future, which can be refined to fit internal culture and the size of the program. The information is from a national survey in the United States but does not necessarily reflect the ideal numbers. The number of clinical support personnel needed will depend on the size of the program, as well as the responsibility of the "transplant" physicians and surgeons to their nontransplant activities and the availability of other nonclinical support. The size of the program needs to take into consideration the number of transplants performed yearly, and the average number of patients evaluated and seen in the follow-up clinic as well as other institution specific issues such as other end-stage lung programs managed by the transplant personnel.

A transplant *database* enhances research, and data management needs to comply with internal and external regulatory requirements and for the quality assurance process.

Table 1 Staffing for Lung Program Performing <20 Transplant and >20 Transplants a Year in the United States

Staffing	Transplant # <20 (FTE)	Transplant # >20 (FTE)
Surgeons	1.6	1.5
Pulmonologist	1.9	2.4
Transplant coordinators	2.5	4
Physician extenders	1.3	0.7
Inpatient coordinator	0.5	0.3
Donor support person	0.3	0.2
Secretaries/Assistants	1.2	1.5
Social workers	0.9	0.8
Case manager	0.0	0.1
Financial coordinator	0.9	0.7
Data coordinator	0.4	0.4
Dietitian	0.4	0.4
Physical therapist	0.1	0.2
Respiratory therapist	0.1	0.6
Pharmacist	0.8	0.5
Administrative support	2.1	1.0
# Transplant (average)/yr	15	33.6
# Transplant evaluations/yr	70.5	101
# Added to waiting list/yr	20.5	44
Clinic visits pre and post/yr	600	1150

Information collated from UNOS, Transplant Administrators Committee Staffing survey based on 2007 data, Adult-only lung transplant programs. Note: only 27% of the centers (17/64) responded to the survey.

An effective working relationship with individuals in key areas of support, such as finance, billing, managed care, marketing, and human resource, is necessary. Many transplant-related ancillary staffs need to be under the direct control of the transplant administration, whether it is organ specific or under the umbrella of multiorgan transplant program. The ancillary staffs include but are not limited to: clerical staff, data entry and information system staff, social workers, dieticians, pharmacist, financial coordinators, billers, and contracting specialists. A time sheet will be needed and maintained for all the staff to account for time carrying out their work, some of which is not billable or apparent to the organization at large. Of utmost importance is the documentation of time spent in transplant activities by any and all parties; direct transplant expenses are reimbursable by medicare and provide a huge financial support for medicare approved programs. It is also important to understand the financial contribution and/or strain the transplant program places upon the institution.

IV. Clinical Effectiveness

Currently, there is consensus in the clinical arena regarding patient selection, transplant procedure, and postoperative management. There are also indicators that lung transplantation is economically favorable, even though this evidence is lacking in the literature. The clinical condition of potential lung transplant recipients can deteriorate while waiting for a suitable donor and requires close monitoring and updating. Available lung

donors, infection, acute cellular rejection, and chronic allograft dysfunction remain the major limiting factors for the growth of lung transplantation and are the main causes of morbidity and mortality. In addition, lung transplant patients are at increased risk of developing infections, renal dysfunction, diabetes, hypertension, and various malignancies that will require close follow-up. Transplant patients also experience a high incidence of psychological complications, including anxiety about rejection and infection, as well as depression. There is no doubt that these limitations demand a multidisciplinary collaborative input from dedicated personnel who have personal knowledge of the lung transplant process and practices. The operational effectiveness depends on how well the core collaborators fit and work together to make the operation successful. Constant communication ought to be maintained between team members regarding any significant change in the clinical condition of the patient. A weekly multidisciplinary transplant board meeting is an irreplaceable communication tool. It is an effective forum to discuss patients who are completing lung transplant workup, as well as patients who are in the process of ongoing workup and require feedback from various members of the team. This also provides an opportunity to obtain consensus regarding management of acute clinical changes of post-transplant patients. In addition, the multidisciplinary board meeting provides a platform for training and education.

The transplant process is complex; therefore, developing protocols and clinical pathways is essential to improve efficiency and consistency. We have observed that a postoperative clinical pathway can facilitate patient care following transplantation and reduce hospital length of stay significantly (13). Reduced hospital length of stay, in turn, reduces the cost associated with lung transplantation. Systematic and standardized processes need to be in place for patient workup, list maintenance, and communication algorithms. This is particularly critical in respect to the actual transplant procedure, as well as specific guidelines for treating rejection and infection. A quality improvement initiative to review the clinical and economic performance is essential. Opportunities for improvement are identified by the variances from protocols, clinical pathway, or benchmarks. A systematic periodic review and update of policies, procedures, and protocols is necessary as new evidence and experience are collected. They should also be updated on the basis of input from physicians, customers, leadership, and any individuals with vested interest. Recommendations can be based on the internally perceived ineffectiveness of various operations or on evidence gathered locally. In addition, the transplant administrative structure needs to cater to the market, define decision-making pathways, leadership roles, and degree of authority. It is critical to develop and implement a strategic plan, which includes developing and implementing marketing as well as an internal and external communication plan.

V. Summary

To be successful, the vision, the mission, and the goals of the institution and transplant program should be well aligned. Necessary support ought to be provided to the transplant leadership to develop the program and allow it to grow. Comprehensive financial management is necessary to capture all opportunities to enhance revenue and control expenses. Finally, a strong multidisciplinary team that is familiar with the protocols and clinical pathways developed by the transplant leadership to provide continuity of care is required. It is essential that the members of the program always incorporate good communication between personnel and possess accountability with an overlap in responsibilities.

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Appendix 1 Staffing and Support System

- Surgical
  - Surgeons: Surgical director and surgeons dedicated to lung transplant to provide cover 24/7
    - Pulmonary interventionalist
    - Physician assistants
  - Procurement coordinators/team
  - Anesthesia: Dedicated to cardiothoracic surgery and transplant programs
  - Perfusionists
- Medical
  - Pulmonologists: Medical director and pulmonologist trained in transplantation to provide cover 24/7
    - Pulmonary bronchocopist/interventionalist
    - Advanced practice nurses
    - Transplant nurse coordinators
  - Clinical director: Oversee staffing levels and qualifications. Maintain high-quality, cost-effective care. As cost containment and quality of care represent important objectives of all health care professionals
- Support Service Providers
  - Patient service coordinator: It is critical for someone to function in the navigator/care coordinator role to assist patients as they move through the transplant process, scheduling appointments etc.
  - Social services
  - Nutritionists
  - PT/OT rehab specialists
  - Financial counselors
  - Research coordinator
  - Clinic RN
  - Respiratory therapy
  - QA/data manager
- Subspecialty providers
    - Pathology: experienced lung histopahtologists
    - Infectious disease team
    - Endocrinology
    - Pharmacy service
  - Psychology/psychiatry
  - GI service, with interventionalist
  - PCP

5
Lung Transplantation for Idiopathic Pulmonary Fibrosis

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I. Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common idiopathic interstitial pneumonitis (IIP) and an increasingly frequent indication for lung transplantation (1). First described in 1872 by von Buhl as "cirrhosis of the lungs" (2), it is now recognized as a progressive, fibrotic process isolated to the lungs (3). Although we are learning much about its course, the primary cause remains unknown. No medical therapy has been shown to be beneficial, and recognizing this, most experts recommend no medical therapy outside of experimental trials. Even with the well-recognized risks and suboptimal outcomes, lung transplantation is the only therapy proven to improve and extend life for IPF patients (4). However, lung transplantation for IPF still remains a developing therapy with many important and controversial questions to be answered.

II. Background of Idiopathic Pulmonary Fibrosis

Although over 200 causes of interstitial lung disease (ILD) have been described, IPF is the most common ILD leading to progressive decline and lung transplantation. Figure 1 displays a differential diagnostic scheme that serves as a framework for the clinician while evaluating patient with ILD referred for lung transplantation. Although any end-stage ILD may benefit from lung transplantation, it is important to establish an accurate etiology of ILD whenever possible, for the following reasons (5).

First, some ILDs are treatable either by removing the causative agent or with medications, most frequently immunosuppressives. It is important to eliminate exposure to silica, asbestos, or one of the many organic or inorganic substances causing hypersensitivity pneumonitis. ILDs associated with systemic illnesses, such as connective tissue diseases (CTDs), are important to be recognized since medical therapy aimed toward the primary illness may improve or stabilize the pulmonary process (6–8). When the environmental exposure, systemic diseases, and genetic predisposition have been eliminated, the patient is labeled as having IIP. At that stage, the prognosis and treatment are dictated by the pathologic pattern demonstrated either on the surgical lung biopsy or as suggested by computerized tomography (CT) imaging (9). Although there is no universally accepted complete list of IIPs, usual interstitial pneumonia (UIP), nonspecific interstitial pneumonitis (NSIP), organizing pneumonia (OP), lymphocytic

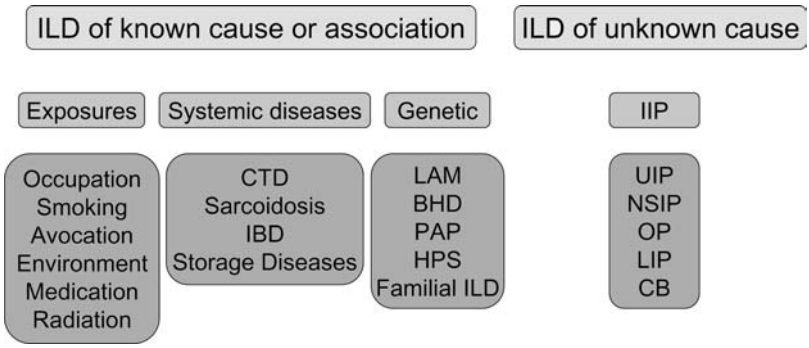

Figure 1 The numerous unrelated interstitial lung diseases can be organized by exposure, associated systemic illness, or ascribed to the idiopathic category and characterized by pattern of injury. *Abbreviations*: IIP, idiopathic interstitial pneumonitis; CTD, connective tissue disease; IBD, inflammatory bowel disease; LAM, lymphangioleiomyomatosis; BHD, Birt-Hogg-Dube; PAP, pulmonary alveolar proteinosis; HPS, Hermansky-Pudlak Syndrome; UIP, usual interstitial pneumonitis; NSIP, nonspecific interstitial pneumonitis; OP, organizing pneumonia; LIP, lymphocytic interstitial pneumonitis; CB, constrictive bronchiolitis.

Table 1 Characteristics of the Idiopathic Interstitial Pneumonitis

IIP	Age (yr)	Onset	Steroid responsive	Five-year survival
UIP	>50	Chronic	No	40%
NSIP	30–60	Subacute	Usually	75%
OP	30–60	Subacute	Usually	75%
LIP	30–60	Subacute	Usually	75%
CB	30–60	Chronic	No	Unclear

interstitial pneumonia (LIP), and constrictive bronchiolitis (CB) are most commonly included categories. These disorders present with indistinguishable symptoms of cough and dyspnea and only relative clinical differences as shown in Table 1.

Second, many ILDs other than IPF are associated with multiple organ involvement, which needs to be recognized both pre and post lung transplantation. Identification of the extent of the disease process prior to the transplantation allows additional treatment opportunities such as reducing aspiration-induced lung injury in the setting of scleroderma or treatment of pulmonary arterial hypertension in sarcoidosis and CTD-associated ILD. It also needs to be recognized that lung transplantation does not eliminate extra pulmonary manifestations of the systemic disease such as lymphangioleiomyomatosis (LAM) or CTD (10–15). Table 2 lists the most common extra-pulmonary manifestations in common non-IPF ILDs.

Finally, an accurate pretransplant diagnosis enables correct assessment of the various ILD courses and prognoses and the correct attribution of outcomes post lung transplantation allowing better decisions in the future.

Table 2 Common Extrapulmonary Manifestations in the Non-IPF ILDs

ILD	Extrapulmonary manifestation	Recurrence in graft
LAM	Angiomyolipoma of abdominal cavity, kidney, or liver Chyloperitoneum Lymphangioleiomyoma Lymphadenopathy Extremity lymphedema	Yes (16, 17)
Tuberous sclerosis-LAM	All of the above plus: CNS cortical tubers Facial angiofibromas Hypomelanic macules (ash leaf spots)	Potentially
Sarcoidosis	Central nervous system Small fiber sensory neuropathy Granulomatous liver disease Granulomatous renal disease Lupus pernio	Yes (18)
Scleroderma	Pulmonary arterial hypertension Esophageal dysmotility and aspiration Small bowel dysmotility Raynaud's disorder	No

III. Course of IPF in Relation to Lung Transplantation

Establishment of a firm pathologic description and accepted criteria for the diagnosis allowed clinical researchers to appreciate the heterogeneous course of IPF despite identical pathology. For unclear reasons, IPF progresses in a saltatory manner with significant number of patients having an acute exacerbation leading to death without antecedent physiologic change (19). Almost all patients have periods of disease quiescence, with stable or minimally worsening cough, lung function, and exercise tolerance. These periods can last from months to years. Recent large placebo controlled trials have demonstrated that approximately 70% of patients with initial mild IPF (FVC% > 50% and DLCO% > 35%) will have perfectly stable lung function, exercise tolerance, and quality of life over the following year. Unfortunately, the remainder of patients will either die or have significant disease progression defined as >10% drop in FVC% or >15% drop in DLCO% (20).

Fractionating patients at diagnosis or initial transplant assessment into those who will be stable, progress, or die has been evaluated in recent years. Two centers have followed large number of patients and shown that those with worsening forced vital capacity (FVC), 6-minute walk distance, or dyspnea will die more frequently in the coming 6 and 12 months (21,22). Although important to recognize in the evaluation of patients who are considering lung transplantation, the data is a tautology since it demonstrates those who are progressing are more likely to progress.

Nonclinical indicators of a higher risk of disease progression and death are currently the focus of much interest. Careful pathologic assessment using morphometry has shown that patients with more fibroblastic foci per area of lung tissue have a shorter survival (23,24), although other studies have failed to verify this finding (25). Analysis of CT images has demonstrated that those with predominant honeycomb cystic changes

rather than ground glass opacities also have shorter survival (26), and this has been seen in other ILDs such as hypersensitivity pneumonitis as well (27).

Biomarkers, either from the blood or bronchoalveolar lavage fluid (BALF), have even a greater promise to predict disease course, impacting several other aspects of lung transplantation. Elevated surfactant protein D in BALF and serum portends worse survival (28). KL-6, a glycoprotein released from proliferating alveolar type II cells is also elevated in patients most likely to worsen in future months (29). Although these findings are intriguing, they are not readily available and need to be confirmed outside of the authoring research centers.

Despite months or years of stability, almost all patients with IPF will experience worsening lung function leading to death in one of the two manners. First, approximately half of patients who die of their pulmonary illness will have moderately paced disease progression over several months—manifest with increasing cough, supplemental oxygen requirements, and exercise intolerance. The other half will have rapidly worsening lung function over the course of days to several weeks progressing from relatively preserved exercise tolerance to death. These events are termed acute exacerbations of IPF and occur in the absence of acute infection and pulmonary emboli. Such exacerbations are thought to be triggered by lung epithelial injury from aspiration of the gastric contents, surgery-associated positive pressure ventilation, or antecedent viral infection (19). Although approximately 50% of deaths caused by idiopathic pulmonary fibrosis occur in the setting of an acute exacerbation, the overall incidence is only 5% to 20% per year. Most worrisome is the unpredictable nature of these events, and that they can occur after months or years of stability, or in patients with preserved lung function and exercise tolerance.

The unpredictable and potentially catastrophic nature of IPF disease progression makes the timing of evaluation and listing for lung transplantation a difficult decision. Recent guidelines appropriately suggest discussing transplantation and a referral to a lung transplant center at the time of initial IPF diagnosis (30). This allows patients to comprehend the gravity of their diagnosis, and risks and benefits of lung transplantation, leading to an informed decision on when to pursue the transplantation.

The timing of performing pretransplant testing is dependent upon many factors and must be individualized. The presence of preformed reactive antibodies (PRAs) or any other identified comorbidity such as renal dysfunction, CTD, coronary artery disease (CAD), or any potential malignancy is promptly investigated and treated. The decision to list is individualized, but in general patients with exercise intolerance requiring greater than 4 L/min of supplemental oxygen with exertion or any supplemental oxygen at rest should have all testing completed and if appropriate, listing for lung transplantation.

IV. Comorbid Illnesses Associated with IPF and Their Relationship to Lung Transplantation

Although IPF is a pathologic process isolated to the lung parenchyma, it also presents with several extrapulmonary manifestations that can impact health pre and post transplantation. Several comorbidities occur owing to the generally advance age of patients and prior smoking. CAD is found more frequently in patients with IPF awaiting lung transplantation than other diseases, including COPD (31). The cause of this is unclear, yet likely related to age, male predilection, profound hypoxemia, and other unknown systemic effects of IPF. Thus, all patients with IPF, irrespective of their age, undergo left heart catheterization early in their evaluation. This allows pretransplant intervention with bare metal stenting or

planning for concomitant coronary artery bypass grafting (CABG), if required (12). Only bare metal stents are preferred since drug-eluting stents require use of clopidogrel for up to one year after the procedure to prevent in situ thrombosis (32). If the stenoses are not amenable to stent placement, single- or multiple-vessel CABG can be performed at the time of transplantation at selected centers. Importantly, the risk of CAD must not be overlooked post-transplantation and should always be considered in the differential diagnosis of dyspnea in lung transplant recipients for IPF.

For identical reasons, lung cancer is also seen with increased frequency in patients with IPF (33). At initial evaluation, CT imaging should be reviewed for lesions suspicious for pulmonary malignancy. Suspicious abnormalities should be investigated with combined PET/CT imaging. Patients with areas of concern should always have pathologic confirmation whenever possible. It is also to be noted that an area of dense fibrosis can mimic cancer and as many as 67% of patients with IPF may exhibit nonmalignant/nonspecific mediastinal adenopathy (34). In addition both of these radiographic mimickers of malignancy can demonstrate low-level activity on PET images (35). Post transplantation, single-graft recipients must be carefully observed for development of malignancy in the native lung.

Gastroesophageal reflux disease (GERD) has been recognized in association with IPF for over two decades (36). GERD symptoms are common in patients with IPF but have not been proven to be associated with disease worsening. Moreover, excepting anecdotal case series (37), acid suppression with proton pump inhibitors (PPI) has not been demonstrated to affect IPF progression. None of the placebo controlled trials for IPF have demonstrated benefit with PPI therapy on subset analysis of the placebo groups. This may be owing to ongoing damage from non-acid elements of gastric secretions despite PPI therapy or true lack of affect of aspiration on the course of IPF.

Although GERD treatment has not been proven to alter the course of IPF, its presence after lung transplantation increases risk of bronchiolitis obliterans (38). In selected patients, anti-reflux surgery such as fundoplication should be considered, either pretransplantation or in the early post-transplant period (39,40). In patients with ILD associated with CTD, esophageal dysmotility and dilatation can lead to macro-aspiration and episodic worsening fibrosis pretransplantation. The presence of esophageal dysfunction and dilatation in patients with previously diagnosed IPF prompts a thorough evaluation for extrapulmonary CTD involvement. Even if none are found, the association is strong enough that these cases should be reclassified as *forme fruste* CTD-associated ILD. Esophageal dysmotility and need for esophageal dilatation is currently considered as a strong contraindication to lung transplantation owing to the near certain development of post-transplant bronchiolitis obliterans syndrome (BOS) despite aggressive medical management. Resolving this contraindication with gastric fundoplication is difficult owing to the likely development of functional achalasia. Experimental surgical therapies such as laparoscopic Roux-en-Y gastric bypass are investigational and applicable to only highly selected individuals (41).

V. IPF and Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is recognized in impacting the course of the illness as well as that of lung transplantation in patients with IPF (42). When present, whether the PAH results from alveolar destruction and fibrosis (direct consequence of IPF) or is a separate pathologic process often remains unknown. The FVC and the degree of PAH in patients with IPF often do not correlate supporting the latter notion, which might be a

separate endothelial pathology. However, FVC is not a perfect marker of IPF severity as it is affected by many elements such as body habitus, concomitant obstructive lung disease, and respiratory muscle strength, making this argument inconclusive at best.

Regardless of this relationship, PAH is frequently detected in patients with IPF. Its existence must be assessed during the pretransplant evaluation to gauge severity of total impairment and urgency for enlistment. Precise pretransplant diagnosis of PAH requires right heart catheterization (RHC), which should be performed in all patients within three months of enlistment. Patients with very early fibrosis and minimal exercise intolerance who otherwise would not be placed on the transplant list should have RHC if non-invasive testing, such as echocardiogram or brain natriuretic peptide (BNP) levels, is found abnormal.

When present, PAH has significant pretransplant and post-transplant implications. Pretransplantation, IPF patients with PAH, whether demonstrated by RHC or elevated BNP, have significantly shorter survival. Evaluation and listing should not be delayed in these patients (43,44). Treatment of PAH in patients with IPF is of unclear benefit, although multiple trials with agents used to treat idiopathic PAH are underway. Importantly, the lung allocation score (LAS) will be increased by the presence of PAH, giving the patients preference for the procedure to reduce wait list mortality. IPF patients who are listed with deteriorating exercise tolerance should have repeat RHC performed to improve their odds of receiving organs.

Presence of PAH also affects the decision of single versus double grafts in IPF patients. Presence of secondary PAH is a risk for primary graft dysfunction (PGD), which results in severe postoperative hypoxemia owing to shunt through the remaining native IPF lung and may potentially reduce survival (45). Somewhat paradoxically, if the patient survives the post-surgical period, PAH in the native lung of single-graft recipients may be beneficial. Native lung PAH will force most pulmonary blood flow to the graft, reducing the likelihood of exercise desaturation from shunting through the native lung. On the contrary, in absence of PAH, patients undergoing single-lung transplantation for IPF may experience desaturation, which may or may not improve with supplemental oxygen therapy. We have experienced this phenomenon frequently in our practice, which needs to be scientifically substantiated.

VI. Controversies in Lung Transplantation for IPF

A. Single- vs. Double-Lung Transplantation for IPF

The decision of listing for single- versus bilateral-lung transplantation is complex one and based on imperfect data. Importantly, exercise tolerance and quality of life are equivalent for single- or bilateral-graft recipients (46,47). Data from a cohort prior to introduction of the United Network for Organ Sharing (UNOS) LAS showed those less than 60 years of age demonstrated improved 3-year survival for single- versus bilateral-graft recipients (48). The authors hypothesized that fewer surgical problems and less graft failure accounted for the improved single-graft survival in this age group. These data, coupled with the American Thoracic Society (ATS) guidelines recommending single-lung grafts for patients older than physiologic 60 years, an age which the majority of IPF patients exceed, point toward single grafts being offered to IPF patients. However, this prima facie conclusion of giving all IPF patients single grafts is starting to be challenged on several fronts.

First is the recognition that when all diseases are combined, double lung transplant have better five-year survival (Fig. 2), which is also seen when IPF patients are evaluated separately (Fig. 3). Data reported from our single-center demonstrates 55% five-year

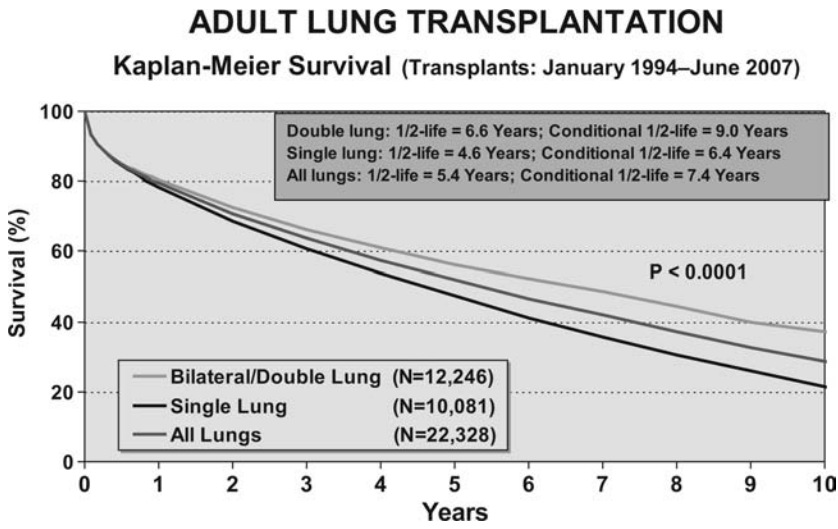

Figure 2 Kaplan–Meier survival by graft type for adult lung transplants performed between January 1994 and June 2007. Conditional half-life is the time to 50% survival for the subset of recipients who were alive one year after transplantation. *Source*: From Ref. 49.

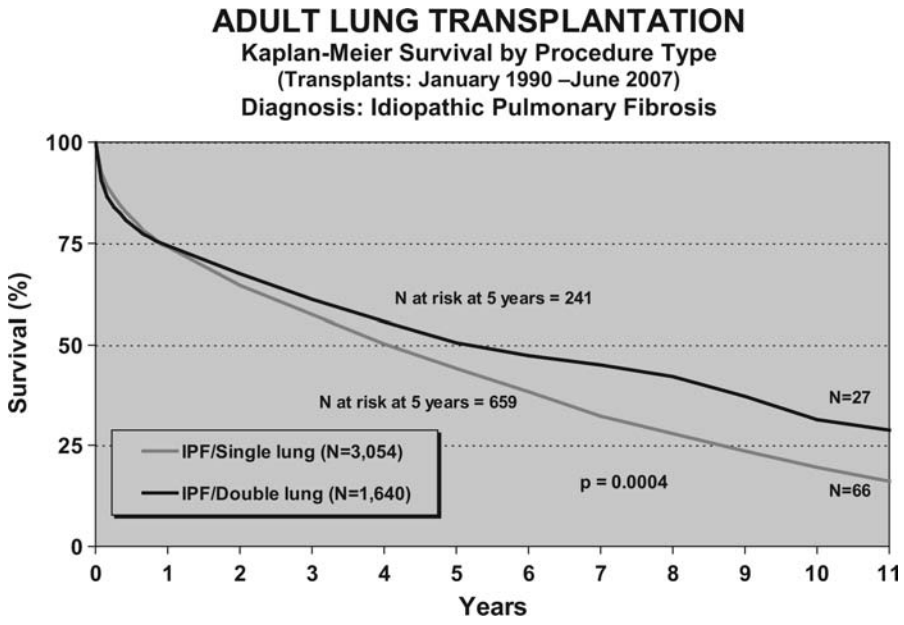

Figure 3 Kaplan–Meier survival for adult IPF patients receiving lung transplants between January 1990 and June 2007. *Source*: From Ref. 49.

survival for double compared with 34% for single-graft recipients (50). These data must be interpreted cautiously as it is tainted by severe selection biases as historically younger and healthier patients with fewer comorbid diseases were more likely to receive two grafts, and they would be more likely to survive longer than the older and sicker patients receiving one graft.

Second, fewer double-graft recipients will develop BOS compared with single-graft patients (51). Freedom from BOS may translate into prolonged survival, but studies have not looked at this in a rigorous manner yet. The mechanism is likely from an immunologic basis since a simple lead time bias from ablative protection of more graft volume would disappear over time. The mechanism of the reduced BOS is unknown, although the authors speculate that the larger graft volume may increase the likelihood of inducing graft tolerance.

We have also observed that the patients with single-lung transplantation for IPF continue to suffer more with dry cough, especially upon exercise, probably arising from the fibrosed native lung. In one instance, a patient required a pneumonectomy as a palliative measure. Once again, this phenomenon needs to be scientifically substantiated.

Unfortunately, double-lung transplantation compared with single-lung transplantation is not without risk or cost. Increased risk is seen both pretransplant and at the time of surgery. Waiting time is longer for two grafts, increasing the risk of death for this disease with unpredictable and rapid decompensation leading to death. Analysis of U.S. transplant data shows that the prolonged wait and increased numbers of deaths while waiting for two grafts counteract the potential survival benefit of receiving two grafts, even with the LAS determining priorities (Dr. S. Nathan, Fairfax, VA, personal communication). Additionally, bilateral surgery is more likely to require cardiopulmonary bypass during the procedure with increased risk of bleeding and post-surgical cardiac dysfunction in this elderly group. Finally, bilateral grafts reduce the number of potential recipients possible with single grafts, leading to more waiting list deaths. With this conflicting data, our center performs single-lung transplantation on patients above 60 years of age without pulmonary hypertension and double-lung transplantation for patients less than 60 years of age and for older patients with PAH, but otherwise in good health. A randomized, multicenter trial is needed, but likely to never occur owing to ingrained bias.

B. Age and Transplantation for IPF

Owing to the age-enhanced hazards of transplant surgery and lifelong immunosuppression, the American Thoracic Society recommends upper age limits for each type of lung transplantation. These expert recommendations are based upon the observed poorer survival for lung transplant recipients starting at age 50 and exponentially increasing with age (Fig. 4). Their recommendations suggest chronologic limits of 55 for combined double-lung and heart recipients, 60 for double-lung recipients, and 65 for single-lung recipients. Recognizing patient variability, these recommendations are not expected to be followed strictly, rather they are suggested extremes on the basis of physiologic age. Numerous centers have extended these limits, especially in advanced age patients without comorbidities, considering them of younger physiologic age. In carefully selected patients, these centers attempt to achieve standard survival and quality of life (52). The absolute upper limit of chronologic age has not been defined, but patients older

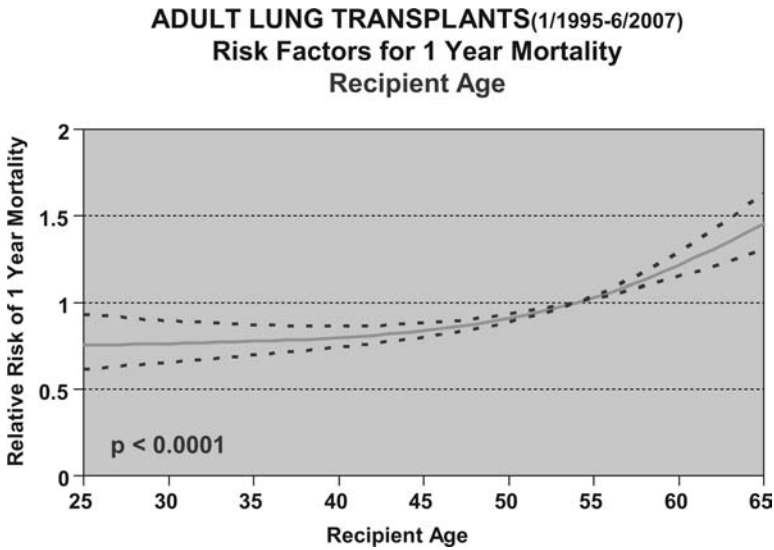

Figure 4 Association of recipient age with the relative risk of death within one year after transplantation for adult lung transplants performed between January 1995 and June 2007. *Source*: From Ref. 49.

than 70 should be transplanted with great caution and awareness that they may have increased risk of poor outcomes based solely on age (53). Recognizing this, patients older than the suggested limits should be referred to centers experienced in transplanting those with advanced chronologic age.

C. Transplantation of the Severely Ill Patient with IPF in the LAS Era

Prior to implementation of the LAS system, IPF patients who were extremely ill or worsening from an acute exacerbation of IPF that required hospitalization, mechanical ventilation, or extracorporeal membranous oxygenation almost always died before they could be evaluated, enlisted, and have organs allocated to them. The LAS allows experienced centers to evaluate, list, and receive organs for these extremely ill patient during this brief window. Although it was not the primary goal of the LAS, several centers have reported successful transplantation in this tenuous group of patients (54). However, these extremely ill patients, when defined as LAS > 46, have poorer one-year survival compared with less ill IPF patients (Fig. 5) (55). Whether the LAS should be modified to discourage the use of grafts in this high-risk population allowing others with a better chance of survival to receive grafts is controversial. Current recommendation is to transfer such high-risk patients requiring advanced life support techniques to centers with experience in their pretransplant management and intra-operative complexities.

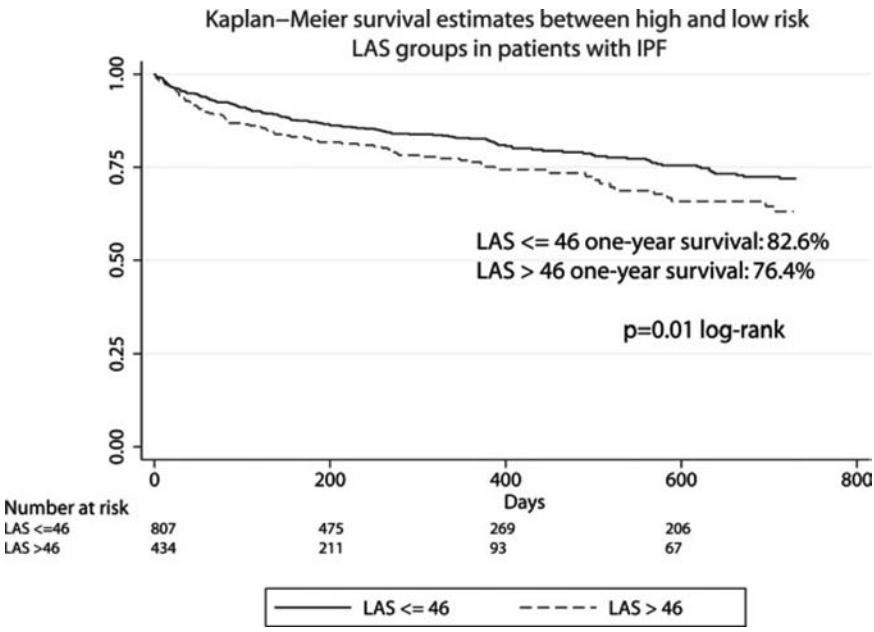

Figure 5 Kaplan–Meier survival estimates between high and low risk. LAS groups in patients with IPF. *Source*: From Ref. 55.

VII. Conclusion

Lung transplantation for IPF is a proven life-extending therapy that achieves improved survival and quality of life in properly selected patients. However, lung transplantation for IPF is hampered by advanced patient age and comorbidities. Most problematic is the unpredictable nature of IPF; in that many patients, even with moderate or severe disease, can have months to a year or two of stable lung function and good survival rates, while others with the same initial degree of impairment will decline within weeks' time and die. Patients with IPF who are physiologically less than age 65 should be referred to a transplant center soon after diagnosis. Despite being an accepted therapy, lung transplantation for IPF has several controversial aspects. Optimal treatment of patient at advanced age, the need for pretransplant life support, and determination whether one graft or two achieves better long-term survival are current controversies requiring future assessment.

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6
Emphysema and α-1 Antitrypsin Deficiency

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I. Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease affecting millions of individuals. Its estimated prevalence ranges from 7% to 19% worldwide. COPD has become the fourth-ranked cause of death in the United States, killing more than 100,000 individuals each year. COPD is associated with impaired physical function, reduced quality of life, an increase in healthcare resource utilization, including frequent physician office visits and hospitalizations because of acute exacerbations, and chronic medical and oxygen therapy (1). Only 15% to 20% of smokers develop COPD, although the majority will develop some degree of airflow obstruction (2). Despite this, COPD remains underdiagnosed (3). Pathologic manifestations of COPD include small airway inflammation (bronchiolitis), lung parenchymal (alveolar) destruction, and loss of the pulmonary capillary bed. Physiologically, these lead to a loss of elastic recoil resulting in airflow limitation and hyperinflation leading to increased work of breathing and dyspnea. An important, underrecognized cause of emphysema is α-1 antitrypsin deficiency, an autosomal codominant disorder because of insufficient production or secretion of α-1 antitrypsin.

Systemic manifestations of COPD include loss of muscle mass and function, depression, anemia, osteoporosis, pulmonary hypertension, and cor pulmonale. It is important that physicians recognize and diagnose COPD early as appropriate management is effective to prevent disease progression and decrease dyspnea, reduce the frequency and severity of exacerbations, and improve exercise capacity. Medical therapy includes drugs, pulmonary rehabilitation and exercise regimens, and the use of supplemental oxygen. With the exception of continuous oxygen use, these forms of therapy have a limited effect on quality of life and survival in these patients. This lack of response to medical therapy has resulted in the development of surgical therapy for the treatment of emphysema (4). These techniques will be discussed in a subsequent chapter.

II. Definition

The *G*lobal Initiative for Chronic *O*bstructive *L*ung *D*isease (GOLD) report produced by the World Health Organization (WHO) and the National Heart, Lung, and Blood Institute (NHLBI) defines COPD as follows (5): "*Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.*" Earlier definitions have distinguished different types of COPD

(emphysema, chronic bronchitis, asthma), a distinction that is not included in the GOLD definition (6–8). While the remainder of this chapter will only discuss emphysema it is important to recognize that substantial overlap exists among the types of COPD. That is, chronic bronchitis and emphysema with airflow obstruction or emphysema with reactive airways disease (asthma) commonly occur together. This overlap may have important implications when evaluating patients with emphysema for lung volume reduction surgery (LVRS) or lung transplantation (4).

III. Clinical Features

A. History

Patients with emphysema typically present in one of three ways. Some are mildly symptomatic but may lead a sedentary lifestyle because of decreased exercise capacity (9). Others present with dyspnea on exertion or cough while others present with an acute exacerbation characterized by increased dyspnea, wheezing, or cough with or without fever. Dyspnea initially occurs only with exertion but eventually becomes more noticeable with progressively less activity or even at rest. The chronic cough is characterized by the slow onset of morning sputum production, which may progress to occur throughout the day. The sputum is typically mucoid, but may become purulent during acute exacerbations that can be incorrectly diagnosed as asthma particularly when associated with wheezing. Conversely, other illnesses such as congestive heart failure, bronchiolitis, or bronchiectasis are often incorrectly diagnosed as COPD exacerbations. Exacerbations become more frequent and life-threatening as the severity of the COPD increases.

B. Physical Examination

The physical examination of the chest varies with the severity of emphysema. Early in the disease, the physical examination may be normal, or may show prolonged expiration and wheezing on forced exhalation. As the degree of the airway obstruction progresses, the physical examination reveals hyperinflation, decreased breath sounds, wheezing, crackles at the lung bases, and/or distant heart sounds (10). In advanced severe disease, diaphragmatic excursion may be depressed or limited in its motion, and the anteroposterior diameter of the chest may be increased. With end-stage emphysema, patients typically lean forward with their arms outstretched and weight supported on the palms to improve the sensation of dyspnea. They use their accessory respiratory muscles of the neck and shoulder girdle, develop pursed lip breathing, and may develop paradoxical retraction of the lower interspaces during inspiration. In far-advanced disease, patients develop cyanosis, asterixis because of severe hypercapnia, and signs of right heart failure.

IV. Diagnosis

The diagnosis of COPD should be suspected in all patients who report any of the following: chronic cough, chronic sputum production, dyspnea at rest or with exertion, or a history of inhalational exposure to tobacco smoke, occupational dust, or occupational chemicals (5,11).

A. Pulmonary Function Tests

Pulmonary function tests (PFTs) are the gold standard for the diagnosis of COPD in those patients who have the features described in the preceding text. PFTs are used to

diagnose COPD, determine the severity of the airflow obstruction, and follow disease progression or the response to therapy. The key parameters measured are the forced expiratory velocity in one second (FEV_1) and the forced vital capacity (FVC). COPD is confirmed when a symptomatic patient is found to have airflow obstruction (FEV_1/FVC ratio < 0.70) and other etiologies associated with airflow obstruction have been excluded. Reversibility, or a reactive airways component is defined as a more than 20% increase in FEV_1 after bronchodilators.

In addition to the FEV_1 and FVC, lung volumes are also determined from PFTs. Lung hyperinflation is characterized by a decrease in inspiratory capacity and vital capacity, accompanied by an increase in total lung capacity, functional residual capacity, and residual volume. Air-trapping is defined as an isolated increase in residual volume. The single breath carbon monoxide diffusing capacity (DLCO) decreases in proportion to the severity of emphysema secondary to loss of the pulmonary capillary bed. The FEV_1, degree of lung hyperinflation and DLCO and degree of reactive airways disease along with exercise capacity are the prime determinants of eligibility for LVRS or lung transplantation.

B. Imaging Studies

Chest Radiography

Plain chest radiographs have poor sensitivity for detecting COPD—only about half of patients with moderate COPD are identified by a plain chest radiograph. Radiographic features suggestive of COPD include rapidly tapering vascular shadows, increased radiolucency of the lung, a flat or inverted diaphragm, a long, narrow heart shadow on a frontal radiograph and an increased, retrosternal airspace on a lateral radiograph. These findings are diagnostic of lung hyperinflation. Bullae are defined as radiolucent areas larger than one centimeter in diameter and may be due to confluent, local severe emphysema and may or may not be accompanied by widespread emphysema. Giant bullae occupy greater than 1/3 of the hemithorax and may be targets for surgical excision in selected patients (4). Pulmonary artery enlargement and encroachment of the heart shadow into the retrosternal space are seen with pulmonary hypertension and cor pulmonale.

Computed Tomography

Computed tomography (CT) has greater sensitivity and specificity than standard chest radiography for the detection of emphysema. CT can determine whether the emphysema is homogeneous or heterogeneous in distribution and whether it is centriacinar or panacinar. Centriacinar emphysema occurs in the upper lobes, producing holes in the center of secondary pulmonary lobules. Panacinar emphysema more commonly involves the lung bases and involves the entire secondary pulmonary lobule and can cause a generalized loss of vascular structures. CT plays an important role in evaluating emphysema patients for LVRS (4).

Arterial Blood Gases

Early in the course of emphysema, arterial blood gases (ABGs) reveal mild or moderate hypoxemia without hypercapnia. ABG abnormalities may also worsen during exercise and sleep or during acute exacerbations. As the disease progresses to an $FEV_1 < 1$ L/sec, hypoxemia becomes more severe and hypercapnia develops. The degree of hypercapnia may have important ramifications on eligibility for LVRS.

Cardiac Studies

Echocardiography or cardiac catheterization is not typically indicated in the evaluation of the patient with COPD. Both can be utilized to rule out cardiac comorbidity in patients with COPD or in the evaluation of patients with dyspnea without readily apparent or mild pulmonary disease. Echocardiography and/or cardiac catheterization are routinely employed in the evaluation of the emphysema patient considered for LVRS or lung transplantation. Evidence of moderate to severe pulmonary hypertension is considered a contraindication for LVRS and likely identifies patients more appropriate for lung transplantation (4).

V. α-1 Antitrypsin Deficiency

α-1 Antitrypsin (AAT) deficiency is a disorder primarily affecting the lung and liver and rarely the skin. AAT is an inhibitor of the proteolytic enzyme elastase (12). At least 100 alleles of AAT are identified and given a letter code based on electrophoretic mobility. They have been categorized into four basic groups: (*i*) M alleles are associated with normal AAT levels and normal function. This normal phenotype is designated MM. (*ii*) Z alleles are associated with AAT levels less than 35% of the average normal level. This allele is carried by approximately 2% to 3% of the Caucasian U.S. population. The deficient phenotype is designated ZZ. (*iii*) Null alleles lead to no detectable plasma AAT levels. These patients have the most severe form of the disease. (*iv*) Dysfunctional alleles produce normal quantities of AAT protein but the protein does not function properly. Population studies suggest a minimum plasma threshold of 50 to 80 mg/dL, below which there is insufficient AAT to protect the lung, leading to a risk of developing emphysema. Most patients below this threshold level have the PI*Z phenotype (i.e., homozygous PI*ZZ) (13,14). Although AAT deficiency is considered rare, estimates suggest that 80,000 to 100,000 people in the United States have severe AAT deficiency, and that the disease is under-recognized (15,16). It is estimated that more than 3 million people worldwide have allele combinations associated with severe deficiency (17). Unrecognized individuals with severe AAT deficiency probably comprise two separate groups: those with no clinical manifestations and those with disease in whom the underlying AAT deficiency has not been diagnosed. The relative proportion of these groups are unknown. Two recent surveys (15,16) demonstrate that the delay between the first symptom and recognition of AAT deficiency has not decreased over the years, indicating that under-recognition persists despite extensive educational efforts and the publication of evidence-based guidelines for diagnosis and management of AAT deficiency (13). The availability of specific therapy for AAT deficiency makes it imperative that patients with persistent airflow obstruction by spirometry or other characteristics be tested (Table 1) (13). As noted earlier, the diagnosis of severe AAT deficiency is confirmed by demonstrating an AAT level below 50 to 80 mg/dL (11 μmol/L) in combination with a severe deficient genotype.

Table 1 Characteristics Suggesting α-1 Antitrypsin Deficiency

Emphysema in young patients (age $\leq$45 years)
Emphysema in a non-smoker or minimal smoking
Emphysema characterized by predominant basilar changes on chest X ray
Family history of emphysema or liver disease
History or clinical presentation of panniculitis
History or clinical presentation of unexplained chronic liver disease

In the lung, severe deficiency of AAT predisposes to emphysema, especially panacinar emphysema. Some series also report an association of AAT deficiency with bronchiectasis and/or asthma, but these associations have not been as firmly established (18). Emphysema because of AAT deficiency is thought to result from an imbalance between neutrophil elastase in the lung, which destroys elastin, and the elastase inhibitor AAT, which protects against proteolytic degradation of elastin. AAT deficient patients may present unique challenges to the choice of LVRS or lung transplantation (4). It is recommended to check AAT levels on all patients with obstructive lung disease.

VI. Staging

The FEV_1 (expressed as percent predicted) is often used to stage disease severity. The FEV_1/FVC ratio is not used for this purpose because measurement of FVC becomes less reliable as the disease progresses (the long exhalations are difficult for the patients) or patients age.

Different clinical practice guidelines use different cut-off values, but most are similar to the GOLD staging system (Table 2) (5). Patients with stage I or mild COPD typically have a chronic cough with or without sputum production and are usually unaware they have abnormal lung function. Those with stage II or moderate COPD have a cough with or without sputum production and shortness of breath with exertion. Because of their symptoms or an acute exacerbation these patients typically come to medical attention in this stage. Patients with stage III or severe COPD have worsening airflow limitation resulting in increased shortness of breath, decreased exercise capacity, and recurrent exacerbations. Those with stage IV or very severe COPD may develop respiratory failure evidenced by severe hypoxemia or hypercarbia and exacerbations may be life threatening. These patients may be considered for evaluation for LVRS or lung transplantation.

The FEV_1-based staging system has been criticized for underestimating the importance of the extrapulmonary manifestations of COPD in predicting outcome. The BODE index addresses this criticism (Table 3). The four factors included in the BODE index are weight (body mass index), airway obstruction (FEV_1), dyspnea (Medical Research Council dyspnea score), and exercise capacity (6-minute walk distance). This index provides better prognostic information than the FEV_1 alone and can be used to assess a therapeutic response (19–22).

Table 2 Classification of Emphysema Severity Based on Post-Bronchodilator FEV_1

Stage I: Mild	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted
Stage II: Moderate	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted
Stage III: Severe	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ predicted
Stage IV: Very severe	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ with $PaO_2 < 60$ mmHg with or without $PaCO_2 > 50$ mmHg breathing room air at sea level

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide.

Table 3 The Body Mass Index, Degree of Airflow Obstruction and Dyspnea and Exercise Capacity (BODE) Index: Variables and Points Used for Its Calculation

	Points on the BODE index			
Variable	0	1	2	3
FEV_1 (percent of predicted)	≥65	50–64	36–49	≤35
6-minute walk distance (m)	≥350	250–349	150–249	≤149
MMRC dyspnea scale	0–1	2	3	4
Body mass index	>21	<21		

FEV1, forced expiratory volume in 1 second; m, meters; MMRC, modified Medical Research Council.

VII. Management of Stable COPD

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends that pharmacologic and nonpharmacologic therapies should be added in a stepwise fashion to control symptoms, decrease the frequency and severity of exacerbations, and improve health status, exercise function, and quality of life (5). It is important to monitor symptoms (e.g., dyspnea, exercise tolerance, cough, sputum production), airflow (i.e., spirometry), the amount of as-needed medication use, and the frequency of exacerbations to determine whether the patient has achieved an adequate response to therapy.

The cornerstone of drug therapy for stable COPD patients are bronchodilators, primarily β-agonists and anticholinergics, and inhaled glucocorticoids. These are generally administered via metered dose or dry powder inhalers and are given alone or in combination depending on the severity of disease and response to therapy. Patient education about the purpose and dosing of medications, timing of short-acting bronchodilators prior to exertion, and instruction as to the proper inhaler technique is essential. Short-acting β-agonists include *albuterol*, *levalbuterol*, and *pirbuterol*. They have been proven in randomized controlled trials and meta-analyses to improve symptoms and lung function (23). Short-acting anticholinergic medications such as ipratropium have been shown to improve lung function, increase exercise capacity, decrease dyspnea, and decrease cough (24). Albuterol and ipratropium have been compared in randomized controlled trials (25–27) and on average, both medications improve lung function to a similar degree. Side effects are unique to each medication class but are minimal at commonly prescribed doses. The degree of bronchodilation achieved by short-acting β-agonists and anticholinergics is additive but combination therapy did not alter the frequency of exacerbations (25).

Short-acting bronchodilators alone or in combination may be insufficient to control symptoms particularly in patients with advanced stages of emphysema. Either a long-acting β-agonist (LABA) or a long-acting anticholinergic are effective. In general, a long-acting anticholinergic is preferred over long-acting β-agonists because most of the effects of the currently available once daily anticholinergic appear to be superior to the twice daily β-agonists that are available for use. LABAs include salmeterol, formoterol, and arformoterol. Multiple studies have demonstrated their benefit in patients with stable COPD (28). The long-acting anticholinergic medication, tiotropium, improves lung function and decreases dynamic hyperinflation, while also decreasing dyspnea and exacerbations (29). In addition, it improves trough airflow (24 hours after

the last dose) and reduces hyperinflation, indicating that its effects are long-lasting (30). Tiotropium may slow the rate of decline in FEV_1. Conflicting evidence has been reported regarding possible adverse cardiovascular effects of anticholinergic therapy in patients with COPD; however, data from a long-term, randomized trial [Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT)] support its safety (31).

Some regimens used in the past are now rarely used. Theophylline, which is only a modestly effective bronchodilator and has more side effects than other bronchodilators, is occasionally used for patients with refractory COPD. Systemic glucocorticoids have long been used for treatment of COPD exacerbations; however, their chronic use can have significant adverse effects and has been associated with an increase in morbidity and mortality (32,33). Therefore, long-term systemic glucocorticoid therapy is not recommended, even for severe COPD. In the uncommon circumstance when they are occasionally used, systemic glucocorticoids should be reduced to the lowest dose possible. Despite the presence of thick secretions, oral expectorants (e.g., guaifenesin, iodides) offer little benefit to patients with COPD (34). Acetylcysteine reportedly thins the secretions of patients with chronic bronchitis. However, it has no effect on airflow or sputum volume and may induce significant bronchoconstriction when given by inhalation. Studies looking at the value of oral acetylcysteine as an antioxidant therapy for COPD were negative (35). Other mucolytic agents include dornase alfa (DNase), exogenous surfactant, various proteolytic agents, and various detergents. These agents require additional study prior to their routine use in patients with COPD. Chronic antibiotic therapy is without benefit in most patients with stable COPD, but there are some exceptions. Patients whose COPD is due to, or associated with, bronchiectasis may benefit from chronic antibiotic therapy.

Many supplemental therapies are important in the management of stable COPD. Many patients with stable severe COPD (especially GOLD Stage IV) have chronic hypoxemia, and it is important to detect this as long-term oxygen therapy improves survival and quality of life in hypoxemic patients with COPD (36–38). Improved survival may be due, in part, to improved pulmonary hemodynamics. Long-term continuous oxygen therapy should be prescribed for all patients with COPD with chronic hypoxemia. Pulmonary rehabilitation, nutrition, and smoking cessation also play an important role in the management of COPD. Clinician advice and encouragement, nicotine replacement therapy, bupropion, varenicline, and counseling have been shown to be effective cessation techniques. The best cessation rates are achieved when counseling is combined with medication therapy. Nonimmunized patients with COPD who are at high risk for contracting influenza and/or have early acute influenza infections may benefit from antiviral therapy. Pneumococcal polysaccharide vaccine should be offered to patients with COPD who are $\geq$65 years old, or who are younger than 65 years with a forced expiratory volume in one second (FEV_1) less than 40% (5). An annual influenza vaccine should also be given to all patients with COPD.

VIII. Management of Acute COPD Exacerbations

It is estimated that 50% to 60% of exacerbations are due to respiratory infections (mostly bacterial and viral), 30% are of unknown etiology and 10% are associated with environmental pollutants (39). Other medical conditions mimic or cause COPD exacerbation including myocardial ischemia, heart failure, pulmonary embolism, or aspiration (5). The patient must be triaged to inpatient or outpatient management following initial

evaluation. Criteria for hospitalization (40) include an inadequate response of symptoms to outpatient management, a marked increase in dyspnea, an inability to eat or sleep due to symptoms, worsening hypoxemia and/or hypercapnia, an altered mental status, the inability to care for oneself (lack of home support), an uncertain diagnosis or the presence of high risk comorbidities including pneumonia, cardiac arrhythmia, congestive heart failure, diabetes mellitus, renal failure, or liver failure. There is general consensus that acute respiratory acidosis justifies hospitalization.

The goals for the successful management of acute COPD exacerbations (41) are (*i*) to identify and ameliorate the cause of the exacerbation, if possible; (*ii*) to optimize lung function by bronchodilators and other pharmacologic agents; (*iii*) to assure adequate oxygenation and secretion clearance; (*iv*) to avert the need for intubation; (*v*) to prevent complications associated with immobility, such as thromboemboli and deconditioning; and (*vi*) to address nutritional needs. Supplemental oxygen is a crucial component of acute therapy. An arterial oxygen tension (PaO_2) of 60 to 70 mmHg should be targeted, with an oxygen saturation of 90% to 94% (5). Most acute exacerbations of COPD do not require high FIO_2 to correct the hypoxemia. The inability to correct hypoxemia with a relatively low FIO_2 should prompt consideration of an alternative diagnosis such as pulmonary emboli, acute respiratory distress syndrome, pulmonary edema, or severe pneumonia as the cause of respiratory failure. Adequate oxygenation must be assured, even if it leads to acute hypercapnia that is generally well tolerated in patients with a chronic elevation in arterial carbon dioxide tension ($PaCO_2$). The development of depressed mental status, profound acidemia, or cardiac dysrhythmias may warrant the institution of mechanical ventilation.

The major pharmacologic treatments for managing an acute exacerbation of COPD include inhaled short-acting bronchodilators, either β-adrenergic agonists or anticholinergic agents, glucocorticoids, and antibiotics (41). Inhaled short-acting β-adrenergic agonists are the cornerstone of therapy for acute COPD exacerbations because of their rapid onset of action and efficacy to produce bronchodilation (42). Despite evidence that a metered dose inhaler may have equal efficacy during acute exacerbations of COPD, many clinicians prefer to use nebulizers on the presumption they have more reliable delivery of drug to the airway (5). Inhaled short-acting anticholinergic agents are often combined with inhaled short-acting β-adrenergic agonists to treat exacerbations of COPD (5). This is based on several studies that found that combination therapy produces bronchodilation in excess of that achieved by either agent alone in patients with a COPD exacerbation, an asthma exacerbation, or stable COPD.

Systemic glucocorticoid therapy improves lung function and treatment success, while reducing the length of hospital stay (43). Intravenous glucocorticoids should be given to patients who present with a severe exacerbation, who have responded poorly to oral glucocorticoids, who are vomiting, or who present with shock. Oral glucocorticoid administration is used in most other patients as they are rapidly absorbed and their efficacy is comparable to that with intravenous therapy. The optimal dose of systemic glucocorticoids for treating a COPD exacerbation is unknown (5) but typical dosing is either methylprednisolone (60–125 mg, two to four times daily) or prednisone (40–60 mg orally, once daily). The duration of systemic glucocorticoid therapy varies by patient and from exacerbation to exacerbation. Most exacerbations are treated with full dose therapy for 7 to 10 days (5). The efficacy of inhaled glucocorticoids on the course of a COPD exacerbation has not been studied in randomized trials. Thus, they are not recommended for use as a substitute for systemic glucocorticoid therapy.

Several other therapies have been utilized for the treatment of COPD exacerbations. Antibiotics are indicated for many patients having a COPD exacerbation. There is little evidence supporting the use of mucolytic agents (e.g., *N*-acetylcysteine) in acute exacerbations of COPD as some mucolytic agents may worsen bronchospasm. Aminophylline and theophylline are not recommended for the treatment of acute exacerbations of COPD as randomized controlled trials of intravenous aminophylline have failed to show efficacy beyond that induced by inhaled bronchodilator and glucocorticoid therapy (42).

IX. Surgical Therapy for Emphysema

Carefully selected patients may benefit from LVRS or lung transplantation (4). These will be discussed in greater detail in another chapter. The National Emphysema Treatment Trial identified patients likely to benefit from LVRS as well as those with increased mortality following the procedure (44). Typically patients have an FEV_1 >20% of predicted and a DLCO >25% with heterogeneous upper lobe, predominant emphysema. The decision to proceed with lung transplantation for severe COPD may be complex. While ample evidence suggests that functional capacity is improved following the procedure, a survival benefit is less clear. One must determine which patients have the most urgent need for lung transplantation and are likely to have the longest survival after transplantation. Guidelines for timing a referral for a transplant evaluation for patients with COPD or emphysema due to α-1 antitrypsin deficiency include (45) BODE index >5, post-bronchodilator FEV_1 <25% of predicted, resting hypoxemia, defined as PaO_2 <55 to 60 mmHg, hypercapnia, secondary pulmonary hypertension, or an accelerated decline in FEV_1. Transplantation is usually deferred until the BODE index is seven or higher, the FEV_1 is below 20% of predicted, the diffusing capacity for carbon monoxide (DLCO) is below 20% of predicted, there is a homogeneous distribution of emphysema, or the clinical course becomes more aggressive with life-threatening exacerbations (45).

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7
Cystic Fibrosis and Bronchiectasis

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I. Introduction

The pretransplant management and evaluation of individuals with cystic fibrosis (CF) and non-CF bronchiectasis is described below. The median predicted age of survival for individuals with CF has now increased to over 37 years (1); yet despite tremendous advances in the management of CF, progressive respiratory failure remains the primary source of morbidity and mortality. Therefore, lung transplantation is an important therapeutic option for CF patients with end-stage lung disease. CF is the third most common indication for lung transplantation in adults (2), after chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), and the most common indication in the pediatric population (3). CF adults have the longest median survival of any group receiving lung transplants (2).

CF is an autosomal recessive genetic disorder that results from a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that encodes a faulty chloride channel (4). CFTR is expressed in multiple organs; and thus, CF is a multisystem disease with comorbidities, such as sinusitis, pancreatic insufficiency, liver dysfunction, and an increased risk of gastrointestinal (GI) malignancies, which impact the management of CF patients referred for lung transplantation (4). Because non-CF bronchiectasis (secondary to idiopathic, primary ciliary dyskinesia, hypogammaglobulinemia) accounts for a very small proportion of all lung transplants performed, and there are limited data on the transplant evaluation and management of these patients, the transplant center approach to non-CF bronchiectasis is similar to that for CF patients (2).

II. Pulmonary Evaluation

CF patients should be considered for referral to a lung transplant program when the forced expiratory volume (FEV_1) falls consistently below 30%, if they have a rapid decline in FEV_1 (especially in young females), or if they have frequent exacerbations (5). Transplantation referral should also be considered for patients with increasing frequency of pulmonary exacerbations or among patients with exacerbations severe enough to require management in the intensive care unit (6). It has also been shown that a partial pressure of arterial oxygen below 55 mm Hg or a partial pressure of carbon dioxide above 50 mm Hg is associated with less than 50% survival in two years (7). The choice to perform lung transplantation in patients with CF is often times a multifactorial decision that takes into account previous infectious history, extrapulmonary CF manifestations, FEV_1, oxygen use, hypercapnia, and pulmonary hypertension. Indications for referral and guidelines for lung transplantation are shown in Table 1.

Table 1 Guidelines for Referral and Transplantation in Cystic Fibrosis

Guidelines for referral
• $FEV_1 < 30\%$ predicted or a rapid decline in FEV_1 (especially in females >20 as they have a poorer prognosis)
• Pulmonary exacerbation requiring ICU stay
• Increasing frequency of exacerbations
• Refractory or recurrent pneumothorax
• Recurrent hemoptysis not controlled with embolization
Guidelines for Transplantation
• Oxygen-dependent respiratory failure
• Hypercapnia
• Pulmonary hypertension

Source: Modified from Ref. 5.

The procedure of choice for individuals with CF is bilateral lung transplantation. Single-lung transplants are not performed because of the risk of infectious organisms from the native lung contaminating the transplanted lung (8). Since the institution of the lung allocation score and decreased waiting times, the need for alternative donors has decreased. In the United States in 2007, there were five lobar-cadaveric and one lobar-living related donor transplants in patients with CF (1).

Two relative contraindications to lung transplant in all individuals, according to the international guidelines, include infection with pan-resistant organisms and mechanical ventilation (5). These topics deserve special consideration in patients with CF as studies suggest that CF patients do well despite these comorbidities.

In general, mechanical ventilation is a relative contraindication for lung transplantation; however, selected CF patients can undergo successful lung transplantation in the setting of pretransplant mechanical ventilation. Four single-center studies suggest that mechanically ventilated patients with CF do not have increased morbidity or mortality after bilateral lung transplantation (9–12). This may not be the case with children as a small, single-center study reported worse one-year survival compared to matched controls (13). The international guidelines recommend that CF patients undergoing mechanical ventilation should be considered for lung transplantation if (*i*) the pretransplant work-up has occurred prior to intubation, (*ii*) there is no other organ failure, and (*iii*) the patient understands that comorbidities may develop during mechanical ventilation (such as renal failure) that would contraindicate lung transplant (5).

A. Infection

The pathogenesis of CF lung disease is a vicious cycle of airway obstruction, infection, and inflammation. CF patients' upper and lower respiratory tracts are often infected with multiple antibiotic resistant organisms. Post-transplant infections are one of the leading causes of morbidity and mortality in individuals with CF. There had been concern that CF patients colonized with infectious organisms such as multiple antibiotic resistant *Pseudomonas aeruginosa* (MARPA), *Burkholderia cepacia* complex (BCC), mycobacterium, and/or fungal organisms would lead to post-transplant morbidity and mortality in the setting of systemic immunosuppression. With the exception of BCC,

Table 2 Kaplan–Meier Median Survival by Diagnosis and Comparison of Survival Between Diagnoses for Adult Lung Transplants Performed Between January 1990 and June 2006

Disease	Median survival (yr)	Survival comparison (CF vs. Disease)
Cystic fibrosis	6.4	
COPD	5.0	$p < 0.001$
AT deficiency	5.9	$p < 0.001$
IPF	4.1	$p < 0.001$
IPAH	4.6	$p < 0.001$
Sarcoidosis	5.1	$p < 0.001$

Source: Adapted from Ref. 2.
Abbreviations: COPD, chronic obstructive pulmonary disease; AT, α-1 anti-trypsin; IPF, idiopathic pulmonary fibrosis; IPAH, idiopathic pulmonary arterial hypertension.

despite the presence of these organisms pre- and post-transplant, survival in CF patients appears to be similar to those with other lung diseases (Table 2).

Prior to transplant, MARPA infection has been associated with an acceleration of CF lung disease and increased rates of transplantation (14). However, several studies have not identified increased peri- or post-transplant morbidity or mortality in patients colonized with MARPA prior to transplant. MARPA colonization does not (*i*) increase the risk of death from perioperative sepsis (15), (*ii*) increase the risk of post-transplant infectious complications (16), or (*iii*) change post-transplant survival (17,18). Aris and colleagues performed a retrospective study in 66 transplanted patients over 6 years and found that patients with pan-resistant *P. aeruginosa* had a 1-year survival of 90% (17).

If pretransplant *P. aeruginosa* colonization has no effect on survival, what is the course of CF patients who become infected with *P. aeruginosa* after transplant? As expected, compared to non-CF lung transplant recipients, *P. aeruginosa* is cultured earlier and more frequently in CF lung transplant patients (19); however, this phenomenon is limited only to the lungs: there is no difference in rates of *P. aeruginosa* bacteremia between these groups. In lung transplant recipients, with and without CF, isolation of *P. aeruginosa* is associated with an intense inflammatory response (19). A small, single-center retrospective study by Vos and colleagues demonstrated that *P. aeruginosa* colonization may be associated with an increased risk of bronchiolitis obliterans syndrome in CF patients (20). However, after adjustment for confounders, there was a trend toward increased risk of bronchiolitis obliterans syndrome, but the results were no longer statistically significant (OR 3.08, 95% CI 0.95 to 9.99, $p = 0.06$). CF lung transplant recipients who have isolated *P. aeruginosa* have an increased inflammatory milieu and a potential association with bronchiolitis obliterans; however, when compared to other post-transplant patients who did not culture *P. aeruginosa*, there is no difference in mortality (19).

While MARPA is not an absolute contraindication to transplant in CF patients, *Burkholderia cepacia* complex has been associated with significantly reduced post-transplant survival. Because of this, some centers do not transplant BCC patients. Early observational studies did not take into account the fact that BCC is comprised of many genomically distinct bacterial species or genomovars (21,22). More recent studies suggest that genomovar III *B. cenocepacia* species is the main contributor to decreased post-transplant survival and that other *Burkholderia* species have mortality rates similar

to uninfected controls (23–25). In the largest of these studies, Murray and colleagues examined 88 BCC-infected lung transplant recipients and compared their post-transplant survival to uninfected controls. The authors concluded that *Burkholderia gladioli* and a subgroup of *B. cenocepacia* had worse mortality, while recipients infected with *Burkholderia multivorans* had mortality similar to uninfected controls.

It is also important to note that BCC can frequently be misidentified in standard laboratories (26). The consequences of a diagnosis with BCC carry significant medical and psychological impact for the patient. Referral of BCC-positive cultures to a Cystic Fibrosis Foundation (CFF) referral center to confirm the diagnosis is strongly recommended (26). Approximately, one-third of centers do not transplant patients with BCC (27); therefore, referral to a center experienced with management of BCC patients is preferred. Lung transplant centers continue to evaluate BCC patients on a case-by-case basis.

There are less data on outcomes from colonization with other organisms. There have not been any large studies detailing the impact of bacterial infections, such as methicillin-resistant *Staphylococcus aureus*, *Achromobacter*, and *Stenotrophomonas*, but colonization with these organisms does not seem to be associated with worse post-transplant outcomes (28). Fungal colonization has not been associated with an increased risk of infectious complications (16), though there may be a higher rate of postoperative infections at the bronchial anastomoses (29). Iversen and colleagues suggest that colonization with *Aspergillus* is not associated with short-term mortality but may be associated with a higher five-year mortality (30). Infection with non-tuberculosis mycobacterium (NTM) post-transplant does not appear to lead to worse survival, though those colonized prior to transplant are at increased risk of recurrence after transplant (31). A single-center retrospective study at The University of North Carolina in Chapel Hill found an association with NTM and increased morbidity post transplant; however, NTM infections were able to be treated successfully despite immunosuppression (31). The odds of an invasive NTM infection was most strongly predicted by pretransplant colonization with NTM; this association was strongest with *Mycobacterium abscessus* (31). *M. abscessus* is a rapidly growing NTM and much more difficult to eradicate than other NTM (32). Case reports of post-transplant infection with *M. abscessus* have shown both response to treatment (33,34) and death from disseminated disease despite pre-, peri-, and postoperative treatment of the infection (35). Cutaneous lesions should be treated with surgical debridement.

No matter what the organism, a key to preventing infectious complications in post-transplant CF and non-CF bronchiectasis patients is to administer perioperative antibiotics targeted at pretransplant and perioperative culture results. In those patients with pan-resistant organisms, consideration should be given to in vitro synergy testing to determine if combinations of antibiotic agents can inhibit the pan-resistant strain (36). Furthermore, as both CF and non-CF bronchiectasis patients are at risk of colonization in the years after transplant, surveillance cultures should be obtained to direct future therapy.

III. Extrapulmonary Manifestations of CF

As CF is a multisystem disease, comorbidities must be taken into consideration during lung transplant evaluation process. These include diabetes mellitus, osteoporosis, gastroesophageal reflux/liver disease, pancreatic insufficiency/malnutrition, and sinusitis. If under good control, these problems are not considered contraindications for transplant.

Diabetes is common in pretransplant CF patients with a prevalence of 20% to 40%. Prevalence increases after transplant, possibly secondary to corticosteroid and other immunosuppressive therapies (37). A pretransplant diagnosis of diabetes does not portend a worse survival after transplant (38). In addition, some centers have performed simultaneous bilateral lung and pancreas transplants with resolution of pancreatic insufficiency and need for supplemental insulin (39).

Osteoporosis is another common disease in end-stage CF patients being evaluated for lung transplant (40). Inflammation and decreased vitamin D absorption lead to increased rates in this population. After transplant, immunosuppressive medications further increase this risk (41). Therefore, it is important to monitor for osteoporosis, provide vitamin D and calcium supplementation, treat with bisphosphonates where appropriate, and try to minimize corticosteroid therapy when possible.

GI issues in regard to lung transplantation include gastroesophageal reflux disease (GERD), liver disease, distal intestinal obstruction syndrome (DIOS), and poor absorption of cyclosporine. GERD is common in pre- and post-transplant CF patients (42). Given the potential association between GERD and the development of chronic rejection (43), medical and surgical treatment of this condition is warranted. In patients with end-stage liver disease, combined lung and liver transplants can be safely performed at experienced centers (44). Another potential complication in the postoperative setting is DIOS. Pretransplant, DIOS tends to occur in adolescent and adult CF patients with underlying pancreatic insufficiency because of a combination of malnutrition and impaired intestinal electrolyte secretion (45); however, DIOS also can develop in children in the post-lung transplant setting (46). Toronto reviewed 75 CF lung transplant recipients and 10 developed perioperative DIOS, with 2 requiring surgical management. The combination of decreased ambulation, decreased oral intake, and opiate medications in the postoperative period increases the risk for DIOS. Aggressive preoperative and post-transplant bowel regimens should be instituted to prevent abdominal obstruction, which can also impair respiratory function. Finally, given issues with absorption in CF patients, cyclosporine has lower bioavailability when compared to other lung transplant patients (47).

Lung transplantation is a viable treatment option for highly selected candidates with severe advanced lung disease secondary to CF or non-CF bronchiectasis. Guidelines for the selection of candidates are based on maximizing survival, which in turn maximizes the utilization of scarce donor organs. Lung transplantation should be offered to those with the greatest need and highest likelihood of obtaining improved survival. This goal can be achieved by early referral to a lung transplant center to allow adequate time to perform a detailed evaluation and appropriately manage pretransplant comorbidities to select the most appropriate candidates for this intervention.

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8
Pulmonary Arterial Hypertension

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Pulmonary hypertension (PH), an abnormal elevation in pulmonary artery pressure, may be the result of left heart failure, pulmonary parenchymal or vascular disease, thromboembolism, or a combination of these factors. Whether the PH arises from cardiac, pulmonary, or intrinsic vascular disease, it generally is a feature of advanced disease. Because the causes of PH are so diverse, it is essential that the etiology underlying the PH be clearly determined before embarking on treatment.

I. Nomenclature and Classification

PH was traditionally divided into primary and secondary. This classification has been replaced by the one proposed by the World Health Organization in 1998 (1). Currently, PH is divided into five major categories with further subdivisions in each category (Table 1). Pulmonary arterial hypertension (PAH) refers to pulmonary vascular disease originating in the arterial side of the pulmonary circulation. PAH can be idiopathic, secondary to other medical conditions or associated with significant venous or capillary involvement. PAH can also be either sporadic or familial. Pulmonary venous hypertension is due to left heart disease with elevated pulmonary capillary artery pressure. PH associated with hypoxemia is due to lung disease and other disorders associated with hypoxemia. PH due to chronic thrombotic or embolic disease is due to prior pulmonary embolism (PE) in the majority of cases. The miscellaneous category of PH includes diverse disorders like sarcoidosis and fibrosing mediastinitis.

II. Pathology

The most common vascular changes in PAH can best be characterized as a hypertensive pulmonary arteriopathy, which is present in 85% of cases (3). These changes involve medial hypertrophy of the arteries and arterioles, often in conjunction with other vascular changes. Isolated medial hypertrophy is uncommon, and when present it has been assumed to represent an early stage of the disease. The intimal proliferation may appear as concentric laminar intimal fibrosis, eccentric intimal fibrosis, or concentric intimal fibrosis. The frequency of these findings differs from case to case and within regions of the same lung in the same patient (4). In addition, plexiform and dilation lesions, as well as a necrotizing arteritis, may be seen throughout the lungs. The fundamental nature of the plexiform lesion remains a mystery. Morphologically, they represent a mass of disorganized vessels with proliferating endothelial cells, smooth muscle cells, myofibroblasts, and macrophages. Several studies have demonstrated the involvement of growth factors that have been implicated in angiogenesis. Whether the plexiform lesion represents impaired proliferation or angiogenesis remains unclear.

Table 1 Clinical Classification of Pulmonary Arterial Hypertension

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic pulmonary hypertension
     - (a) Sporadic
     - (b) Familial
   - 1.2 Associated with
     - (a) Connective tissue disease
     - (b) Congenital heart disease
     - (c) Portal hypertension
     - (d) Human immunodeficiency virus infection
     - (e) Drugs/toxins
       - (1) Anorexigens
       - (2) Other
   - 1.3 Persistent pulmonary hypertension of the newborn
   - 1.4 Pulmonary veno-occlusive disease
   - 1.5 Pulmonary capillary hemangiomatosis
2. Pulmonary venous hypertension
   - 2.1 Left-sided atrial or ventricular heart disease
   - 2.2 Left-sided valvular heart disease
   - 2.3 Extrinsic compression of central pulmonary veins
     - (a) Fibrosing mediastinitis
     - (b) Adenopathy/tumors
   - 2.4 Other
3. Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Sleep-disordered breathing
   - 3.4 Alveolar hypoventilation disorders
   - 3.5 Chronic exposure to high altitude
   - 3.6 Neonatal lung disease
   - 3.7 Alveolar-capillary dysplasia
   - 3.8 Other
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
   - 4.1 Thromboembolic obstruction of proximal pulmonary arteries
   - 4.2 Thromboembolic obstruction of the distal pulmonary arteries
   - 4.3 Pulmonary embolism (tumor, ova parasites, foreign material)
5. Pulmonary hypertension due to disorders directly affecting the pulmonary vasculature
   - 5.1 Inflammatory
     - (a) Schistosomiasis
     - (b) Sarcoidosis
     - (c) Histiocytosis X
     - (d) Other

Source: Modified from Ref. 2.

III. Pathobiology

PAH has a multifactorial pathobiology (5) (Fig. 1). Abnormalities in molecular pathways regulating the pulmonary vascular endothelial and smooth muscle cells have been described as underlying PAH. These include inhibition of the voltage-regulated potassium channel (7), mutations in the bone morphogenetic protein-2 receptor (8),

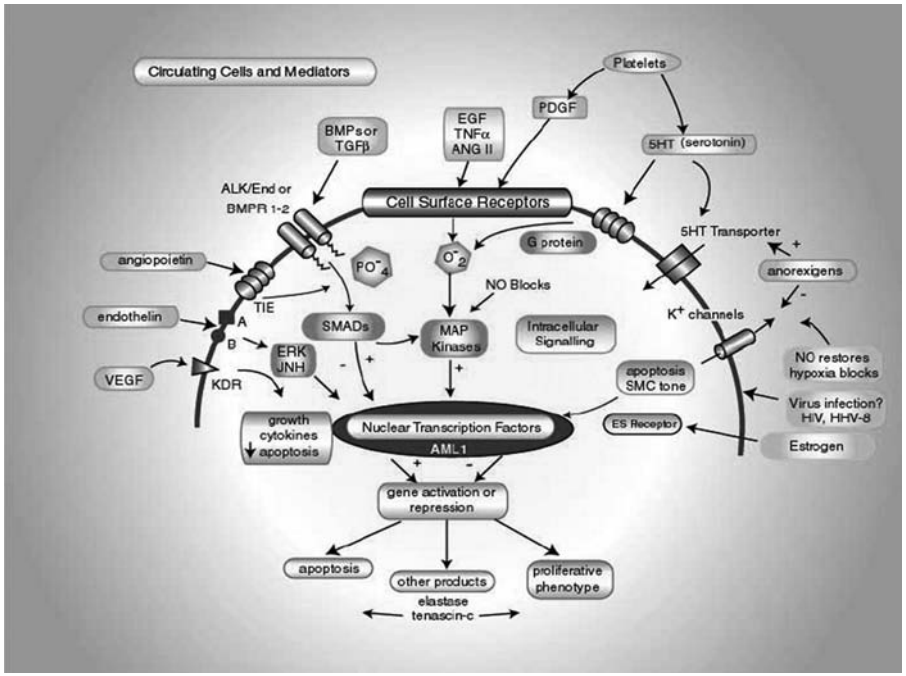

Figure 1 (*See color insert*) The complex pathobiology of pulmonary hypertension. Extracellular mediators and cell surface receptors, ion channels, intracellular signaling, and nuclear responses are illustrated. Many pathways span the extracellular, membrane, cytosolic, and nuclear domains. Intracellular transduction of these pathways is poorly understood. *Source*: Adapted from Ref. 6.

increased serotonin uptake in the smooth muscle cells (9), increased angiopoietin expression in the smooth muscle cells (10), and excessive thrombin deposition related to a procoagulant state (11). As a result, there appears to be loss of apoptosis of the smooth muscle cells allowing their proliferation, and the emergence of apoptosis-resistant endothelial cells that can obliterate the vascular lumen. Vasoconstriction, remodeling of the pulmonary vessel wall, and thrombosis contribute to increased pulmonary vascular resistance in PAH. The process of pulmonary vascular remodeling involves all layers of the vessel wall and is complicated by cellular heterogeneity within each compartment of the pulmonary arterial wall. Each cell type (endothelial, smooth muscle, and fibroblast), as well as inflammatory cells and platelets, may play a significant role in PAH. Pulmonary vasoconstriction is believed to be an early component of the pulmonary hypertensive process. Excessive vasoconstriction has been related to abnormal function or expression of potassium channels and to endothelial dysfunction (7). Endothelial dysfunction leads to chronically impaired production of vasodilators such as nitric oxide and prostacyclin along with overexpression of vasoconstrictors such as endothelin (12). Recent genetic and pathophysiologic studies have emphasized the relevance of several mediators in this condition, including prostacyclin (13), nitric oxide (14), endothelin (15), angiopoietin (10), serotonin (16),

and members of the transforming growth factor (TGF)-β superfamily (8). Disordered proteolysis of the extracellular matrix is also evident in PAH.

IV. Pathophysiology

The right ventricle responds to an increase in resistance within the pulmonary circulation by increasing RV systolic pressure as necessary to preserve cardiac output. Over time, chronic changes occur in the pulmonary circulation, resulting in progressive remodeling of the vasculature, which can sustain or promote PH even if the initiating factor is removed. The ability of the right ventricle to adapt to increased vascular resistance is influenced by several factors including age and the rapidity of the development of PH. For example, a large acute pulmonary thromboembolism can result in RV failure and shock, whereas chronic thromboembolic disease of equal severity may result in only mild exercise intolerance. Coexisting hypoxemia can impair the ability of the ventricle to compensate. Several studies support the concept that RV failure occurs in PH when the RV myocardium becomes ischemic due to excessive demands and inadequate right ventricular coronary blood flow (17). The onset of clinical RV failure, usually manifest by peripheral edema, is associated with a poor outcome (18).

The anatomical disposition and geometry of the right ventricle allow it to adapt very well to wide variations in preload, but poorly to increases in afterload. In the

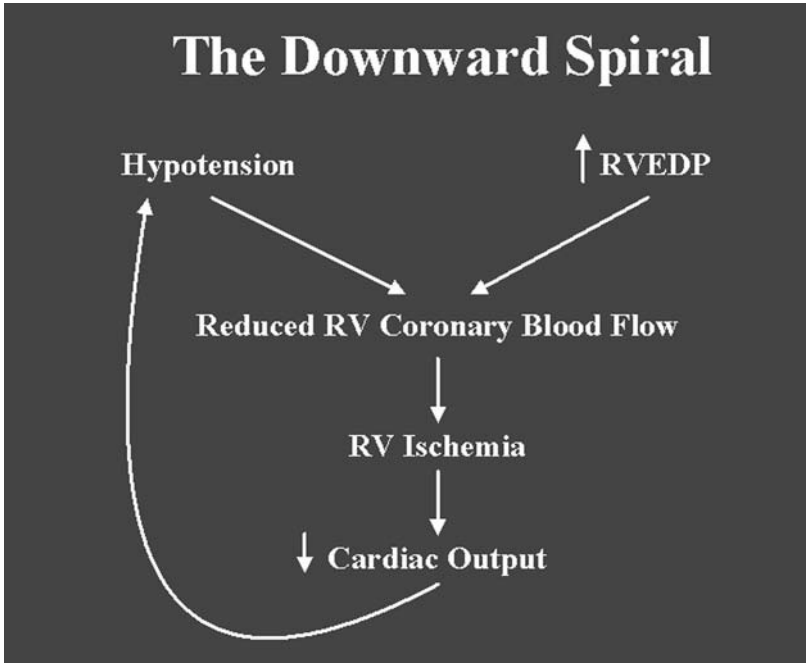

Figure 2 The lethal vicious circle of acute right ventricular failure from chronic pulmonary hypertension. In the absence of treatments that selectively improve right ventricular performance, it can be very difficult to improve cardiac output without worsening RV function.

presence of increased afterload, RV stroke volume decreases linearly with increasing resistance and the ventricle eventually dilates. This dilation is then responsible for further RV failure due to decreased right coronary artery flow at a time when myocardial oxygen consumption is increased (17). Furthermore, RV dilation shifts the interventricular septum to the left, decreasing left ventricular preload and compliance and, hence, the cardiac output. An often-lethal vicious circle is induced (Fig. 2). The main therapeutic goals aimed at breaking this circle are restoration of adequate oxygen delivery to the myocardium and diminution of RV afterload.

V. Diagnosis

Patients with PH can present with varied cardiopulmonary symptoms (19). Exertional dyspnea is the most frequent symptom and unexplained dyspnea should always raise the suspicion of PH. PH may be asymptomatic in the early stages and may be an incidental finding on echocardiogram performed for other reasons. Chest pain and syncope are usually late symptoms. Patients may present with symptoms of right heart failure such as peripheral edema or ascites. A family history of PH, use of fenfluramine appetite suppressants, cocaine or amphetamines, prior history of deep vein thrombosis (DVT) or PE, chronic liver disease or portal hypertension, risk factors for HIV, thyroid disease, splenectomy, and sickle cell disease should be sought in all patients suspected to have PH.

The physical examination typically reveals increased jugular venous pressure, a reduced carotid pulse, and a palpable RV impulse. Most patients have an increased pulmonic component of the second heart sound, a right-sided fourth heart sound, and tricuspid regurgitation. Peripheral cyanosis and/or edema tend to occur in later stages of the disease.

A. Laboratory Findings

The goals of work-up in PH include confirmation of diagnosis, establishing an underlying cause, and quantifying severity with hemodynamics and functional impairment. *Electrocardiographic* features of significant PH include right axis deviation, right atrial enlargement, and right ventricular hypertrophy. The *chest X ray* (CXR) may show enlarged main and branch pulmonary arteries with attenuation of peripheral vascular markings. CXR changes of obstructive or restrictive lung disease or pulmonary congestion may be helpful in elucidating the cause of PH. *Echocardiography* is helpful in confirming the diagnosis as well as excluding left-sided cardiac lesions as the etiology of PH. A thorough study is needed to delineate cardiac anatomy and function, great arterial vessels, systemic and pulmonary veins, and to assess the severity of PH and its hemodynamic effects. *Pulmonary function testing* is done to evaluate for possible obstructive or restrictive lung disease. *Ventilation/perfusion scan* is recommended as initial investigation to evaluate for chronic thromboembolic pulmonary hypertension (CTEPH). *Computed tomography* (CT) scan of chest may show various abnormalities in CTEPH, including irregular pulmonary arteries, organized thrombus, webs, increased bronchial artery collateral flow, lung scars from prior infarction, and mosaic perfusion pattern. CT scan may also show airway or parenchymal changes suggestive of underlying lung disease as the etiology of PH. Blood work-up should include antinuclear antibody tests, liver function tests, thyroid function tests, and HIV testing.

Cardiac catheterization is required to confirm the diagnosis, assess its severity, guide medical therapy, and provide prognostic information. This procedure is mandatory

for accurate measurement of pulmonary artery pressure, cardiac output, and LV filling pressure, as well as for exclusion of an underlying cardiac shunt. Care should be taken to measure pressures only at end expiration. It is also recommended that patients with PAH undergo drug testing with a short-acting pulmonary vasodilator at the time of cardiac catheterization to determine the extent of pulmonary vasodilator reactivity (20). Inhaled nitric oxide, IV adenosine, and IV epoprostenol appear to have comparable effects in reducing pulmonary artery pressure acutely. Nitric oxide is administered via inhalation in 10 to 20 parts per million. Adenosine is given in doses of 50 μg/kg/min and increased every 2 minutes until side effects develop. Epoprostenol is given in doses of 2 ng/kg/min and increased every 30 minutes until side effects develop. A positive vasodilator response is defined as a decrease of at least 10 mmHg in mean PAP and achieving mean PAP $<$ 40 mmHg, and an increase or no change in cardiac output, and no significant fall in blood pressure (21). Patients who respond can often be treated with calcium channel blockers and have a more favorable prognosis (22). In some patients, left heart catheterization is also performed if there is suspicion of left heart disease. All the hemodynamic data is obtained at baseline as well as after giving a short acting pulmonary vasodilator.

VI. Idiopathic Pulmonary Arterial Hypertension

Idiopathic pulmonary arterial hypertension (IPAH), formerly referred to as primary PH, is uncommon, with an estimated incidence of two cases per million. There is a strong female predominance, with most patients presenting in the fourth and fifth decades, although the age range is from infancy to >60 years (19).

Familial IPAH accounts for up to 20% of cases of IPAH and is characterized by autosomal dominant inheritance, variable age of onset, and incomplete penetrance. The clinical and pathologic features of familial and sporadic IPAH are identical. Heterozygous germline mutations that involve the gene coding the type II bone morphogenetic protein receptor (BMPR II), a member of the TGF-β superfamily, appear to account for most cases of familial IPAH. The low gene penetrance suggests that other risk factors or abnormalities are necessary to manifest clinical disease (23).

VII. Natural History

The natural history of IPAH is uncertain, and because the predominant symptom is dyspnea, which can have an insidious onset, the disease is typically diagnosed late in its course. Prior to current therapies, a mean survival of two to three years from the time of diagnosis was reported (18). Functional class remains a strong predictor of survival, with patients who are in New York Heart Association (NYHA) functional class IV having a mean survival of less than six months. The cause of death is usually RV failure, which is manifest by progressive hypoxemia, tachycardia, hypotension, and edema.

VIII. Treatment

A. General Recommendations

Because the pulmonary artery pressure in PAH increases dramatically with exercise, patients should be cautioned against participating in activities that demand increased physical stress. Diuretic therapy relieves peripheral edema and may be useful in

reducing RVEDP. Resting and exercise pulse oximetry should be obtained as oxygen supplementation helps to alleviate dyspnea and RV ischemia in patients whose arterial oxygen saturation is reduced. Hypoxemia is a potent pulmonary vasoconstrictor, and all activities leading to hypoxemia need to be avoided in such patients. Anticoagulant therapy is advocated for all patients with PAH on the basis of retrospective and prospective studies that demonstrated that warfarin increases survival of patients with PAH (24). The dose of warfarin is generally titrated to achieve an INR of two to three times control. Influenza and pneumococcal vaccination is strongly recommended to prevent respiratory infections. All medication use including over the counter and herbal medications should be discussed with the physician prior to their use. All vasoconstrictor medications including pseudoephedrine containing compounds should be avoided. Appetite and diet pills should also be avoided due to their association with PH. Oxygen supplementation is recommended in patients who are hypoxemic. Patients whose SaO_2 is less than 89% at rest, during sleep or with ambulation, should be provided supplemental oxygen therapy to keep SpO_2 more than 90% at all times.

B. Drug Treatment for PAH

Calcium Channel Blockers

Patients who have substantial reductions in pulmonary arterial pressure in response to short-acting vasodilators at the time of cardiac catheterization should be treated initially with calcium channel blockers (22). Typically, patients require high doses (e.g., Nifedipine, 240 mg/day, or Amlodipine, 20 mg/day). Patients who respond favorably usually have dramatic reductions in pulmonary artery pressure and pulmonary vascular resistance associated with improved symptoms, regression of RV hypertrophy, and improved survival now documented to exceed 20 years (25). However, less than 20% of patients respond to calcium channel blockers in the long term. These drugs should not be given to patients who are unresponsive as they can result in hypotension, hypoxemia, tachycardia, and worsening right heart failure.

Endothelin Receptor Antagonists

The endothelin receptor antagonists bosentan (26) and ambrisentan (27) are approved treatments of PAH for patients who are NYHA functional classes III and IV. In randomized clinical trials, they improved symptoms and exercise tolerance as measured by an increase in six-minute walk distance. Bosentan is initiated at 62.5 mg b.i.d. for the first month and then increased to 125 mg b.i.d. thereafter. Because of the high frequency of abnormal hepatic function tests associated with drug use, primarily an increase in transaminases, it is recommended that liver function be monitored monthly throughout the duration of use. Bosentan is also contraindicated in patients who are currently on cyclosporine or glyburide. Ambrisentan is used as 5-mg or 10-mg doses on the basis of clinical response. The safety profile of ambrisentan appears to be better than that of Bosentan.

Phosphodiesterase-5 Inhibitors

Sildenafil, a phosphodiesterase-5 inhibitor, is approved for the treatment of PAH patients who are functional class II and III (28). Phosphodiesterase-5 is responsible for the hydrolysis of cyclic GMP in pulmonary vascular smooth muscle, the mediator through which nitric oxide lowers pulmonary artery pressure and inhibits pulmonary

vascular growth. Randomized clinical trials have shown that sildenafil improves symptoms and exercise tolerance in PAH. The recommended dose is 20 mg t.i.d. The most common side effects are headache and stuffy nose. Sildenafil should not be given to patients who are taking nitrate compounds.

Prostacyclins

Iloprost, a prostacyclin analogue, is approved for PAH patients via inhalation who are functional class III and IV (29). It has been shown to improve symptoms and exercise tolerance. Therapy can be given at either 2.5 or 5 mcg per inhalation treatment. The inhaler must be given by a dedicated nebulizer. The most common side effects are flushing and cough. Because of the very short half-life (<30 minutes), it is recommended to administer treatments as often as every two hours. Epoprostenol is approved for the treatment of PAH patients who are NYHA functional class III or IV (30). Clinical trials have demonstrated an improvement in symptoms, exercise tolerance, and survival even if no acute hemodynamic response to drug challenge occurs (31,32). The drug is administered intravenously and requires placement of a permanent central venous catheter and infusion through an ambulatory infusion pump system. Side effects include flushing, jaw pain, and diarrhea, which are generally tolerated by most patients.

Treprostinil, an analogue of epoprostenol, is approved for patients with PAH who are NYHA functional classes II to IV (33). Treprostinil has a longer half-life than epoprostenol (four hours), is stable at room temperature, and may be given intravenously or subcutaneously through a small infusion pump that was originally developed for insulin. Clinical trials have demonstrated an improvement in symptoms and exercise capacity. The major problem with the subcutaneous administration has been local pain at the infusion site, which has caused many patients to discontinue therapy. Side effects are similar to those seen with epoprostenol.

The IV prostacyclins have the greatest efficacy as treatments for PAH, and often will be effective in patients who have failed all other treatments (34). Favorable properties include vasodilation, platelet inhibition, inhibition of vascular smooth muscle growth, and inotropic effects. It generally takes several months to titrate the dose of epoprostenol or treprostinil upwards to optimal clinical efficacy, which can be determined by symptoms, exercise testing and catheterization. The optimal doses of these drugs have not been determined, but the typical doses of epoprostenol range from 25 to 40 ng/kg/min and from 75 to 150 ng/kg/min for Treprostinil. The major problem with IV therapy is infection related to the venous catheter, which requires close monitoring and diligence on behalf of the patient.

Although most clinical trials have focused on patients with advanced symptoms, it is recommended that every patient diagnosed with PAH be treated. While no treatment has been demonstrated to be superior as first-line therapy, patients often prefer to initiate their treatment with an oral or inhaled form of therapy. In the clinical trials, full clinical benefit was generally manifest within the first two months of therapy. Patients who fail to adequately improve should have the treatment discontinued and started on a different therapy. Equally important is that delaying a more effective treatment may allow the disease to progress and become less responsive. The use of these drugs in combination has become popular. However, the only randomized controlled trial of combination therapy demonstrating efficacy has been the addition of oral sildenafil to stable patients with PAH on IV epoprostenol. Patients with declining status in spite of treatment with IV prostanoids should be considered for lung transplantation.

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9
Connective Tissue Disorders

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I. Introduction

Lung transplantation is an effective therapeutic option for a variety of end-stage lung diseases. Chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), and idiopathic pulmonary hypertension (IPAH) are among the more common advanced lung disorders for which lung transplantation is performed. From the 2009 Registry of the International Heart and Lung Transplant Society (ISHLT) report for the period of January 1995 through June 2008 (1), IPF accounts for 21%, or about 5000 lung transplants. Not included in this IPF group is the diagnosis of connective tissue disease related interstitial lung disease (CT-ILD), comprising only 0.8%, or 181 lung replacement procedures. This number has risen from 0.5% as reported from the ISHLT registry of 22nd annual report (2).

Review of the literature related to the timing of listing, indication for single lung transplant (SLT) or bilateral lung transplant (BLT), complications, and survival reveals few similarities and variable outcomes for the category of CT-ILD. Further, the majority of available data is scant and based on one transplant center's 10 to 20 years experience with other programs reporting as few as one to four transplants per center: specifically for systemic sclerosis (SSc), the idiopathic inflammatory myopathies; polymyositis (PM) and dermatomyositis (DM), systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), and rheumatoid arthritis (RA) (3–10). No global statistics have been reported for survival with respect to this specific cohort of patients neither by The Scientific Registry for Transplant Recipients (SRTR), the United Network for Organ Sharing (UNOS), nor by the ISHLT. However, the 2009 ISHLT annual registry shows that patients transplanted with non-IPF pulmonary fibrosis have nearly 2.5 times the risk of death by the first year after lung transplantation when compared to the cohort with the lowest one-year mortality, that is the COPD population (1). Variables found to significantly worsen the one-year survival include increased age, bilirubin levels, supplemental oxygen requirements at rest, decreased cardiac output, and low transplant center volume (1). Also, center specific data reports primarily short-term outcomes at one and three years. Not much is known about 5-and 10-year morbidity and mortality in patients transplanted for CT-ILD.

The indications, contraindications, absolute contraindications, and timing for referral and listing for transplantation for patients with COPD, IPF, CF, and IPAH have been recently published (11). However, the same for CT-ILD are still evolving because of a dearth of experience. Historically, patients with CT-ILD have been considered to have a "systemic disease" and as such have been excluded as candidates for lung

transplantation. This systemic disease stems from the autoimmune nature of their underlying disease that has been previously felt to pose a risk for lung transplantation. Although the indication stems primarily as an ILD in patients with CT-ILD, the potential for other manifestations of respiratory dysfunction is significant with these autoimmune diseases. These manifestations include myopathy with respiratory muscle dysfunction, recurrent aspiration or at least the potential for recurrent aspiration from esophageal dysmotility, thromboembolic events from a hypercoagulable state (i.e., antiphospolipid membrane antibody in SLE patients), upper airway dysfunction by inflammation of the cricoarytenoid joints (patients with RA), pulmonary hypertension (either secondary from hypoxic vasoconstriction, autoimmune vasculitis, or from chronic thromboembolic disease) and the development of bronchiectasis. Bronchiectasis without any of the aforementioned problems with CT-ILD is not necessarily problematic other than mandating the need for bilateral sequential lung transplantation. In addition to the respiratory ailments that could complicate the work-up of the CT-ILD patients for lung transplantation, the unrecognized or unidentified possibility of extrapulmonary organ involvement, progression of underlying disease, possible recurrence of disease in the transplanted lung, and the unforeseen risk for early postoperative complications have previously rendered this population ineligible for lung transplantation (6,11,12). However, as early as 1998, the ISHLT consensus statement stated lung transplantation is legitimate for ILD related to collagen vascular diseases provided no contraindications exist, patients have failed an adequate course of medical therapy and systemic disease is quiescent (4).

II. Systemic Sclerosis

Since the introduction and use of angiotensin-converting enzyme inhibitors (ACE inhibitors) for renal disease in patients with scleroderma, life-threatening and life-ending renal crisis has been strikingly reduced and relegated to the past. Now, lung involvement in patients with SSc has become the formidable threat to the lives of these patients. SSc lung involvement is the major cause of death and therefore is the primary indication for lung transplantation. Surveillance of disease progression and consideration for listing is primarily according to the decline in vital capacity and diffusion capacity. Exclusion criteria to transplantation derived from two transplant centers in the United States whose combined experience with systemic autoimmune disease complicated by ILD and PH are the largest volume reported in 29 patients include creatinine clearance less than 50 mL/min; chest wall sclerosis; non-healing, open skin wounds; and severe gastroesophageal reflux disease unresponsive to medical therapy (13).

Lung transplantation in patients with SSc carries an early increased risk of mortality at six months after lung transplantation when compared with patients transplanted for IPF. Survival following lung transplantation becomes comparable to the IPF patients near the two-year mark at approximately 60%. The leading cause of death in the first six months post-lung transplantation is largely attributed to primary graft dysfunction, which is especially true with a diagnosis of pulmonary hypertension (4,13). Many of these early fatal complications could quite likely be related to covert pulmonary hypertension, the greatest threat to early postoperative outcomes in lung transplantation (1,14).

For patients transplanted with pulmonary hypertension without evidence of parenchymal lung diseases, approximately ¼ of the SSc patients were dead within one

month after lung transplantation, again related to primary graft dysfunction (13). Overall, 9 of 29 patients survived less than six months post transplant. Of these, six patients underwent SLT. A total of five were transplanted prior to the year 2000. The six month survival for the SSc cohort from this report and the IPF group reported by ISHLT was 69% and 80%, respectively. The two-year survival for SSc was 61% which was similar to the 64% seen in the IPF group from the ISHLT registry. The leading causes of death however were similar in both reports (13).

Specifically, the Johns Hopkins group reported no difference in survival at four years when comparing the SSc group to the IPF population (8). In their experience of nine patients there was no evidence of recurrence of disease, no difference in infection rates, and fewer acute rejection episodes. Late deaths in patients with SSc have been reportedly similar to those as observed in non-scleroderma patients: cancer, PH, infection, cardiac events, and bronchiolitis obliterans (15). There appears to be no survival advantage with respect to type of procedure, SLT versus BLT for patients with SSc. Nevertheless, survival at two and three years after lung transplantation does not differ from other lung transplant recipients. Interestingly, there is a decreased rate of acute rejection. Questions exist as to whether pre-transplant immunosuppression plays a role in the decreased incidence of acute rejection, however no difference in the rate/risk of obliterative bronchiolitis (OB) was identified (15).

III. Idiopathic Inflammatory Myopathies, PM and DM

There are no established treatment protocols for DM- and PM-associated ILD. Incidence of lung involvement reportedly ranges from 10% to 65% of patients with DM (4,16). Autoantibodies to the enzyme histidyl-tRNA-synthetase (anti-Jo1, anti-PL7, anti-PL-12, KJ, or M1-2) are present in the majority of patients with ILD associated with DM or PM. These antibodies are present in fewer than 20% of patients without ILD. Further, these autoantibodies are rarely present in other connective tissue diseases. Lung transplantation is reserved for patients with severe, progressive ILD who have good muscle strength or very little residual effect, no specific contraindications and quiescent systemic disease (4).

There are two reports of patients, both males, with idiopathic inflammatory myopathies, one with DM (16) and one with PM (17). Both patients developed acute onset of respiratory symptoms rapidly progressing (within 7 weeks to a few months) to a state of deterioration requiring venovenous and venoarterial extracorporeal membrane oxygenation (ECMO), respectively (16,17).

During the time from diagnosis to requiring extracorporeal lung assist, these patients failed medical therapy with pulse cyclophosphamide, intravenous immunoglobulin, cyclosporine, rituximab, and steroids. Both patients underwent BLT. Despite prolonged use of this therapy as a bridge to transplant and experiencing multiple complications including sepsis, infections, right-heart failure, and disuse atrophy, both patients survived to at least one-year post transplant. One patient, the younger of the two (38 years of age) with PM is reported to be alive at three years post transplant with a reasonable quality of life (17).

IV. Systemic Lupus Erythematosus

The available information regarding lung transplant for SLE is extremely limited, thus any opinion is the sole bias of these authors as best interpreted from the existing literature. For SLE, the center-specific data dates back to over 15 to 20 years ago where

the primary indication for lung transplantation was for pulmonary hypertension rather than ILD. In the Papworth experience of three patients with SLE (6), two underwent lung transplantation primarily for thromboembolic pulmonary hypertension. Both of these patients died early in the postoperative course as a result of complications because of mesenteric thrombosis resulting in bowel infarction and multisystem organ failure. These patients tested positive for anticardiolipin antibody, an antiphospholipid antibody. One patient died on postoperative day 60 following heart-lung transplant (HLT) and the other died on postoperative day 18 after single-lung re-transplantation for progressive OB occurring 20 months post-HLT. The third patient from this group of three transplanted with SLE was still alive after SLT with concomitant α-1 antitrypsin-related emphysema and an NYHA functional class II.

A case report from the Harefield Hospital in the United Kingdom involved a 23-year-old woman whose HLT was indicated for pulmonary hypertension with SLE as well (5). Complications included two episodes of acute rejection within the first postoperative month and OB at 18 months that stabilized. She was reported alive four years post without disease recurrence and highly functional. Neither of these reports (5,6) discussed the timing of listing nor their centers' protocol for determining the suitability of these patients with only one patient surviving more than three years after transplantation.

For patients with SLE, up to 70% will reportedly develop APS. Patients transplanted with APS associated pulmonary hypertension have an increased risk of mortality because of of early postoperative thrombotic events. Potential candidates should be carefully considered on a case by case basis, evaluating the underlying disease for variants that could pose a threat in their early postoperative period. These experiences are limited and it would be simultaneously premature or an overstatement to determine if disease recurrence becomes a complication.

V. Antiphospholipid Syndrome

APS, the most common acquired cause of thrombophilia, is an autoimmune disease characterized by the formation of antibodies reacting against proteins bound to phosphoplipids in cell membranes. Clinically, this syndrome can result in arterial and venous thrombosis with diffuse microvascular injury. Similar to most other autoimmune diseases, it is more common in women than in men. Antiphospholipid antibodies are detected in up to 5% of young healthy patients with higher detection rates among elderly patients with coexistent chronic diseases (18). In patients with SLE, more than half can develop the APS; however, about a third of SLE patients with antiphospholipid antibodies have no evidence of the APS over an average follow-up of seven years (18,19). There is a case report of a patient who underwent single-lung transplantation secondary to CT-ILD with APS who developed capillaritis and pulmonary hemorrhage in the transplanted lung within two months of transplantation (7).

VI. Rheumatoid Arthritis

Although 80% of patients with RA have lung involvement, 50% are symptomatic. The progression of CT-ILD in patients with RA is relatively slow when compared to the rapid decline and high mortality in the symptomatic IPF population. Known factors associated with pulmonary fibrotic lung disease in patients with RA are male gender, age

above 60 years, history of smoking, variant α-1 antitrypsin deficiency, and HLA-B40. Pulmonary function results are variable, as is the course of their disease. In any event, given the frequency of lung involvement in such a common autoimmune disease, severe debilitating articular disease is a contraindication to transplantation and limits those who may benefit from a respiratory standpoint (4).

The lung transplant group at the University of Colorado published in 1998 four patients who experienced pulmonary capillaritis as a complication of lung transplantation (10). One of these patients underwent SLT for bronchiolitis obliterans associated with RA with no reported complications at discharge on post operative day 8. One week later she became symptomatic with fatigue, shortness of breath, hemoptysis, oxygen desaturation, and an infiltrate in the transplanted lung. There was evidence of bronchial mucosal inflammation and capillaritis with diffuse alveolar hemorrhage. This was complicated by tissue culture positive for *Staphylococcus aureus*. This infection was treated and the immunosuppression was augmented with high-dose steroids and antilymphocyte globulin that was later replaced by OKT-3 on day 4 of admit when she developed recurrent massive diffuse alveolar hemorrhage and severe hypoxemia. Following plasmapheresis and prolonged OKT-3 for 13 days the condition abated. She was extubated on day 15 of admit. She was re-admitted within two days of discharge with a similar presentation and was treated with OKT-3, nitric oxide, and cyclophosphamide. Total lymphoid irradiation was administered for refractory rejection. At 12 months post transplant she was reportedly doing well requiring small amounts of supplemental oxygen with activity and sleep. Antineutrophil cytoplasmic antibodies were negative. Retrospective cross-match was performed, which proved to be negative.

Treatment of pulmonary capillaritis associated with autoimmune diseases such as Wegener's granulomatosis, microscopic polyangiitis, SLE, and Goodpasture's syndrome often consists of immunosuppression with steroids and cyclophosphamide. However, the above case and the other three patients (including α-1 antitrypsin deficiency, pulmonary hypertension, and cystic fibrosis) developed capillaritis despite this therapy. Three of these cases were fulminant and there were two deaths, one of which was shy of one year post transplant for PH due to ventricular septal defect (10).

These issues highlight the importance of the original underlying disease playing a role in the development of pulmonary capillaritis such as in the above patients with RA. Also, patients with pauci-immune capillaritis, microscopic polyangiitis, SLE, and Goodpasture's syndrome might recur after lung transplantation. However, reports of the patients with α-1 antitrypsin deficient emphysema, pulmonary hypertension, and cystic fibrosis have led the Colorado group to suggest that capillaritis could be another manifestation of acute lung rejection.

As a result, with the dearth of information on replacing lungs in patients with RA, no specific recommendation can be made other than to individualize the evaluation keeping in mind that much of the disfiguring changes could limit the mobility of these patients under consideration for lung transplantation.

VII. Special Considerations

In the process of evaluating patients with diffuse parenchymal lung diseases for lung transplantation in some instances a previous biopsy or the explanted lung will show nonspecific interstitial pneumonitis (NSIP). Patients with NSIP, particularly the fibrotic phase, have a prognosis nearly identical to patients with IPF, and with no available

therapies to alter its natural history, lung transplantation is the only therapeutic option in selected patients. NSIP has been considered the most common lung injury pattern identified in patients with connective tissue disease (20). Therefore, attempting to diagnose an underlying connective tissue disorder that may take years to manifest (20) or never emerge as an unintended consequence of immunosuppression from transplantation should obviate the need for a serologic survey other than a careful history and physical examination and an "end-organ" workup during transplantation evaluation with special attention to the thrombotic disorders, musculoskeletal system, esophagus, and age-appropriate cancer screening.

Regarding the esophagus and potential threat to the lungs, a recent report from a single institution describes a systematic evaluation of the esophagus in a series of 23 patients with CTD-ILD referred for lung transplantation (21). 83% had pathologic distal reflux by ambulatory 24-hour pH monitoring and 78% had impaired or absent peristalsis by esophageal manometry. This paper underscores the importance of carefully assessing the esophagus in patients with CTD-ILD undergoing an evaluation for lung transplantation. However, this descriptive series and others like it have never prospectively confirmed or refuted the role the esophagus has in affecting the lungs before and after transplantation. Moreover, all patients with advanced lung disease may very well have significant esophageal disorders when carefully evaluated. Are esophageal disorders in patients with lung disease a mere consequence of advanced lung disorders, especially if the esophagus is the most compliant structure in the thorax of patients with interstitial lung disease? Or do esophageal disorders initiate, perpetuate, or intensify the fibrosis seen in patients with diffuse parenchymal lung diseases? Perhaps the answer is yes to both propositions.

VIII. Conclusion

Overall the duration of follow-up in this highly specific population of patients with CT-ILD is relatively short, numbers are low, and a great deal of the data is relatively antiquated with the recent rapid advances in lung transplantation. A guideline for appropriate timing of listing is difficult to establish because of the paucity of long-term outcome data (4). The ISHLT registry of 2009 for a period from January of 1995 through June 2008 states acute rejection rates have decreased (1). The most widely used calcineurin inhibitor today is tacrolimus. There is a trend toward using induction with interleukin-2 receptor antagonists, antithymocyte globulin, and alemtuzumab. Analysis of risk factors for mortality establishes that transplant era remains a risk factor. Significant improvements in early outcomes has been witnessed in the more recent eras presumably from refined surgical techniques, procurement strategies including preservation, perioperative and early postoperative management as well as long-term management (1). Therefore, many patients with CT-ILD are potentially suitable candidates for lung transplantation, once no contraindication has been identified through an evaluation essentially identical to the evaluation of patients with IPF. Specific caveats that must be considered for patients with CT-ILD undergoing evaluation in order of seriousness include potential thrombophilic states, limited ability to undergo physical rehabilitation from debilitating articular disease, concomitant pulmonary hypertension, and severe esophageal disease that could conceivably threaten the allograft and the lives of these patients after lung transplantation. While patients with SLE, especially those with APS, and patients with RA are less likely to be candidates for lung transplantation,

patients with SSc, and the idiopathic inflammatory myopathies (PM and DM) especially those with the antisynthetase syndrome are more likely to be candidates following an appropriate workup for lung transplantation.

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10
Patient Selection

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I. Introduction

Over the last 40 years, lung transplantation has become an accepted and increasingly utilized therapeutic option for patients with select end-stage lung diseases. With improved perioperative and early transplant outcomes, increasing numbers of patients are undergoing evaluation and listing for lung transplantation. Although the availability of donor lungs has increased since the inception of lung transplantation, the increase has not kept pace with the demand for donor allografts. Scarcity of suitable donor lungs continues to limit patient access to lung transplant procedures and necessitates careful patient selection. With limited organs to transplant, transplant teams aim to maximize patient survival and quality life while accounting for medical urgency. The patient selection process is a crucial first step in improving patient outcomes, as measured in survival benefit and quality of life, through lung transplant procedures.

The first surgically successful human lung transplant was performed in 1963 on a patient with squamous cell cancer of the left main bronchus (1). In the ensuing 40 years, nearly 26,000 lung transplants have been reported to the International Society of Heart and Lung Transplantation (ISHLT) Registry. Although there is no single authoritative body to set rules governing patient selection for lung transplantation, transplant physicians realized there was a need to standardize patient selection to improve patient outcomes and optimize impact of donor organs. In addition, standardized guidelines would bring justice and equity to the patient selection process while facilitating the evaluation process for patients as transplant centers would have similar criteria to approve patients for transplantation.

In 1998, transplant physicians representing the ISHLT, the American Society of Transplant Physicians, the American Thoracic Society, The European Respiratory Society, and the Thoracic Society of Australia and New Zealand convened and agreed on the first set of international guidelines for patient selection (2). They divided the guidelines into general medical conditions impacting eligibility and disease-specific criteria. These guidelines were to assist with timing of lung transplant referral as well as laying out general principles by which referred patients should be selected by individual transplant teams. The document did note, though, that each individual case should be viewed separately and that circumstances not covered by the guidelines would impact patient selection.

In 2005, the United States introduced a new lung allocation system that prioritizes patients on the wait list by a numerical score that accounts for likely post-transplant

survival and presumed wait list mortality as opposed to the historical reliance on wait list seniority (3,4). Additionally, in the interval after the first set of guidelines, the number of pulmonary transplants increased greatly, facilitating the ability to study and understand patient outcomes on the basis of transplant indication, pretransplant medical condition, and post-transplant course. With these changes in understanding and process, the international transplant societies met again in 2006 and created updated general and disease-specific guidelines for patient selection, reflecting the changing landscape in lung transplantation (5). Again, they emphasized that the guidelines were based on consensus expert opinion and retrospective single and multicenter studies, not prospective randomized trials.

II. Patient Selection

A. General Indications

The goal of transplant is a survival benefit with an improved quality of life. Only the patients with advanced illnesses in which transplant is thought to provide a survival benefit and improve quality of life should be considered for transplant. Patients with chronic end-stage lung diseases should have already received maximal medical management prior to pursuing lung transplantation. Patients must be informed of the risks and benefits of the procedure and demonstrated with a clear understanding of these complex issues that vary from disease to disease. In addition, patients must have demonstrated an ability in the past and a willingness in the future to follow medical guidelines as set by their transplant team (Table 1).

Table 1 Guidelines for Referral and Listing in Lung Transplantation

Chronic obstructive pulmonary disease

Referral:

- BODE index >5

Listing:

- BODE index of 7–10 or at least one of the following:
  - Hospitalization with exacerbation ($P_{CO2} > 50$ mmHg)
  - Pulmonary hypertension, cor pulmonale or both despite oxygen therapy
  - FEV1 <20% and either DLCO <20% or homogenous emphysema

Pulmonary fibrosis

Referral:

- Histologic or radiographic evidence of UIP (irrespective of vital capacity)
- Histologic evidence of fibrotic NSIP

Listing:

- Radiographic or histologic evidence of UIP and any of the following:
  DLCO <39% predicted
  10% or greater decrement in FVC over 6 mo
  Desaturation below 88% during 6-MWT
  Honeycombing on HRCT with fibrosis score >2
- Histologic evidence of NSIP and any of the following:
  DLCO <35% predicted
  10% or greater decrement in FVC over 6 mo
  15% or greater decrement in DLCO over 6 mo

(*Continued*)

Table 1 Guidelines for Referral and Listing in Lung Transplantation (*Continued*)

Cystic Fibrosis
Referral:
- FEV1 <30% predicted or rapid decline (particularly in young women)
- Exacerbation of pulmonary disease requiring ICU stay
- Increasing frequency of exacerbations requiring ICU stay
- Refractory or recurrent pneumothorax
- Recurrent hemoptysis not controlled by embolization

Listing:
- Oxygen-dependent respiratory failure
- Hypercapnia
- Pulmonary hypertension

Pulmonary arterial hypertension
Referral:
- NYHA functional class III or IV, irrespective of ongoing therapy
- Rapidly progressive disease

Listing:
- Persistent NYHA class III or IV despite maximal medical therapy
- Low (<350 m) or declining 6-MWT
- Failing therapy with intravenous epoprostenol or equivalent
- Cardiac Index less than 2 L/min/m^2
- Right atrial pressure exceeding 15 mmHg

Sarcoidosis
Referral:
- NYHA functional class III or IV

Listing:
- Impairment of exercise tolerance and any of the following:
  - Hypoxemia at rest
  - Pulmonary hypertension
  - Elevated right atrial pressure exceeding 15 mmHg

Lymphangioleiomyomatosis and pulmonary Langerhans cell histiocytosis
Referral:
- NYHA functional class III or IV

Listing:
- Severe impairment in lung function and exercise capacity
- Hypoxemia at rest

Source: Adapted from Ref. 5.

B. General Contraindications

Although it is impossible to come up with a complete list of all individual clinical conditions that would contraindicate transplantation for a patient, certain illnesses are more prevalent and play a greater role in disqualifying potential transplant recipients. As

Table 2 Contraindications to Lung Transplantation

Absolute contraindications:

- Malignancy in last 2 yr except squamous and basal skin cancers
- Untreatable advanced dysfunction of nonpulmonary major organ system
- Noncurable chronic extrapulmonary infection
- Documented nonadherence or inability to participate in medical care
- Untreatable psychiatric or psychological condition leading to nonadeherence
- Absence of reliable, consistent social support network
- Substance addiction, active or within last 6 mo

Relative contraindications:

- Age greater than 65
- Clinical instability (shock, mechanical ventilation, ECMO)
- Severely limited functional status with poor rehabilitation potential
- Colonization with resistant or virulent bacteria, fungi, or mycobacteria
- Severe or symptomatic osteoporosis
- Mechanical ventilation
- Severe obesity, BMI >30 kg/m^2

Source: Adapted from Ref. 5.

stated, the end goal of transplantation is prolonged and improved quality of life. As a result, any medical condition that can greatly increase perioperative mortality would contraindicate transplantation. In addition, illnesses that in their own right are potentially terminal or require ongoing invasive therapy are also contraindications to transplant. The new ISHLT guidelines specifically lay out clinical scenarios that would prevent patients from being selected as demonstrated below (Table 2) (5).

A prior malignancy in the two years preceding transplant evaluation is an absolute contraindication with the exception of squamous and basal cell cancers of the skin. Many transplant physicians believe it prudent to demonstrate a five-year disease-free period prior to listing for lung transplantation. Historically, patients have received lung transplants for bronchoalveolar cell lung cancers. This practice is significantly diminishing as these malignancies can recur, although individual patients have received significant survival benefit.

Untreatable end-stage dysfunction of a second organ system in addition to chronic, advanced lung disease contraindicates lung transplant. In the setting of coronary artery disease, vascular lesions that are not amenable to percutaneous intervention or bypass grafting contraindicate transplant. In special circumstances, patients with organ failure in a second organ other than the lung can undergo dual organ transplant when considered appropriate by the treating physicians.

Patients with chronic, noncurable extrapulmonary infections should not receive lung transplants. These infections include chronic active viral hepatitis B, hepatitis C, and HIV. It is thought at this time that the addition of immunosuppression in the face of these ongoing infections would lead to excessive infection-related morbidity and potentially mortality.

Lastly, patients with advanced chest wall or spinal deformity are contraindicated from lung transplantation. These deformities complicate the surgical procedure itself and result in undue perioperative risk for the patient such that it is believed that survival benefit favors medical management over transplant.

In addition to the physical conditions that contraindicate lung transplantation, the new ISHLT guidelines included psychosocial absolute contraindications to lung transplantation (5). Inability to adhere to a complex medical regimen and schedule are contraindications. This includes both prior documented nonadherence as well as untreatable psychological or psychiatric conditions that would prevent adherence. Absence of a sustained and reliable social support network is also a contraindication as patients require both emotional and logistical support. Finally, substance addiction including, but not limited to, alcohol, tobacco, and recreational drugs with ongoing use or use within the last six months is considered a contraindication.

In addition to the absolute contraindications listed in the new selection guidelines from 2006, the group of transplant physicians compiled relative contraindications. These circumstances and medical conditions have the potential to increase patient morbidity and mortality, especially when patients have more than one of them but were not considered strong enough indicators of poor outcome to individually preclude transplant (5).

Older patients have increased mortality following lung transplantation (6). As a result, age greater than 65 is a relative contraindication to lung transplantation. Age as an entity itself is likely not an issue, although older patients are more likely to have multiple comorbidities that may impact transplant outcome and postsurgical recovery. Older patients require careful and thorough screening in addition to extended physician-patient discussions regarding risk and benefit.

Critical illness and clinical instability are relative contraindications. Examples of these include shock, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO), although mechanical ventilation in carefully selected patients with solitary respiratory insufficiency is not a contraindication (7). Patients able to participate in rehabilitation programs while on mechanical ventilation have been transplanted successfully. This potential recipient population requires careful screening.

In general, poor functional status with limited rehabilitation potential is considered a relative transplant contraindication. Anecdotal evidence suggests that patients with poor rehabilitation potential prior to transplant do not demonstrate improved physical rehabilitation potential after transplant. Similarly, patients with severe obesity as demonstrated by a BMI greater than 30 to 35 kg/m^2 are considered less optimal transplant candidates as are those with symptomatic osteoporosis.

Patients colonized with highly resistant or highly virulent bacteria, fungi, or mycobacteria are at risk for severe post-transplant infections that may be difficult to control in the immunosuppressed patient. This comes into play in particular in cystic fibrosis (CF) as well as bronchiectasis in general. When recognized preoperatively, these infectious processes can be treated appropriately at the time of transplant and need not result in excess morbidity and mortality.

Lastly, patients underlying medical conditions that have yet to result in significant end organ damage require adequate treatment and stabilization prior to selection for lung transplantation. Diabetes mellitus treatment must be optimized and blood pressure be controlled. Gastroesophageal reflux disease and peptic ulcer disease should be treated as

reflux and aspiration have been correlated to chronic rejection (8,9). All ischemic heart diseases should be treated before or during the transplant procedure.

C. Disease-Specific Criteria

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) affects approximately 14 million people in the United States and is the fourth leading cause of death (10). COPD is an illness marked by progressive obstruction of airflow during expiration secondary to dilation of airspace with loss of lung parenchyma, decreased lung elasticity, and closure of small airways. Most commonly, COPD is associated with current or former tobacco smoking.

COPD remains the most common indication for lung transplantation (6,11). Despite this, there is still debate as to whether lung transplantation provides a survival benefit for patients with end-stage COPD (12–14). Prognosis is difficult to determine as patients with advanced COPD often survive for years while severely symptomatic. As a result, transplantation in the setting of COPD can at times become an issue of improved quality of life.

In general, increasing mortality in COPD patients correlates with advancing age, increasing hypoxemia, hypercapnia, increasing pulmonary hypertension, decreasing diffusing capacity (DLCO), and decreasing BMI, although there is no specific algorithm of these factors to calculate predicted mortality in an effort to determine potential transplant benefit (15,16). Additionally, hospitalization resulting from acute COPD exacerbations with hypercapnia has been associated with approximately 50% mortality (15). Historically, though, FEV1 has been utilized to follow patient trajectory and determine the point at which survival benefit may favor lung transplantation, but it is now appreciated that health-related quality of life can be an independent predictor of mortality in COPD (16,17).

Accounting for both disease state and quality of life issues, the BODE index attempts to stratify COPD patients through a standardized scoring system. This index is a composite of body mass index, airflow obstruction, dyspnea, and exercise tolerance with patients receiving a numerical score for each category. Elevated BODE scores of 7 to 10 on a scale from 0 to 10 have been associated with a median survival of three years (Table 3) (11,18). Given that median survival with lung transplantation is five years, these patients with high BODE scores will receive a survival benefit from transplantation. Similarly, the National Emphysema Treatment Trial (NETT) looking at lung volume reduction surgery identified a group of COPD patients with FEV1 less than 20% and either a DLCO less than 20% or homogenous emphysema with a median survival of three years who did not receive a survival benefit from lung volume reduction surgery. This population would also receive a survival benefit from lung transplantation (19). Further investigation of the NETT patient population demonstrated that patients with a one-point increase in their BODE index over a 6- to 24-month period exhibited a twofold increase in mortality in the medically managed group and a threefold increase within the lung volume reduction cohort (20). In addition to absolute BODE score, serial measurement may provide insight into timing of patient referral and ultimate listing.

As demonstrated, timing of referral for transplant evaluation can be challenging in COPD as patient clinical trajectory can be difficult to predict. The new ISHLT guidelines suggest that patients with BODE scores greater than 5 should be referred for transplant evaluation if they have interest. These same guidelines suggest that BODE

Table 3 BODE Index Calculation System

	Score			
	0	1	2	3
Body mass index	>21	≤21		
Obstruction (FEV1 % of predicted)	≥65	50–64	36–49	≤35
Dyspnea (modified Medical Research Council scale)	0–1	2	3	4
Exercise tolerance (6-MWT distance in meters)	≥350	250–349	150–249	≤149

Source: Adapted from Ref. 18.

index greater than 7 is an indication for transplant listing. In addition, history of hospitalization with a Pco_2 greater than 50 mmHg, pulmonary hypertension or cor pulmonale despite oxygen therapy, and FEV1 less than 20% and either DLCO less than 20% or homogeneously distributed emphysema are all individual indications for transplant (5). As with all disease states, though, each patient must be viewed and evaluated separately with these guidelines as a reference but not a rule.

Pulmonary Fibrosis (Idiopathic Pulmonary Fibrosis and Nonspecific Interstitial Pneumonia)

Pulmonary fibrosis is a general term referring to destruction of lung parenchyma and airways with resultant fibrotic transformation (21). These architectural changes are most often associated with idiopathic interstitial pneumonias (IIPs) but can also occur as end-stage changes in other infectious and inflammatory diseases. Of the IIPs, idiopathic pulmonary fibrosis (IPF) with its characteristic usual interstitial pneumonia (UIP) pattern of histopathology carries the worst prognosis with median survival of 2.5 to 3.5 years after initial diagnosis and is the second most common indication for lung transplantation (11,22). With the implementation of the new lung allocation score system in the United States, IPF has become the most prevalent indication for lung transplantation in the United States (11).

It is important to note that not all patients with a UIP pattern on surgical lung biopsy have IPF. Multiple different disease processes can result in a UIP pattern including collagen vascular diseases, chronic hypersensitivity pneumonitis, and drug reactions, although the presence of a UIP histopathology often notes an end-stage process and signals patients with increased mortality (21,23–25). Similarly, nonspecific interstitial pneumonia (NSIP) is a histopathology that can mark multiple disease states, although the clinical course of patients with NSIP varies greatly and depends on both the cause of the pulmonary pathology as well as the subset of NSIP present (26,27). Patients with fibrotic NSIP have increased short-term mortality in comparison to those with cellular NSIP. A subset of fibrotic NSIP patients with severe functional impairment at presentation or a decrease in objective pulmonary function, most notably DLCO, after 6 to 12 months of therapy have 2-year mortalities equaling that of IPF patients (28,29). Unlike IPF, NSIP may respond to therapeutic interventions, and all patients should be offered a trial of therapy before consideration of lung transplantation. This real potential for clinical improvement in the setting of NSIP results in uncertainty in the timing of transplant referral and listing.

Historically, patient pulmonary function played an integral role in determining optimal timing for transplantation in patients with pulmonary fibrosis (30). Patients with forced vital capacities less than 60% predicted were thought to have increased mortality, although it is now appreciated that patients with preserved pulmonary function have similar mortalities resulting from acute exacerbations of IPF (31). Decline in pulmonary function over time has been correlated to decreased survival in both IPF and fibrotic NSIP and can be instructive as to determining when survival benefit favors transplantation (23,28,30–34).

In addition, imaging and exercise capacity have been evaluated as diagnostic tools in the timing of transplantation in pulmonary fibrosis. Patients with radiographic changes demonstrating classic features of UIP with honeycombing and without significant ground glass opacities have increased mortalities (5,34–37). As a result, multiple fibrosis score systems based on pathognomonic radiographic changes have been created, all of which have correlated with impaired survival and have the potential to assist in timing of transplantation. Similarly, exercise capacity in the form of the six-minute walk test (6-MWT) has proven to be clinically prognostic and can assist in risk stratifying potential transplant recipients. Desaturations to less than 88% and inability to walk more than 679 ft have both been correlated to increased mortality (38,39).

A special subgroup of patients are those with pulmonary fibrosis, whether it be UIP or NSIP by histopathology, secondary to collagen vascular disease. Complicating their pre- and post-transplant course is the systemic nature of the underlying illness driving their pulmonary pathology. Scleroderma, Sjogren's disease, rheumatoid arthritis, and mixed connective tissue disease all may result in pulmonary fibrosis of either the UIP or NSIP histopathology. Collagen vascular disease is now a rare indication for transplantation accounting for less than 1% of lung transplants (11). There is little data regarding the pre- and post-transplant course of these patients. Each patient must be viewed individually, although patients with active systemic disease, especially active vasculitis, should not be referred for transplant.

The most recent ISHLT guidelines from 2006 suggest referral for all patients with radiographic evidence or histopathology suggestive of UIP and for those with histopathology demonstrating fibrotic NSIP. Listing for transplantation is recommended when these patients with UIP have a DLCO less than 39% predicted, a greater than 10% decrease in FVC over six months, a desaturation to less than 88% on a 6-MWT, or honeycombing on CT scan with a fibrosis score of greater than 2. For those patients with NSIP, transplant listing is recommended when DLCO is less than 35% predicted; DLCO decreases by 15% over six months or FVC decreases by 10% over six months (5).

Cystic Fibrosis

CF is an autosomal recessive genetic disorder with varying penetrance resulting in multiorgan pathology symptomatic in the lung with bronchiectasis and its related infectious and anatomic complications (40,41). CF remains the third most common indication for lung transplantation despite recent concerns regarding survival benefit in the pediatric population (11,42). The multiorgan nature of CF also complicates potential transplantation as can chronic infections with antibiotic-resistant pathogens. Even with these varied potential post-transplant complications, CF patients when taken as an entirety have equal or improved outcomes in comparison to other transplant recipients (12–14,43–45).

When weighing the potential survival benefit of transplant, the risk of infection with drug-resistant organisms must be considered in the CF population as these infections can be challenging to treat in the post-transplant immunosuppressed patient. Many CF patients prior to transplant are colonized or chronically infected in both the upper and lower airways as well as the sinuses. These chronic low-level processes are not contraindications to transplant, although patients with active infections resulting in fever and leukocytosis immediately prior to surgery have increased postoperative sepsis (46). Patients with overt sepsis preoperatively should not be transplanted.

Colonization with different organisms results in varying post-transplant risk. Known colonization with multidrug-resistant *Pseudomonas aeruginosa* is not considered to be a transplant contraindication. Studies have demonstrated no impact of this infection on short-term post-transplant survival (46–49). While data is lacking, methicillin-resistant *Staphylococcus aureus*, resistant gram-negative bacilli, and *Aspergillus fumigatus* are not thought to impact early post-transplant survival and are not considered contraindications (5).

Unlike with the above organisms, observational data demonstrate worse one-, three-, and five-year survival in patients known to be colonized with *Burkholderia cepacia* with a 30% to 40% increased mortality at all three time points (44,46,49–51). However, colonization with *B. cepacia* complex is not an absolute contraindication to transplant as patients colonized with this organism have undergone successful transplantation (5). Retrospective studies have linked *B. cepacia*-related mortality to *B. cenocepacia* (or the genomovar III species) (49,52–54). As a result, some transplant centers opt not to transplant patients with genomovar III species of *B. cepacia* necessitating careful speciation of pathogens (55,56). When patients are known to be colonized with resistant organisms, antibiotic susceptibility should be completed at routine intervals while patients are on the transplant waiting list. This will allow for appropriately directed antibiotic regimens in the peritransplant period.

Patients with CF have clinical courses that can also be complicated by liver disease. No specific guidelines exist to determine severity of liver disease at which lung transplantation would be contraindicated without combined liver-lung transplantation (5). Lung transplantation has been safely performed in patients with controlled portal hypertension and preserved hepatic function in the setting of CF (57). For the general population, a model of end-stage liver disease (MELD) score of 24 signifies advanced liver disease requiring transplantation, although this number has not been validated in CF patients.

Many patients with CF have actively advancing respiratory disease and may eventually require mechanical ventilation. At this time, there is no consensus in relation to transplantation of CF patients receiving mechanical ventilation (5). For the general transplant population, the ISHLT registry demonstrates that pretransplant mechanical ventilation is associated with increased post-transplant mortality. In the setting of CF, single center studies as well as the UNOS database suggest that this increased post-transplant mortality may not correlate with pretransplant mechanical ventilation in the CF population (44,58,59). Initiating mechanical ventilation remains a challenging clinical decision in CF patients listed for transplant as these patients often go on to develop sepsis with acute multiorgan disease and can no longer participate in potentially necessary end of life discussions and decisions. The most recent ISHLT guidelines recommend that lung transplantation should only be considered in CF patients requiring mechanical ventilation if they have been evaluated and listed for transplant prior to

initiation of mechanical ventilation, they have been notified and understand that clinical deterioration after intubation may contraindicate transplantation, they have single organ (pulmonary) failure, and they agree to mechanical ventilation (5).

Predicting survival in CF patients can be difficult. Historically, survival estimates were based on a single center study with mortality thought to correlate with FEV1 less than 30% predicted and to a lesser extent $Paco_2$ greater than 55 mmHg, Pao_2, age less than 18 and female gender (60). More recent data from national and single center registries has been utilized to create multivariate mathematical models predicting mortality in the CF population. Initial comparison to transplant outcomes demonstrated five-year survival advantage through transplantation in the patient population with predicted five-year survival less than 50% and without *B. cepacia* and CF arthropathy (51). Later studies utilizing the same model with a different and larger cohort did not confirm the above findings and provided no predictive benefit over the historical prognostic reliance on FEV1, although some do question this later study as it evaluated two-year mortality as opposed to five year (37,61). This difficulty in predicting outcome in CF patients likely reflects the variation in organ involvement and severity within the larger CF population.

The most recent ISHLT guidelines recommend referral for evaluation when CF patients have an FEV1 less than 30% predicted or a rapid decline in FEV1 particularly in young female patients (5,62–64). Increasing frequency of exacerbations requiring antibiotics as well as an exacerbation requiring care in an intensive care unit are also indications for referral. In addition refractory or recurrent pneumothorax and hemoptysis not responsive to embolization are considered indications for referral. The current guidelines recommend transplantation for oxygen-dependent respiratory failure, hypercapnia, and pulmonary hypertension (5). At this time, there are no recommendations in the guidelines pertaining to non-CF bronchiectasis due to lack of sufficient data.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a disease characterized by increased resistance of the pulmonary vasculature, resulting in potentially fatal right-heart failure with patients experiencing dyspnea and edema (65). Pulmonary hypertension can be idiopathic or secondary to either pulmonary parenchymal disease, chronic thromboses, or systemic inflammatory disorders (66). The majority of our understanding of PAH derives from studies of idiopathic or primary PAH, although the heterogeneous nature of this disease creates complexity in categorizing patients and their potential clinical outcomes. Many new therapies are available for the treatment of PAH, making it challenging to prognosticate mortality and determine optimal timing for transplantation. Ultimately, poor prognosis is linked to degree of right heart failure as opposed to an absolute value of the pulmonary hypertension.

The etiology of pulmonary hypertension plays a role in determining pretransplant mortality. PAH secondary to pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis carry the worst prognosis as they lack medical therapies (5). On the other end of the spectrum, patients with congenital left to right shunts have decreased wait list mortality at one, two, and three years in comparison to those with idiopathic PAH (67). Even in the setting of epoprostenol therapy, PAH secondary to systemic sclerosis has a greater wait list mortality than idiopathic PAH, likely as a result of the systemic nature of the disease process (68,69).

Cardiopulmonary symptoms as assessed by the New York Heart Association (NYHA) and World Health Organization (WHO) functional class and the 6-MWT correlate with survival in idiopathic PAH (70). Those patients with NYHA class III/IV heart failure have increased mortality. Additionally, patients unable to walk greater than 332 m on a 6-MWT regardless of therapy have increased mortality (70). The 6-MWT remains the mainstay evaluation of clinical functional status in this disease process.

Patients with PAH undergo hemodynamic testing as part of their routine care. Through these procedures, severity of pulmonary hypertension and right heart compromise can be measured while acute reversibility with vasodilator therapy can be determined. Although acutely reversible patients are more amenable to medical therapy, it is not considered a predictor of increased survival (5). While 12% of idiopathic PAH patients respond to vasoreactive testing, only 6% have long-term responses to calcium channel blockers, and these patients do not receive a survival benefit in relation to patients with congenital right to left shunts that do not respond to vasoreactive testing (71).

Patients with more severe pulmonary hypertension and right heart compromise have increased mortality. The National Institute of Health Registry of Pulmonary Hypertension demonstrated that untreated patients with a cardiac index of 2 L/min/m^2 or less had greater mortality than those with a cardiac index of 4 L/min/m^2 or greater (72). Similarly, those with a right atrial pressure of greater than 20 mmHg exhibited increased mortality over those with right atrial pressure of 10 mmHg or less as did those with mean systolic pulmonary artery pressure of 85 mmHg in relation to those with a mean systolic pulmonary artery pressure of less than 55 mmHg (72). These increased indices, though, do not predict responsiveness to medical therapies and were determined from a cohort of untreated patients.

Continuous IV epoprostenol improves outcome including survival in idiopathic PAH (71,73). This treatment benefit has not been redemonstrated in secondary PAH (68). There is hope that newer medical therapies including bosentan and treprostinil may enlarge the patient population receiving survival benefit from medical intervention. Large clinical trials are still lacking to prove this theory.

The most recent ISHLT guidelines recommend referral for transplant evaluation in all patients with PAH and NYHA functional class III/IV irrespective of therapeutic interventions. In addition, all patients with rapidly progressive disease should be evaluated for transplant. Patients should be considered for transplant listing if they have persistent NYHA functional class III/IV despite maximal medical therapy, low ($<$350 m) or declining 6-MWT, cardiac index of less than 2 L/min/m^2, or right atrial pressure exceeding 15 mmHg. Those patients who are failing therapy with IV epoprostenol or equivalent should also be considered for immediate listing.

III. Special Considerations

A. Retransplantation

Retransplantation of a second pulmonary allograft has been attempted in the setting of primary graft dysfunction, chronic rejection, and nonreversible anatomic airway complications. With primary graft dysfunction, outcomes following retransplantation have been suboptimal, and retransplantation in this setting is not encouraged (74–76). Patient courses following retransplantation for airway complications such as dehiscence or strictures are mixed (74,76). Chronic rejection, or bronchiolitis obliterans syndrome, is the one scenario in which patient outcome after retransplantation approaches that of

initial transplantation (74–76). Additionally, the new allocation score system with its emphasis on wait list urgency has made retransplantation a more viable option for patients with chronically worsening lung function because of bronchiolitis obliterans syndrome. Since the development of the new lung allocation system, retransplantation for chronic rejection has increased markedly (75).

B. Organ Allocation

Historically, seniority, or accrued time, on the transplant wait list was the main criteria by which potential recipients where chosen to receive appropriately matched organs. In 2005 in the United States, the new lung allocation score system came into effect. At the time of listing, patients receive a numerical score with higher scores signifying increased priority. These scores take into account medical urgency and net transplant benefit with medical urgency also being a component of net transplant benefit (3). This new emphasis on urgent medical necessity has altered the demographics of patients receiving lung transplants with IPF becoming a more common indication and COPD decreasing in prevalence, although COPD still remains the most common indication worldwide for lung transplantation at this time (11). While the selection guidelines require vigorous patient evaluation, it is thought that this emphasis on transplanting patients with more advanced disease processes may be resulting in transplantation of a less-healthy patient population. At this time, it still remains unclear what impact this is having on long-term patient outcomes.

IV. Summary

While lung transplantation is becoming an increasing reality for many patients with end-stage lung disease, allograft availability continues to limit patient access to this life-saving procedure. Patient selection remains a crucial first step to maximize benefit from each donor allograft. Additionally, the selection process assists in ensuring that potential recipients gain survival and quality of life advantage through lung transplantation. Patients are evaluated to determine if their disease has progressed to a state where they benefit from transplantation but have not progressed to the point where perioperative risk would be too great. Those patients thought to benefit from a pulmonary perspective, then receive a thorough evaluation of their nonpulmonary health status as well as their social situation. When patients' pulmonary and general health picture favors quantity and quality of life through transplantation, they are then selected for lung transplantation.

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11
Recipient Management Pretransplant

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I. Introduction

Advanced pulmonary disease (APD) refers to a group of chronic, non-neoplastic lung disorders characterized by progressive decline in lung function, impaired quality of life (QOL), and premature mortality (1). Medical comorbidities in this population are common and may adversely affect prognosis before and after lung transplantation (LT). When severe, nonpulmonary disorders may be considered relative contraindications to transplant candidacy (2). We will review selected medical comorbidities including coronary artery disease (CAD), malnutrition, osteoporosis, and deconditioning, with particular attention to the available evidence for pretransplant optimization.

II. Coronary Artery Disease

In the 2008 International Society for Heart and Lung Transplantation registry, cardiovascular disease is reported as the cause of death in 11% of patients in the first month after transplant and 3% to 6% in subsequent years (3). As defined by more than 50% stenosis in a major epicardial coronary artery, up to 17% of patients referred for LT evaluation will have asymptomatic CAD (4–6). While the majority of patients studied carried a diagnosis of chronic obstructive pulmonary disease (COPD), a similar prevalence of 12% has been reported in patients with pulmonary fibrosis (7).

Medical management of CAD in LT candidates includes treatment of modifiable risk factors such as hypertension, hyperlipidemia, and diabetes mellitus. Treatment is complicated in COPD, where medications including beta-agonists and anticholinergics have been associated with an increased risk of arrhythmia, myocardial infarction, and death in some but not all studies (8,9). Despite data demonstrating the efficacy and safety of cardioselective beta-blockers (10), they are often withheld from this population.

Invasive management includes preoperative revascularization with percutaneous coronary intervention or concomitant coronary artery bypass grafting (CABG). Operative times for sequential CABG and LT are similar to standard single or double LT where noted (6). Longer intensive care and hospital length of stay (LOS) have been reported in some concurrent CABG and LT patients when compared to standard LT patients (4,6). Complications include myocardial infarction, in-stent restenosis, supraventricular arrhythmia, re-exploration for postoperative bleeding, and prolonged mechanical ventilation (6,11). Long-term follow-up is limited, but one study

demonstrated similar mean survival in patients with revascularized CAD versus those without CAD (12).

III. Nutrition

The National Heart, Lung and Blood Institute defines an underweight person to have a body mass index (BMI) of less than 18.5 kg/m^2 and an obese person to have a BMI $\geq$30 kg/m^2. Twenty-two percent of adult cystic fibrosis (CF) patients (13) and up to 75% of LT candidates with CF are malnourished (14). In a European CF registry, indicators of poor nutrition were associated with a greater than 10% decrease in FEV_1 compared to normal weight patients (15). The effect on mortality is controversial, as some reports indicate a correlation with survival independent of lung function (16). In stable outpatients with COPD, 10% to 30% have nutritional depletion, although one study of LT candidates showed a prevalence of 58% (14,17,18). Underweight COPD patients have an increased risk of hospitalization and higher all-cause mortality independent of lung function (17,18). Because of its prognostic value, BMI has been incorporated into the multidimensional BODE index that predicts mortality in COPD (19). In LT recipients, preoperative malnutrition predicts poor post-transplant outcomes, including increased length of mechanical ventilation, longer intensive care stay, and worse survival (14,20).

For malnourished patients with COPD, caloric intake should be 150% of normal (21), but nutritional supplementation is of limited efficacy (22). Dietary counseling may promote weight maintenance and improve dyspnea and QOL (23). Studies of pharmacologic supplementation have not shown consistent improvements. Other targets include optimization of pulmonary function, controlling exacerbations, limiting prednisone use, and treatment of depression and anxiety.

In CF, energy intake should be 110% to 200% of normal with a goal to maintain BMI in women $\geq$22 and in men $\geq$23 (13). A standard diet with 35% to 40% of calories from fat is recommended. Patients with weight loss should be evaluated for inadequate caloric intake, malabsorption, and diabetes mellitus. In those who do not respond to dietary or behavioral interventions, oral supplementation should be considered, although the limited data do not suggest a significant benefit (24). In patients who fail oral supplementation and dietary counseling, nocturnal supplementation has been shown to be effective in weight gain and stabilization of pulmonary function (25). Despite the prognostic importance of malnutrition, dietary supplementation has not been shown to directly improve post-transplant outcomes in any patient population.

The prevalence of obesity in patients with APD is poorly defined. Obesity has been shown to increase both short- (26) and long-term mortality (27) following LT. Because of its prognostic implications, obesity is considered a relative contraindication to transplant (2), and weight loss is strongly recommended before listing.

IV. Osteoporosis

The World Health Organization defines osteoporosis as bone mineral density (BMD) greater than 2.5 standard deviations (SD) below the mean of peak bone mass in young adults, also known as the T score. Osteopenia is present when the BMD falls between 1 and 2.5 SD below the mean. Risk factors for osteoporosis include older age, female gender, Caucasian race, personal or family history of osteoporosis or fragility fracture,

low body weight, tobacco and alcohol use, and physical inactivity. Secondary causes of osteoporosis include hypogonadism, thyroid and parathyroid disease, vitamin D deficiency, medications (notably steroids), and chronic systemic medical conditions.

Adolescents with CF fail to reach peak bone mass and young adults demonstrate accelerated bone loss rather than maintenance, at rates nearing those of postmenopausal women (28). In CF patients, the prevalence of osteopenia is 36% to 53% and osteoporosis is 9% to 18% (29,30). In COPD patients, osteopenia is present in 30% to 52% and osteoporosis in 9% to 41%; it is associated with disease severity, BMI, and steroid use (31,32). For all diagnoses, the lowest levels of BMD are seen in patients undergoing LT evaluation (33). Vertebral and other fractures are feared consequences of low BMD. A decrease in BMD of one SD increases the risk of fracture by a factor of 1.5 to 3 depending on the site (34). Each vertebral compression fracture decreases FVC by 9.4% (35), and up to 60% of patients with COPD and CF will experience at least one vertebral fracture (36,37).

All patients with APD should be assessed for bone loss with dual x-ray absorptiometry (DEXA) scans. Thoracic spine radiographs are the gold standard for detection of vertebral fractures. If low BMD is noted, secondary causes of osteoporosis should be evaluated. Treatment should be initiated in patients with osteoporosis, or osteopenia with risk factors for bone loss, and treatment starts with adequate calcium (>1200 mg/day) and vitamin D (>800 IU/day) intake as well as modification of risk factors. Patients with vitamin D deficiency should be repleted, with attention to serum and urinary calcium excretion. Bisphosphonates are considered first-line pharmacologic therapy and improve BMD with a decreased fracture risk in postmenopausal women and glucocorticoid-induced osteoporosis (38,39). Bisphosphonates have been studied in CF patients with significant improvements in BMD (40). In patients with severe disease or those who cannot tolerate bisphosphonates, teriparatide can be used, although cost and SC administration are limitations (41).

V. Deconditioning

Dyspnea and exercise limitation are universally present in patients with APD. The etiology of impaired exercise capacity is multifactorial, including cardiovascular, musculoskeletal, and psychological factors in addition to ventilatory and gas-exchange limitations. Exercise capacity predicts mortality in COPD patients as a component of the BODE index (19). In CF, improved aerobic capacity is predictive of survival, independent of age, sex, BMI, and FEV_1 (42). The degree of exercise intolerance is related to pulmonary function and nutritional status in both CF and COPD (43,44).

Comprehensive pulmonary rehabilitation (PR) is the standard of care for patients with APD, and recommendations have been published (45,46). PR is comprised of exercise training, education and self-management, and psychosocial and nutritional support. A recent meta-analysis of PR in COPD for 4 to 52 weeks demonstrated an improvement in exercise capacity and QOL (47). These benefits decline over time, although differences persist for at least 12 months. PR after a COPD exacerbation decreases hospital readmission by 87% and mortality by 61% (48). Randomized and uncontrolled trials have also shown that comprehensive PR decreases exacerbation frequency (49) and reduces hospitalization, hospital LOS, and physician visits (50).

Studies in CF demonstrated a trend toward stabilization of pulmonary function following PR (51). PR for patients with diffuse lung disease results in modest gains in

exercise tolerance and improved indices of dyspnea; these effects, however, are not sustained at six months (52). In patients with pulmonary arterial hypertension, exercise has traditionally been viewed as potentially detrimental. However, one trial of submaximal exercise training in these patients showed improved exercise capacity as measured by a mean increase in the 6-MWD of 111 m (53). Preoperative PR is recommended for all candidates undergoing evaluation for LT, although it is unclear to what extent preoperative PR affects post-transplant outcomes.

VI. Conclusion

Medical comorbidities of APD are frequent in LT candidates. Early identification and treatment of these inter-related, cormorbid disorders has the potential to improve pre- and post-transplant outcomes. A multidisciplinary team approach is required to provide comprehensive care to this complex patient population.

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12
Lung Donor Allocation Systems

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I. Introduction

The first human lung transplant was performed by Hardy at the University of Mississippi in 1963 after years of laboratory work using canine models (1). Success with lung transplant eluded thoracic surgeons until the introduction of cyclosporine A allowed for clinical success with heart-lung transplant at Stanford in 1981 (2), and isolated lung transplant at Toronto in 1983 (3). Early organ transplant efforts were complicated by a lack of consensus regarding brain death. Eventually, the medical community accepted the definitions proposed by an ad hoc committee from Harvard medical school (4) and they were adopted across the country. In 1984, the National Organ Transplant Act (NOTA) created the Organ Procurement and Tissue Network (OPTN) in the United States. The United Network for Organ Sharing (UNOS) was awarded the contract to run the OPTN in 1986 and has maintained it ever since.

In the 1980s, Toronto continued to champion isolated lung transplantation, while Stanford championed heart-lung transplantation as the preferred method to implant lungs. The first successful isolated lung transplant in the United States was performed by Raju at the University of Mississippi in 1987 (5). The technique of isolated bilateral-lung transplant developed at the University of Toronto (6) was improved by Noirclerc, in Marseilles, France, to address the problem of ischemic airway complications (7) and was later modified by Cooper's group after his move to Washington University in St. Louis from Toronto in 1988 (8). Isolated lung transplantation had come of age in the United States and became increasingly popular in Europe as an alternative to heart-lung transplantation in the early 1990s.

II. History of Lung Allocation in the United States

In 1990, responsibility for distribution of lungs for transplant in the United States was assumed by the OPTN, and UNOS developed policies specific to lung allocation. The UNOS Thoracic Organ Transplantation Committee decided that lungs should be distributed in a manner similar to that for hearts. Prospective candidates were prioritized for lung offers on the basis of accumulated waiting time. Lung offers were made first within the donation service area of the local organ procurement organization (OPO), then to candidates registered at transplant centers within concentric 500-nautical mile circles from the donor hospital. Within each allocation zone, offers were made first to ABO-identical recipients, then ABO-compatible recipients. Initially, the definition of "local" was interpreted by many programs to mean that individual programs had priority when

the donor was within their own hospital. This was later clarified by UNOS policy to define "local" as within a local OPO (9). UNOS thoracic organ policy provided for a "UNOS/STAT" designation for recipients judged to be at imminent risk of death. This designation allowed OPOs to "jump the list" and offer an organ to a program with a patient who was desperately ill. The "UNOS/STAT" designation was removed from UNOS policy in 1992 and was ultimately replaced by a system that allocated hearts by urgency status codes. Lungs continued to be allocated on the basis of waiting time. The demonstration of increased mortality among patients waiting for lung transplant with a diagnosis of idiopathic pulmonary fibrosis (IPF) [published years later (10)] prompted the UNOS Thoracic Organ Committee to change policy in 1995 to provide IPF patients listed for lung transplant 90 days of additional waiting time to attempt to direct organs to these patients because of their higher risk of wait-list mortality.

As the number of lung transplant programs grew in the 1990s, the number of suitable lungs from the conventional organ donor pool could not keep pace with the demand, and deaths on the waiting list quickly grew to 500 per year in the United States. Strict listing criteria were espoused (11), in part because of the donor shortage. An unintended consequence of employing waiting time for allocation was frustration experienced by OPOs trying to place lungs. The turndown rates in match run data were much higher for lungs than for hearts and livers, perhaps because intended lung recipients able to wait the longest could afford to wait even longer.

In 1998, the Department of Health and Human Services (DHHS) published the Final Rule on organ allocation (12). This required the OPTN to implement policies that (*i*) fostered broader geographic sharing of organs; (*ii*) reduced the importance of waiting time in allocation; and (*iii*) created equitable organ allocation systems focused on the use of objective medical criteria and medical urgency. The Institute of Medicine responded to the Final Rule with a report corroborating that organ allocation should be based on measures of medical urgency while avoiding futile transplants, should minimize the effect of waiting time, and should encourage broader geographic sharing of donor organs (13). The OPTN/UNOS Thoracic Organ Transplantation Committee established both Lung and Heart Allocation Subcommittees to recommend policy refinements in 1999. Meanwhile, the UNOS/OPTN Liver Committee devised the "MELD/PELD" system that allocated livers on the basis of a score related to recipient severity of illness (14).

III. Development of the U.S. Lung Allocation Score

The Lung Allocation Subcommittee's deliberations began in 1999. There was consensus that waiting time was not the most appropriate criterion for distribution of potentially life-saving organs. However, there were divergent opinions concerning potential remedies, the practicality of more widespread organ sharing because of concerns about ischemic time and its impact on outcome, and concerns about local program autonomy. Ultimately, the Subcommittee sought to develop a method of prioritizing candidates for lung transplant on the basis of principles of urgency and utility. After considerable discussion, four ethical principles (15) were considered: *equity*, a sense of fairness or impartiality, to eliminate bias or discrimination in selecting a recipient for a potential donor; *justice*, the principle of rendering to each individual what is due to him or her; *beneficence*, the requirement that physicians and surgeons act in ways reliably expected to result in a greater balance of clinical good over harm for their patients; and *utility*, the principle of making the best use of a scarce resource. The IOM report emphasized that it

was critical to balance justice with utility so as not to waste the precious resource of donor organs in short supply (13). The new system needed to be fair and to appear to be fair and, as much as possible, to be based on objective, evidence-based data. Although it was recognized that lung transplantation offers an opportunity to substantially improve quality of life among survivors, this is notoriously difficult to quantify, and reliable objective data on quality of life for wait-listed and transplanted patients in the United States was simply not available.

The Subcommittee believed that an ideal allocation system would minimize deaths on the waiting list and maximize the benefit of transplant by somehow incorporating post-transplant survival into the algorithm. This was a novel concept, not part of the MELD liver allocation system. The Subcommittee established these goals for the future lung allocation system: (*i*) reduction of lung waiting-list mortality; (*ii*) prioritization of candidates on the basis of urgency while avoiding futile transplants; (*iii*) de-emphasizing the role of waiting time; (*iv*) de-emphasizing geography within the limits of ischemic time; and (*v*) providing the ability for the algorithm to adapt to new information as therapy for end-stage lung disease and transplant practice changed (16).

In an effort to provide an evidence-based allocation system, the Subcommittee requested analyses by UNOS staff and later by the Scientific Registry of Transplant Recipients (SRTR), administered under federal contract by the University Renal Research and Education Association with the University of Michigan. These analyses used data collected at the time of listing and at the time of transplant to identify predictors of death on the waiting list and predictors of death after transplant. An obvious deficiency was that data was only available when patients were listed or transplanted and that the data submission at the time of listing was not mandatory, resulting in missing data fields. The Subcommittee decided to mandate data entry as a condition of listing to enable calculation of a score (as was the new policy for liver transplant recipients) and to mandate follow-up data entry to ensure that programs were in compliance with OPTN policies. As much as possible, the Subcommittee wished to exclude from the algorithm any factors that might be "gameable" or easily manipulated by patients or physicians, such as whether patients were on specific medications, such as steroids, or whether they were in hospital. Details of these analyses are reported elsewhere (17). The factors that were incorporated into the algorithm are listed in Table 1.

Table 1 Factors in Original Lung Allocation Score for U.S. Lung Allocation

Factors used to predict waiting-list survival	Factors used to predict post-transplant survival
FVC (% predicted)	FVC (% predicted)
PA systolic pressure	PCW mean pressure $\geq$20 mm Hg
O_2 required at rest (L/min)	Continuous mechanical ventilation
Age at offer	Age at transplant
Body mass index (BMI)	Serum creatinine (mg/dL)
Diabetes	NYHA Functional Status
NYHA functional status	Diagnosis
Six-minute walk distance $<$150 ft	
Continuous mechanical ventilation	
Diagnosis	

The next challenge was to decide how to incorporate factors that predicted wait-list and post-transplant survival probability into an allocation system. The Subcommittee adopted a new principle in organ allocation policy, to include "benefit" in determining a prioritization scheme to make donor offers to potential candidates. The risk factors were used to predict survival probability curves both with and without a transplant when a size-appropriate donor became available. Transplant benefit was defined as the difference in days of survival a lung transplant would theoretically add, based on estimated survival with or without a transplant. Because wait-list survival figures into both determination of urgency and transplant benefit, the system prioritizes wait-list survival, as a surrogate for urgency, more than post-transplant survival. However, the lung allocation algorithm is the only U.S. organ allocation algorithm that incorporates post-transplant survival probability into allocation policy to reduce the probability of performing futile transplants.

A lung allocation score (LAS) is calculated for each possible recipient when a donor is available based on clinical data provided by transplant centers. This data can be updated at any time to allow the score to reflect current probabilities of waiting-list and post-transplant survival probabilities. Certain data elements *must* be updated every six months. A Lung Review Board was created to review situations in which a treating physician has a reason to believe that an LAS may not adequately reflect the needs of a particular candidate or where diagnostic data needed to calculate a score were not available for a particular candidate.

IV. Impact of the LAS on Lung Transplant in the United States

In June 2004, the OPTN/UNOS Board of Directors adopted the new lung allocation policies proposed by the Thoracic Committee. U.S. transplant centers had to submit updated clinical data, and OPTN computer programmers had to transform the concept into executable code. Five years after the Lung Allocation Subcommittee's deliberations began, the new Lung Allocation System was introduced on May 4, 2005. There was an immediate change in the "mix" of patients being offered lungs for transplant, with substantially more patients with IPF being transplanted. There was a dramatic reduction in deaths on the waiting list, and a 40% increase in the number of lung transplants performed (Fig. 1).

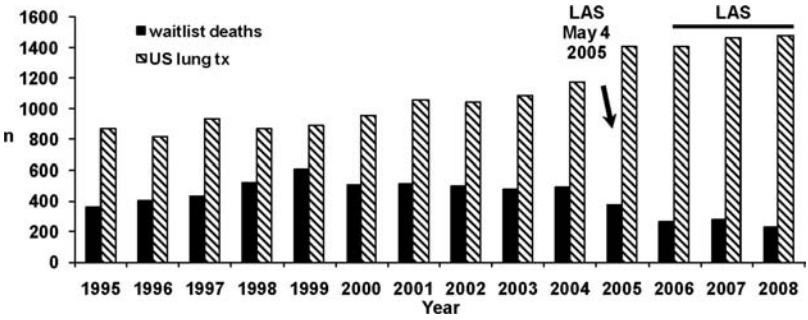

Figure 1 Number of deaths on the OPTN waiting list (*black bars*) and number of lung transplants performed (*hatched bars*) by year in the United States. *Source*: From Ref. 18.

Although the "Donor Collaborative" that began in 2003 was responsible for some increase in overall organ donor numbers, the sudden increase in lung transplant activity in 2005 was more likely attributable to the new lung allocation policy directing lung offers to patients at high risk of dying without a transplant. The median number of lung donor offers made by OPOs to place lungs fell from 10 to 3, making placement of lungs more efficient (19) and possibly increasing the utilization of "marginal" lungs for patients who were desperately in need. Despite the fact that patients receiving lung transplant are presumably sicker (more at risk of death on the waiting list) and there is a higher percentage of patients with IPF receiving transplant, one-year survival after transplant has been remarkably unchanged. Although a small number of patients with a very high LAS score have a higher one-year mortality than other patients (20), these individuals would likely have expired on the waiting list under the previous system that allocated lungs on the basis of waiting time. Despite the controversy surrounding development and implementation of the new system, the lung allocation system appears to have met its initial objectives, although further modifications will improve it (21). Ironically, as deaths on the waiting list fall, the ability to accurately identify hazards for death among wait-listed patients will also diminish.

It was the intent of the Subcommittee that the algorithm undergo modification every six months on the basis of analysis of the most recent three-year cohort of wait-listed and transplanted patients. However, very few modifications have been made. Recent revisions include the addition of pCO_2 to calculation of the LAS because changes in pCO_2 were shown to be associated with increased risk of wait-list mortality for candidates. The system still allows for local allocation first (within a local OPO) before more wider geographic offering, although simulation models predict a 15% reduction in wait-list mortality if lungs are allocated to potential recipients within 500 nautical miles instead of first within a local OPO (22). Ironically, this same simulation model predicted the same modest reduction in wait-list mortality with introduction of the new lung allocation system so the impact of doing away with primary allocation within a local OPO may be more beneficial than predicted by simulation. The arguments in favor of local allocation being favored because of the benefit of shorter ischemic time are no longer valid in the era of Perfadex™ (Vitrolife, Kungsbacka, Sweden), which has increased the safe cold preservation time (23). Indeed, ischemic time is no longer a risk factor for early death after lung transplant (24).

V. Lung Allocation in Other Countries

Other countries have dealt with similar issues in allocation of too few lungs to meet the demands of growing numbers of patients with end-stage lung disease and have developed allocation policies for patients who require heart-lung transplants. There appears to be growing interest in exploring systems similar to the American lung allocation system to allocate lungs for transplant on the basis of urgency rather than waiting time. Subjective criteria defining urgency vary in different countries. The role of geography in allocation is quite variable. However, given the difference in size of countries, that is not surprising. Although cold preservation times might allow "national" allocation systems, the cost of rapid long-distance transportation and the logistics need to be factored in. In the United States, it may not be practical to ship a lung from Seattle to Miami ($\sim$3000 miles), although this is currently performed for a "six antigen match" kidney.

Below is a brief summary of lung allocation practices in various locales as of 2009.

A. The United States

Unlike other countries, the United States has a "for profit" health care system, so centers compete with one another to perform transplants and other procedures. In 2008, 66 U.S. hospitals performed lung transplant procedures (18). Lungs are allocated to recipients of age 12 and older by LAS, calculated on the day of offer from updated data provided by lung transplant centers. Allocation is made first to recipients within a local OPO [the United States has 58 OPOs, with little relationship to state borders (18)], then within concentric 500-nautical mile circles. Lung allocation to pediatric recipients under age 12 is on the basis of waiting time.

B. Canada

Canada has five lung transplant programs. Organs are allocated first within geographic zones corresponding to the location of the transplant centers. Subjective criteria (defined by transplant team members) are used to stratify potential recipients on the basis of severity of illness.

C. Eurotransplant

Eurotransplant includes Austria, Belgium, Croatia, Germany, Luxembourg, Slovenia, and the Netherlands. Member countries share lungs for potential recipients with a high urgency status. This status is requested by individual programs according to subjective criteria and approved by a multinational oversight group. Otherwise, lungs are used in the country of the donor. Unused organs in each country are offered to centers in other countries. There are varied organ donation rates among the countries, different rates of requesting high urgency status, and differences among countries' willingness to accept lungs from Maastricht Category 3 (25) Donation after Cardiac Death Donors (DCDs), but the system attempts to foster cooperation and direct lungs to those judged most in need.

D. France

Ten lung transplant centers are served by four geographic regions. Allocation is local (within a transplant hospital), then regional, national, and international. Within regions, offers are made on a rotational basis to centers. If an offer is declined, that center moves to the bottom of the rotation. If all centers decline, lungs are offered to centers in other regions on a rotational basis. If an offer is accepted, the lung transplant team chooses the recipient on the basis of urgency. Recipients can be classified as "super urgent" for eight days, only twice. Super urgent status varies by diagnosis (on ventilator or ECMO for CF or pulmonary fibrosis, refractory to medical therapy for PPH; >18 hours noninvasive ventilation for CF). For super urgent recipients, donor allocation is national and takes precedence over local or regional allocation. Pediatric donors (<18 years or weight <50 kg) are allocated nationally. Pediatric recipients (<18 years) have no time limit on super urgent status.

E. Italy

Eight lung transplant centers are served by three geographically defined donor areas, roughly dividing the country into thirds. Lungs are allocated first across zones to patients listed as emergent, then within zones to centers on a rotational basis. At individual centers, recipients are selected on the basis of surgeon preference.

F. Scandia Transplant

There are five lung transplant programs in four Scandinavian countries that make up Scandia Transplant: Copenhagen (Denmark), Oslo (Norway), Helsinki (Finland), Lund, and Gotheborg (Sweden). Sweden has three geographic organ procurement areas. In the Stockholm area, donated lungs are allocated alternately to the two lung transplant centers, but the centers cooperate to allocate lungs to very ill patients. At each center, surgeons and other physicians have discretion to allocate donors to recipients judged the most deserving. Unused lungs are offered to other Scandinavian countries on a rotational basis. Scandia Transplant has recently begun a two-year trial of sharing organs for emergent recipients that take precedence over "in country" lung utilization. Each country can allocate three patients per year as "high priority," who will be offered lungs first irrespective of country of citizenship.

G. Spain

Seven lung transplant programs serve Spain, two of which are in Madrid. Donated lungs are allocated within six geographic areas and are shared if not used in the local area. Allocation is based on severity of illness, as determined by members of the transplant team. Waiting time is not a factor.

H. Switzerland

For the nation's two lung transplant programs, organs are allocated nationally on the basis of urgency (on a ventilator), followed by diagnosis (pulmonary fibrosis and pulmonary hypertension), age, and waiting time.

I. United Kingdom

The United Kingdom has five lung transplant centers, all in England. Newcastle performs lung transplants for patients in Northern Ireland and Scotland. Lungs are allocated regionally within the zone surrounding the transplant center and rotated to other centers if not used locally. Centers choose recipients on the basis of severity of illness, judged subjectively. Waiting time only factors in if all potential recipients are thought to be equivalently ill.

J. Australia/New Zealand

Four lung transplant programs serve both countries' eight states per regions. Donors are allocated first to local transplant programs, then on a rotational basis. Programs choose potential recipients on the basis of clinical criteria judging severity of illness, with some judgment of utility at the discretion of the transplant center medical staff. Recipient waiting time is a factor for individuals judged to be equivalently ill.

K. South Korea

Lungs from brain-dead donors are allocated to recipients on the basis of a scoring system that includes recipient age, proximity to the donor, whether a recipient's family member has been an organ donor, certain diagnoses as a surrogate for disease severity, and waiting time in three-month increments out to six months.

L. Japan

Transplantation is limited by cultural and legal issues. An individual must elect to be an organ donor before brain death occurs; the next-of kin cannot make this election after

brain death. Although brain death was legalized in 1997, there are still some cultural hurdles, so the majority of lung transplants performed in Japan have been living lower lobe donor transplants. Lungs from brain-dead donors are allocated on the basis of waiting time.

VI. Conclusions

Organ transplantation is a feature of health care systems predominantly in developed countries, in part due to cost of the procedure, logistics, and the high cost of immunosuppression. Organ allocation systems often share similar goals, but there are clearly cultural differences, as well as differences in health care systems and health care economics that define priorities for organ allocation. Currently, there are not enough lungs to meet the need for patients with end-stage lung disease, but surgeons may be unduly cautious about lung utilization (26). Solutions to the lung-donor shortage include more utilization of marginal donors, perhaps after ex vivo resuscitation of lungs thought initially to be unsuitable (27), and more widespread use of lungs retrieved after death from non-heart-beating donors (28). Ex vivo organ perfusion may become the future of organ transplantation. Ex vivo perfusion of marginal kidneys results in more transplants with acceptable function (29), and recently ex vivo perfusion of kidneys from conventional donors showed superior graft function compared to matched kidneys that were transplanted after retrieval (30). Eventually, ex vivo perfusion will afford an opportunity to treat organs, possibly reducing ischemia-reperfusion injury when the organ is transplanted, perhaps increasing opportunities for tolerance induction (31). Soon, immunosuppression will be more affordable as generic drugs become more widely available. Organ transplantation is becoming increasingly performed in countries in Eastern Europe, Asia, Latin America, South America, and Mexico as economies expand. If strategies to increase the number of lung donors succeed [particularly lung retrieval from Maastricht Category 1 donors (25)], then the lung donor shortage may be abolished and lung allocation policies may be moot.

VII. Disclosures

The author founded a not-for-profit corporation, Lung Banks of America, whose mission is to promote lung retrieval from non-heart-beating donors (Maastricht Category 1) and develop and perform techniques of lung assessment to determine transplant suitability. The author also founded, holds equity in, and serves as president of X-In8 Biologicals Corporation, a for-profit corporation developing agents to reduce ischemia-reperfusion injury.

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13
Donor Management

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I. Pulmonary Management of the Potential Organ Donor

The major limiting factor in clinical lung transplantation is the shortage of suitable donor organs. This results in longer waiting times for listed patients and an increased risk of dying before a suitable organ becomes available (1). Using traditional selection criteria less than 20% of multiorgan donors become pulmonary donors (2).

The most common reason for rejection of lungs is donor hypoxemia (3). However, in a recent study using physiological, microbiological, and histological methods, Ware et al. (4) found that 41% of rejected lungs are potentially suitable for transplantation. Furthermore, use of early and aggressive donor management protocols yields more organs for transplantation (5–7).

Understanding the mechanisms of donor lung injury is essential in the current treatment of the brain-dead donor and in the development of future management strategies. There are a number of factors that compromise pulmonary function and lead to a low procurement rate. These include direct lung trauma, aspiration of blood or gastrointestinal fluid, shock with ischemia reperfusion injury, pulmonary arterial thromboembolism, transfusion-related acute lung injury, as well as pulmonary insults that occur after the institution of mechanical ventilation such as atelectasis, ventilator acquired pneumonia, barotrauma, volutrauma, and the effects of oxygen toxicity.

It is now well established that the process of brain death significantly impairs respiratory function and pulmonary physiology; this impacts on the management process. Brain death is associated with an autonomic crisis. The sympathetic storm, dominated by the release of noradrenaline, results in acute systemic vasoconstriction and a rise in systemic vascular resistance. This leads to a decrease in left ventricular output and an increase in left atrial pressure. At the same time vasoconstriction results in redistribution of blood volume. Systemic venous return increases leading to an increase in right ventricular output. Blood is therefore shifted to the more compliant pulmonary circulation (8). The sudden increase in left-atrial pressure and pulmonary blood flow lead to a transient massive increase in pulmonary capillary pressure and alveolar odema as a result of elevated hydrostatic pressure and stress failure of the pulmonary capillary membrane. Animal models have demonstrated that 72% of the circulating volume may be stored in the pulmonary circulation immediately following brain death (9). Pulmonary venous constriction that occurs because of sympathetic stimulation can further contribute to the increase in pulmonary capillary pressure (10,11). In addition to the blast injury theory described earlier, there is evidence to suggest that direct sympathetic

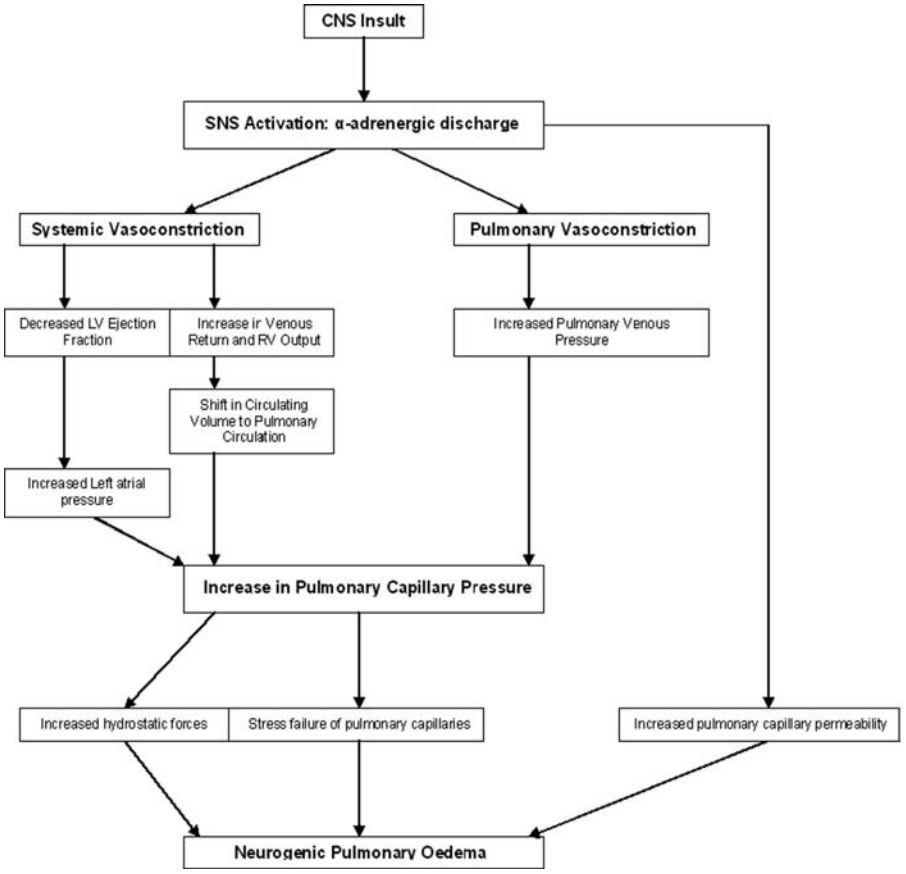

Figure 1 Mechanism of neurogenic pulmonary edema. *Abbreviations*: SNS, sympathetic nervous system; LV, left ventricular; RV, right ventricular.

nervous stimulation increases pulmonary capillary permeability leading to neurogenic pulmonary odema (12,13) (Fig. 1).

The sympathetic discharge that accompanies brain death triggers a systemic inflammatory response syndrome (SIRS). Acute lung injury can arise where the primary insult is distant to the lung. An acute systemic inflammatory response appears to play an integral role in the development of such injury by initiating infiltration of activated neutrophils into the lung providing the potential for massive localized tissue injury (14). Fisher et al. have compared potential organ donors with non-smoking ventilated controls and demonstrated a significant increase in the neutrophil concentration (30.85% vs. 3%) and bronchoalveolar lavage levels of IL-8 (12588 vs. 102 pg/mL) (15). The extent of neutrophilic infiltration correlated with the IL-8 level.

In a subsequent study, Fisher et al. correlated the extent of IL-8 expression and neutrophil infiltration in the donor lung with recipient graft function and survival. The IL-8 signal in the donor correlated with the percentage of neutrophils in the

bronchoalveolar lavage fluid, the degree of graft impairment and oxygenation, the development of severe early graft dysfunction, and early recipient mortality (16). Furthermore we have also demonstrated in an animal model that SIRS can be attenuated by treatment, prior to brain death, with the α-adrenergic antagonist phentolamine (17), which suggests that there is a link between the adrenergic and inflammatory mechanisms of donor lung injury.

II. General Principles of Donor Management

The process from identification of a potential organ donor to recovery of organs for transplantation may take up to 24 hours. Brain death needs to be certified according to the local code of practice and informed consent needs to be obtained from the next of kin. As soon as a multiorgan donor is identified, contact with donor transplant coordinators should be established. This has been demonstrated to improve the rate of recovery of lungs for transplantation (18).

Guidelines for the critical care management of the potential organ donor suggest that after the declaration of brain stem death, treatment strategy should be shifted from a strategy of cerebral protection to a strategy aimed at preserving solid organ perfusion and function (19). Some principles apply generally whereas others are targeted at a specific organ. The aim is to recover as many organs as possible and thus the team in charge of the donor must consider a proposed treatment in the best interest of all organs.

General management focuses on maintenance of body temperature, acid/base balance, electrolytes, intravascular volume, and prevention of infection and pulmonary embolism.

III. Hemodynamic Management

Therapeutic strategies to preserve pulmonary function require careful consideration of cardiopulmonary interactions. Fluid loading has traditionally been recommended to improve hemodynamics in brain-dead donors. In a prospective study, we investigated the effect of fluid resuscitation with lactated Ringer's solution on pulmonary function in 26 potential donors (20). In 13 patients, a central venous pressure (CVP) of 8 to 10 mmHg was achieved while in the remaining patients a CVP of 4 to 6 mmHg was maintained. A significant increase in the alveolar arterial oxygen gradient occurred in those patients who were fluid loaded to achieve a CVP of 8 to 10 mmHg. As brain death is associated with an increase in pulmonary capillary permeability, Starling's forces will dictate there will be an increase in alveolar edema with deleterious effects on oxygenation.

However, a strict reliance on CVP to guide donor maintenance may be detrimental to the lungs. We have demonstrated a disparity between right and left-sided filling pressures following brain death, with right ventricular filling pressures underestimating left ventricular filling pressures. This potentially puts donors at risk of elevated left atrial pressure and pulmonary odema (21). Similar disparities between left and right ventricular function have been demonstrated in animal models of brain death (22).

Current expert consensus recommends the use of a pulmonary artery flow catheter to optimize right- and left-sided filling pressures (23). Early invasive hemodynamic monitoring and optimization can prevent endothelial injury secondary to fluctuations in blood pressure. Brain death tests should therefore not be delayed and, upon confirmation, treatment redirected at the optimization of donor organ perfusion with the lowest

possible myocardial oxygen demand. This may require the use of vasopressors and inotropes. A retrospective analysis showed that the use of systemic catecholamines in the donor was predictive of worse gas exchange in the recipient following transplantation (24). Donors were categorized according to catecholamine use from the time of referral for donation to surgery. No exogenous administration of catecholamines (EAC) was defined as the use of dopamine at less than 2.5 μg/kg/min and included those patients receiving vasopressin as a vasoconstrictor. Donors receiving dopamine at 2.5 μg/kg/min or greater, epinephrine, or norepinephrine during the retrieval period were categorized as recipients of EAC. Both EAC and non-EAC groups had a fall in PaO_2/FIO_2 ratio between retrieval and six postoperative hours ($p < 0.01$). This fall was greater in the EAC group ($p < 0.05$). Furthermore, a study from our own laboratory has demonstrated that arginine vasopressin has a similar anti-inflammatory effect to noradrenaline in the correction of hypotension following brain death (25). Low-dose vasopressin infusion has been shown to improve hemodynamics and reduce inotropic requirements (21) leading to an increased rate of recovery of all organs for transplantation (26).

IV. Hormonal Resuscitation

Brain death commonly, although not always, causes dysfunction of the hypothalamopituitary axis. Levels of circulating hormones such as corticosteroids, insulin, triiodothyronine, and antidiuretic hormone may be low or inappropriately low.

Hormonal resuscitation using high-dose methylprednisolone and tri-iodothyronine (27) has been demonstrated to increase organ viability (23). An animal study from our group has demonstrated that the administration of intravenous methylprednisolone within five minutes of brain death significantly reduces the systemic and pulmonary inflammatory responses to brain death. This results in improved donor oxygenation and superior graft function following transplantation of lungs to recipient animals (28). In addition, a retrospective clinical study reported increased yield and improved oxygenation at organ recovery following the early administration of 15 mg/kg of methylprednisolone (29). While these findings have not been reproduced in a prospective randomized controlled trial, steroids have been associated with a reduced accumulation of extravascular lung water, even when administered several hours after the declaration of brain death (5).

Triiodothyronine (T3) is commonly used to improve donor heart function (27, 30). Improved cardiac function with reduced left atrial pressure might limit lung water accumulation, and in addition, T3 increases alveolar fluid clearance (AFC) (31). However, in a recent prospective trial T3 did not seem to confer any benefit for the pulmonary donor, although this study may have been underpowered to detect any small differences (5).

V. Additional Pharmacological Strategies

In addition to the administration of loop diuretics to treat fluid overload and pulmonary edema, stimulation of AFC may help to improve donor oxygenation. In ex vivo human donor lungs, β_2-adrenergic stimulation with aerosolized terbutaline has been shown to accelerate AFC (32). In the same study, treatment of the donor with low-dose dopamine was associated with faster AFC and administration of diuretics was associated with

lower extravascular lung water-to-dry weight ratios. Furthermore, investigators from Leuven have also demonstrated that endotracheal instillation of terbutaline is not only associated with an increase in AFC (33) but it also modulates the pulmonary inflammatory to brain death (34). In the absence of clinical studies, nebulized β_2-agonists cannot be recommended for routine use. However, results are awaited of an ongoing multicenter, double-blind, randomized-controlled trial by the California Transplant Donor Network investigating the efficacy of albuterol on oxygenation in brain-dead donors (BOLD study: β-agonist for oxygenation in lung donors).

VI. Ventilation Strategy

The traditional approach to mechanical ventilation of the organ donor is variable (35) with the use of pressure or volume-controlled ventilation with or without the use of positive end expiratory pressure (PEEP). Guidelines for the critical care management of the potential organ donors suggest that after the declaration of brain stem death, treatment strategy can be shifted from a strategy of cerebral protection to a strategy aimed at preserving solid organ perfusion and function (19). However, the recommended strategy for potential lung donors is similar to the one proposed for brain injured patients: maintenance of arterial PO_2 of 100 mmHg by the use of low levels of PEEP and $PaCO_2$ of 30 to 35 mmHg by the use of high tidal volumes (36). This strategy is potentially harmful. Brain death triggers a systemic inflammatory response (17) and can potentially lead to acute lung injury or acute respiratory distress syndrome (37), which may be precipitated or exacerbated by ventilator induced lung injury. Nevertheless, Gabbay et al. increased lung procurement with a high tidal volume strategy (7). The aggressive approach toward donor management in this study also included the use of PEEP, chest physiotherapy, attention to fluid balance, bronchial toilette, antibiotics, and bronchoscopy. Approximately 29% of potential organ donors had a PaO_2/FIO_2 ratio of less than 300 mmHg; 31% of these were clearly unsuitable because of poor oxygenation. Those remaining were subjected to aggressive pulmonary organ donor management. Approximately 50% were able to subsequently achieve a PaO_2/FIO_2 ratio of more than 300 mmHg and were successfully recovered and transplanted, with outcomes identical to the ideal lung.

Contemporary methods of mechanical ventilation have been driven by evidence from studies of ARDS (38), supporting the use of low–tidal volume ventilation. No prospective randomized controlled trial has been performed to determine if one mode of ventilation is superior to another in the management of the brain-dead organ donor. The use of pressure controlled ventilation has however been compared to volume-controlled ventilation in a randomized study of patients suffering from ARDS (39). In this trial, the mode of mechanical ventilation was not independently associated with patient mortality.

Recently, it has been demonstrated that the implementation of a management protocol for potential pulmonary donors led to an increased rate of procurement without a detrimental effect on 30-day and one-year survival rates (40). To implement the San Antonio Lung Transplant protocol, transplant pulmonologists met with staff involved in organ recovery to deliver training sessions on donor selection and management. Specific elements of the donor management strategy included performing ventilator recruitment maneuvers, restricting crystalloid fluids, administering diuretics, and implementing techniques for the prevention of aspiration. Alveolar recruitment was undertaken when the initial blood gas analysis demonstrated a PaO_2/FIO_2 ratio of less than 300 mmHg,

the presence of pulmonary infiltrates/pulmonary edema, and/or atelectasis. Recruitment strategies consisted of pressure control ventilation with an inspiratory pressure of 25 cmH_2O and a positive end-inspiratory pressure of 15 cmH_2O for two hours. The ventilatory mode was subsequently returned to conventional volume control ventilation with a tidal volume of 10 mL/kg and positive end-inspiratory pressure of 5 mmHg. Successful recruitment was defined by an improvement in PaO_2/FIO_2 ratio to at least 300 mmHg and significant improvement in the chest radiograph. Aspiration risk was diminished by elevating the head of the bed to 30° and inflating the balloon to the endotracheal tube to 25 cmH_2O. Bronchoscopy was performed in all patients with bilateral bronchioloalveolar lavage to evaluate areas of pulmonary infiltrates, contusion, or aspiration on the chest radiograph. These management processes were continued until lung procurement.

Recruitment maneuvers are an important component of donor optimization. Atelectasis is a common finding in the lungs of cadaveric donors because of prolonged ventilation in the supine position (41). In animals, donor lungs develop microatelectasis and a reduction in pulmonary compliance and functional residual capacity despite PEEP and a relatively short ventilation period (42). To prevent loss of alveolar recruitment higher levels of PEEP should be used immediately after recruitment maneuvers (43). Furthermore, some consideration should be given to performing suction through a closed ventilator circuit rather than an open one (35). In the absence of a randomized controlled trial, we would advocate the use of a low tidal volume ventilation strategy with appropriate use of PEEP and recruitment maneuvers (Fig. 2).

Infection or colonization of the lower airways with bacteria or yeast is common. In a study from our institution, recipients with donor BAL culture positive for bacteria had lower mean oxygenation index in the first six hours compared to recipients of lungs with negative bacterial culture. They also had longer median intensive treatment unit stay, median time of mechanical ventilation and inferior survival. There was no difference in the above parameters between recipients with gram-negative and recipients with gram-positive bacteria in the donor BAL (44) (Fig. 3). Given these findings it is recommended that every potential pulmonary donor undergo bronchoscopy for therapeutic bronchial toilet, and to isolate potential pathogens to guide antibiotic therapy in both the donor and the recipient (19). However, the benefit of empirical antibiotic administration prior to the diagnosis of pneumonia has only been demonstrated in a canine model (45). There is no current support for the empirical use of antibiotics in the human donor. General principles dictate that antibiotic use be limited to the narrowest spectrum antibiotic necessary to treat isolated pathogens.

VII. Ex Vivo Lung Perfusion

The purpose of donor management is to identify reversible causes of poor oxygenation and prevent further injury to the lungs. Traditional organ procurement practice only allows a limited amount of time for donor management and organ assessment. Furthermore, during this period lungs are immersed in a proinflammatory milieu. A novel approach to lung evaluation is ex vivo lung perfusion (EVLP). This technique was developed by Steen et al. to assess the quality of lungs from donation after cardiac death (DCD) donors (46,47). The EVLP circuit enables us to remove lungs from the potentially harmful environment of the brain-dead donor and maintain them so that reparative processes can be initiated. Successful transplantation following EVLP has been

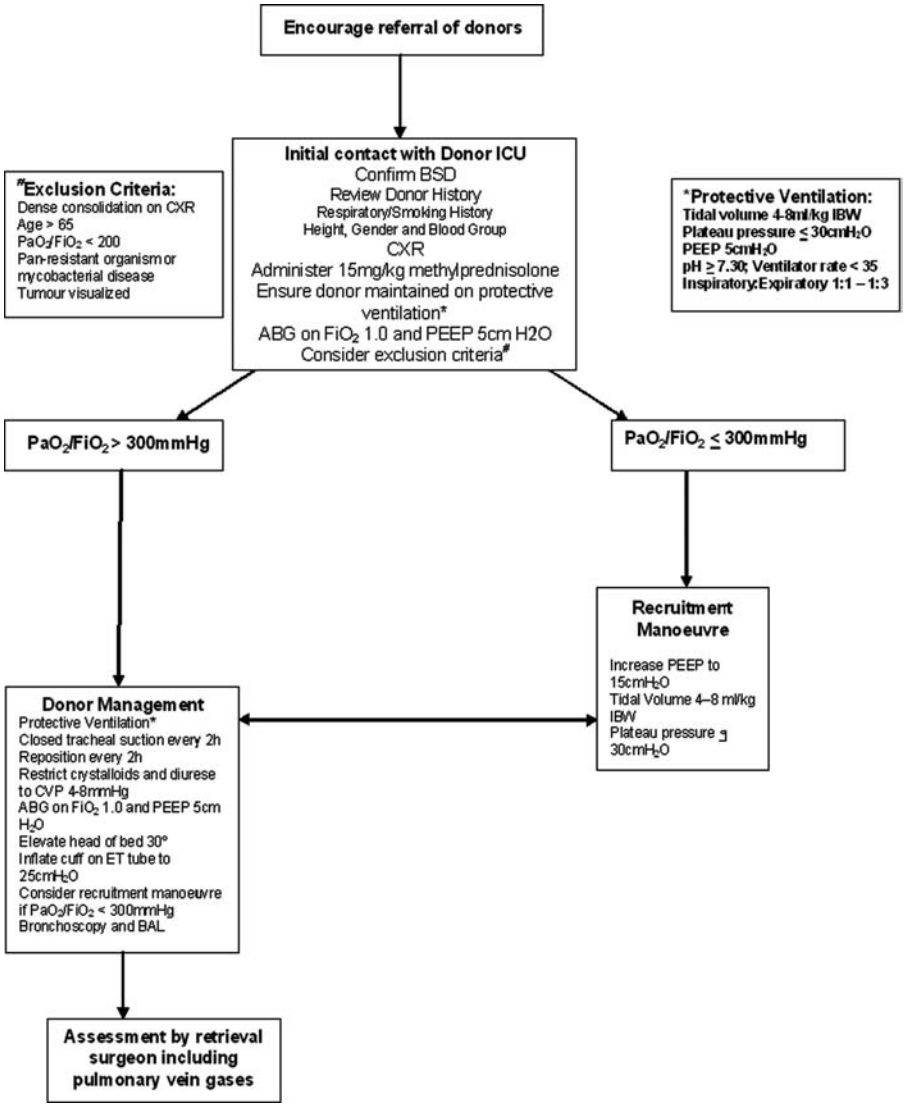

Figure 2 Algorithm for the respiratory management of the brain-dead donor. *Abbreviations*: BSD, brain stem death; CXR, chest X ray; FiO_2, inspired fraction of oxygen; PEEP, positive end expiratory pressure.

described in both animal studies and human recipients (48,49). The application of this donor maintenance strategy will serve as good platform for the development of therapies to repair or recondition lungs, and will allow sufficient time for prognostic testing. This may facilitate pulmonary transplantation by expanding the number of suitable lungs and by improving postoperative outcome.

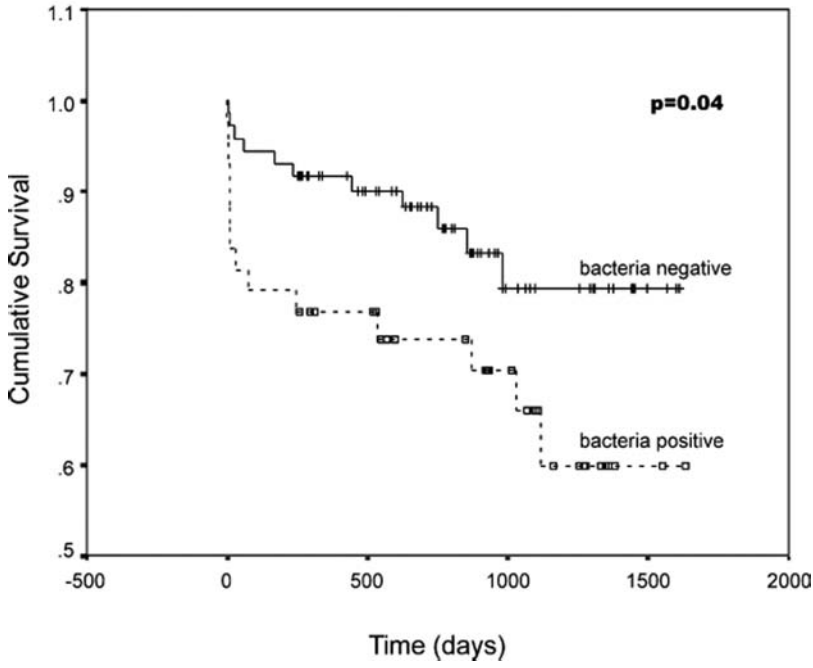

Figure 3 Kaplan–Meier survival curves for the groups with donor BAL positive and negative for bacteria. □ and + mark censored cases.

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14
Lung Donor Selection Criteria

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I. Introduction

At the inception of clinical lung transplantation, strict parameters of lung donor criteria were developed (Table 1) (1), and these criteria helped establish the field of safe lung transplantation. However, acceptance rates for donor lungs were relatively low and the number of patients awaiting donor organs began to far exceed the number of accepted organs. Since that time, initial and long-term survival rates have continued to improve, and lung transplantation is now a routine option for end-stage lung failure. Given the improvements in clinical results for lung transplantation, the generally accepted criteria for donor organ selection are continually being challenged and expanded, allowing for the utilization of organs that were historically rejected. Some parameters have become validated while others retain unclear utility. Despite selection criteria, borne from experience and expert opinion, the process of donor lung selection continues to as well as depend on subjective assessment and judgment. In this chapter, we outline the major parameters for lung donor selection and review these criteria in light of the current literature.

II. Institutional Algorithm

When a donor offer is received, the organ is initially evaluated in terms of ABO and size. While ABO incompatibility is an absolute contraindication, significant donor-recipient size discrepancies are considered. Once these criteria are met and a suitable recipient identified, functional characteristics are reviewed. Extreme findings, such as radiographic evidence of persistent and significant infiltrates or severe contusions, infection, PaO_2 values less than 200 mmHg, may delay acceptance or lead to offer rejection. At this point, should the cumulative evidence not warrant an immediate offer rejection, clinical management of the donor should be actively pursued to improve the lungs. Frequently, strategies to optimally recruit donor lung atelectasis while avoiding excess barotrauma will be instituted. Liberal use of a computed tomography (CT) scan of the chest may be performed to help evaluate the lungs, especially in a donor with a significant smoking history or possible contusions. Finally, a procurement team is deployed to make an onsite assessment and possibly improve some clinical parameters. Frequently, abnormal findings at the time of initial offer will be resolved at the time of onsite evaluation through careful donor management or through maneuvers performed during the onsite evaluation. Once onsite, routine clinical parameters and donor management plan are reviewed and appropriately modified. A repeat bronchoscopy is performed to assess presence of airway injury and/or infectious process. The thorax and

Table 1 Lung Donor Criteria

Age < 55
ABO compatibility
Clear chest radiograph
$PaO_2 > 300$ on $FiO_2 = 1.0$, PEEP—5-cm H_2O
Tobacco history < 20 pack years
Absence of chest trauma
No evidence of aspiration/sepsis
No prior cardiopulmonary surgery
Sputum gram stain—absence of organisms
Absence of purulent secretions at bronchoscopy

lungs are physically inspected for trauma, which may have escaped initial physical examination and radiographic studies. Any areas of atelectasis are recruited and followed to determine permanence of recruitment efforts. The entirety of the lungs is palpated for nodules not detected on chest radiographs. Compliance is subjectively assessed through valsalva and complete removal from the ventilatory circuit. The decision to accept or reject is made on the basis of cumulative evidence. Clinical trials will as well soon begin to assess the effectiveness of ex vivo lung perfusion modification as the final step in improving donor lung acceptance and utilization.

Finally, acceptance of lungs may depend to some extent on donor-recipient matching.

Some extended donors may not be best utilized in patients with significant postoperative predictors of lung failure such as severe primary pulmonary hypertension, And some parameters such as donor age may depend on expected ischemic times as well as recipient risk factors.

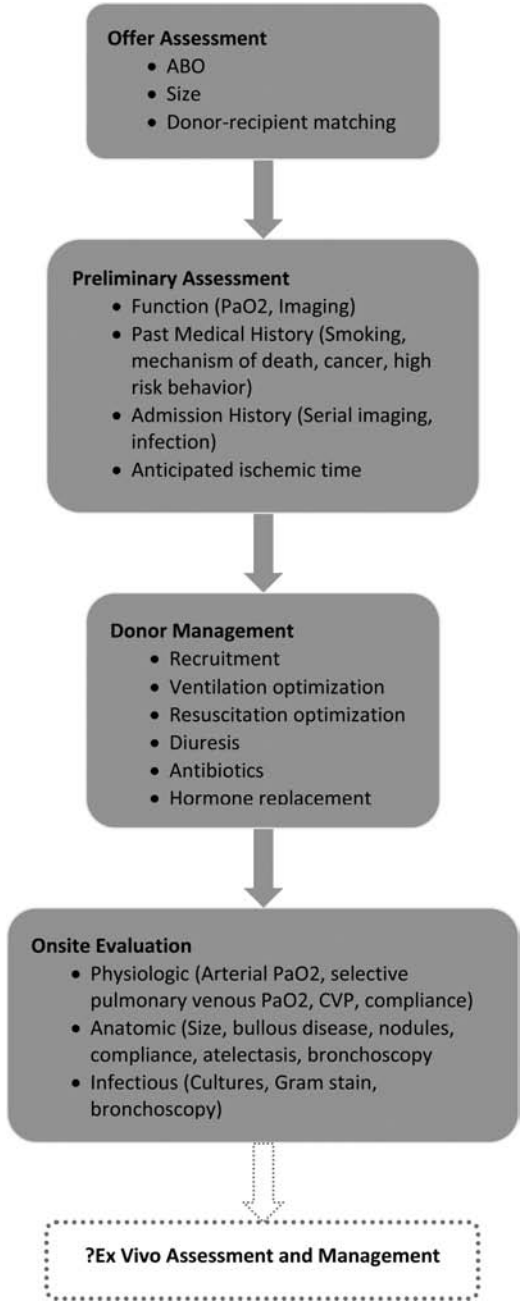
III. Selective Donor Criteria

A. ABO Compatibility

While ABO incompatibility is an absolute contraindication for transplantation, the significance of identical versus compatible donor-recipient blood types remains unclear. In a single institutional study, Yu et al. compared recipients of ABO-identical versus ABO-compatible donor lungs. They found no statistically significant differences in intensive care unit (ICU) and hospital lengths of stay, incidence of acute and chronic rejection, median time and grade of rejection, maximal FEV1 post transplantation, or one-year survival (2). Various older studies of the immunologic consequences of ABO-compatible transplantations demonstrated that nonidentical matches could lead to increased incidences of post-transplantation hemolysis (3,4). These studies, however, did not demonstrate any differences in post survival. To date, primary ABO compatibility is the primary determinant of acceptance.

B. Size

Donor-recipient size matching has long been considered an important factor in favorable transplant outcomes; despite its importance, the limits of donor-recipient mismatch and the rubric by which an appropriate match should be assessed continue to be debated. Historically, concerns over size mismatching were over two possibilities: a small donor


Offer Assessment
• ABO
• Size
• Donor-recipient matching
Preliminary Assessment
• Function (PaO2, Imaging)
• Past Medical History (Smoking, mechanism of death, cancer, high risk behavior)
• Admission History (Serial imaging, infection)
• Anticipated ischemic time
Donor Management
• Recruitment
• Ventilation optimization
• Resuscitation optimization
• Diuresis
• Antibiotics
• Hormone replacement
Onsite Evaluation
• Physiologic (Arterial PaO2, selective pulmonary venous PaO2, CVP, compliance)
• Anatomic (Size, bullous disease, nodules, compliance, atelectasis, bronchoscopy
• Infectious (Cultures, Gram stain, bronchoscopy)
?Ex Vivo Assessment and Management

lung transplanted into an excessive large thoracic cavity would lead to persistent pneumothorax, while an excessively large donor lung transplanted into a smaller thoracic cavity would lead to persistent atelectasis and subsequent infection development. While some evidence have highlighted the adverse consequences of extreme size mismatches, studies have demonstrated that recipients can tolerate significant size mismatches, with relatively low rates of complication.

In a recent retrospective study of a single institution's data, Mason et al. reviewed 469 patients who underwent lung transplantation over a 17-year time period. Analyzing the ratio of the predicted total lung capacities for the donor and recipient, they compared transplantation outcomes from donor-recipient pairings with the highest and lowest ratios (15% each) to the 70% of recipients whose pairings were closer to parity. While they found no overall survival difference, disease-specific survival analysis revealed that recipients with emphysema who received lungs from donors with extreme size mismatch resulted in significantly lower survival rates (5).

Downsizing of donor lungs by lung-wedge resection and lung-volume reduction surgical techniques is an effective maneuver to adapt larger lungs to a smaller chest cavity. Although with extreme size mismatches, formal lobectomies of the upper lobes may be required, stapled downsizing of the right middle lobe or lingula may sufficiently enable closure of the chest and appropriate size matching. At Columbia, we subjectively use younger age donor lungs as well for extremes of mismatch as the lungs tend to be significantly more compliant and adaptable.

C. Age Less Than 55

Lung function generally deteriorates with age. However, the consequences of accepting well-functioning lungs from older donors and the upper limits of donor age as a determinant of post-transplantation outcomes remain unclear. With the liberalization of donor selection criteria, there has been a trend toward accepting organs from older donors. In 1997, the average lung donor age was 45, whereas in 2007 it was 49.8 years (6). Review of older UNOS data correlated a higher post-transplantation mortality with increased donor age (7). Contemporary single institution data revealed a similar correlation between older donors and primary graft dysfunction (8). In a study specifically looking at donors older than 60 years of age, the Toronto group did not find a difference in post-transplant mortality. In their study, however, they note that these older donors were carefully selected with lower incidence of trauma-related deaths and shorter ventilator support times. Additionally, higher rates of primary graft dysfunction were found when donors older than 60 years were used for patients with primary pulmonary hypertension.

At present, it is unclear if any absolute donor age should be a contraindication for declination of lungs. Factors that may affect their use include smoking history among other medical issues and inability to tolerate longer ischemic times. Long-term follow-up of donor lungs older than 60 years at present is lacking.

D. Chest Radiograph

In donor lung evaluation, chest radiographs serve as qualitative surrogates for parenchymal pathology such as atelectasis, contusions, edema, effusion, or infection. As a qualitative measure, any finding is subject to interobserver variability. Bolton et al. studied the relationship between donor chest radiographic findings and the actual

clinical outcomes of donor lungs and determined a concordance rate of 64.2%. Given a positive predictive value of 78.3% for acceptance and a negative predictive value of 36.3% for rejection, they concluded that due to the subjective nature of radiographic evaluation, chest radiographs had a limited role in assessing transplant suitability (9).

Another potential confounding factor is the evolution of predonation radiographic findings. As these patients are subject to various donor management protocols, these findings are likely to change during the management period. In a retrospective evaluation of donor organs, McCowin et al. revealed that upwards of 50% of significant radiographic densities completely resolved, and 45% of radiographic evidence of edema completely resolved during the evaluation period. They discovered that radiographic deterioration correlated with organ rejection while radiographic improvement did not have a similar effect on acceptance (10).

E. PaO_2

One of the most relied upon measures to donor lung functional assessment is the PaO_2:FiO_2 ratio. The significance of this variable was first recognized by Harjula et al. in their determination of lung donor selection criteria (11). In an analysis of contemporary, single institutional data, Botha et al. demonstrated a strong correlation between the PaO_2:FiO_2 ratio of pulmonary vein gas and primary graft dysfunction. Furthermore, they demonstrated a correlation between the numbers of pulmonary vein gas PaO_2 less than 300 mmHg and primary graft dysfunction. Interestingly, there was a poor correlation between arterial PaO_2 values at the time of referral and pulmonary vein gas PaO_2 values at the time of donor organ evaluation (12).

F. Tobacco History Less Than 20 Pack Years

Given the numerous pulmonary complications associated with smoking, donor lungs of smokers are scrutinized during donor evaluation. Christie et al. evaluated smoking as a potential risk factor for primary graft failure; as a dichotomous variable, smoking did not correlate with primary graft failure in univariate or multivariate analysis (13). In another single institutional study, Oto et al. reviewed the smoking habits of lung donors who were stratified by the intensity of cigarette use. They found a dose-dependent effect on post-transplant PaO_2:FiO_2 ratio, ventilatory support period, and ICU stay; however, these effects did not extend to long term. Moreover, the intensity of smoking did not impact survival (14). Nonetheless, an extended history of smoking warrants thorough investigation of possible lung cancer or emphysema. At Columbia, it is a routine to require a chest CT on any donor with greater than 20 pack year smoking history to make a better assessment of unusual nodules or emphysematous disease.

G. Sex

The International Society for Heart & Lung Transplantation (ISHLT) data continue to demonstrate a difference in one- and five-year survival rates of female recipients compared to other donor-recipient combinations. The 2008 ISHLT data show that a male donor and female recipient combination had a one-year mortality RR = 0.88, and female donor and female recipient combination had a greater five-year advantage with an RR = 0.80 (6). In a review of their institutional experience, Roberts et al. showed that donor-recipient gender mismatch conferred a statistically significant survival advantage with male donor-male recipients having the shortest survival periods. The mechanism underlying this finding is

unknown; however, the authors hypothesize that organ size, functional reserve, immunological, hormonal, and/or mechanical factors may play a role (15). In a review of contemporary ISHLT data, Sato et al. compared all donor-recipient gender combinations taking recipient diagnosis, donor-recipient lung capacity ratios, recipient and donor ages, recipient body mass index, donor age, transplant procedure, and blood type into account. Female recipients, regardless of donor gender, had improved survival compared to male recipients, with male recipients of female donor organs having the highest hazard ratios for death (16).

IV. Cause of Death

Traumatic injury to the chest grossly causing structural damage to the lungs themselves—lacerations, contusions, etc.—may be a contraindication to donor organ selection. Death, due to trauma that does not involve the chest, does not have a negative impact on post-transplant survival. In a retrospective review of a single institutional experience, Ciccone et al. compared the outcomes of lungs procured from donors with traumatic brain injury to those procured from donors whose deaths did not involve trauma. In a series of 295 trauma-related donations and 205 nontrauma-related donations, there were no significant differences in the immediate postoperative outcomes and long-term survival. There was a statistically significant difference, however, in the occurrence of bronchiolitis obliterans syndrome (BOS) in the trauma-related donor organs (17). Ciccone's findings are corroborated by a more contemporary study in which Ganesh et al. reviewed data on all lung transplantations in the United Kingdom. Analysis of 580 lung transplantations, which occurred between 1995 and 2002, revealed no significant impact of trauma as a cause of donor death on recipient survival. While the study did not reveal significant differences in BOS incidence, the authors suggest that the negative findings may be secondary to incomplete data (18).

Potential donor lungs with suspected chest trauma or contusions should undergo CT scanning to rule out deep, significant contusions. In our institutional experience, subpleural contusions, with primary retained pulmonary parenchyma, are acceptable for transplantation.

V. Asthma

Generally, an on-going history of asthma in lung donors has been a contraindication to donor organ selection, the concern focusing on persistent airway reactivity and primary graft failure. However, donor lungs from asthmatics who have mild or well-controlled disease or in whom the history is distant have been transplanted with good success. In a retrospective analysis of a single institutional experience, Oto et al. reviewed 743 consecutive lung donors, of which 74 had a history of asthma. Twenty-seven of the 74 asthmatic lungs were transplanted. The selection criteria was stringent; in 17 donors, asthma was the only negative donor characteristic, while in 10 donors, there was a history of smoking in addition to asthma. Abnormal findings in chest radiographs and low PaO_2 were reasons for organ rejection. Recipients of lungs from donors who were on asthma treatment at the time of donation had better outcomes compared to recipients of lungs from donors not on asthma treatment. Recipient survival was not significantly different from overall lung transplant survival rates with one- and five-year survival rates between treated and nontreated donor lungs of 74%/69% and 74%/60%, respectively. Both patients who received lungs from donors whose causes of death were

directly related to asthma died—one due to early graft failure and the other due to possible acute rejection. Interestingly, only one recipient of a lung from an asthmatic donor had persistent clinical symptoms of asthma post-transplantation (19).

VI. Cytomegalovirus (CMV)

The significance of donor-recipient CMV status has evolved with advances in transplant patient management. In their review of UNOS data, Russo et al. analyzed all possible donor-recipient CMV pairings over successive time periods. In a multivariate analysis of UNOS data (2000–2004), donor-recipient CMV status had no statistically significant impact on post-transplant survival rates. They did note, however, that this finding was different from previous eras (1990–1994, 1995–1999) when donor-recipient CMV status had a significant impact on post-transplant survival (20). In the most recent review of the ISHLT registry (up to July 2007), a donor-recipient CMV mismatch in which CMV-recipients receive lungs from CMV+ donors had a 1.2 relative risk of one-year mortality— down from an RR = 1.37 in 2002 (6,21). The authors point, however, that these results were not adjusted for potentially confounding factors such as age.

VII. History Prior to Chest Surgery

In conventional donor selection criteria, the ideal donor does not have a history prior to chest surgeries. The rationale behind this restriction is the increased likelihood of heart and/or lung injury during the procurement process. Specifically, in the processes of entering the chest through the usual midline sternotomy and the necessary mobilization of the lungs, the lungs may incur surgical injury rendering the organs unsuitable for transplantation. Furthermore, injury to the heart may jeopardize the entire procurement process for all organ procurement teams. While no studies have examined the feasibility of routinely utilizing lungs from donors with previous chest surgeries, a case series of two patients are reviewed by Toyoda et al. Both donors, with prior histories of mitral valve repairs, were noted to have mild-to-moderate adhesions in the pleural cavities. The procurement procedures were not significantly different from standard practice. Toyoda, however, pointed out that increased care must be taken to minimize the possibility of organ injury, which can be achieved by minimizing the amount of dissection—particularly behind the sternum (22).

VIII. Anticipated Ischemic Time

While anticipated ischemic time impacts donor organ allocation and the logistics of procurement/transplantation coordination, its potential influence on transplantation outcomes plays a large role in donor selection. An older study of a single institutional experience by Gammie et al. retrospectively reviewed 392 first-time lung transplantation patients between 1988 and 1998. Donor ischemic times, which ranged from 65 to 538 minutes, were stratified into three categories—0 to 4 hours, 4 to 6 hours, and greater than 6 hours. Multivariate analysis did not reveal an independent relationship between graft ischemic time and post-transplantation survival. In addition, no correlation between ischemic times and diffuse alveolar damage, episodes of acute rejection, duration of intubation, and bronchiolitis obliterans were demonstrated (23). In a multicenter center study of lung transplantation patients from 1987 to 1998, Thabut et al. reviewed data of 752 patients from 7 centers and found a relationship between graft ischemic time and

post-transplant PaO_2 and long-term survival in non-heart-lung recipients (24). Multivariate analysis demonstrated that the hazard ratios for death in single- and double-lung transplant patients rose dramatically once graft ischemic times exceeded six hours. The hazard ratios of single- and double-lung transplantations with graft ischemic times of four hours were 1.57 and 1.51, respectively. When ischemic times were increased to 8 and 10 hours, the hazard ratios increased to 2.96 and 2.70 and to 8.50 and 7.10 for single- and double-lung transplantations, respectively. Novick et al. reviewed UNOS data from lung transplantations performed between 1987 and 1997. In their multivariate analysis, no independent association was found between graft ischemic time and survival. However, when interacting age with graft ischemic time, an age-dependent association was found. In grafts from donors less than 10 and greater than 51 years of age, early recipient survival was influenced by ischemic time. Once again, there was a correlation between ischemic time and one-year survival when the impact of donor age was taken into consideration, with one-year survival rates significantly diminished when transplantations involved older donors with increased ischemic times (7).

IX. Infectious Considerations

Evidence of infection in donor organs raises concern of transferring the infection to immunosuppressed recipients. Radiographic and bronchoscopic findings suggestive of infection that are corroborated by evidence of functional impairment usually lead to lung offer rejection. Bronchoscopic findings should be carefully assessed to differentiate retained old secretions frequently found in donors versus distal purulent evidence of pneumonia. Additionally, in donors less than 24 hours from death, significant evidence of aspiration may be a worrisome finding as the effects of aspiration may not become clinically evident for 48 hours.

Several studies have evaluated the correlation between donor organisms and recipient post-transplant outcomes. In a single institutional study, Weill et al. reviewed 60 consecutive lung donors, which resulted in 90 transplantations between 1989 and 1990. Three patients who did not survive more than 30 days were excluded from the study. Of the 60 donors, 43 (72%) had a positive diagnostic Gram's stain prior to graft procurement. Of these 43 Gram's pos donor lungs, there were 5 cases (12%) of post-transplantation pneumonia. From the 44 donor cultures of gram-negative organisms, 9 (20%) recipients developed post-transplantation pneumonia. Weill and colleagues also found that 38 of the 60 donors were noted to have erythematous central airways on bronchoscopy (25). In another single institutional study, Bonde et al. reviewed infection data on 80 consecutive single- and bilateral-lung transplantations, which occurred between 1998 and 2001. Pediatric patients and recipients who did not survive at least 3 days were excluded from the study, with 71 remaining study patients. Of 61 donor lungs, 57 (89%) grew organisms, 46 (80%) of which were polymicrobial. The most common donor culture organisms were *Staphylococcus* sp. (61.4%), *Streptococcus* sp. (57.9%), *Haemophilus* sp. (28.1%), *Candida* (24.6%), and *Pseudomonas* sp. (7%). Of the 71 recipients, 24 developed post-transplant pneumonia, with *Pseudomonas* the most common causative agent 13 (54.2%). Nineteen of these 24 recipients (79.2%) received grafts that had positive donor cultures; however, in only 5 of the 19 cases (26.3%) were the causative organism identified in the donor cultures. Their analysis showed that identified donor organisms had a sensitivity of 0.75 and a specificity of 0.04 in predicting post-transplantation pneumonias (26). From their analysis, Bonde et al. concluded that given

the low sensitivity and specificity of donor culture results, traditional infection criteria should be reassessed in the selection process for donor organs.

Functionally, donor cultures alone unless they are significant hospital-acquired pathogens should not absolutely deter lung acceptance. However, positive donor cultures combined with radiographic evidence of infiltrate or bronchoscopy with distal purulent secretions may obviate lung acceptance.

X. Conclusion

Donor lung criteria are an important guide to the assessment and objective analysis of results of lung transplantation. It is now clear that significant liberalization of the original donor criteria can be done with excellent short-term results. Long-term results especially in donors of extreme age and smoking history are yet to be determined. It will be important to the field of lung transplantation that we track these variables of extended donor criteria for 5- and 10-year follow-up of functional results. It is important to note that presently the use of extended criteria should only be used with full recipient consent, and the anatomical or donor history that accounts for the extended donation status should clearly be reflected on the operative consent. Finally, the exciting field of ex vivo lung assessment and modification is in evolution. Thus, shortly, lungs with certain defined defects may be modified ex vivo post harvest and should greatly expand the donor pool and ultimately the results of lung transplantation.

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15
Non-Heart-Beating Donor: Lung Transplantation with Donation After Cardiac Death (Controlled DCD) Allografts

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I. Introduction

Outcomes after lung transplantation have significantly improved over the last decade. Single- and bilateral-lung transplantations are now well-established treatment options for many end-stage respiratory diseases. The primary limitation to increased utilization of lung transplantation continues to be the availability of suitable allografts. After the initial limited clinical experience with lung transplantation in the early 1960s, performed with allografts from donors after cardiac death, the legal definition of brain death in the late 1960s promoted the shift to utilize organs from donors with maintained circulation and verified brain stem death (1). Furthermore, lungs from brain-dead donors may sustain diffuse damage secondary to catecholamine surge, endothelial activation, and inflammatory injury. Overall, lung utilization rates from donors after brain death remains about 20% worldwide, resulting in deaths on the waiting list, worsening clinical status of the patients waiting, and limiting wider application of lung transplantation to decrease the burden of lung disease.

Donation after cardiac death (DCD) provides a readily available alternative source of lungs for transplantation. Defined as allografts available from donors after complete cessation of cardiac function, these donors require a modified approach to achieve procurement of viable lungs. Current results of DCD lung transplantation suggest very satisfactory early and midterm outcomes. Widened application of DCD lung transplantation is now justified with strict adherence to local organ procurement protocols and an appropriate informed consent process for potential recipients.

This chapter defines the DCD donor population and provides evaluation criteria for the assessment of controlled DCD lung allografts. We provide protocols for procurement of such lungs with particular emphasis on the logistics and principles of DCD organ acquisition. The clinical evidence for DCD lung transplantation available to date is critically appraised in this chapter. Finally, we discuss the clinical context and ethical propriety of DCD lung transplantation.

II. Background

The evolution of lung transplantation has followed the pattern of other solid organ transplantation and has now become a widely established therapeutic option in selected cases of end-stage pulmonary disease (2). Early survival has improved significantly over

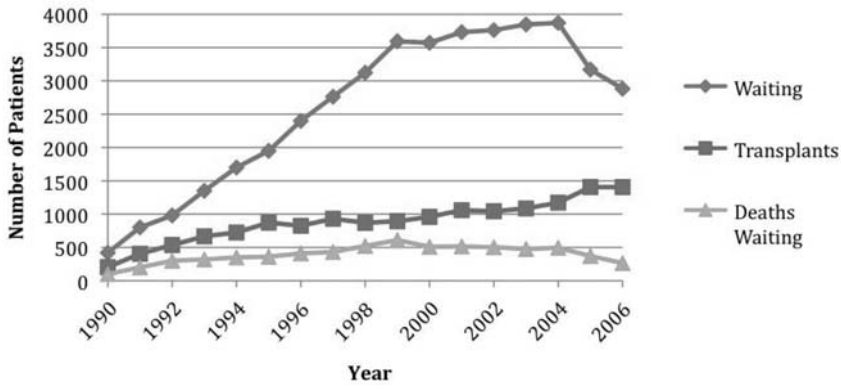

Figure 1 Lung transplantation in the U.S. 1990–2006.

the last decade because of advances in surgical techniques, donor management, procurement protocols, and perioperative care (3,4). The waiting-list mortality, however, remains unacceptably high. In the United States, up to one-third of patients currently registered for lung transplantation may not receive allografts and succumb to their disease while waiting for a suitable organ for transplant (5) (Fig. 1).

Liberalization of the standard criteria for lung transplantation from brain-dead donors resulted in more frequent acceptance of "marginal" allografts (6,7). These generally do not fulfill one or more of ideal pulmonary function parameters or systemic donor criteria (8,9). These extended criteria brain-dead donors are now frequently utilized to meet the increasing demand for lung transplantation (10). Improved lung recovery rates have been achieved as a result of focused efforts on the delivery of transplant care through National Healthcare Improvement Initiatives such as the Transplant Collaborative in the United States (10). The primary limitation to increased lung transplantation, however, remains the scarcity of donors and the fact that currently only 20% of these are deemed suitable for lung transplantation (11). One alternative source of transplantable organs is from donors who do not meet the standard brain death criteria and are allowed to progress to cardiac death prior to organ harvest (12,13).

The potential for DCD has been recognized, and this has improved prospects for candidates of other solid organ transplants (14). Excellent results have been achieved in renal transplantation utilizing established DCD protocols (15). There are, in fact, those that argue that there are physiologic advantages to avoid procuring lungs from patients who have suffered brain death and the pulmonary sequelae of brain death (16–24). This has provided impetus for other solid organ programs to reconsider DCD transplantation (25,26). Scientific reviews and results from experimental models have helped to establish the clinical approach for DCD lung transplantation. These have become a realistic alternative for candidates waiting for lung transplants (27–30). This has the potential to substantially reduce the waiting-list mortality for selected lung transplant candidates.

Established DCD donor procurement protocols for *controlled donors* (Maastricht Category III) therefore provide a unique opportunity to increase the rate of lung

transplantation and reduce the waiting-list mortality (31). In view of the paucity of clinical information reported for DCD lungs transplanted, we include data from our cohort of 24 consecutive DCD allografts transplanted, currently the largest series available.

The evaluation of donor data, the development of a procurement protocol, and documentation of DCD lung recipient outcomes have provided a model for other lung transplant programs to incorporate this valuable source of donor lungs into clinical practice (28,32–34). This chapter would be incomplete without the consideration of the recipients of DCD lungs. A brief data analysis will focus on early and midterm survival and the incidence of clinically evident primary graft dysfunction (PGD) in this cohort.

III. DCD Lung Donors

All potential DCD lung donors are referred and assessed according to UNOS guidelines. Procurement offers are assessed in detail with the donor family's wishes respected at all stages. DCD procedures are performed in strict adherence with each local Organ Procurement Organization (OPO) protocol. The series reported here serves to provide basic information for a cohort of *controlled* non-heart-beating donors (category III Maastricht classification) (35) (Table 1). Lungs from *uncontrolled* DCD donors (Maastricht category I or II) have been transplanted less frequently and involve more complex physiologic and cultural issues. Category I DCD lung transplants have not had the same encouraging early and midterm outcomes; in particular a higher PGD rate has been reported. The feasibility and specific clinical concerns of *uncontrolled* DCD lung transplantation have been reported by Verela et al. but are not the focus of this chapter.

During the 1990s and early part of this decade, our experience with DCD lung transplantation was utilized almost exclusively in patients with the highest-risk profiles (36). The recipients in this series may not have otherwise survived the waiting time associated with standard allograft availability. The consenting process should reflect the degree of uncertainty regarding *long-term* graft function, although early experience with

Table 1 Classification and Potential for DCD Lung Donation

DCD Donors	Status on assessment	Availability	Consideration for LTX
Category I	Donor declared dead on arrival (DoA)	Potentially vast numbers	Poor donor risk profile assessment
Category II	Declared donor after unsuccessful resuscitation	Large increase in donor pool	Very limited donor risk evaluation, better than Category I
Category III	Awaiting cardiac death, after withdrawal of treatment	Estimated 30% donor expansion	Good risk assessment, logistic concerns, time/progression issues
Category IV	Cardiorespiratory arrest after previous diagnosis of brain death	Less frequent occurrence	Additive BD and DCD procurement factors present

Source: Modified from Kootstra et al., Maastricht Criteria for NHBD Revised 2003.

DCD lungs transplanted has been very reassuring. Potential candidates have to be given balanced advice regarding their risks associated with waiting for a transplant on the one hand and the limited, but positive, experience with DCD on the other. Because of the unpredictability of such organ availability and the need then to make decisions in a timely manner, it has been our practice to have the specific consent for DCD lung transplantation completed in advance (37).

This chapter covers the management of DCD category III asystolic donors and is applicable also to category IV cases where donor families request that their loved ones be removed from life support measures soon after giving consent for donation.

The final decision to accept or decline a DCD lung offer should be made by a senior transplant surgeon on the basis of information regarding each individual potential DCD lung recipient (38). Minor variations regarding procedural protocols and organizing withdrawal of artificial life support in DCD donors have to be known a priori (37,39). Similarly, timing and administration of some routine premortem DCD donor care may require adjustment to comply with local regulations. Recommended UNOS guidelines and specific DCD lung allograft criteria were applied for selection of potential donors (Table 2).

Assessment for potential contraindications included the following criteria for all DCD donors with clear emphasis to observe the failure of the donor to progress within the stipulated warm ischemic time less than 60 minutes (Table 3).

Table 2 DCD Lung Donation Criteria

Factor	Criterion
Age	<55 yr
Chest radiograph	Free of consolidation within 24 hr
Oxygenation	PO_2/FiO_2 ratio >300
Exclusion	No concurrent diagnosis incompatible with lung transplantation
Condition	Progression of DCD donor likely

Source: Adapted from UNOS.

Table 3 Contraindications to DCD Lung Donation

Factor	Criterion
History	Previous lobectomy
	Active tuberculosis
Serology	Positive HIV, HTLV, positive hepatitis B core antibody, hepatitis C positive
Chest radiograph	Consolidation c/w pneumonic infiltrate or contusion
Oxygenation	PO_2 repeatedly <300 mmHg at FiO_2 of 1.0
IV/illicit drug use	<6 months
Condition	Donor sepsis
	Failure to progression to cardiac arrest
Family	Withdrawal of consent at any stage

Source: Adapted from UNOS.

Table 4 University of Wisconsin/Loyola University Medical Center Clinical Protocol for DCD Lung Procurement

1. *Advance* revision of procedure for DCD lung procurement with local staff, anesthesiologist and abdominal procurement team.
2. Move the donor to the operating room with consent to withdraw artificial life support in the operating room if possible.
3. Placement of femoral cannulae *if permitted by local DCD protocol*.
4. 300 U/kg heparin and 10 mg phentolamine or 1 mg PGE given IV in central line *permitted by local DCD protocol*.
5. Postmortem heparinization by cardiac massage. Risk reduction of microthrombus formation. Median sternotomy, pulmonary artery (PA) exposure.
6. 10 mg phentolamine (or 1 mg PGE) injected into the PA followed by open cardiac compressions for 1 min.
7. Cannulation of main PA with 6.5 F cannula directed back at the pulmonic valve.
8. Flush with 4 L of cold pulmoplegia solution with phentolamine 10 mg/L.
9. Left atrial (LA) appendage vented, confirming good pulmoplegia run off obtained.
10. Pleurae opened, lungs inspected for adequacy of inflation and pulmoplegia flush, cold N/saline into chest during flush.
11. En bloc removal of heart and lungs with lungs moderately inflated prior to stapling trachea.
12. The heart is removed on the back table, placed back in the chest or sent for valves.
13. 2–4 L of pulmoplegia solution with 10 mg/L phentolamine flushed *retrograde THROUGH EACH pulmonary vein*; inspection of parenchyma and effluent from PA.
14. Separation of R and L lungs with final inspection as to quality of flush, inflation, and weight of each lung *prior to final decision* to begin recipient operation.
15. Lungs packed in cold sterile solution and ice in outer packs for transport.

A detailed procurement protocol was used for all DCD donors at the University of Wisconsin and Loyola University Hospital and is provided in Table 4 (25). At least one bronchoscopy was performed in all donors to assess graft adequacy and remove airway secretions. Reintubation was required for all DCD lung donors after completion of the stipulated "hands-off" period (5 minutes) after irreversible cessation of cardiac function. The specific DCD definitions applied were according to the Crystal City Report recommendations.

In our experience, the DCD procurement procedure varied minimally and only to adhere to local protocols. The median DCD donor age in this series was 35. Motor vehicle accident with multiple trauma was the predominant reason for donor admission and subsequent cause of death. Donor oxygenation at baseline at FiO_2 0.4 was PaO_2 (mean) 135.5 mmHg and after O_2 challenge at inspired FiO_2 1.0 was 474.4 mmHg (63.3 kPa). The final mean PaO_2 prior to withdrawal of artificial ventilatory support was 406.4 mmHg (54.2 kPa). Ischemic times were defined as warm ischemia (WIT), encountered from discontinuation of artificial life support to the time of administration of cold pulmoplegia: 35.5 minutes (range: 18–93 minutes) and cold ischemia (CIT) defined as cold flush completion until in vivo reperfusion in the recipient: 364 minutes (221–610) (Table 5).

ABO compatibility was assured and size matching confirmed within 20% BMI or absolute height of the recipient. CMV mismatch was tolerated and reflected in altered

Table 5 21 Consecutive DCD Lung Allograft Donors

Donor #	Age	CoD+	WIT	CIT
1	46	CVA	40	235
2	12	Anoxia	21	221
3	50	CVA	19	389
4	22	Anoxia	35	290
5	21	MVA/CHI	27	247
6	10	MVA/CHI	19	289
7	32	MVA/CHI	42	455
8	32	MVA/CHI	42	537
9	17	MVA/CHI	40	370
10	39	MVA/CHI	93	360
11	18	MVA/CHI	20	480
12	44	Asphyxia	18	395
13	44	Asphyxia	18	610
14	20	CHI	27	370
15	23	CVS arrest	27	380
16	22	MVA/CHI	29	420
17	17	Hanging	45	425
18	35	CHI	80	190
19	55	CVA	44	275
20	19	Anoxia	35	406
21	22	CHI	24	300
Median/mean	35 yr		35.5 min	364 min

induction regimen and early screening as well as surveillance protocol in the recipient. Clinical DCD lung transplantation was reintroduced with our first case in 1993, for a patient with PGD, supported on ECMO after a single-lung transplant.

Patient demographics and pulmonary diagnoses in this cohort of 24 DCD recipients were comparable to recipients of lungs from traditional brain-dead donors, however lung allocation scores (LAS) were significantly higher, on average, when compared to national means for lung transplant candidates receiving standard criteria allografts (mean 52.6 vs. 38). Operative approaches for either single or bilateral sequential lung transplantation were performed according to routine implant procedures. Cardiopulmonary bypass was utilized when required for safe facilitation of the implant procedure.

IV. Outcomes in DCD Lung Transplantation

Several DCD lung transplant case series have now been reported internationally. The early and midterm outcomes have been comparable to lung transplantation from brain-dead donors. Most reports published to date summarize the findings of less than 10 cases, and early adopters of this technique have now advocated its widened application (40–43). The results at the University of Wisconsin and Loyola University Medical Center presented in this series have provided clinical evidence of the feasibility, excellent survival data, and good midterm graft function despite significantly higher

recipient LAS scores. It is noteworthy that only two patients in this cohort had clinically severe PGD (ISHLT grade 3) with prolonged recovery times and a third had less profound grade 2 PGD. This is in line with the evolving international experience with DCD lung transplantation and may well emerge as a beneficial aspect of DCD lung transplantation, if confirmed in larger series.

Long-term survival in this cohort was mostly limited by BOS and nontransplant-related mortality. It is reasonable to expect improved long-term prognosis in this group of patients with adequate surveillance and tailored immunosuppressive regimens (44,45).

V. Discussion

The rationale for utilizing DCD donors is apparent when considering the increasing disparity between acceptable donors and candidates waiting on lung transplantation lists. The scientific basis and experimental evidence has now provided insights confirming that lung parenchyma may be less vulnerable to ischemia if procured carefully with adherence to careful protocols to preserve the organs. Early clinical experience with category III and IV DCD has been very encouraging (27).

Recent guidelines reviewed the criteria for DCD donation and provided ethical propriety of this approach and specific critical care recommendations have been issued. The National Conference on DCD in the United States affirmed DCD as an "ethically acceptable practice of end-of-life care, capable of increasing the number of deceased-donor organs available for successful transplantation" (30,31,46).

Skepticism regarding detrimental pulmonary consequences of circulatory arrest has not been borne out in reality. The nonventilated lung may become atelectatic, and tissue hypoxia will certainly ensue after cessation of circulation, but the metabolic demands of the lung interstitium and the integrity of parenchymal tissue appear satisfactory for DCD to be performed. Thrombotic complications have not been observed with the routine systemic administration of heparin and brief internal cardiac massage to distribute it into the pulmonary vascular bed. The distribution after direct PA administration maybe variable as shunting secondary to atelectasis is likely to be a limiting factor. Swift reexpansion of lungs after reintubation status post withdrawal of life support, therefore, is of paramount importance.

More subtle consequences of the pathophysiologic effects of circulatory arrest on lung parenchyma have not been studied prospectively in human trials. These topics include apoptosis, likely to be triggered during warm and subsequent cold ischemia, inflammatory insults leading to capillary leakage and alveolar sequestration of neutrophils, alterations in innate immune regulation, and class II MHC upregulation, all of which may affect the incidence of rejection and the development of BOS. We have not observed clinically detectable manifestations of these potential factors in this cohort.

Further prospective evaluation is needed to provide confidence and advise potential recipients of DCD allografts about the potential inherent risks of this approach compared with experience in standard cadaveric donor organs. In fact, the consent process offering DCD allografts to lung transplant candidates has to be based on the assumption that we currently lack substantial evidence to predict long-term outcomes and associated complication rates.

At our center, we have resorted to DCD allografts predominantly in recipients with high risk of mortality on the waiting list when even ECD lungs would be unlikely to

be found in time for transplantation. Much remains to be learned about the best practice of DCD lung transplantation. How to optimize such donor lungs and increase the number of transplants performed is the primary concern. Ex vivo functional assessment of DCD allograft, once clinically standardized, will no doubt facilitate the DCD procurement process (27,30,47). Ex vivo resuscitation of lungs prior to transplantation has now been achieved with success in Europe and Canada.

With increasing experience and validation of the clinical application with ex vivo assessment, DCD lung transplantation may become a primary source of allografts in lung transplantation and provide a realistic alternative for many patients waiting for lung transplantation (48,49). Continued public and professional education as well as clinical and basic science research applied to DCD as a potential significant source of lungs is essential.

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16
Preservation of the Donor Lung

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I. Introduction

The increased success of lung transplantation over the past 25 years owes much to the advances made in donor lung preservation. Donor organ ischemia and reperfusion are obligatory steps in all solid organ transplantation, but preservation-related injury during this time remains a major contributor to primary graft dysfunction. Since the first successful clinical lung transplant in 1983, the paradigm of lung preservation has evolved from hypothermic atelectatic immersion to hypothermic static flush preservation, all the way to normothermic ex vivo lung perfusion. The optimal method of lung preservation, however, remains unclear today, and 20% of lung transplant recipients still suffer from significant ischemia-reperfusion-induced injury (IRI). We will review the current standard of care for lung preservation and discuss lung preservation techniques of the future.

II. Preprocurement Strategies for Lung Preservation

Even prior to the onset of ischemia, brain-dead individuals maintained for lung donation must be carefully managed in the ICU to avoid injury to the lung prior to procurement. A protective ventilation strategy should be utilized (V_T = 6–8 mL/kg, PEEP = 5 mmHg, $FiO_2 < 0.5$) where possible. Frequent turning and suctioning for pulmonary toilet along with regular recruitment maneuvers should be performed to reduce the likelihood of pneumonia and atelectasis. Because of the cytokine storm of brain death, a methylprednisolone bolus at 15 mg/kg has been shown to improve post-transplant outcomes. To avoid pulmonary edema, central venous pressure monitoring should be employed to maintain central venous pressure (CVP) between 4 and 10 mmHg. Pulmonary artery catheterization should be considered if left heart dysfunction is present as CVP may be misleading.

III. Lung Preservation Strategies During Procurement

The majority of the strategies developed for lung preservation are applied during the procurement operation. We will first discuss how current lung preservation strategies are employed and will follow with a discussion on the development of these strategies.

A lung protective ventilation strategy should be maintained throughout the procurement operation (tidal volume of 6–8 cc/kg, an FiO_2 of 50%, and a PEEP of 5-cm H_2O). Following sternotomy, the lungs are exposed and any atelectatic areas are

reexpanded with ventilatory recruitment. The donor should then be anticoagulated with IV heparin (300 units per kg). After cannulation of the pulmonary artery, a bolus of prostaglandin E_1 (PGE_1, alprostadil, 500 μg) is then administered into the main pulmonary artery. This dilates the pulmonary microvasculature, and a significant drop in systemic blood pressure is observed. In sequence, the superior vena cava is ligated, the inferior vena cava is transected, the left atrial appendage vented (2 cm orifice), and the aorta cross-clamped (1). The pulmonary artery flush is carried out using 60 mL/kg of low-potassium dextran (LPD) solution (Perfadex®) mixed with 500 μg of PGE_1 cooled to 4°C to 8°C. Ventilation is continued while the flush solution is infused into the main pulmonary artery. To assure a low-pressure, high-volume flush, the flush solution should be hung at 30 cm (not any higher) above the patient and allowed to flow in by gravity alone. This usually takes approximately 20 minutes to complete. Following the flush, the heart is removed taking care to leave a cuff of left atrium with the lungs. An inflated 16Fr Foley catheter is then inserted into each of the pulmonary veins in sequence; 250 mL of Perfadex is instilled into each vein for the retrograde flush. Clots and other embolic material can often be seen to exit via the pulmonary artery and should be suctioned out. Just prior to removal from the body, the lungs are inflated to a peak airway pressure of 20 cm H_2O with an FiO_2 of 50% and the trachea is stapled with a TA-30 stapler and transected. If a flight is required to return to the recipient hospital, care is required to not overinflate the lungs prior to stapling of the trachea as airplane cabins are generally pressurized only to an altitude of 8000 ft, and this can cause significant expansion of the lungs (barotrauma) during flight. The lungs are then excised, packed in organ bags containing 2 L of the preservation solution, and placed on ice for transportation.

IV. Special Considerations for a Non-Heart-Beating Donor

A slightly different initial sequence is used for non-heart-beating donors (2). The process does vary depending on local institutional practice preferences. The first step is systemic heparinization, which is usually given 30 minutes prior to withdrawal of clinical support. In some jurisdictions, ethical considerations have limited the use of pre-withdrawal heparin administration. Some early data suggests that this may not impact outcomes, but further study is warranted. Following the declaration of death and the obligatory hands-off period, reintubation and ventilation of the lung is performed simultaneously with the median sternotomy, pulmonary artery cannulation, and flush. Immediately prior to flush, 500 μg of PGE_1 is instilled into the pulmonary artery and the heart squeezed three or four times. After flushing, the procedure is same as for donation after brain death, as described earlier.

V. Lung Preservation Strategies During Implantation

Prior to the time of implantation into the recipient, the lung is stored cold and inflated, and few additional strategies for lung preservation have been employed during this phase of aerobic, hypothermic lung preservation. Minimizing warm ischemia and atelectatic time is the key principle during implantation. One strategy has been to employ a cooling jacket around the lung during implantation to slow the warming of the lung. Following implantation, gradual reinstitution of pulmonary arterial blood flow during reperfusion by increasing pulmonary artery flow in a stepwise manner over a 10-minute period has been shown to improve the outcomes (3).

VI. Details of Preservation Methods

A. Preservation Solutions

The optimal lung preservation solution, storage temperature, inflation volume, oxygen concentration, and pharmacologic additives needed to enhance lung graft success will of course continue to evolve as more is learned about the underlying injuries and effective strategies to prevent them. However, several lung preservation techniques have been developed to protect the procured donor lungs from the major insults of ischemia, cold storage, and reperfusion that may contribute to IRI and long-term mortality (4,5). The principle of a hypothermic pulmonary artery flush is to cool the lung tissue uniformly and remove blood from the pulmonary vascular bed, thereby preventing thrombosis and endothelial injury from retained neutrophils. Experimental work and clinical reports have favored the use of extracellular type solutions over intracellular (high-potassium, low-sodium crystalloid) type preservation solutions (6–22). Examples of extracellular solutions include the most commonly applied LPD-glucose solution [e.g., Perfadex (Vitrolife, Sweden)] that was developed specifically for lung preservation, and Cambridge solution, Celsior, and Papworth. Papworth contains mannitol, albumin, and donor blood. Euro-Collins and University of Wisconsin are intracellular solutions.

The key components of LPD solutions are the dextran and the low concentration of potassium. Dextran-40 in the LPD solution functions as an oncotic agent, helping to keep water within the intravascular compartment, thereby decreasing interstitial edema formation. Dextran-40 also reduces the aggregation of erythrocytes and circulating thrombocytes, which may improve the microcirculation and reduce cellular activation (16). The low-potassium concentration maintains normal pulmonary artery pressures during infusion. A further development was the addition of glucose to the dextran-based extracellular solution. The addition of glucose is designed to support aerobic metabolism and maintain cell integrity during prolonged ischemia. Perfadex is an LPD-glucose solution that is now available worldwide and used by most lung transplant centers. The addition of glucose to a lung preservation solution takes advantage of the unique aspect of lung physiology in transplantation; the inflated lung has an oxygen supply for its parenchyma even during storage (23).

Several studies have reported better outcomes with extracellular solutions in terms of various parameters, such as frequency of primary graft dysfunction, duration of ventilator dependence, and 30-day mortality. One of the largest studies retrospectively examined the likelihood of primary lung graft dysfunction among 157 consecutive patients whose donor lungs were preserved with one of three lung preservation solutions (Perfadex, Euro-Collins, and Papworth). Perfadex was superior in prevention of moderate-to-severe primary graft dysfunction, and it trended toward superiority in other early post-transplant outcomes (17). Several other studies have supported the preferential use of Perfadex (18–21).

B. Pharmacologic Additives

Two pharmacologic agents, prostaglandins and glucocorticoids, have been broadly used for lung preservation (24–26). These drugs have been given as pretreatment of the donor before flushing since part of the flush perfusate itself and as a treatment for the recipient during and after reperfusion.

Prostaglandins

Prostaglandin E_1 (PGE_1, alprostadil) and I_2 [PGI_2, prostacyclin, iloprost (a PGI_2 analog)] were originally chosen for lung preservation because their vasodilator activity offset the cold-induced vasoconstriction of the preservation solution and allowed a more even distribution of perfusion (22). Subsequent study has found that PGE_1 has additional properties, particularly downregulation of proinflammatory cytokine expression, which are probably more important in ameliorating ischemia-reperfusion injury (26,27). Many centers routinely inject PGE_1 into the pulmonary artery just before flushing with preservation solution, although clinical study data in humans is lacking.

Methylprednisolone

High-dose methylprednisolone has become an empirical adjunct to most clinical protocols because of its anti-inflammatory actions (28–30). Methylprednisolone, 15 mg/kg, is typically administered intravenously as soon as possible to the donor before procurement and to the recipient immediately before reperfusion.

Temperature of Preservation Solution

While the optimal temperature has been debated, most centers use a flush temperature of 4°C to 8°C (4). Hypothermia reduces metabolic activity such that cell viability can be maintained in the face of ischemia (5% of the metabolic rate at 37°C). Essentially, the process of dying is slowed down. Cold temperature preservation thus continues to be an important cornerstone of lung preservation (31).

Anterograde and Retrograde Flushes

Anterograde flush refers to the administration of flush solution through the pulmonary artery with drainage from the pulmonary veins. Retrograde flush refers to the administration of the flush solution to each pulmonary vein, with drainage through the pulmonary artery. The combination of both flushes appears to achieve better lung function and most transplant centers now combine an anterograde flush with a retrograde flush (32). Once again, care is taken to ensure that the maximum perfusion pressure is less than 30 cm H_2O.

In an experimental model, a retrograde flush improved lung preservation, compared with anterograde flush alone (33). This effect was attributed to a more effective clearance of red cells within the capillaries and better distribution of the flush solution. It also provides the added advantage of removing any clot or emboli in the pulmonary arteries.

Volume of Preservation Solution

Although scientific data are limited regarding the ideal volume of preservation solution, typically about 50 to 60 mL/kg of perfusate is infused after lung extraction as this successfully clears the lungs of blood cells and uniformly cools the lungs (4). Usually this takes 15 to 20 minutes to complete.

Pressure of Preservation Solution Infusion

Data are limited regarding the optimal pulmonary artery pressure for infusion of the preservation solution. The need for complete clearance of the vascular bed has to be balanced against the risk of injury to the low-pressure pulmonary vasculature (4) particularly while the organ is cooling. We typically use a perfusion pressure in the lower range (10–15 mm Hg) (34,35). Once the vascular bed has been flushed, perfusion is discontinued during storage.

Lung Inflation

Inflation of the lungs with an oxygen mixture during the ischemic period appears to protect the lung; however, scientific information regarding ideal oxygen concentration and inflation pressure is limited (36,37). On the basis of studies in animal models, three primary mechanisms are thought to contribute to the protective effect of inflation with oxygenated air:

- Energy efficient aerobic metabolism is maintained.
- Integrity of pulmonary surfactant is preserved.
- Epithelial fluid transport is improved.

Lung inflation is generally limited to 50% of the total lung capacity or to an airway pressure of 20 cmH_2O to avoid overdistention (36,37). Usually, an inspired oxygen tension (FiO_2) ranging from 30% to 50% is used. Once the lungs have been inflated, the trachea is stapled for storage.

Storage Temperature

The ideal temperature for donor lung storage remains unclear. Preservation at 4°C to 8°C decreases cellular metabolic activity and preserves the cellular function; however, cold storage may actually compound some aspects of IRI (4). Specifically in the lung, hypothermia may result in increased extravascular fluid and pulmonary vasoconstriction, contributing to diminished oxygen exchange and increased vascular resistance after reperfusion. Some experimental work has suggested that lungs preserved at 10°C instead of 4°C had superior lung function after transplantation (38). However, the most common and practical temperature for lung storage continues to be 4°C as the logistics of transportation may prolong storage time and necessitate a margin of safety provided by the lower temperature.

Ischemic Time

The maximal acceptable ischemic times for donor lungs are not known, although in general, the longer the ischemic time, the greater the risk of significant primary graft dysfunction. Ischemic times up to eight hours are generally considered acceptable. The risk of primary graft dysfunction and 30-day mortality increases with more than 8 hours of ischemia; however, ischemic times of up to 10 to 12 hours have been successfully reported (4,39–41). Therefore, the decision to accept lungs with longer ischemic times is made with the consideration of the constellation of other predictive risk factors in the lung donor (e.g., age, clinical variables, smoking history, etc.) and also consideration of the status or condition of the recipient.

VII. New Approaches to Organ Preservation

Maintaining organ viability during preservation is an important prerequisite for successful outcome after transplantation. A variety of different approaches to reducing lung injury during storage are under investigation. Some examples are as follows:

A. Experimental Pharmacologic Agents

Several pharmacologic and biologic agents have shown some benefit in experimental models of lung transplantation but have not been validated in human studies (26,27,42–49):

- Prostaglandin E_2 (PGE_2)
- Oxygen-free radical scavengers such as superoxide dismutase and catalase
- Glutathione, allopurinol, dimethylthiourea, and deferoxamine
- Verapamil
- Platelet-activating factor antagonists
- Complement inhibitors (sCR-1)
- Pentoxifylline
- Inhaled nitric oxide, nitroglycerin, and nitroprusside
- Phosphodiesterase-5 inhibitors (e.g., sildenafil)
- Exogenous surfactant
- Endothelin-1 (ET-1) receptor antagonists
- Adenosine A2a receptor agonists

B. Normothermic Perfusion

The cold static preservation system described above was developed in an era with younger organ donors and good-quality organs. However, to increase the availability of donor organs, older and sometimes injured donor organs are being used. The need to use donor lungs that do not meet standard criteria and difficulties with assessing lung function in non-heart-beating donors have made it necessary to explore alternative preservation techniques (50).

Hypothermic preservation inhibits cellular metabolism and eliminates the possibility of substantial reparative processes occurring after donor organ injury. For this reason, normothermic (37°C) or near-normothermic (25–34°C) ex vivo organ perfusion is becoming popular as a preservation alternative in kidney and liver transplantation (51–56).

Attempts at using a ventilating and perfusing machine for lung preservation have failed in the past largely due to the development of lung edema and increased pulmonary vascular resistance (57,58). However, investigators have since used a large animal model to develop a perfusion system that allows for evaluation of lung function ex vivo (59). A key part of ex vivo perfusion has been the development of a specific solution (Steen® solution, Vitrolife) that allows for ex vivo perfusion of lungs without development of pulmonary edema. In an animal model and a single human case, after a short period (60–90 minutes) of ex vivo evaluation, lungs were successfully transplanted (60).

An acellular EVLP technique that can maintain donor lungs for at least 12 hours at body temperature without inducing significant injury has been tested in porcine and human lungs (61,62). After prolonged EVLP, lung function after transplantation was excellent. The acellular perfusion technique also allows evaluation of lung function ex vivo. This preservation modality opens the door to treatment opportunities to repair or pre-prepare the donor lung in the ex vivo phase prior to transplantation (63).

VIII. Summary

Much of the experimental work in lung transplantation in the past has focused on optimizing methods of lung preservation to reduce the impact of ischemia-reperfusion injury on post-transplant lung function. Cold, static aerobic flush preservation with Perfadex solution has become the standard of care in clinical lung preservation at most lung transplant centers. As we gain improved understanding of the underlying injury processes and the biology of the transplanted lung, we need to shift the focus away from

simply slowing down the dying process of the donor lung to actively and specifically treating and repairing the injured donor lung. Ultimately, we will also be able to immunologically pre-prepare the donor lung before it is implanted into the recipient. Recent exciting developments in successful normothermic ex vivo lung perfusion have opened the door to the potential for superior lung preservation, diagnostic and physiologic evaluation, and repair of injured donor lungs. This strategy will hopefully not only increase the number of donor lungs that can be used, but also improve the quality and outcomes of the lung transplants performed.

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17
Donor Procurement

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Donor suitability for transplant and donor/recipient matching is usually well established by the time the procurement team reaches the donor center. However, the most critical part in donor assessment takes place at the time of harvest. Clear communication between the donor and the recipient teams about organ quality, expected time of cross clamping, and time of arrival to the recipient hospital plays a crucial role in coordinating the onset of the recipient surgical procedure to minimize ischemia time.

I. Donor Evaluation

The evaluation consists of examination of the hospital records, flexible bronchoscopy, in addition to a visual and manual examination of the lungs.

The process starts with verification of the history, hospital course, brain death note, and the presence of consent for organ donation. Attention is then directed to the confirmation of blood group compatibility between the donor and recipient and a detailed review of the pertinent donor blood work. Examination of the available chest radiological studies, including a chest X ray within the last 24 hours, is an important step in excluding disqualifying abnormalities.

Detailed flexible bronchoscopy is done next to assess the airway for any anatomical abnormalities. It is very common to find significant secretions in the donor's bronchial tree. The sputum should be cleared completely and a sample is collected for gram staining and cultures. The quality of the underlying mucosa is examined for evidence of infection or intense erythema. Secretions that clear with the bronchoscope revealing a normal underlying mucosa are not a source of major concern (1).

The ventilator is set at a tidal volume of 8 to 10 cc/kg of body weight, PEEP of +5 cm H2O and FiO_2 of 1.0 (2). Normal lung compliance is assured by observation of peak and plateau airway pressures. A sample of arterial blood for gas analysis is sent 15 to 20 minutes after bronchoscopy to confirm adequate gas exchange.

For the manual and visual examination, the lungs are accessed through a median sternotomy incision. The pleural spaces are opened widely and the lungs are examined. After complete circumferential inspection, lung compliance is assessed again by disconnecting the endotracheal tube from the ventilator at end inspiration to observe the lungs for normal, instantaneous deflation (3). The lungs are palpated thoroughly for evidence of nodules or masses while in a deflated state.

After communication with the other organ procurement teams regarding their time needs, the cross clamp time is estimated and the information is shared with the recipient

team to help them plan the timing of their procedure with the goal of keeping the total ischemia time to less than six to eight hours (4).

At the end of the assessment, the pulmonary artery is separated from the ascending aorta to define the pulmonary bifurcation. The ascending aorta should be dissected circumferentially to separate it from the right pulmonary artery posteriorly. The superior vena cava is dissected circumferentially to a point just superior to the Azygus vein entry and a 0-Silk tie is placed around it. The inferior vena cava is freed circumferentially inside the pericardium. Electric cautery on low setting can be used for most of the dissection.

Throughout the course, fluid administration to the donor should be kept to an absolute minimum to prevent pulmonary edema.

The importance of courteous communication with the cardiac harvest team cannot be overstated. There should be a clear agreement on the cannulation site of the pulmonary artery, the line of incision of the left atrium and pulmonary artery, and the preferred venting site of the left atrium.

II. Cannulation

After completion of the abdominal dissection, the donor is given 250 to 300 units/kg of Heparin as an intravenous bolus (3). The pulmonary artery is cannulated through a 4-0 Prolene U stitch proximal to the bifurcation (Fig. 1). To assure an even distribution of the flush solution to both lungs we use a 6-mm Sarns™ aortic cannula with a Soft-Flow™ tip (Terumo, Ann Arbor, Michigan).

III. Lung Perfusion and Preservation

Low potassium Dextran (Perfadex®) is the current lung perfusion fluid in our program. Although the choice of perfusion fluid is controversial (5–8), there is some evidence that Perfadex might be superior to the other options (9–11).

Donor lungs are pretreated with the infusion of 500 mg of prostaglandin E_1 (Alprostadil) just prior to the application of the aortic clamp. An 18-gauge needle is used to inject the drug directly into the pulmonary artery over a period of 10 to 15 seconds (3). A significant drop in systemic blood pressure is expected as a result of the initial infusion. Several heart beats are allowed to take place before the superior vena cava is ligated, the inferior vena cava is clamped or incised and the aortic cross clamp is applied. The left atrium can be vented by resection of the tip of the left atrial appendage. Alternatively, Sondergaard's plane can be dissected with a #15 blade and the left atrium entered after assuring about 4 or 5 mm of left atrial cuff anteriorly on the right-sided pulmonary veins (Fig. 2).

We use Perfadex® at a temperature of 4°C to 10°C (kept on ice in a cooler during transport). Perfadex® dose is about 60 cc/kg of donor body weight. An additional 500 mg of Alprostadil is added to the first liter of flush. The flush bag is hung on an IV pole at about 200 cm above the floor level and infused by gravity; this will result in a perfusion pressure of 15 to 20 mmHg (12). The lungs are ventilated during the entire process. If the lungs are interfering with good visibility during the procedure, the tidal volume can be lowered by half.

The main method for cooling the donor lungs is the administration of cold pulmonary flush. Cooling is enhanced with the local application of slush saline during the

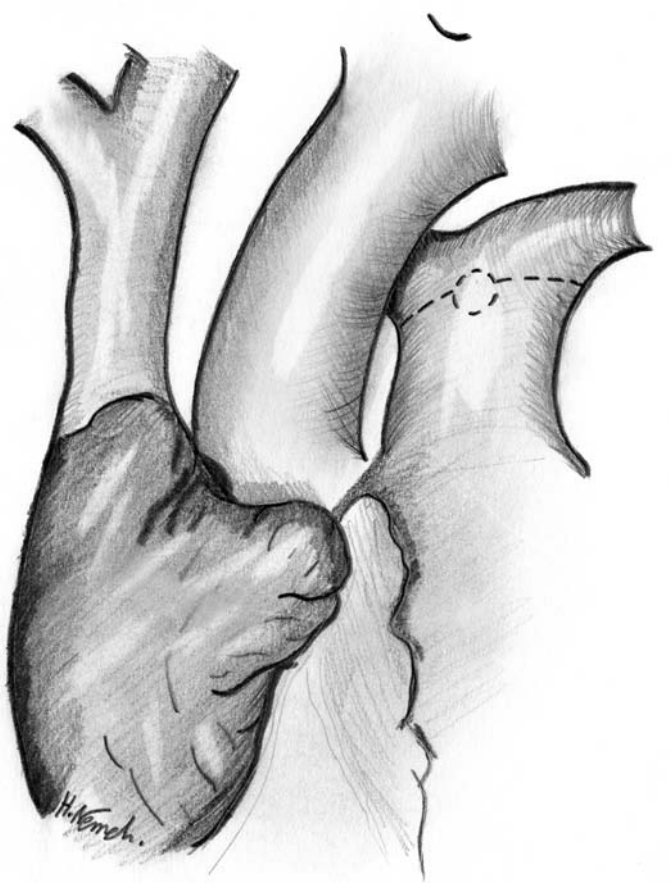

Figure 1 Point of cannulation and resection line of the dissected pulmonary artery.

flush. Air in the ventilated lungs acts as a barrier to fully cooling the organ by topical cold fluid alone.

During the infusion, the heart is not manipulated. The effluent from the left atrial venting site is observed to assure the return of clear fluid as a sign of adequate lung perfusion.

When the inferior vena cava is opened in the pericardial well, it is very important to advance the tip of high-power suction into the open end of the vessel to aspirate the abdominal flush effluent and prevent it from reaching the heart or the lungs.

After removal of the lungs as a block, retrograde Perfadex® is administered through the pulmonary veins on the back table with the use of a 14 Fr. self inflating balloon tipped retrograde cardioplegia catheter (Edwards Lifesciences, Irvine, California). Approximately, 250 cc of Perfadex® is infused in each pulmonary vein. Infusion continues until the return from the open pulmonary artery becomes clear. It is very common to see small to medium size pulmonary emboli exiting the pulmonary artery during this

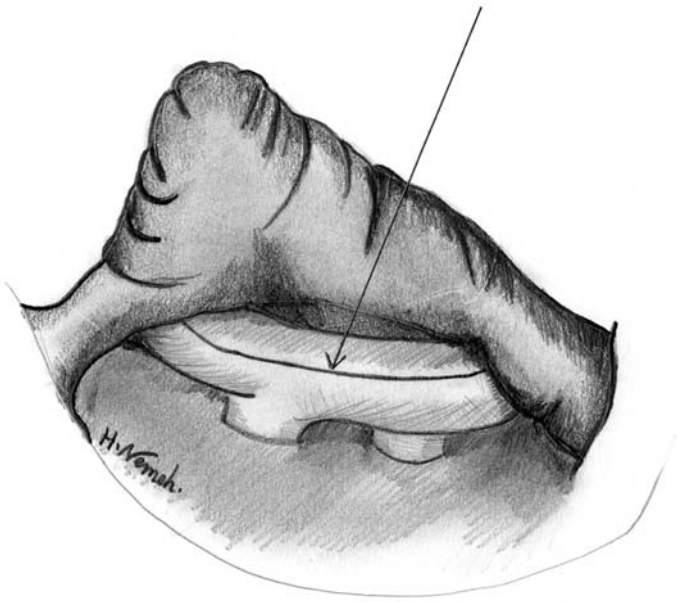

Figure 2 Sondergaard's plane after dissection. The arrow is pointing to the line of entry into the left artium.

process (13). The benefits of retrograde flush are suggested in both the experimental and clinical literature (14–16).

IV. Resection

After delivery of the cardiopulmonary flush, the pericardial well is cleared. The inferior vena cava is fully transected at the pericardial reflection. The inferior edge of the right inferior pulmonary vein is cleared from the attached soft tissue to prevent injury to the vein during harvest (17). The heart is elevated to expose the left inferior pulmonary vein. A #11 blade is used to enter the left atrium halfway between the left inferior pulmonary vein and the coronary sinus. With the use of a pair of scissors, the left atrial incision is extended toward the base of the left atrial appendage leaving the entire left atrial appendage attached to the heart (Fig. 3). Then, the incision is extended inferiorly and across the midline toward the right-sided pulmonary veins. Visualization of the pulmonary veins from inside the atrial cavity allows for leaving adequate left atrial margins on both the heart and the pulmonary veins. A rim of about 4 to 5 mm of left atrial tissue is usually sufficient for the recipient anastomosis. Prior dissection of Sondergaard's plane facilitates the development of the right-sided pulmonary venous cuff.

The pulmonary artery is incised anteriorly at the site of cannulation (base of the bifurcation) (Fig. 1). The incision is then extended carefully to the sides and to the back wall under direct vision from inside of the pulmonary artery to keep the bifurcation ridge on the lung side and to avoid unnecessary shortening of the artery.

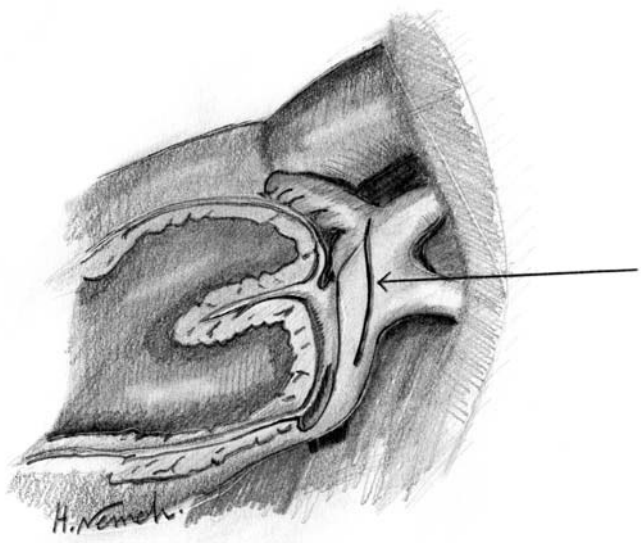

Figure 3 The heart is elevated to the right side of the donor exposing the left sided pulmonary veins. The arrow is pointing to the line of entry into the left atrium halfway between the coronary sinus and the left sided pulmonary veins.

After complete removal of the heart from the field, the pericardium is incised laterally at the level of the diaphragm down to the inferior pulmonary ligaments. The inferior pulmonary ligaments are taken down to the inferior pulmonary veins. Each lung is delivered, in turn, medially and the mediastinal pleura is incised posterior to the hilum i.e., at the level of the descending aorta on the left and the level of the esophagus on the right all the way up to the chest apices. The esophagus is carefully freed posteriorly from the trachea to avoid injury to the membranous trachea.

The trachea is exposed anteriorly at the base of the neck. It is usually necessary to transect the innominate vein and artery to fully expose the trachea. The trachea is freed circumferentially with care to avoid injury to the membranous part posteriorly. An umbilical tape is passed around the trachea to facilitate the passage of the stapler. The endotracheal tube is palpated through the trachea and the anesthesiologist is asked to pull it back slightly if necessary to have a free segment for the application of the stapler. At this point, a TA-30 Auto Suture stapler with 4.8 mm staples is placed securely around the trachea. The lungs are hand inflated with 100% FiO_2 until all atelectasis is eliminated. Then the lungs are allowed to deflate just enough to avoid hyperinflation (12) (deflated to normal inspiratory tidal volume) and the stapler is closed. Ventilation is discontinued and the trachea is stapled twice. The trachea is transected with a knife blade between the two staple lines. The posterior wall of the trachea is mobilized gently all the way down to the carina with blunt and sharp dissection. The pericardium is transected inferiorly and the remaining soft tissue attachments superior to the pulmonary arteries on both sides are incised sharply. Care is taken when freeing the superior aspect of the left pulmonary artery to avoid injury at the level of the ligamentum arteriosum. The lungs are removed from the field as a block.

We prefer to separate the lungs on the back table prior to packing them by transecting the pulmonary artery at the bifurcation and the left atrium in the center between the right-and left-sided pulmonary veins. The left main bronchus is transected at the level of the carina with a GIA-60 Auto Suture stapler with 4.8 mm staples.

Each lung is placed in a separate bowel bag with 1 L of cold Perfadex®. The bag is tied securely after complete evacuation of air. The initial bag is placed in two more bags, each containing cold saline. The last bag is clearly labeled for laterality and placed in ice inside a cooler to keep the temperature of the organ at about 4°C during transport to the recipient hospital (12).

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18
Ex Vivo Management of Lungs

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Summary
This chapter outlines the recently described technique of ex vivo lung perfusion, its potential applications to increase the number of lung transplantations, and the worldwide clinical experience so far.

I. Introduction
Lung transplantation as the ultimate treatment for selected patients suffering from any form of benign end-stage lung disease is limited by the number of suitable brain-dead donors (1). Various strategies have been applied to increase the potential lung donor pool, including living lobar transplantation, split-lung transplantation, the use of extended criteria donors, as well as donors after cardiac death or so called non-heart-beating donors (1,2).

Ex vivo reperfusion of lungs was reported in historical papers as a method to assess the quality of the graft (3) and as a technique to preserve heart and lungs during distant procurement (4). Recently, renewed interest has been shown in use of ex vivo lung perfusion (EVLP) as a technique to evaluate lungs prior to transplantation. The first case report of successful lung transplantation after EVLP was published by Steen and colleagues in 2001 (5). A left single lung was transplanted into a 54-year old female recipient with chronic obstructive lung disease after previous lung volume reduction surgery. The donor was a Maastricht category II non-heart-beating donor who was declared dead after unsuccessful resuscitation following myocardial infarction. The lungs were topically cooled in the intact body for three hours initiated 65 minutes after death. The heart-lung block was removed and functional performance of both lungs were assessed in an ex vivo reperfusion system for one hour, then cooled and further stored for 12 hours prior to transplantation. The function of the transplanted lung has been good for the first five months of follow-up. This unique case report for the first time demonstrated that lungs can be transplanted successfully after a period of warm ischemia, ex vivo perfusion and evaluation, and cold storage.

The experimental work performed in Steen's lab in Lund, Sweden (6), has stimulated many research groups worldwide to further investigate the technique and the role of EVLP as a method to increase the number of lungs available for transplantation (7–11).

The objective of this review is to describe the technique of EVLP, its potential applications to increase the number of lung transplantations, and the worldwide clinical experience so far.

II. Technique of EVLP

Our group at the University of Leuven has previously reported on a feasibility study with EVLP of 20-paired human lungs from heart-beating donors (12). The set-up that is used in our laboratory to evaluate human lungs declined for primary transplantation is shown in Figure 1. The closed circuit contains a blood reservoir, a centrifugal pump, a leukocyte filter, a gas exchanger, an inline blood gas analyzer, and a heater/cooler. An endotracheal tube and perfusion cannulas are inserted for inflow of venous blood through the pulmonary artery and outflow of saturated blood from the left atrium before the human double lung block is mounted in a plexiglas box (Fig. 2). Lung ventilation with 50% oxygen starts when lungs are rewarmed up to 32°C. Full perfusion of the lungs at a perfusion pressure equal or less than 15 mmHg are done at 37°C with Steen Solution® (Vitrolife AB, Gothenburg, Sweden) mixed with a red blood cell concentrate up to a hematocrit of 15%. Functional assessment is performed during a period of two hours with measurement of gas exchange, hemodynamic and aerodynamic parameters, and indicators of lung edema.

Figure 1 (*See color insert*) Isolated reperfusion circuit for ex vivo assessment of pulmonary grafts. From the hard shell reservoir (**a**) the perfusate is recirculated by a centrifugal pump (**b**) passing a leukocyte filter (**c**) and a membrane oxygenator (**d**) before entering the lung block (**e**). The heater/cooler (**f**) is connected to the membrane gas exchanger. Blood gases and pulmonary artery flow are continuously measured using an inline blood gas analyzer (**G**) and an electromagnetic flow meter (**h**), respectively.

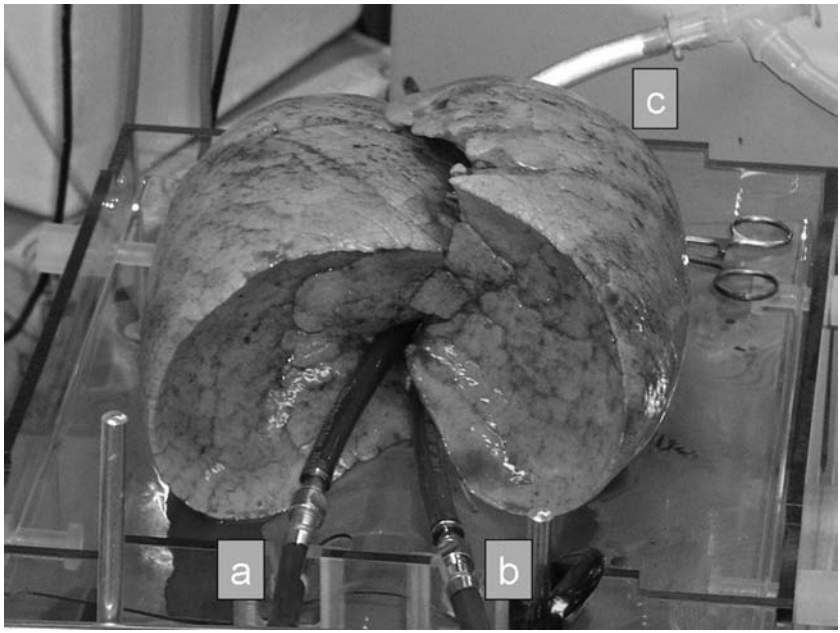

Figure 2 (*See color insert*) The human double lung block is mounted in a plexiglas box for ex vivo perfusion and ventilation. The inflow cannula (**a**) is positioned in the pulmonary artery bringing deoxygenated blood to the lungs and the outflow cannula (**b**) is draining oxygenated blood from the left atrium back to the reservoir. Both lungs are ventilated via an endotracheal tube (**c**).

We have found that reperfusion was possible for at least two hours even in poor quality lungs. Using a rigorous protocol of controlled reperfusion and ventilation, no significant changes over time in any of the measured parameters (pulmonary vascular resistance, pulmonary artery flow, oxygenation, and airway pressures) were observed during two hours of reperfusion, reflecting stable graft function with no visible edema formation. Other groups have also published their experience with human lungs using a similar ex vivo reperfusion set up (11,13,14).

The basic principle of ex vivo reperfusion is that lungs can be assessed without additional injury reflected by edema formation. In our opinion, key elements for successful EVLP are the use of an albumine-based extracellular solution with an optimal colloid pressure mixed with deleukocyted red blood cells up to a hematocrit of 15% as described by Steen and coworkers (6), the use of a leukocyte filter (8,15), and the technique of controlled reperfusion (16,17), and controlled ventilation (18). In our feasibility study (12), lungs were, therefore, slowly rewarmed by gradual increase of perfusion flow rates and ventilation of the graft in the ex vivo circuit was not started until the temperature of the effluent had reached 32°C. It is also our belief that full flow is not necessary to adequately assess the performance of the lungs. We therefore did not attempt to increase the flow rate higher than 1.5 to 2 L/min by accepting a mean pulmonary artery pressure around 15 mmHg to avoid hydrostatic pulmonary edema. We have used a completely closed reperfusion circuit by connecting a donor aortic patch to

the remnant of the left atrium, in case the heart was previously extracted, to avoid direct contact with ambient air. The pressure on the outflowing line was kept at 0 mmHg. Other groups have used an open system with free drainage of the reperfusion solution (14) or with a positive (3–5 mmHg) left atrial pressure by adjusting the height of the reservoir to prevent collapse of the pulmonary veins and to maintain venous afterload to keep the microcirculation open (11). A lung-protective strategy of mechanical ventilation is used gradually increasing ventilatory parameters in the first 30 minutes to a tidal volume of 10 mL/kg, a positive end-expiratory pressure of 5 cm H_2O, a respiratory rate of 10 breaths/min, and an inspired oxygen fraction of 50%.

Further studies are needed to answer remaining questions on the best technique (pulsatile vs. non-pulsatile flow) and on the optimal solution (cellular vs. acellular) needed to reperfuse human lungs for several hours without edema formation.

Portable machines similar to recently developed heart support systems (19) are currently designed for EVLP to make these potential applications a practical reality. Experimental and clinical data assessing the feasibility and safety of these transport devices are still awaited.

III. Potential Applications of EVLP

EVLP was originally developed by Steen as a method to evaluate lungs from uncontrolled non-heart-beating donors prior to transplantation (5). Besides (re)assessment of donor lungs, EVLP as a technique is hoped to bring new applications that may expand the donor pool and change clinical practice in the future. Firstly, EVLP could become a technique for prolonged (>12 hours) preservation of lungs so that the transplantation can be done as a planned procedure. Secondly, as many donor lungs are currently rejected because of the injury sustained in the hours after brain death (edema, aspiration, infection, atelectasis), EVLP could become a technique to resuscitate the lungs and to improve their quality and performance so that some of these can still become transplantable. Finally, as bronchiolitis obliterans resulting from chronic allograft rejection remains the major limiting factor for long-term survival after lung transplantation, EVLP is hoped to become a technique that may help to induce tolerance in the recipient to the pulmonary graft by ex vivo immunotherapy.

A. Lung Assessment

In the past, human lungs deemed unsuitable for transplantation have been evaluated after retrieval using microbiological, histological, and limited physiological methods (20–23). The ex vivo system provides an excellent environment for re-expansion of atelectatic lung areas and alveolar recruitment, for cleaning of bronchial secretions, and for removal of clots in the pulmonary circulation. The graft can be inspected and palpated and evaluated bronchoscopically and radiographically, enabling the transplant surgeon to carefully exclude the presence of tumors, areas of contusion and infection, bullae or interstitial parenchymal pathology. EVLP is a technique that offers the possibility to (re)assess lungs for transplant suitability under better conditions compared with the in vivo situation. Bronchial lavage and tissue specimens can easily be obtained during reperfusion for further microbiological, molecular, and morphological analysis. Studying noninvasive objective indices of donor lung injury may help to rationalize the selection process of suitable organs in the future (24,25). Finally, graft performance including gas exchange, hemodynamics, and ventilatory parameters can be assessed in an isolated reperfusion circuit.

B. Lung Preservation

Hypothermic preservation has traditionally been an important prerequisite for successful outcomes after lung transplantation. Machine preservation is currently being proposed as an alternative and superior preservation method for other solid organs such as kidney (26), liver (27), and heart (28). Past attempts at prolonged machine preservation of lungs have largely failed because of the inability to maintain the integrity and normal barrier functions of the vasculature and epithelial membranes, leading to progressive deterioration in vascular flow and the concurrent development of edema (4,9,29). The modern success of EVLP without edema formation is in part due to the use of a buffered, extracellular solution with an optimal colloid osmotic pressure as the lung perfusate developed by Steen et al., now commercially available as Steen Solution (Vitrolife AB, Gothenburg, Sweden).

Much experimental work was recently carried out at the University of Toronto by the group lead by S. Keshavjee. Studies in pig lungs demonstrated that 12 hours of EVLP at physiologic temperature using an acellular perfusate were achievable and maintained the donor lungs without inflicting significant added injury (10,30). This long period of EVLP opens perspectives to preserve and to treat donor lungs for a longer period of time. Further studies in pig lungs after 12 hours of cold storage demonstrated that ongoing lung injury was prevented during 12-hour EVLP when compared with a control group with further 12-hour cold storage (31).

C. Lung Resuscitation

Many donor lungs get injured before and after the onset of brain death as a result of contusion, atelectasis, aspiration, infection, or neurogenic edema formation. Research is conducted to investigate whether the quality of nonacceptable lungs can be adequately improved during EVLP before transplantation by direct intervention with the graft via an endotracheal or intravascular route. Possible pharmacological applications in the ex vivo circuit include utilizing high osmotic perfusates or β-adrenergic drugs (32) to accelerate removal of lung edema or bronchodilating and vasodilating agents to improve ventilation-perfusion mismatch, drugs to inhibit the pro-inflammatory response, perfusing the lung with high-dose antibiotics to help sterilize pneumonias and with fibrinolytics to help remove pulmonary emboli.

Our group has previously investigated the prophylactic role of the anti-oxidant *N*-acetyl cysteine in non-heart-beating donor pig lungs subjected to three hours of warm ischemia. Functional performance (33) and inflammatory response (34) assessed during EVLP was attenuated compared with the nontreated control group. The Zurich group investigated the role of EVLP in reconditioning pig donor lungs that were injured by acid aspiration (35). Ex vivo administration of surfactant via lavage resulted in improved graft function when compared with a control group. The same group found that adding the fibrinolytic drug urokinase to the reperfusion solution resulted in improved graft function with decreased pulmonary vascular resistance and better oxygenation (36). Investigators at the University of Hamburg also demonstrated that pig lungs damaged by acid aspiration could be repaired during EVLP (37). In another study using a porcine model of brain death–induced lung injury the same authors were able to demonstrate that ex vivo reperfusion for six hours allowed reconditioning with reversal of histological damage and clinical dysfunction (38). In a series of human donor lungs determined to be unsuitable for transplantation by the Toronto group, five lungs were subjected to

12 hours of normothermic EVLP and treated by transbronchial gene therapy with the anti-inflammatory interleukine IL-10 (39). Improvements in oxygenation capacity, restoration of alveolar barrier integrity and attenuation of lung inflammation were noticed compared with the untreated group (40).

D. Lung Conditioning

Gene therapy provides the exciting potential to immunologically prepare the donor lung prior to exposure to the recipient immune system response. No experimental data have been published so far using EVLP to prevent acute of chronic allograft rejection.

IV. Clinical Experience with EVLP

Recently, the group from Steen in Lund reported on a series of six successful double lung transplantations with lungs that were initially rejected (41,42). The donor lungs were reconditioned ex vivo in an extracorporeal membrane oxygenation (ECMO) circuit with Steen Solution mixed with erythrocytes to form a hyperoncotic solution that is able to dehydrate edematous lung tissue. Functional evaluation was performed with deoxygenated perfusate by varying the inspired fraction of oxygen. After the reconditioning, the lungs were kept immersed at 8°C in the perfusate on the ECMO circuit until the moment of transplantation.

A clinical trial is currently ongoing in Toronto to assess the feasibility and safety of EVLP in extended criteria donor lungs with the hope to increase their utilization rates and to improve outcome after transplantation. So far 22 human lungs from nonstandard criteria donors (brain dead or non-heart-beating) were placed in an ex vivo circuit (Toronto XVivo^{TM} system) and perfused normothermically with Steen solution for two to four hours for physiologic reassessment (43). Lungs that fulfill the criteria of good oxygenation capacity, low compliance, and airway pressures during EVLP are considered transplantable in a preclinical trial. A few lungs have been successfully transplanted so far (S. Keshavjee, personal communication).

V. Conclusion

EVLP is a new promising tool that allows assessment, preservation, repair, and conditioning of donor lungs prior to transplantation. It may become a method in the near future that helps to maximize the number of available lungs for transplantation. Further technological developments and research on the optimal technique and solution for long-term ex vivo reperfusion as well as further clinical trials are needed before EVLP will become an established technique in daily lung transplantation.

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19
Assessment and Management of the Sensitized Patient

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I. Introduction

The presence of antibodies to human leukocyte antigen (HLA) in the blood of a potential solid organ transplant recipient places such a patient at risk for the development of hyperacute allograft rejection. A "sensitized" patient was initially described in kidney transplantation in the 1960s, and subsequently, HLA antibodies have been associated with antibody-mediated allograft rejection (AMR) and poor outcomes (1). The first published account of hyperacute rejection following lung transplantation was described by Frost and colleagues in 1996 when pretransplant crossmatching was not routine (2). Close attention to panel reactive antibody (PRA) testing and prospective crossmatching of potential lung donor lymphocytes with recipient serum has virtually eliminated this event. The awareness of this circumstance and the development of improved techniques to detect and identify the specificities of anti-HLA antibodies have lead to the implication of donor-specific antibody (DSA) involvement in acute and chronic AMR (3). While evidence for AMR is strong in kidney and heart transplantation, only recently have publications in lung transplantation supported an association of anti-HLA antibodies with recurrent acute rejection (4), bronchiolitis obliterans syndrome (BOS) (5), and poor post-transplant survival (6,7). Between 10% and 17% of lung transplant recipients are presensitized to HLA antigens (7,8). Risk factors for sensitization include prior blood product transfusion, pregnancy, and previous organ transplant. ABO blood type and donor size are the primary considerations when accepting a potential organ allograft. However, patients with a positive PRA traditionally require a prospective crossmatch between donor lymphocytes and recipient serum. Allograft ischemic limitations and the inherent delay due to the crossmatch procedure place these patients at a disadvantage by limiting the donor pool to the local area. Newer more sensitive techniques used for the detection of anti-HLA antibody specificities have allowed the expansion of available donors to outside zones by matching donor HLA type and recipient serum anti-HLA antibody specificities (virtual crossmatch) (9). Despite the virtual crossmatch, patients with high PRA levels (>25%) still find it difficult to find an appropriate donor match. Desensitization techniques using IV immunoglobulin (IVIg), plasmapheresis, and medications to suppress the T- and/or B-cell response (mycophenolate mofetil, rituximab) have been successfully utilized to reduce anti-HLA antibodies both before and

after transplantation (10). Herein, a description of the approach to the sensitized lung transplant recipient is discussed.

II. Histocompatibility Evaluation

Prior to transplant listing of potential lung transplant recipients, a histocompatibility evaluation should include HLA typing of HLA class I (A, B, Cw) and class II (DR, DQ) antigens as well as screening and characterization of anti-HLA antibody specificities. As part of the determination of risk to be sensitized, a complete history including previous transfusion of blood products, pregnancy, or previous organ transplant is important. Recent infections, vaccinations, or an autoimmune disease is also relevant due to the potential rebound of anti-HLA antibodies and/or the development of autoreactive antibodies (11). Sensitization is defined as the presence of anti-HLA antibodies in patient serum and historically has been detected by measuring PRA and the strength of reactivity (12). Several laboratory techniques are used for antibody identification with variable sensitivity and specificity.

The complement dependent cytotoxicity (CDC) assay is the most widely used traditional test for antibody screening (Fig. 1). Patient serum is tested against lymphocytes from donors (30–50 donors) including a broad representation of HLA class I and class II specificities. Rabbit complement, ethidium bromide, and acridine orange are added prior to incubation. Complement-dependent cell lysis results in cell death when

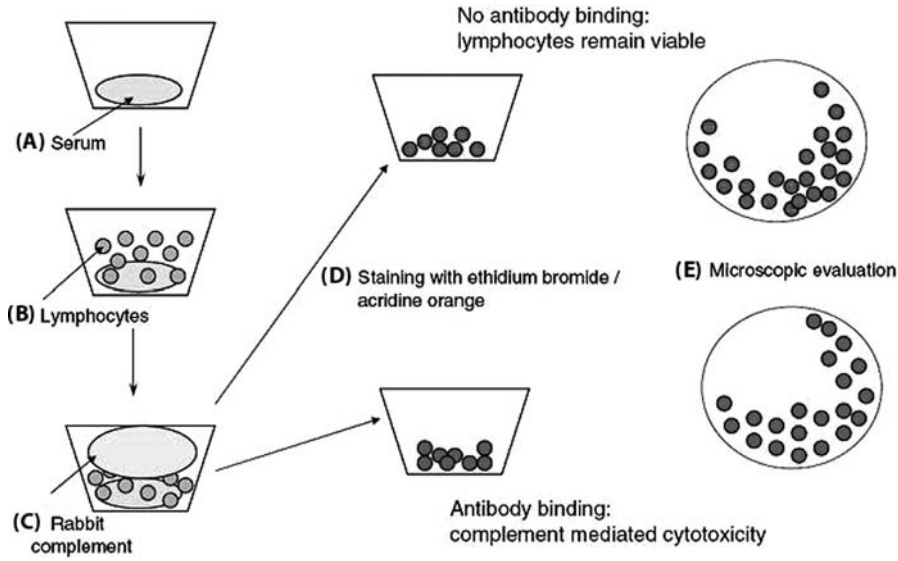

Figure 1 (*See color insert*) Complement-dependent cytotoxicity assay for the detection of anti-HLA antibodies. Recipient serum (**A**) is incubated with (**B**) lymphocytes of known HLA type. Rabbit serum is added as a source of complement after allowing for antibody antigen binding. (**C**) The presence of anti-HLA antibodies results in cell death and is visualized microscopically after the addition of stains (**D**) differentiating viable and dead cells. (**E**) The number of lysed cells expressed as a percentage is the reported panel reactive antibody (PRA). *Source*: From Ref. 13.

antibody binding occurs and is visualized by microscopic evaluation (13). The percentage of cell lysis gives an indication of the strength of the anti-HLA antibody reactivity with the HLA antigens of the tested donor. The percentage of antibody reactivity with a cell panel from a local pool of donors represents the PRA and is expressed as a percentage (%PRA). The assay can also be used to identify anti-HLA antibody specificities. However, the CDC assay is not as sensitive as microbead-based assays for the identification of anti-HLA antibody specificity and PRA levels; for this reason, it is no longer the recommended test of choice (14).

A prospective crossmatch in "real time" is done when a donor has been identified for a sensitized recipient. Using the CDC assay, actual donor lymphocytes are incubated with recent recipient serum prior to transplantation. A positive crossmatch should negate the transplant. Disadvantages of this assay include the nondetection of noncomplement-fixing antibodies, detection of IgM antibodies that are directed against non-HLA antigens (autoreactive antibodies), and the detection of alloantibodies (13). Interpretation of this test is subjective, adding to a lower sensitivity and specificity compared to newer solid phase assays. The addition of a second antihuman immunoglobulin (CDC-AHG) increases the sensitivity of this assay (3). However, the flow cytometry crossmatch is the method of choice for assessing HLA compatibility (15).

Solid phase methodologies use a solid matrix coated with purified recombinant or solubilized HLA class I or class II antigens. Optical detection methods are utilized, optimizing sensitivity and specificity (3,13). Both complement fixing and noncomplement fixing anti-HLA antibodies are detected by these technologies that include flow cytometry (flow PRA) and Luminex methods.

Flow cytometry assays use purified HLA class I or class II antigens coated on individual microparticle beads. Recipient serum is added and fluorescence conjugated secondary antibody directed against human immunoglobulin is used to detect antibody binding (Fig. 2) (3,13). Detection is done by flow cytometry and comparison of the fluorescence signal to the negative control provides an indication of the strength of antibody reactivity (13). Different sets of microparticle beads coated with HLA antigens can be used for anti-HLA antibody screening and PRA determination (3). Microbeads coated with single specific antigens can be used for anti-HLA antibody specificity testing (13).

Luminex technology also utilizes HLA class I or class II antigen—coated microparticles, except these microparticles are colored with a combination of two dyes arranged in different proportions so the beads can be distinguished (13). Each microparticle is coated with a single HLA antigen, providing higher resolution and sensitivity than microparticles coated with multiple antigens. Up to 100 particles can be utilized. HLA-specific antibody binding is detected using R-phycoerythrin-conjugated antihuman immunoglobulin. Lasers within the Luminex instrument excite the internal dyes to identify each microparticle and quantify the level of reaction (Fig. 3) (13). Following the detection of anti-HLA class I and class II antibody specificities by flow cytometry or Luminex assay, a calculated PRA is reported.

The sensitivity levels for each assay vary, and there may be antibodies present below the level of detection of the technique. Although some of these antibodies may not be clinically relevant, a case of hyperacute rejection occurring after negative PRA screens performed by enzyme-linked immunosorbent assay (ELISA) has recently been reported (15). Class I DSA was retrospectively detected using both flow cytometry and Luminex techniques (15).

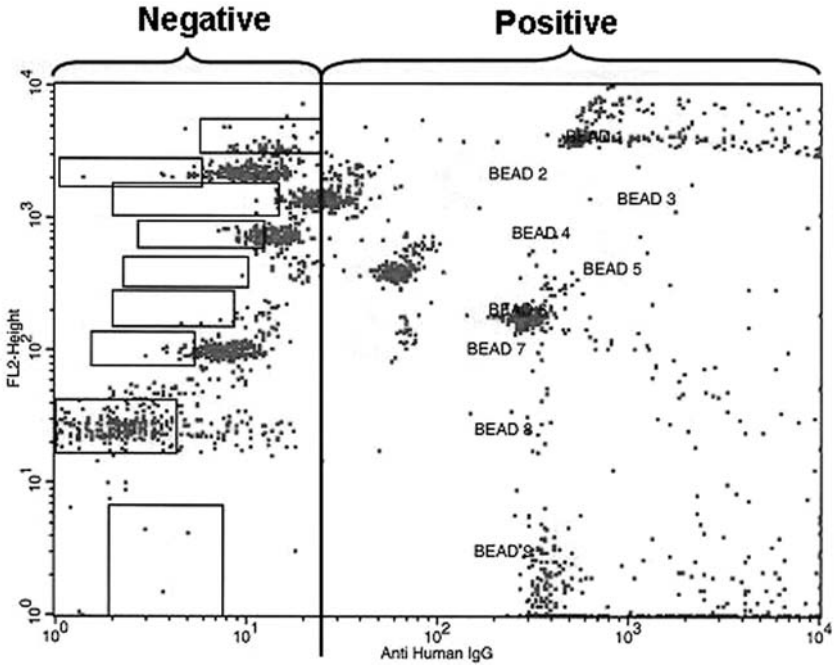

Figure 2 Flow cytometry antibody screening for the detection of anti-HLA antibodies. Microbeads are coated with purified HLA molecules from lymphoblastoid cell lines. The panel of these beads consist of 32 HLA class I or class II beads arranged in four groups, each group includes eight cells of different HLA class I (A, B, Cw) or class II (DR, DR51, DR52, DR53, and DQ) specificities plus one negative control bead (bead #8). Only one group of beads is shown in this figure. Beads corresponding to various cells of different HLA phenotypes are stained with a different level of red fluorescence. Using flow cytometry, each of these beads (numbered from 1 to 9) and hence each HLA phenotype can be distinguished (FL-2). After incubation with the patient's serum, binding of anti-HLA class I or class II antibodies can be distinguished using FITC-conjugated antihuman IgG (green fluorescence). Antibody binding and specificity can be determined by analyzing the red and green fluorescence. The proportion of positive fluorescent beads in this assay corresponds to percentage PRA. *Abbreviation:* FITC, fluroscein isothiocyanate.

Antibody strength is quantitated by fluorescent intensity responses in relation to a negative control. By flow cytometry, this is determined by the channel shift (shift to the right) of a specific bead compared to a normal control (Fig. 2). Fluorescent intensity as detected in the Luminex assay is measured by the mean florescent intensity (MFI) (e.g., the greater the antibody strength, the higher the intensity) (16). Antibody strength should be determined by each center's own cutoff values on the basis of clinical practice and transplant outcome data. For example, at our institution, we have set antigen strength for specific antibodies detected by Luminex screening assays as "high" with an MFI greater than 3000, "medium" with an MFI between 1000 and 3000, and "low" with an MFI less than 1000. This is based on the observation that a positive CDC-AHG crossmatch is usually observed in sera with MFI values greater than 7000; MFI values between 1000

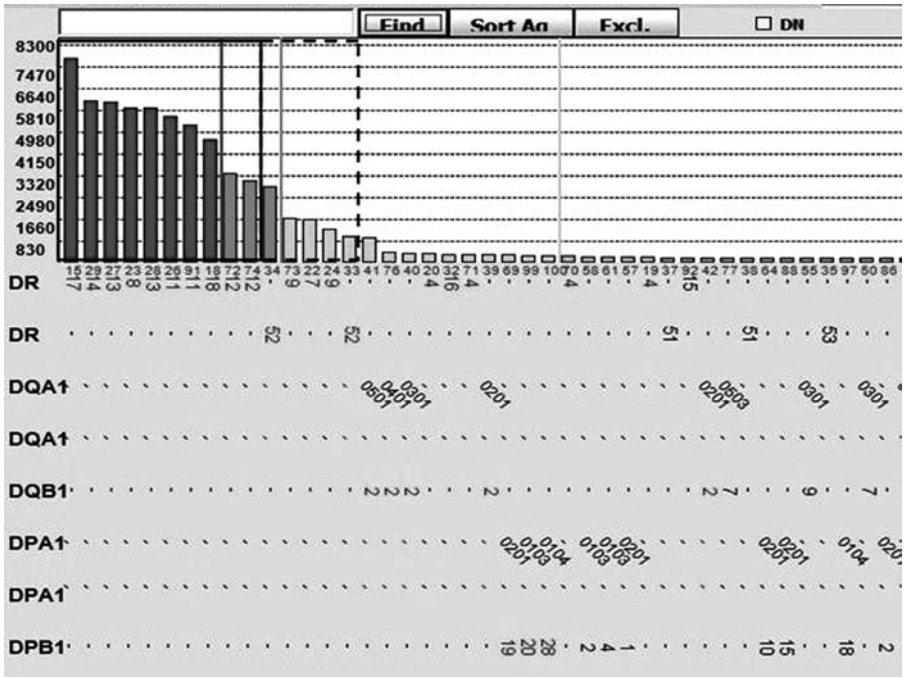

Figure 3 Single-antigen bead assay using Luminex technology. Recipient serum is incubated with beads coated with recombinant single-HLA antigens. Antihuman IgG tagged with a fluorescent protein detects antigen-bound anti-HLA IgG. Laser stimulation excites the color-coded single antigen beads and fluorescent-tagged IgG to detect and specify the presence of anti-HLA antibodies. Antibody strength is determined by the level of fluorescence. Antigens that have a mean fluorescent intensity (MFI) of greater than 3000 are deemed "unacceptable" antigens (*solid line box*) for virtual crossmatch. Those with an MFI between 1000 and 3000 are to be "avoided" if feasible (*dashed line box*). Unacceptable DR8, DR11, DR12, DR13, DR14, DR17, DR18. Avoid if feasible DR7, DR9, DR52.

and 3000 are usually not detected by CDC-AHG but are often associated with a weak flow cytometry crossmatch, and an MFI less than 1000 is usually not detected by either CDC-AHG or flow cytometry crossmatch (Table 1).

III. Pretransplant Assessment

When the PRA is positive and specific HLA class I and class II antibodies have been identified, a prospective crossmatch between donor lymphocytes and recipient serum is performed to identify the presence of donor-directed antibodies and prevent donor-recipient incompatibility. A positive crossmatch results in denial of the organ. This process delays the acceptance of the donor organ, requires collection of donor lymphocytes, may increase donor allograft ischemic time, and therefore, limits the donor pool to the local region. While this is the "traditional test" to prevent hyperacute rejection in transplant recipients, the high sensitivity and specificity of solid phase

Table 1 Comparison of Antibody Testing Methodology

Luminex specificity or single antigen beads	Flow cytometry	Complement-dependent cytotoxicity	Listing of HLA unacceptable antigens
Purified or recombinant HLA antigens	Fresh cells	Fresh cells	
Negative: MFI < 1000	Negative	Negative	No
Weak: MFI $= 1000$–3000	Variable	Negative	Variable
Positive: MFI $= 3000$–7000	Positive	Negative to weakly positive	Yes
Strongly positive: MFI > 7000	Positive	Positive	Yes

MFI values may vary with the assay kit used. This variation can be due to changes in the density of HLA antigens coated on the beads and/or the characteristics of the conjugated antihuman IgG used in the assay. Therefore, MFI values should not be used as absolute numbers and the interpretation of cutoff values should be done in consultation with the histocompatibility laboratory.
Abbreviations: HLA, human leukocyte antigen; MFI, mean fluorescent intensity.

techniques provide the ability to predict a crossmatch outcome in conjunction with donor HLA typing. This "virtual crossmatching" strategy is utilized successfully in kidney transplantation (17,18) and has been applied to lung transplant recipients with up to 100% accuracy (9). By eliminating real-time prospective crossmatching, this approach can reduce wait times and wait list mortality by exposing a sensitized patient to a larger donor pool (3,9).

Virtual crossmatching should not be used for organ allocation if HLA antibody specificities are not definite due to technical issues or if the patient has received a blood transfusion since the last PRA sample was drawn. Determination of unacceptable antigens is dependent on the strength of the anti-HLA antibody as measured by the intensity of fluorescence of anti-HLA antibodies, history and dates of sensitization, and severity of clinical illness. Review of unacceptable and acceptable antigens must be done at the time of donor offer by the transplant center to determine risk-benefit effect associated with low and moderate antibodies. HLA specificities with an MFI greater than 3000 are usually designated as unacceptable. While medium (MFI 1000–3000) level antibodies should be avoided, the exclusion of these unacceptable antibodies must be made at the discretion of the transplant center on the basis of the patient's allo-sensitization history and severity of patient illness (Fig. 3). A retrospective crossmatch (flow cytometry or CDC-AHG) should be performed on all sensitized cases after transplantation to guide post-transplant therapy.

Patients listed for transplant must be screened periodically to ensure that cross-match recommendations and unacceptable antigen assignments are current. Patients with no anti-HLA antibody and no recent blood product transfusion usually will have repeat PRA testing every three months. Patients who have received a blood product transfusion, experienced a severe infection, or have received a vaccination should have repeat anti-HLA antibody testing two weeks post event and then one month later. Patients with a high PRA and high lung allocation score (LAS) should obtain a PRA every one to two months to keep unacceptable antigen assignments up to date.

IV. Post-Transplant Injury

The presence of anti-HLA antibodies increases the risk of hyperacute rejection, antibody-mediated acute allograft rejection, early BOS, and worse survival after lung transplantation (2,4–7,15,19–21). Hyperacute rejection occurs almost immediately after transplantation and presents with hypoxemia, pulmonary edema, and pink, frothy secretions (2,15,19,20). Histopathologically, findings of diffuse alveolar damage, interstitial and intra-alveolar hemorrhage with extravasation of fibrin, and neutrophilia are seen (2). The perivascular lymphocytic inflammation found in T cell-mediated allograft rejection is absent and immunofluorescent staining for IgG, C3, and C4d is evident on endothelial surfaces, alveolar spaces, and alveolar septae (2,20).

Antibody-mediated rejection (AMR) has been studied extensively in renal transplantation and is a distinct clinicopathologic entity that requires (*i*) clinical evidence of graft dysfunction, (*ii*) histologic evidence of tissue injury, (*iii*) immunopathologic evidence of antibody action (usually C4d deposition, a stable marker of complement activation), and (*iv*) serologic evidence of anti-HLA or antidonor antibodies at the time of biopsy (11). The role of AMR in lung transplantation is less clear. Magro and colleagues have described an association between C4d and C3b deposition with acute and chronic lung allograft rejection; however, anti-HLA antibodies were not detected (22,23). Lau et al. described alveolar capillaritis with C3 deposition in a patient with an elevated PRA, confirming the role of humoral involvement in allograft injury (5). While early studies showed no relationship between sensitization and the development of BOS (24,25), contemporary publications have found an increased risk of BOS (5,21) and death (6,7). Interestingly, the de novo development of anti-HLA antibodies in nonsensitized lung transplant recipients has been found to be significantly associated with the development of BOS (21).

V. Desensitization and Treatment

A sensitized patient who receives a donor without incompatibilities is at low risk for antibody-related allograft injury. While most patients will qualify for transplant in this category, some with a PRA greater than 80% will find it difficult to obtain a crossmatch compatible donor. The main mechanism of injury in AMR is caused by antibody-mediated activation of the complement cascade (10). Treatment to prevent and manage antibody-mediated injury is focused on the inhibition of antibodies and their effector function (IVIg), suppression of T-cell and B-cell response (mycophenolic acid, antilymphocyte globulins), elimination of circulating antibodies (plasmapheresis), and suppression or depletion of B cells (rituximab) (10).

IVIg has potent immunomodulatory effects and is effective in reducing anti-HLA antibodies in kidney transplant recipients (10,26,27). IVIg is prepared from pooled human plasma of 50,000 to 100,000 screened donors and is composed of 90% immunoglobulin G including antibodies with specificities against class I and class II HLA molecules, costimulatory molecules, cytokines, and T-cell receptors (10). Mechanisms of action by IVIg include anti-idiotypic antibody binding to B-cell receptors that result in downregulation of B-cell proliferation and induction of apoptosis, binding of C3b and C4b fragments thereby preventing complement-induced tissue injury, inhibition of antigen presenting cells by interactions with Fc receptors, and inhibiting cytokine gene activation and anti-cytokine activity (28). The serum half-life of IVIg is approximately three weeks and comparison of the inhibitory effects of IVIg preparations reveal the

largest inhibition of lymphocytotoxicity occurs using IgM/IgA containing IVIg preparations (10,29). Side effects develop in less than 5% of patients and include headache, chills, rigors, fever, myalgias, nausea, abdominal pain, hypotension, and hypertension. Serious rare events include aseptic meningitis, anaphylaxis due to IgA sensitization in patients with IgA deficiency, renal insufficiency, thrombosis, and volume overload (10,26). Dosing varies between 100 mg/kg in conjunction with plasmapheresis and 2 g/kg (up to 140 g) when used alone for desensitization (10,28,30). Hyperimmune cytomegalovirus (CMV) IVIg has been advocated by Montgomery et al. in conjunction with plasmapheresis for renal transplant desensitization. This product is thought to provide enhanced antimicrobial titers and improved batch-to-batch consistency as it is procured from a stable donor pool (30). Administration of 2 g/kg of IVIg must be given with caution in potential lung transplant recipients to prevent volume overload. It is administered between two and five days monthly, for at least four months to accomplish desensitization (28). Postoperatively, Jordan and colleagues advocate one dose of IVIg to ensure PRA reductions one month after transplantation (28). IVIg is efficacious when used in conjunction with plasmapheresis and high-dose immunosuppression to treat AMR and hyperacute rejection (31).

Suppression of the B-cell response is vital to maintaining a reduction in anti-HLA antibodies. Antilymphocyte globulin preparations not only have T-cell antibody specificities but also target B cell (i.e., CD 20) and plasma cell antigens (i.e., CD 38 and CD 138), thereby suppressing B-cell proliferation (10). Mycophenolate mofetil (MMF) inhibits proliferation of T and B lymphocytes and decreases the primary antibody response mechanism, which may result in hypogammaglobulinemia (10,32,33). It has been shown to reduce sensitization in renal transplantation and has been reported to decrease anti-HLA antibody production in a sensitized cardiac transplant recipient (33–35). More recently, traditional transplant immunosuppressive agents such as the calcinurin inhibitors and sirolimus have been found to exhibit significant B-cell inhibition (10). MMF has been the preferred antiproliferative agent in protocols for desensitization and treatment of AMR and can be used in conjunction with IVIg to desensitize lung transplant recipients (10). Antilymphocyte globulin treatment as well as calcinurin inhibitors are traditionally applied at the time of transplantation to prevent both traditional T cell–mediated rejection and the reemergence of anti-HLA antibodies in the sensitized recipient.

Therapeutic plasma exchange by plasmapheresis removes antibodies from the plasma, allowing reduction of immunoglobulins to approximately 50% (36). The procedure usually consists of the removal of one plasma volume that is replaced by albumin and/or fresh frozen plasma. Side effects include volume contraction, depletion of essential plasma components such as clotting factors leading to bleeding diathesis, allergic reactions, and viral contamination (10,36). Immunoadsorption allows the selective removal of antibodies using adsorbent membranes that bind antibodies through hydrophobic and electrostatic bonding; however, its use is limited by high cost and availability (10,36). Plasmapheresis is most effective when used in conjunction with additional antibody inhibition therapies to prevent rebound antibody elevation (10). This procedure in conjunction with IVIg is an effective desensitization modality in renal transplantation for living donor procedures; however, it is impractical for cadaveric renal and lung transplantation when timing of the transplant is unpredictable (31,37). This therapy is used effectively peri- and postoperatively to prevent and treat AMR due to elevated donor-specific antibodies.

Rituximab is a genetically engineered chimeric mouse-human monoclonal antibody directed toward CD20, a transmembrane protein expressed on pre-B and mature B lymphocytes (10,38,39). Rituximab depletes B cells through antibody-dependent complement-mediated lysis and is approved for the treatment of relapsed or refractory B-cell non-Hodgkin's lymphoma (40). A phase-one trial evaluating the pharmacodynamics of rituximab in sensitized renal patients found rapid B-cell depletion within 48 hours of medication administration with only partial recovery at one year despite dose escalation from 50 to 375 mg/m^2 (40). Acute side effects include transient hypotension, fever, and arthralgias (38). Infectious complications have also been reported, especially when used in conjunction with other immunosuppressive agents and include septic shock, histoplasmosis, fungal pyelonephritis, and polyoma virus nephropathy (10,40). Rituximab has been reported to be effective as induction therapy for sensitized renal transplant recipients and refractory acute renal rejection (10). Stegall and colleagues compared two plasmapheresis regimens with low-dose IVIg and rituximab to high-dose IVIg alone for renal desensitization. They found that the plasmapheresis/rituximab regimen was a more effective desensitization treatment resulting in lower allograft rejection rates (41). Rituximab has been reported to treat vascular rejection in heart transplant recipients using 375 mg/mg^2 once or up to four times weekly (42,43). Anti-CD20 antibody has also been an effective adjunct for the emergency treatment of ABO incompatibility in lung transplantation requiring a regimen of plasmapheresis, MMF, antithymocyte globulin, immunoadsorption, and IVIg (44,45).

Bortezomib is a new unique proteosome inhibitor that interferes with intracellular signaling resulting in plasma cell death (46). By targeting the source of antibody production, bortezomib is very effective at reducing DSA. The successful treatment of AMR using this new agent has been reported in both kidney and lung transplant recipients (46,47).

Successful desensitization and treatment of antibody-associated allograft injury requires a management strategy that targets the inhibition and elimination of circulating anti-HLA antibody, blocking of B- and T-cell activation, and the prevention of B-cell proliferation.

VI. Approach to a Sensitized Patient

Our center uses solid matrix technologies for HLA detection and specification. The Luminex assay technique is applied for antibody screening and characterization. Unacceptable antigen assignments are made on the basis of Luminex MFI value. Recommendations for prospective versus virtual crossmatching are made after discussion with the HLA laboratory director and the transplant program directors. Flow cytometry is the technique of choice for crossmatching. Virtual crossmatching is recommended for most patients.

The risk of donor allograft and recipient incompatibility requires the assessment of (*i*) sex (females have higher antibody variability and change in antibodies), (*ii*) history of blood transfusions and pregnancy, (*iii*) history of recent infection or inflammatory state (result in increased development of antibodies), (*iv*) race (African-Americans develop a higher range and change in antibodies), (*v*) estimation of the number of potential donors per month for a particular patient on the basis of calculated PRA (CPRA), (*vi*) severity of illness (determination of risk to take regarding PRA), (*vii*) previous transplant (previous transplantation incurs a higher risk and higher range of

antibodies), and (*viii*) risk of receiving blood transfusions after transplantation (high risk if patient is to be transplanted on cardiopulmonary bypass). In sensitized patients with a high LAS, our center begins IVIg (1–2 g/kg) monthly initially for four months in conjunction with MMF (1000–1500 mg twice daily). Donor-specific antibodies are monitored three weeks after IVIg infusion. Plasmapheresis is considered in patients when there is minimal response to treatment and donor offers are moderate to high. These difficult patients may receive an allograft across DSA with MFI values in the low-to-moderate range. These patients are closely monitored and treatment with anti-lymphocyte globulin, plasmapheresis, IVIg, and bortezomib or rituximab are initiated if required. Patients are monitored until PRA stability ensues.

VII. Conclusion

Patients sensitized to HLA class I and II antigens are challenging to transplant. High-sensitivity and specificity solid phase assays have increased the detection of donor anti-HLA antibodies and permit virtual crossmatching to accurately predict the outcome of a crossmatch while increasing the available donor pool for the sensitized patient. Effective strategies aimed at inhibiting and eliminating circulating antibodies, blocking B- and T-cell proliferation, and depleting B-cell production provide adequate desensitization to allow transplantation in some of these individuals. Although AMR is well defined in renal transplantation and less clear in lung transplantation, increasing evidence is supportive of the detrimental role of both donor- and nondonor-specific anti-HLA antibodies in the lung transplant recipient.

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Anesthesia for Lung Transplantation

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I. Introduction

The first human lung transplant was performed in 1963; however, it was not until the 1980s when improvements in surgical technique and immunosuppression regimens turned lung transplantation into the gold standard treatment for a variety of end-stage lung diseases. The number of lung transplants performed since then has been steadily increasing with over 2000 transplants performed at approximately 150 centers as reported in 2008 to The Registry of the International Society for Heart and Lung Transplantation (ISHLT) (1). Survival rates have also gradually improved over the past three decades, and there has been increased interest in recent years regarding the anesthetic management of patients undergoing lung transplant and how it contributes to patient outcomes (2–6). Anesthesiologists taking part in these procedures need to have specific skills with respect to lung isolation (including both technical concerns in achieving lung isolation and physiological concerns with oxygenation during one-lung ventilation), the interpretation and use of invasive monitoring including transesophageal echocardiography (TEE), and the management of respiratory and myocardial impairments. This chapter will provide an overview of these perioperative anesthetic management considerations.

II. Preoperative Evaluation/Induction

Criteria for patients to be considered for lung transplantation are reviewed elsewhere in this textbook, but it is important for the anesthesiologist to realize that organ allocation in the United States is now based on a priority system that balances the likelihood of survival after transplantation with the risk of death while on the waiting list (7). The result is that while all patients will have some degree of functional impairment as a result of their underlying disease, the degree of hypoxia/oxygen requirements can vary among them, impacting their perioperative management.

Patients will also present with a variety of underlying pulmonary disorders. Chronic obstructive pulmonary disease (COPD) is the leading indication for lung transplantation worldwide, but idiopathic pulmonary fibrosis, primary pulmonary hypertension, and cystic fibrosis are other leading diseases that may result in patients requiring transplantation (Table 1) (1). Careful consideration of the underlying disease is important because it can impact the surgical procedure [single- vs. bilateral-lung transplant) and intraoperative techniques employed (e.g., the use of cardiopulmonary

Table 1 Common Diagnoses for Adult Lung Transplant Recipients (January 1995–June 2007)

Diagnosis	Total ($N = 19{,}792$)
Chronic obstructive pulmonary disease/emphysema	7186 (36%)
Idiopathic pulmonary fibrosis	3969 (20%)
Cystic Fibrosis	3218 (16%)
α_1-Anti-trypsin deficiency emphysema	1509 (~8%)
Idiopathic pulmonary arterial hypertension	689 (3.5%)
All others (including sarcoidosis, congenital heart disease, etc.)	3221 (~16%)

Source: Available at: www.ishlt.org. Accessed April 20, 2009.

bypass (CPB)], which in turn can impact anesthetic management with respect to lung isolation management and the use of epidural anesthesia.

It has been proposed that the use of epidural anesthesia be considered in all lung transplant patients as this technique has been associated with improved pain control and improved pulmonary function after transplantation (2,8). However, complications with epidural anesthesia can include the risk of hematoma and careful consideration needs to be given as to the likelihood of CPB use (with the inherent utilization of anticoagulation) and if the patient is on other anticoagulants that may preclude preoperative placement of a thoracic epidural (9).

Usually, there is sufficient time between when the donor is identified and when the surgery will begin to review the patient's history, labwork/tests (pulmonary function tests, echocardiograms, etc.), and establish an optimal timeline for the ensuing operation. Communication with the organ recovery team/site and the recipient site to minimize organ ischemic time is vital and times planned for anesthetic induction, cross-clamp, and surgical incision should be discussed as well. Particular emphasis should be placed on the airway exam as these patients will not generally tolerate prolonged periods of apnea that may be associated with difficulty in securing airway access. Contingency plans for potential difficult airway access should be well planned out and a variety of endotracheal tubes be readily available for placement if necessary.

In reviewing with the patient/family the anesthetic plan, risks/benefits, etc., they should be counseled as to the steps in the process including the potential for a lengthy wait depending on donor site operating room availability and bronchoscopy of the donor lungs to assess viability that may result in the procedure being cancelled. During this time, a decision regarding epidural placement can also be made taking into account the aforementioned considerations. In securing IV access, labwork can be obtained if recent labwork is not available, and the patient should be type/crossmatched for blood products.

It is our practice to not routinely sedate patients in preoperative holding, even for epidural placement, as these patients' oxygen requirements/functional status may result in exaggerated responses to IV sedation including further hypoxia or hypercarbia related to depression of their respiratory drive that will be poorly tolerated. In placement of preinduction arterial lines and thoracic epidurals, the authors employ local anesthetic liberally and counsel the patients extensively as to the technical aspects of these procedures to minimize discomfort in place of large doses of sedation.

When the patient is brought to the operating room, American Society of Anesthesiologists (ASA) standard monitors are applied, oxygen is administered via face mask (preoxygenation), and the arterial line connected. The induction of general anesthesia is

a time period during which hemodynamic instability leading up to cardiac arrest has been reported in these patients (10,11). It should be recognized that most patients will have elevated pulmonary artery pressures and increases in $PaCO_2$ or hypoxia can trigger dramatic increases in pulmonary vascular resistance precipitating right ventricular failure. Adequate preoxygenation and avoidance of apnea/hypercarbia is essential during this period.

It is our practice to employ a "cardiac" style induction that relies heavily on narcotics (fentanyl or sufentanil) and benzodiazepines (midazolam). Depending on the patient's underlying disease and baseline hemodynamic profile, etomidate may also be administered. At all times, vasoactive medications should be available for hemodynamic support and resuscitation. Neuromuscular blockade is administered and the airway secured rapidly (choice of endotracheal tube is discussed below).

Central line placement is typically done postinduction as most patients may not tolerate trendelenberg positioning while awake as a result of their underlying pathology. A pulmonary artery catheter is also placed as well as a TEE probe. The use of TEE intraoperatively is well established in lung transplantation and can benefit in evaluating ventricular function, volume status, and verify flow from the pulmonary veins into the left atrium after surgical anastomosis (4). The use of TEE can also identify potential complications such as the presence of air and thrombus formation (12,13).

A baseline arterial blood gas is also obtained after the initiation of mechanical ventilation with 100% oxygen as a large A-a gradient may predict difficulty during a bilateral-lung transplant and suggest that the use of CPB may be of benefit for the procedure. Antibiotic and immunosuppressant regimens should be initiated.

III. Intraoperative Management

A. Ventilation Strategies

Intraoperative management often depends on the underlying disease present as it influences anesthetic management. For example, mechanical ventilation strategies have been described for lung transplant patients who have obstructive disease that follow guidelines for patients with adult respiratory distress syndrome (5). These include using tidal volumes of 6 to 8 mL/kg and the careful administration of positive end expiratory pressure (PEEP). The use of PEEP can be associated with decreased venous return and with positive pressure ventilation can raise pulmonary vascular resistance and right ventricular strain.

Patients who have pulmonary fibrosis and low compliance may suffer from barotrauma in association with mechanical ventilation. It may be preferable to use pressure control ventilation modes rather than volume control modes in patients undergoing thoracic surgery to decrease the airway pressures transmitted to the diseased lungs (14,15). However, it should be recognized that while there is a reduction in airway pressure associated with positive pressure ventilation, the only randomized trial comparing the two modes of ventilation found no improvement in oxygenation when pressure controlled ventilation was used during one-lung ventilation (16). A limitation of this study was its relatively small size, and additional work in this area is needed.

Care should be taken when ventilating the transplanted lung; initially there may be a period of low compliance associated with reinflating the donor lung, but as the compliance improves, pressure control ventilation may result in higher tidal volumes than desired. In general, goals of mechanical ventilation should be aimed at maintaining

normocapnia and avoiding hypoxia while exposing the lungs to minimal airway pressures. This is especially important after the transplanted lungs are being ventilated as high airway pressures/tidal volumes may be associated with trauma to bronchial anastamoses.

The underlying disease process also often predicts the type of surgery planned. For example, patients with COPD or idiopathic pulmonary fibrosis often undergo single-lung transplant (SLTx), whereas patients with cystic fibrosis will undergo bilateral-lung transplant because the transplanted lung can become contaminated by the native lung. Most bilateral-lung transplants are now bilateral-sequential-single-lung transplants (BSSLTx), and the considerations for the type of surgical procedure planned are reviewed elsewhere in this textbook.

In cases not involving CPB, one-lung ventilation is necessary. As aforementioned, the authors typically use left-sided double lumen tubes as they have been described as being more favorable for lung transplant (17). Right-sided tubes may be considered for left SLTx but can interfere with ventilation of the right upper lobe, even with proper placement because of the variability of location of the right upper lobe orifice. Proper tube position is confirmed with fiberoptic bronchoscopy. Double-lumen tubes also offer the advantage of more facile suctioning and application of continuous positive airway pressure (CPAP) when compared to bronchial blockers. However, double-lumen tubes need to be replaced at the end of the procedure with a single-lumen tube for bronchoscopy, which may be less than ideal especially with a difficult initial intubation. In these situations, you may leave the double-lumen tube until extubation or when the intubation with a single lumen can be safely placed.

Physiologically, the initiation of one-lung ventilation can produce hemodynamic instability. Shunting can worsen hypoxia, hypercarbia, and acidosis, all of which can worsen right ventricular function by increasing pulmonary vascular resistance. Coupled with the prospect of ventilating lungs with significant underlying pathology, these factors can make the maintenance of adequate oxygenation challenging. Treatment strategies for hypoxia during one-lung ventilation include the use of CPAP to the nonventilated lung and PEEP to the ventilated lung, though both have drawbacks. Surgical exposure can be impaired with CPAP application to the nonventilated lung, while the potential disadvantages of PEEP have been outlined earlier. In addition to these, the use of PEEP on the ventilated lung can negatively affect hypoxic pulmonary vasoconstriction so its use needs to be titrated carefully to the desired effect of improving oxygenation while minimizing these potential negative effects.

Clamping of the pulmonary artery by the surgeons during the removal of the diseased lung can improve the intrapulmonary shunt; however, it also has the effect of increasing right ventricular afterload. The use of TEE can help determine if the right ventricle will tolerate the clamping of the pulmonary artery, and the initiation of CPB should be considered if it appears that the patient will not be hemodynamically stable during this period.

After the implantation of the donor lung and anastamoses are completed, and once the lung is reperfused the lung is gently reinflated. Aggressive reexpansion of the lung can result in pulmonary edema or barotrauma (18). At our institution, inhaled nitric oxide (iNO) is administered in selected patients with preoperative pulmonary hypertension during this period. iNO has been demonstrated to reduce pulmonary artery pressure without affecting systemic blood pressure, thereby reducing the workload on the right ventricle while maintaining perfusion of the ventricle (19,20). The routine use of iNO

has recently been called into question as a randomized, controlled trial in 30 bilateral-lung transplant patients did not demonstrate any reduction in extravascular lung water or improvement in gas exchange associated with the use of iNO (21). It should be recognized, however, that this was a small trial focusing only on bilateral-lung transplant patients; further work in this area needs to be completed to determine definitively the benefits of iNO in this patient population.

Hypotension can also occur as a result of plegia solution/metabolites from the ischemic lung entering into the circulation and air entering the coronary arteries. Even more challenging is the fact that air is more likely to enter the right coronary artery given its anatomical location, and this can impair right ventricular function further. This period often requires vasoactive support to maintain adequate perfusion pressures. It is our practice to have infusions of vasoconstrictors such as norepinephrine or phenylephrine for hemodynamic support if hypotension persists. Dopamine is also administered for its benefits in improving myocardial contractility (especially the right ventricle) and its effects on increasing blood pressure.

If the procedure entails BLSSTx, it is important to assess the first transplanted organ to rule out technical issues that may affect adequate ventilation/perfusion of the transplanted lung during the explant of the remaining diseased organ. These include potentially evaluating flow through both pulmonary arteries and veins via TEE to rule out any immediate stenosis (5). Bronchoscopy can rule out kinking of the bronchial anastamoses.

B. The Use of CPB

The use of CPB in lung transplantation is a source of considerable debate (22–28). Proponents of the use of CPB tout the greater hemodynamic stability it affords, the avoidance of one-lung ventilation (which can be technically difficult in some patients and physiologically poorly tolerated in others) and that it provides a safe and controlled reperfusion period (28). Opponents of routine use of CPB state that its use is associated with longer periods of postoperative ventilation, increased blood transfusions, increased pulmonary edema, and early graft dysfunction (24,27). More recent studies in patients with COPD have suggested a survival benefit and no adverse outcomes associated with the use of CPB (25,26). It should be recognized that there are no randomized, controlled trials involving the use of CPB for lung transplantation. Available studies for the most part have been small/retrospective and that given the heterogeneity of patients' underlying pathology/severity of their disease process that any one study's results may not be broadly applicable. Overall, the role of CPB as an independent risk factor for early graft dysfunction remains controversial.

For the anesthesiologist, cases involving CPB obviously necessitate a different approach. If CPB is planned from the outset, a single-lumen tube can be placed as one-lung ventilation will not be necessary. However, we still commonly place double-lumen tubes for cases involving CPB at our institution. The reason is that if a complication such as pulmonary hemorrhage occurs, lung isolation will be required and would be more difficult to establish with a single-lumen tube in a patient whose airway has now been compromised with blood. Additionally, if known preoperatively that CPB is likely or planned, decisions regarding epidural placement in the preoperative period may be altered (see earlier). Even if CPB is not initially planned, perfusion teams should be readily available and the anesthesiologist prepared for the initiation of CPB as hemodynamic instability during the procedure (as described earlier) may necessitate its use.

IV. Anesthetic Maintenance

There have been several reports of centers' anesthetic maintenance regimens during lung transplantation (5,29,30). Most of these have described the use of benzodiazepines and narcotics in large doses (so called "cardiac" induction/maintenance). Myles et al. described the use of IV propofol infusions or volatile anesthetics in their series of patients undergoing lung transplantation as part of their anesthetic maintenance, while Raffin advocated no volatile anesthetics be administered because of concerns regarding decreased hypoxic pulmonary vasoconstriction during one-lung ventilation and potential for reperfusion injury associated with their use (29,30). Another advantage of administering an anesthetic involving higher doses of narcotics is blunting of the stress/sympathetic response to surgery and that these agents do not depress myocardial function to the same degree as the volatile anesthetics.

In cases involving CPB, the anesthesiologist needs to consider the pharmokinetics of narcotics as related to the bypass circuit. The initiation of CPB is associated with a decrease in plasma concentration of all the narcotic agents (31). In addition, the lungs themselves contribute to a "first-pass" effect on narcotics. The combination of these factors suggests that narcotic concentrations decrease when the lung is removed and when the transplanted lung is reperfused. Therefore, these agents should be redosed during this period. In addition, agents to help blunt awareness (propofol, volatile anesthetics, benzodiazepines) should be titrated in during this time as their concentrations may be decreased as well. It should be noted that this period is also associated with potential hemodynamic instability, and patients may not tolerate increases in volatile anesthetic or propofol administration; thus, the anesthesiologist should be prepared to titrate in benzodiazepines/narcotics as tolerated.

In our institution, patients are typically administered an anesthetic that relies more heavily on narcotic and benzodiazepine administration, with volatile anesthetics titrated to the patient's hemodynamics. Propofol infusions are not typically administered during the procedure, but low-dose infusions (20–50 μg/kg/min as tolerated) initiated on transport to the intensive care unit (ICU) for sedation purposes. If an epidural has been placed preoperatively, its use is dependent on the hemodynamic status of the patient. If hypotension is a concern, it is prudent to delay epidural dosing until hemodynamic stability is achieved. Typically, epidural infusions are started postoperatively at our institution after consultation with the acute pain service. Epidural anesthesia has been associated with earlier extubations, improved pain control, and catheters are typically left in place until after the chest tubes are removed (5).

Hemodynamic instability can occur at various points during the procedure (see earlier). Usually patients undergoing lung transplant procedures have preserved left ventricular function, but right ventricular function may be diminished, especially during periods of increased afterload (e.g., clamping of the pulmonary artery). Dopamine and dobutamine infusions augment right ventricular contractility and may increase systemic blood pressure as well. Phosphodiesterase inhibitors can also provide some inotropic support while reducing pulmonary vascular resistance, though decreases in systemic vascular resistance may limit their use. The use of iNO is discussed earlier, the principle advantage it offers is reduction in pulmonary vascular resistance and thus right ventricular workload without having any systemic effect.

Hypotension is not tolerated well and may worsen right ventricular function secondary to inadequate perfusion because of the elevated right ventricular pressures these patients often have. Given the preserved left ventricular function, infusions of

vasoconstrictor agents such as norepinephrine or phenylephrine can increase systemic vascular resistance and blood pressure.

In addition to protective lung ventilation strategies, fluid restriction is typically described in the literature as being beneficial in reducing pulmonary complications (29,32). Increased central venous pressure has been associated with prolonged mechanical ventilation and increased mortality (32). In addition, a recent retrospective review found an inverse relationship between the volume of intraoperative colloid administered and early graft dysfunction/reduced rate of extubation (3). However, fluid restriction strategies can necessitate the use of vasoconstrictor infusions, and the anesthesiologist needs to carefully balance judicious fluid administration with the use of vasoconstrictors to optimize end-organ perfusion.

V. Postoperative Care

While the ICU management of these patients is addressed elsewhere in this book, the immediate postprocedural care of these patients begins in the operating room. At the conclusion of the procedure, the anesthesiologist needs to be prepared for several facets of the patients care:

1. Changing the double-lumen endotracheal tube (if placed) to a single-lumen endotracheal tube
2. Maintaining anesthesia for bronchoscopic evaluation of the transplanted lung(s)
3. Preparing the patient for transport to the ICU
4. Signing out care to the ICU team

In changing the double-lumen endotracheal tube to a single-lumen one, the anesthesiologist needs to consider the initial intubating conditions, fluid administration intraoperatively, and anticoagulation status of the patient. If the initial intubating conditions were ideal, fluid restriction employed (reducing the risk of oropharyngeal edema) and the patient is not currently anticoagulated, direct laryngoscopy is often the technique of choice. However, if any of these factors are less than ideal, use of an airway exchange catheter can be considered. Care should be taken as trauma can be associated with the use of these catheters and the bronchial anastamoses may be susceptible to traumatic injury (33). A final option may be to leave the double-lumen tube in place until correction of edema, anticoagulation, etc., but ICU care teams may not be as familiar with these devices so they should be carefully educated as to their differences with respect to single-lumen tubes.

As patients will remain intubated at the end of the transplant for bronchoscopy and remain intubated for immediate postoperative care in the ICU, there should not be attempts made for emergence from general anesthesia. The authors typically maintain the patient's anesthetic (including neuromuscular blockade) through the bronchoscopy and initiate low-dose propofol infusions for sedation en route to the ICU and for immediate postoperative ICU care. Reversal of neuromuscular blockade prior to extubation is vital and can be initiated either in the operating room or in the ICU prior to discontinuing sedation.

Transport of critically care patients to/from the ICU is associated with potential complications and recommendations include providing patients with same care/monitoring as they would have in the ICU/operating room (34). Given that patients may be requiring hemodynamic support in the form of vasopressors and that adequate

oxygenation needs to be ensured, essential monitoring during transport includes electrocardiogram, arterial line pressure, and pulse oximetry. In addition, the anesthesiologist should be prepared with emergency airway equipment and resuscitative drugs. Finally, coordination with various members of the transport team is necessary and the responsibility of the anesthesiologist to ensure a safe transport. This includes communicating with surgical team members and respiratory therapists so that the patient can be transported with iNO if it is being administered.

Finally, transfer of care to the ICU team (including the nurses and intensivists who will care for the patient) involves detailed reporting of intraoperative events and the current hemodynamic state of the patient. Intraoperative fluid administration should be noted, any vasoactive infusions verified, and the status of antibiotics/immunosuppressant regimens as well as neuromuscular blockade status relayed to the ICU team. Ventilator settings should keep in mind the goals of protective lung strategy and minimizing airway pressures while maintaining oxygenation. If an epidural catheter is in place or is planned on being placed postoperatively, a discussion with the acute pain service as to the patient's intraoperative response to anesthetic administration should take place. The hemodynamic status of the patient at the time of transfer of care to the ICU team should be documented prior to the anesthesiologist signing off.

VI. Conclusion

Lung transplantation procedures will continue to increase as advances in technology and pharmacology combined with liberalization of donor/recipient criteria will allow for a greater number of patients to benefit from this therapy. From helping coordinate the optimal time of anesthetic induction minimizing organ ischemia to safely guiding the patient psychologically, physiologically, and hemodynamically through a challenging operation, the perioperative role of the anesthesiologist is vital in contributing to the good outcomes of these patients.

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21
Single-Lung Transplantation

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I. Background

Lung transplantation may be the only hope for survival in most patients with end-stage lung disease (ESLD). The challenges inherent to lung transplantation are shortage of available donor organs, primary graft dysfunction, rejection, infection, and perioperative strategies including technical issues and critical care. While both bilateral and single-lung transplants are widely used in a variety of ESLD, single-lung transplantation may be the mostefficient means of transplanting a suitable donor (1). This chapter describes the history, technique, and outcomes of single-lung transplantation.

II. History

The history of thoracic transplantation begins in the laboratories of the University of Chicago where Alexis Carrel pioneered the technique of blood vessel anastomosis and orthotopic heart transplantation in canines (2). The first human lung transplant was performed by Dr Hardy at the University of Mississippi in 1963 for isolated lung cancer (3). It was not until the introduction of cyclosporine and cardiopulmonary bypass that lung transplantation became a viable and increasingly safe treatment option for patients with ESLD. The first single-lung transplant with prolonged postoperative survival is credited to Dr Joel Cooper in Toronto General Hospital in 1983 (4). Since then, refinements in technique, immunosuppression, and perioperative care have made single-lung transplantation routinely available for many patients with ESLD.

III. Indications for Single-Lung Transplantation

The general indications for lung transplantation include COPD, α-1 antitrypsin deficiency–related lung disease, idiopathic pulmonary fibrosis (IPF), pulmonary hypertension, septic lung diseases such as cystic fibrosis and bronchiectasis, and lung disease associated with connective tissue disorders. Disease-specific guidelines must be considered on an individual basis when considering lung transplantation (5). Except for patients with septic lung disease a single lung transplant may be considered in all other ESLD. In patients with pulmonary hypertension and in patients with potential native lung hyper-inflation a bilateral lung transplant would be the preferred choice (for detailed account, see chaps. 5–10). Single-lung transplants offer the advantage of preserving the contralateral donor organ for an additional recipient. They also offer, in some instances, shorter waiting times, shorter operating times, and rapid recovery. In some instances, the contralateral native lung may provide backup to

the recipient for gas exchange if there is any significant primary graft dysfunction while the donor lung recovers. The advocates of bilateral lung transplant cite several advantages including the long-term survival benefit, the lack of concern for native lung-induced donor compromise, and the decreased incidence of bronchiolitis obliterance (6,7). However, some studies have shown that single-lung transplantation has a survival advantage in select settings such as IPF, particularly in the absence of secondary pulmonary hypertension (8,9). This particular patient population appears to be increasing in numbers since the introduction of the lung allocation score in the United States (10). In addition, recent data suggests that bilateral lung transplant has little benefit over single-lung transplant in patients 60 years of age and older with a diagnosis of COPD (11,12). Thus, it is important to individualize the transplant strategy and to consider factors such as the underlying lung disease, age, and associated comorbidities. There is no doubt that the strategies of single- and bilateral-transplants will continue to evolve as more evidence emerge. In summary, single-lung transplantation is a viable option for many recipients and provides good short- and long-term outcomes in patients with ESLD.

IV. Technique

A. Donor Pneumonectomy

The donor selection (chap. 14) and procurement (chap. 17) is addressed in detail in the book elsewhere. During donor evaluation a flexible bronchoscopy is always performed to examine the airways and remove any secretions. Invariably the lung donor procurement is in the setting of a multiorgan procurement. The surgical approach is via a midline sternotomy. Initially the lung is inspected to evaluate its suitability for transplantation checking for pathology including evidence of trauma, infection, tumor, or other parenchymal disease. Usually the following surgical steps are followed. After the sternotomy, the pleura is opened on both sides without injuring the lungs. Following the inspection of the lung, if the pericardium is not already opened by the cardiac team the pericardium is opened and stay sutures are applied. The superior vena cava (SVC), inferior vena cava (IVC), and aorta are mobilized. The azygos vein is isolated and then divided flush with the SVC. 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 pulmonary plegia that also contains vasodilator medications. The lung block is dissected by digital dissection and sharp division of investing structures. The pericardium, inferior pulmonary ligament, and mediastinal pleura anterior to the esophagus and descending aorta are divided from an inferior approach. The trachea is identified posterior to the SVC and innominate artery and encircled by a tape. The trachea is divided four to five rings above the level of the carina using a stapling device while the lung is inflated close to predicted tidal volumes. The main pulmonary artery is divided at the bifurcation. The 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 for implantation. Then the ligamentum arteriosum is divided toward the descending aorta. This will allow the entire lung block to be dissected away from the descending aorta and esophagus. At the back table, the lungs are separated from each other by incising the left main bronchus, left pulmonary artery, and left atrium between the right and left pulmonary veins.

B. Recipient Procedure

Once a donor is verified and deemed to be suitable for transplant, the recipient is brought into the operating room for transplantation. In general, the lung with the least pulmonary

reserve is excised, leaving the healthier lung to support the recipient during the transplantation and later with the new lung. We prefer to have a thoracic epidural placement prior to the transplantation, and test doses of the epidural are avoided at this stage. General anesthesia is provided and patient is ventilated with a double lumen endotracheal tube. Tube position is verified by fiberoptic bronchoscopy. Arterial and venous access lines, including a pulmonary arterial catheter, are placed. At this stage we also place a transesophageal ECHO (TEE) probe. The patient is placed in a lateral decubitus position or in a semi-lateral position with the assistance of a bean bag while the upper arm is supported on a cradle. It is important that an axillary roll be placed under the axilla of the dependent arm to prevent brachial plexus injuries. A body-warming device is used for the lower part of the body (Bear hugger). The chest, abdomen, and the upper groins are exposed and this field is prepared with antiseptic solution and draped in a sterile fashion.

Incisions

A number 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. In patients with obstructive airway disease, where the recipient's chest cavities are large, we perform a muscle sparing lateral thoracotomy or a submammary incision sparing division of all muscles. In patients where the chest cavities are small, such as in severe IPF, we perform a posterolateral thoracotomy, partially dividing the lattisumus dorsi muscle but preserving the serratus anterior muscle. The level of incision is placed in such a way that it is over the hilum of the lung, either entering the pleural space through the fifth or the sixth intercostal space depending on the size of the chest cavity. The incisions are ideally made higher for the smaller chest cavities and lower for the larger chest cavities.

Recipient Pneumonectomy

The recipient is prepared while the donor is procured, but the lung is not excised until the donor organs are in the recipient operating room. Adhesions between the lung and chest wall are taken down with electrocautery. The hilum is dissected while preserving the phrenic nerves. Injury to the phrenic nerve may occur during the division of the inferior pulmonary ligament, the dissection of the hilum, the placement of vascular clamps, or during excessive retraction. The right phrenic nerve is more vulnerable due to its position adjacent to the hilum. Vagus neurovascular bundles ought to be 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 this injury. Electrocautery should be used at the minimum settings while dissecting close to these nerves.

The pulmonary artery and veins are dissected as distally as possible from surrounding tissues and isolated with vessel loops. Dissection around the main bronchus is kept to the minimum to preserve its blood supply. The pericardium is opened around the veins to release the left atrium for placement of a future proximal vascular clamp. When the donor lung is in the room the recipient is given 5000 units of heparin intravenously. After adequate circulation of the heparin, the pulmonary veins and artery are divided at the distal portion of the main artery with a linear cutting vascular stapler. The right main bronchus is divided at the lobar branch level with electrocautery. Once the lung is explanted the bronchus is divided with a knife at the level of the proximal main bronchus

three to four rings away from the carina. This division should be shorter on the right side than the left. Any bronchial vessels are identified and cauterized or clipped with a metal clip. Studies have demonstrated the feasibility of bronchial arterial anastamoses. While this is an intriguing concept, it is not routinely done at our institution since it adds time to the transplant with no clear benefit (13).

Back Bench Preparation of Donor Lung

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 any bronchial attachments. Any extrapulmonary artery is not trimmed at this point but the final length is determined in situ at the time of anastomosis. We perform a retrograde flushing of the pulmonary vascular bed prior to implantation. This step is also performed at the donor hospital on the back table. The main bronchus is opened and microbiological specimens are collected. Then the bronchus is divided with a knife leaving two or three rings of cartilage from the origin of the upper lobe bronchus. The brochus is lavaged with small amounts of cold normal saline if necessary.

Implantation

The donor lung is then brought to the operative field. The bronchus is anastamosed end to end first. We believe that doing the bronchial anastomosis first "frames" the lung, as this is the most rigid of the three anastomoses. We routinely use two separate techniques of suturing for the bronchial anastamosis. The membranous portion of the bronchus is anastomosed using a running 4-O absorbable monofilament suture (Maxon US Surgical, Connecticut, U.S.) while the cartilaginous portion is secured with interrupted figure of eight of the same type suture (Fig. 1). Single–running suture techniques have also been

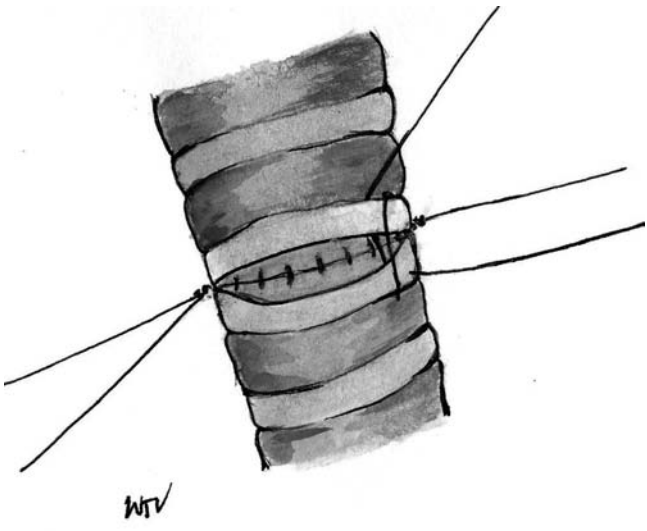

Figure 1 We routinely use figure of eight sutures for the cartilaginous portion and continuous suturing for the membranous portion using a monofilament absorbable suture (4-O Maxon).

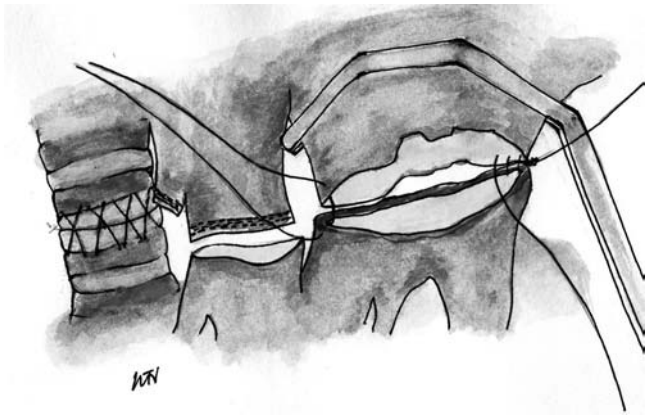

Figure 2 This figure shows the pulmonary venous anastomosis, using an atrial cuff technique (4-O polypropylene).

described in the literature and appear to be equally efficacious. This is most useful when both bronchi are fairly pliable. The "telescoping technique" is rarely if ever indicated anymore (14).

Next, attention is turned to the venous anastomosis. After placing the vascular clamp to include a portion of the left atrium, the recipient left pulmonary vein orifices are connected by dividing the bridge of atrial wall to create an 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-O polypropylene suture (Fig. 2).

Finally, the pulmonary artery is prepared for the final anastomosis. This anastamosis is left for last since it is the most delicate of the three anastamoses. Excess length of pulmonary artery is removed after appropriately sizing the vessel, to prevent any kinking or tension on the anastomosis. 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-O polypropylene suture (Fig. 3). Occasionally, a size mismatch exists where the recipient pulmonary artery is lager 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 our practice we administer 500 mg of solumedrol intravenously prior to reperfusion of the graft. This is best done by having anesthesia infuse the medication while performing the last anastomosis. In preparation for reperfusion, patient is placed on Trendelenberg position and a cross-clamp is placed distal to the anastomosis on the donor pulmonary artery. Air, clots and debris are vented through the pulmonary artery anastomosis. 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 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 α-agonists. The chest is inspected carefully for hemostasis. The color of the lung is observed and the lungs are inflated while monitoring the left atrium on the TEE. A leak

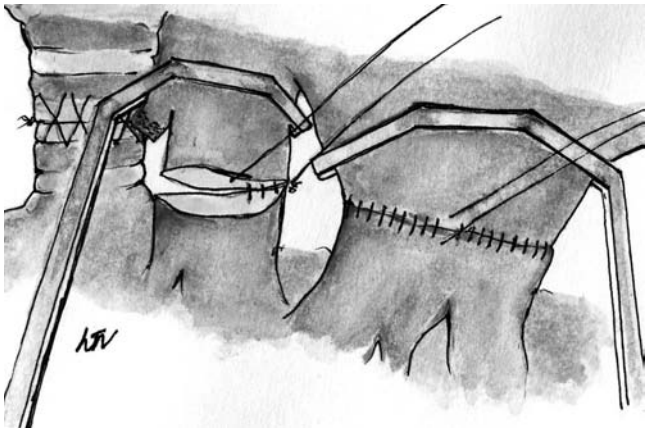

Figure 3 Pulmonary arterial anastomosis is performed end to end; however at times the recipient pulmonary artery is large and the larger lower trunk is anastomosed end to end to the donor (5-O polypropylene).

test may be performed at this time by carefully ventilating the new lung with the bronchus submerged in normal saline and inspecting for bubbles. The irrigation is evacuated and a single chest tube is placed posteriorly to the apex. Once stable hemodynamics and good oxygenation are achieved, the ribs are approximated using interrupted #1 Dexon pericostal sutures. The fascia and skin are approximated with running 2-O and 4-O Dexon. With the patient in the supine position the double-lumen endotracheal tube is changed to a single lumen tube and a fiberoptic bronchoscopy is performed to inspect the bronchial anastomosis and remove any clots or secretion present in the bronchial tree.

Cardiopulmonary Bypass

Cardiopulmonary bypass is rarely necessary when doing single-lung transplantation. One of the groins is usually prepared into the sterile field during the draping in case there is a need to cannulate the groin. When doing a right-sided lung transplantation the aorta and right atrium can be easily accessed for cannulation from the chest and therefore the groin cannulation is rarely needed. When left single-lung transplantion is performed the groin provides the best access for cannulation if cardiopulmonary bypass is required. It is our practice to have a perfusionist available in the hospital during lung transplants in all cases. Most often when cardiopulmonary support is required for single-lung transplantation, partial bypass suffices and rarely is full flow required.

Troubleshooting

During the harvesting it is critical to preserve an adequate donor left atrial cuff around the confluence of the superior and inferior pulmonary veins. However, because of technical error, the donor lung may sometimes have little or no atrial tissue around the venous confluence. A “neoatrial cuff” made of donor pericardium may be created with a running 5-O polypropylene around the divided edges of the two pulmonary veins. The resultant pericardial cuff is trimmed to match the recipient left atrium. More complex donor vein reconstructions have been described with excellent outcomes (15,16).

Occasionally, donor lungs will have congenital venous anomalies. For instance, the donor right upper lobe pulmonary vein may be seen draining into the SVC or the inominate vein. The normal donor inferior veins can be anastomosed to the recipient inferior pulmonary vein. The donor and recipient superior veins may then be anastomosed individually to each other with a conduit of donor iliac vein or autologous pericardium (17). Anomalous bronchial patterns have also been described. In one report the apical segmental branches were found to originate from the donor trachea. In this case, the anomalous segmental bronchus may be excised from the donor trachea with a cuff, which is then incorporated into the bronchial suture line (17).

IPF patients pose a particular challenge since their intrathoracic volumes tend to be restricted. Using donors with smaller lung volumes may be helpful in this setting. In addition, strategies to depress the diaphragm using either a suture placed on the dome of the diaphragm retracted through the potential chest tube site or a malleable retractor may be helpful during implantation.

V. Outcomes

Single-lung transplantation offers the advantage of shorter operating times, no cardiopulmonary bypass, and an efficient use of the already scarce donor pool. The donor shortage is the prime reason for long waiting list times and fewer available lung transplants. Thus, single-lung transplant should be offered to the appropriate patients with ELD. In a retrospective review of 1656 transplant recipients from 1998 to 2004, there was no survival benefit noted between single and double lung transplant recipients. Overall 30-day and 1-year survivals were 95% and 77%, respectively. IPF and donor cigarette smoking for greater than 20 years were independent predictors of mortality (12). In another study on IPF, patients transplanted over a 10-year period by Meyers et al. noted no significant advantage for bilateral lung transplantation (9).

VI. Conclusion

Single-lung transplant is an efficient and perhaps an economical way to treat patients with ESLD in need of thoracic transplantation. The technique can be executed in a minimally traumatic manner through a muscle sparing thoracotomy. Single-lung transplantation yields a comparable survival benefit to double lung transplantation in a significant number of patients with ESLD and is an excellent means of utilizing the scarce lung donor pool in appropriately selected patients.

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22
Bilateral Sequential Lung Transplantation: Technical Aspects

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I. History

The University of Toronto Lung Transplant team described their experience with the first successful long-term surviving lung transplant in 1983 (1). Subsequently, en bloc double-lung transplant was devised for patients with cystic fibrosis and emphysema where a tracheal anastomosis was performed, but this technically complex procedure was plagued with problems of airway anastomotic healing (2). This led to the development of bilateral sequential lung transplant where two separate airway anastomoses were performed close to the hilum to improve collateral airway blood supply on the donor side (3). Dr. Cooper provides an excellent account of the early days of evolution of the technique of lung transplantation (4).

Airway anastomotic healing has been the most vulnerable technical aspect of lung transplantation and often dictated survival in the early days of the procedure. Efforts to mitigate this problem have included avoiding high-dose steroids in the early postoperative period (5), using cyclosporine that did not impair bronchial healing (6), bronchial artery revascularization (7), and the use of omental wrap of the airway anastomosis (8). Bronchial artery revascularization and the omental wrap are no longer in routine clinical practice, and steroids are routinely used perioperatively without the fear of compromised airway healing.

Subtle changes have been made to incisions, exposure techniques, choice of suture materials, anastomotic technique, and overall conduct of the operation as experience has accumulated. For nearly two decades now, the bilateral sequential approach is the preferred operation for double-lung transplantation.

There is a continuing debate on the choice of operation for patients with pulmonary fibrosis and emphysema. In general, single-lung transplantation provides equivalent short- and medium-term results compared with bilateral-lung transplantation, but long-term survival appears to favor bilateral-lung transplantation. In the end, the choice of operation in a patient depends on the number of available organs, institutional preference, and specific factors unique to the donor or the recipient. Our own preference is to perform a bilateral-lung transplant whenever possible.

II. Salvage Techniques for Suboptimal Procurements/ Anatomic Aberration

Many injuries to hilar structures in the donor organs are related to suboptimal procurement and thus avoidable. It is of utmost importance that the heart and lung procurement teams

work in coordination and follow well-established routines. The procurement operation is described elsewhere.

A. Pulmonary Artery Injuries

The bifurcation of the pulmonary artery (PA) should remain with the lung graft. The right PA is at a greater risk for injury due to its course behind the aorta and the superior vena cava, but due to its greater length, an injury to the right PA under the aorta often does not require repair. The artery is simply trimmed distal to the laceration. For more distal lacerations of the right PA or injuries to its upper lobe branch, lateral repair with 5.0 polypropylene suture often suffices. If a more complex reconstruction of the truncus anterior is required, a patch or complete reimplantation with vein can be used. The repair can be performed with a segment of donor cava, azygous vein, or extra segment of PA.

B. Atrial Cuff and Pulmonary Vein Injuries

Procurement-related pulmonary venous injuries are more common than arterial mishaps. Injuries most frequently involve the right inferior pulmonary vein, occurring during the division of the left atrial cuff or division of the inferior vena cava. Other common mechanisms of pulmonary venous injuries are excessive dissection of the inferior pulmonary ligament or unnecessary intrapericardial dissection of the atrial cuff. These maneuvers should be avoided.

When a pulmonary vein orifice has been lacerated, we start the repair by dividing the pericardium overlying the vein back to the lung parenchyma. Small branches of the vein that might have been divided if the vein orifice has been entered are identified and oversewn to prevent bleeding at reperfusion. More complex reconstruction may require creating a new cuff around pulmonary vein orifices that are completely separated. Autologous or donor pericardium, PA segment or azygous vein may be utilized for this. Oto and colleagues have observed a need for pulmonary vein reconstruction in 2.7% of their patients and have elegantly illustrated their techniques (9) (Fig. 1).

C. Upper Lobe Bronchus Arising from Trachea

A tracheal upper lobe bronchus may be a segmental or a lobar bronchus. If the bronchus is determined to be a segmental bronchus, we oversew the bronchial orifice and proceed with standard bilateral-lung transplantation. The segment to the upper lobe receives adequate collateral airflow, and we have observed no problems with this technique. Other groups have elected to reimplant the anomalous segmental bronchus by incorporating it into the bronchial anastomosis (10). If the entire right upper lobe bronchus arises as an abnormal tracheal bronchus, the options are donor right upper lobectomy, left single-lung transplantation, or incorporating the bronchus intermedius and the aberrant upper lobe bronchus into a modified anastomosis with the recipient bronchus.

D. Aberrant Pulmonary Venous Anatomy

Anomalous pulmonary venous drainage in the donor can be rerouted to the recipient atrium during lung transplantation. On the left side, an aberrant pulmonary vein can be anastomosed directly to the left atrial appendage (11), carefully avoiding injury to the left circumflex coronary artery when placing a vascular clamp on the LA appendage.

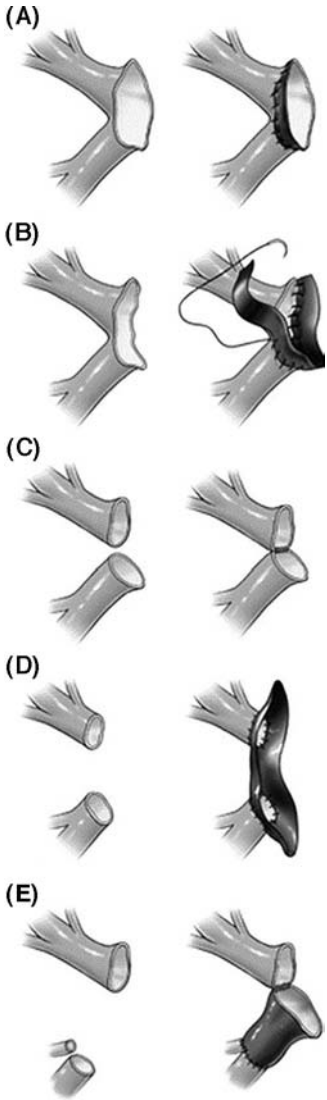

Figure 1 Reconstruction for an inadequate left atrial cuff. (**A**) Anterior pericardial patch augmentation. (**B**) Anterior and posterior pericardial patch augmentation. (**C**) Separated but close venous orifices united by suture repair to create oval cross-sectional cuff. (**D**) Widely separated veins, cuff reconstruction using pericardium. (**E**) Donor pulmonary artery used to reconstruct inferior vein at segmental level. *Source*: From Ref. 9.

E. Size-Mismatched Lungs

Lungs from acceptable donors that are larger than the recipient can be safely accepted. Our preferred technique of downsizing is an anatomic lobectomy on the back table (12). If, however, the size mismatch is appreciated only after implantation, wedge resection of the lingula and middle lobe using stapling devices are an appropriate strategy.

III. Incisions

A. Bilateral Anterolateral Thoracotomy

Bilateral anterolateral thoracotomy is our preferred incision for bilateral sequential lung transplant. Leaving the sternum intact prevents significant incision-related morbidity (13). The skin incision follows the inframammary crease at the level of the fourth intercostal space and extends from the lateral sternal edge to the anterior axillary line. The breast tissue is raised up and the pectoralis major muscle is divided sparing the fibers of the serratus anterior in the lateral part of the incision. The chest cavity is entered in the fourth interspace. Bilateral internal mammary arteries are ligated and divided. Alternatively, the internal mammary arteries can be preserved if a 1-cm segment of costal cartilage of the fourth rib is resected at the sternal border, allowing upward mobility of the fourth rib when retracted. Further mobility for retraction is obtained by dividing the intercostal muscles from within the pleural space laterally to the paraspinal muscles. Optimal exposure is obtained by placement of two chest wall retractors at 90° angles to one another (Fig. 2).

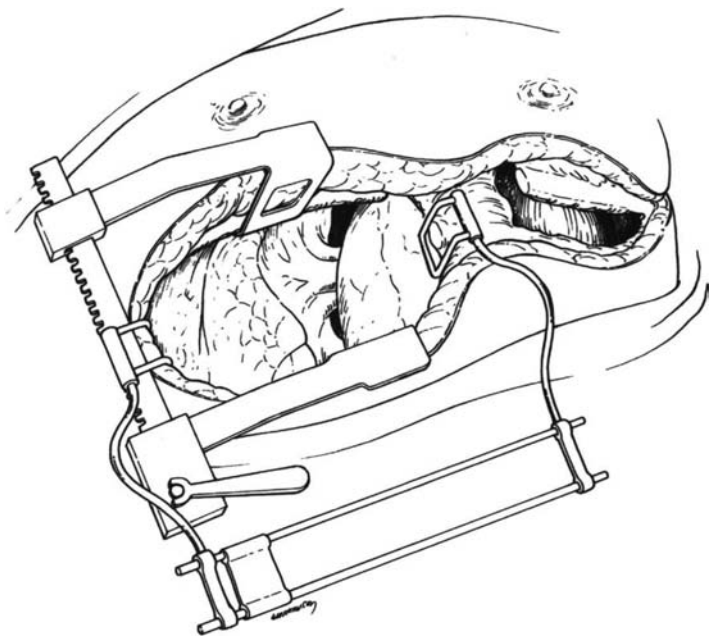

Figure 2 Bilateral anterolateral thoracotomy with the use of two retractors placed at right angles. *Source*: From Ref. 14.

B. Clam-Shell Incision (Sternothoracotomy)

This incision involves connecting the bilateral anterolateral thoracotomy incisions across the midline by dividing the sternum. Both mammary arteries are divided in this approach. This incision provides excellent exposure. This incision is useful when a concomitant cardiac procedure is performed or when cardiomegaly or a relatively small chest cavity (e.g., recipients with restrictive lung disease) makes hilar exposure difficult. The sternum is reapproximated using two figure-of-eight sternal wires.

C. Median Sternotomy

This incision is used if the recipient is undergoing concomitant cardiac surgery. In a retrospective comparison of the median sternotomy to clamshell incision for bilateral-lung transplantation, significantly fewer wound-related complications were seen in the sternotomy group (15).

IV. Recipient Pneumonectomy

Prior to recipient pneumonectomy, the donor lungs should be readied for implantation. The lung with the lesser physiologic contribution is transplanted first as the other lung will more likely support single-lung ventilation. Prior to either lung being explanted, hilar dissection is completed bilaterally and pleural adhesions mobilized while maintaining meticulous hemostasis. This allows speedy removal of the second lung, thus minimizing the amount of time that the freshly implanted contralateral lung is exposed to the entire cardiac output. Close attention is paid to protecting the phrenic, vagus, and recurrent laryngeal nerves.

The inferior pulmonary ligament is divided and hilar dissection initiated. The PAs and the pulmonary veins are dissected beyond their first bifurcations to preserve the length centrally. The right PA is transected about 1 cm beyond the truncus anterior branch and the left PA beyond the second branch to the left upper lobe. This provides adequate length centrally while downsizing the recipient PA to prevent any size mismatch. Vascular staplers are used on the central side of division while simple ties suffice peripherally. The first branch (ligated) of the recipient PA also provides an anatomic landmark for orientation during the anastomosis.

Similarly, the pulmonary veins are divided at secondary branch points. The peribronchial tissue is divided and bronchial arterial bleeding controlled with cautery or ligatures. The bronchus is divided just proximal to the upper lobe origin and the lung removed. All posterior mediastinal and posterior chest wall bleeders need to be dealt with this point. We now set up hilar exposure. The PA is gently grasped in a clamp, freed centrally, and retracted anteromedially. The superior and inferior pulmonary veins are grasped in clamps, the pericardium around them widely opened, and the veins retracted anteriorly. We are now ready for lung implantation.

V. Implantation

The donor lung is covered with a cold sponge and placed in a bed of ice slush into the thoracic cavity. The anesthesiologist advances a small suction catheter into the ipsilateral recipient airway to keep the field clean. We start with an end-to-end bronchial anastomosis using two strands of 4-0 PDS (polydioxanone) suture in running fashion. A retraction suture (0 silk) is placed into the anterior aspect of the recipient bronchus. The

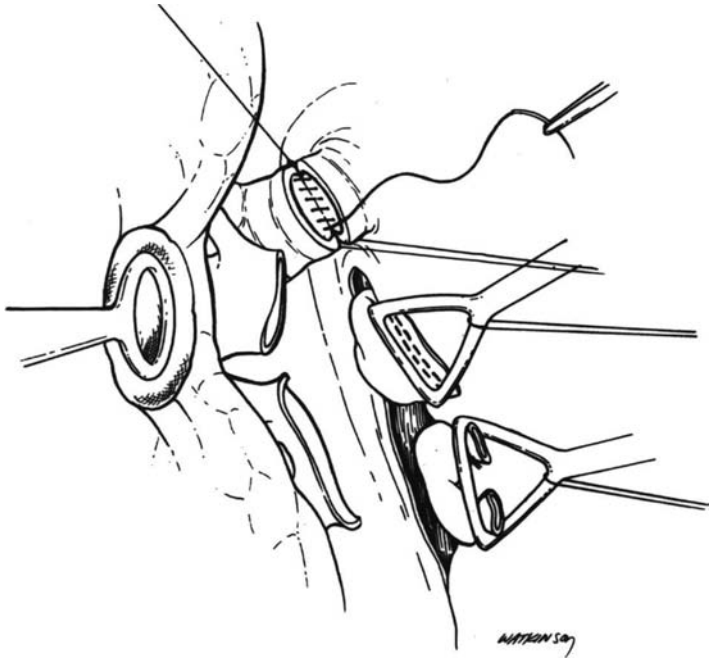

Figure 3 Retraction on the pulmonary artery and pulmonary vein stumps provides exposure for the airway anastomosis. The bronchial anastomosis being performed with 4-0 PDS suture. *Source*: From Ref. 14.

anastomosis is started on the membranous part in running fashion and carried around over the anterior cartilaginous part with the second suture to prevent a purse-string effect (Fig. 3).

If there is significant size mismatch, the membranous portion is completed as above, while the cartilaginous part is approximated with simple interrupted 3-0 vicryl sutures.

The peribronchial tissue on the donor and recipient sides is approximated to cover the anterior aspect of the anastomosis and isolate it from the vascular anastomoses in case of bronchial dehiscence. End-to-end airway anastomosis has been found to be superior to the telescoped anastomosis technique (16).

Next, a vascular clamp is placed centrally on the recipient main PA and the staple line resected. Donor and recipient PAs are trimmed as necessary to prevent excessive length and possible kinking. An end-to-end anastomosis is constructed using a continuous 5-0 polypropylene stitch (Fig. 4).

Both vein stumps are then retracted laterally and a Satinsky clamp is placed centrally on the recipient left atrium. An umbilical tape is passed between the rings on the clamp to prevent accidental dislodgement. The recipient pulmonary venous stumps are amputated and the two openings connected to create the atrial cuff. Gentle lateral traction on the Satinsky clamp improves the exposure for this anastomosis. Alternatively, a retraction suture placed in the pericardium 2 to 3 cm above the inferior

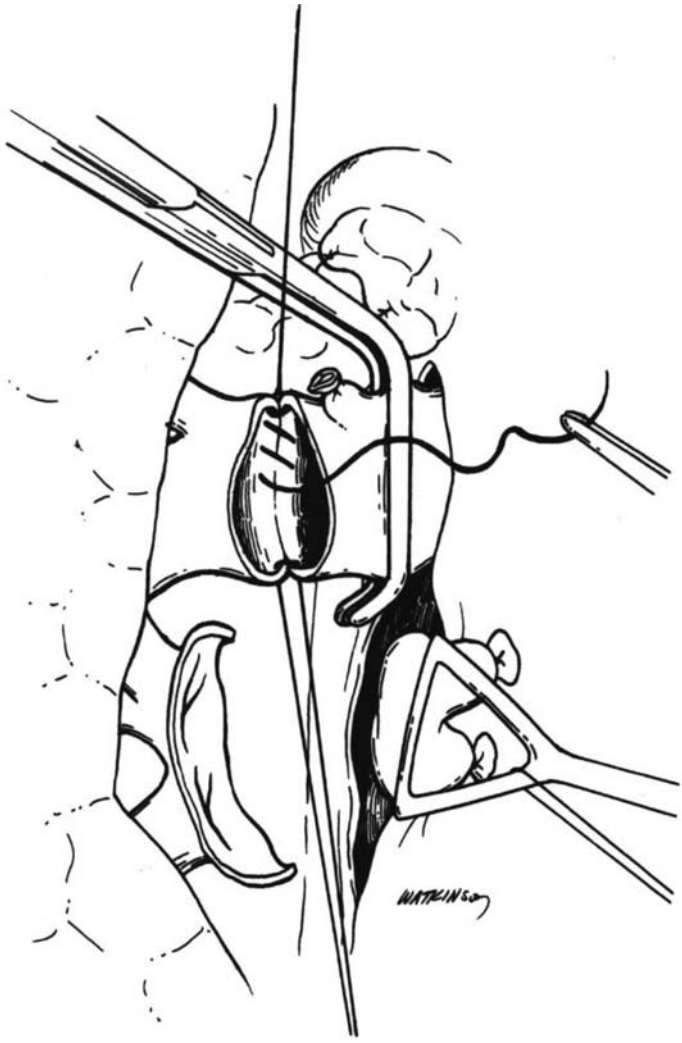

Figure 4 The PA anastomosis is fashioned using a running 5-0 polypropylene suture. *Source*: From Ref. 14.

pulmonary vein, carefully avoiding the phrenic nerve, can improve exposure too. The anastomosis is fashioned with continuous 4-0 polypropylene suture. Stitches are placed in a mattress technique, which achieves intima to intima apposition and excludes thrombogenic atrial muscle (Fig. 5).

The last few sutures are left loose, the lung partially inflated, and the PA clamp is released momentarily. This maneuver flushes out residual perfusate from the lung. The left atrial clamp is then opened to de-air the atrium. The atrial suture line is pulled up tight and tied down. All clamps are removed.

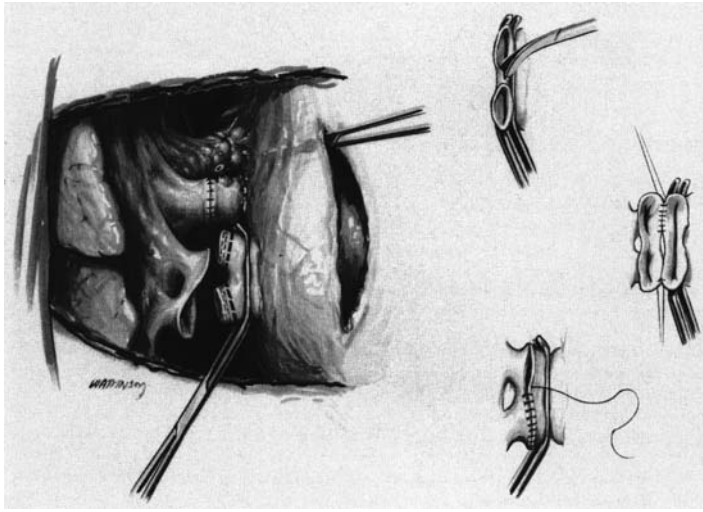

Figure 5 A large Satinsky is placed centrally across the left atrium. Both vein stumps are amputated and the bridge between connected to create a left atriotomy suitable for anastomosis. *Source*: From Ref. 17.

If the operation is being performed without cardiopulmonary bypass (CPB), it is important to stabilize the patient after the first lung is implanted. Initial pulmonary hypertension may be due to hypercarbia and a period of dual lung ventilation may be required to normalize the $PaCO_2$. This frequently avoids the use of CPB for implantation of the second lung.

Each pleural space is drained with two #24 Blake drains (Ethicon, Somerville, New Jersey, U.S.), one placed apically and one along the diaphragm. If significant postoperative bleeding is expected, two 28 Fr conventional chest tubes are preferred. The ribs are reapproximated with heavy interrupted figure-of-eight monofilament non-absorbable suture and sternal closure has been discussed previously. The wound is closed in layers with absorbable suture.

We routinely perform flexible bronchoscopy after exchanging the double-lumen tube for a single-lumen tube. The airway anastomoses are inspected and secretions are suctioned out. The patient is now transported, intubated, to the ICU.

VI. Cardiopulmonary Bypass

We employ CPB electively in children and small-statured patients (single-lung ventilation not available), lobar transplants, concomitant cardiac procedures, and most patients with pulmonary hypertension. CPB is initiated emergently for hemodynamic or respiratory compromise. When CPB is electively used, we perform most of the dissection prior to heparinization. We are careful in making a limited pericardiotomy to prevent herniation of the heart outside the pericardial sac and difficulty in closing the pericardium. Standard aortic and two-stage venous cannulation is performed. CPB is initiated and both lungs excised. We try to avoid the use of pump suckers.

VII. Difficult Exposure

Inadequate exposure of the left hilum may be the only indication for CPB. We have used the Urchin heart-positioning device (Medtronic, Inc., Minneapolis, Minnesota, U.S.) to improve exposure (18). This device is commonly used in off-pump coronary artery bypass surgery to retract the heart and provides excellent exposure of the left hilum without use of CPB.

A small chest cavity, usually in patients with restrictive lung disease, can make exposure arduous. A traction suture, placed in the fibrous portion of the diaphragm can improve hilar exposure.

VIII. Summary

Sequential bilateral-lung transplant is the procedure of choice for double-lung transplantation. A well-planned approach and meticulous attention to technical detail are the cornerstones of success in this operation.

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23
Heart-Lung Transplantation

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I. Introduction

Since the first successful human heart-lung transplant (HLT) was carried out at Stanford University Medical Center in 1981 (1), the International Society of Heart of Heart and Lung Transplantation (ISHLT) reports that more than 3300 (2) of these procedures have been performed worldwide. The Organ Procurement and Transplantation Network (UNOS) report that approximately 1000 HLTs transplants were performed between 1988 and 2008 in the United States. A total of 178 HLTs were carried out at Stanford University Medical Center during the same time period. Although the frequency of HLT has decreased in recent years, a subset of patients with end-stage cardiopulmonary disease remains, which benefit immensely from this procedure. The current practices at Stanford University Medical Center pertaining to HLT follow.

II. Indications for Transplantation

The most common diagnoses prompting HLT during recent years include congenital heart disease (CHD) and primary pulmonary hypertension (PPH) (3). Less common diagnoses include cystic fibrosis, chronic obstructive pulmonary disease; among others. Appropriate patients with end-stage pulmonary disease are more frequently treated with lung transplantation alone; however, those with cor pulmonale and combined end-stage heart and lung failure are better served by HLT.

III. Heart-Lung Bloc Procurement/Preservation

Appropriate donor evaluations must be thorough and include history and physical exam, serologies, chest X ray with lung dimensions, arterial blood gas values on 40% and 100% fraction of inspired oxygen, bronchoscopic evaluation, sputum cultures, 12-lead EKG, and an echocardiogram. Coronary angiograms are advisable in donors older than 40 years of age. CT scans of the chest are not mandatory but are frequently helpful in the evaluation of patients with blunt trauma, marginal arterial blood gas values, or in those donors suspected of having ventilator-associated pneumonia. Because distant procurements tend to be the norm, it is difficult to directly participate in donor management prior to arrival at the site of graft retrieval. As a result it should be emphasized to the placement/management agencies that excessive volume administration should be avoided prior to organ retrieval so as to prevent pulmonary edema. Serial blood gas values should be made available for the immediate hours preceding organ harvest.

In general, suitable donors are less than 50 years of age, are HIV negative, have a minimal smoking history, and have normal or near-normal radiographic images. Oxygen pressures of at least 100 and 350 mmHg on 40% and 100% fraction of inspired oxygen, respectively, are expected and sputum Grams stains should be free of bacteria and fungus or significant numbers of white blood cells. Overall donor-recipient heights are helpful, but of more importance are the heights of the lungs themselves. Donor lung heights at end-inspiration should approximate recipient values, as placement of oversized lungs can result in poor function. Donor hearts should be free of hypertrophy and structural abnormalities (excluding the presence of a patent foramen ovale) and should demonstrate normal ventricular function on minimal inotropic support. Weight matching is less of an issue with HLT donors because right ventricular failure is rarely observed.

Upon arrival to the operating suite, flexible bronchoscopy should be performed to evaluate for gross airway lesions or purulent collections. Mucous plugs should be evacuated and the patient should be maintained on 40% fraction of inspired oxygen during the procurement procedure. Large-bore intravenous access should be assured and pulmonary arterial lines are removed. A median sternotomy is performed and the pleural spaces are opened widely, and the lungs are inspected for pigmentation and the presence of nodules, blebs, contusions, and visceral pleural injuries. The pericardium is opened and the heart is inspected for size, contractility, and the presence of palpable epicardial vessel lesions. If the organs appear satisfactory the procurement team should notify the recipient surgical team so that coordination of subsequent surgical steps can ensue.

Donor preparation includes mobilization of the ascending aorta and innominate artery as well as the superior vena cava. The azygos vein should be ligated and divided. Division of the innominate vein is optional but may facilitate dissection of the trachea. However, in patients being transplanted for complex congenital disease it is preferable to leave the innominate vein intact and to harvest it in continuity along with the bloc. Tissue over the airway is divided longitudinally and just enough so that the trachea can be encircled with an umbilical tape. Excessive tracheal dissection should be avoided so as to reduce the risk of injuring peribronchial vessels. Heparin is administered systemically (300 U/kg) and purse-string stitches are placed on the distal ascending aorta and main pulmonary artery for securing a cardioplegia needle and a blunt large bore perfusion cannula, respectively. Alprostadil (500 μg) is injected directly into the pulmonary artery in order to counteract the vasoconstrictor effects of subsequent preservation fluid administration and then the distal superior vena cava is ligated. The left atrial appendage is amputated and the inferior vena cava is cut at its union with the right atrium. Blood is suctioned from the field and the aorta is clamped when it is empty. Cold crystalloid cardioplegia (1000 cc for adults or 10 cc/kg for children) is given into the aortic root to arrest the heart and 3 L of cold low-potassium dextran (Perfadex) solution is delivered by gravity into the main pulmonary artery to flush the lungs in antegrade fashion. Cold saline is introduced into the thorax to facilitate rapid cooling and the lungs are gently ventilated with half-normal tidal volumes of room air during the antegrade perfusion process (both lungs should clearly blanche).

While it is generally accepted that adjunctive retrograde pulmonary perfusion improves post-transplant lung function, our preference has been to use antegrade perfusion alone when procuring heart-lung blocs. However, retrograde perfusion is feasible by making a small incision in the central inferior aspect of the left atrium for introduction of a perfusion cannula. The effluent is evacuated through the small defect originally made in the main pulmonary artery for antegrade pulmonoplegia

administration. Upon completion of the perfusion process the lungs are deflated and the left and right pericardial sheets are excised down to the level of the phrenic nerves. The posterior pericardium is divided transversely to expose the esophagus and then the left lung is medialized and the hilar structures are protected while inferior ligament and other avascular attachments anterior to the esophagus are divided. Working in a superior direction, the aorta is divided at the isthmus and then the pedicle containing the phrenic nerve and subclavian artery is transected. A finger is inserted into the aorta for inferior retraction and then the arch vessels and attachments are divided until the esophagus is seen thus completing the left side of the dissection. In analogous fashion, the right side of the dissection is performed, which should leave the heart-lung bloc completely freed with the exception of the tracheal attachment. The lungs are gently ventilated until no atelectasis is observed and then they are inflated to three-fourths normal vital capacity volume and the trachea is stapled with a transverse device. The bloc is freed after division of the more proximal trachea and is completely submerged in sterile bags containing cold Physiosol solution. The bloc is transported in sterile transport box contained within a large cooler filled with ice. Grafts procured in this manner have been transplanted successfully with total ischemic times of six hours.

IV. Operative Technique for Combined Heart-Lung Transplantation

HLT is unique in that it is a surgical procedure that requires familiarization with all major structures within the chest. Successful outcomes require intraoperative efficiency and rigorous attention to detail. Moreover, frequent communication between the surgical, anesthesia, perfusion, procurement, and nursing teams are of paramount importance.

Recipient preparation in the operative suite should begin once the deployed procurement team visually inspects the donor graft and ensures adequate function. The recipient is anesthetized and appropriate invasive monitoring lines and a transesophageal echo probe are inserted. Median sternotomy is performed and the pericardium is opened widely. Both pleural spaces are entered and if necessary pulmonary adhesiolysis is performed prior to heparinization assuming hemodynamic stability can be maintained. Division of bilateral inferior pulmonary ligaments should be performed cautiously so as to avoid injury to the aorta and esophagus (division of the left ligament and posterior pleural adhesions may be deferred until the patient is placed on cardiopulmonary bypass if appropriate). The Argon Beam Coagulator (ConMed Corp, Utica, New York, U.S.) is occasionally helpful in achieving chest wall hemostasis in the patients who have undergone prior pleurodesis.

Bilateral anterolateral aspects of the pericardium are carefully dissected and entirely preserved. Preservation of bilateral phrenic nerves is critical and every effort should be maintained to separate the inferolateral aspects of the pericardium away from the pulmonary hila as close to the vascular structures as possible. Once a “window” is created it should be carefully extended deep to the course of the phrenic nerves in a longitudinal fashion. Patients transplanted for end-stage CHD and PPH tend to have well-defined surgical planes with clearly visualized phrenic nerves. However, this is not often the case in patients with inflammatory diseases and the tissue between the phrenic nerves and the nearby hilar structures tends to be inflamed, friable, and contracted making separation and the creation of the subphrenic, perihilar pericardial incision difficult. The ultimate goal is creation of bilateral pericardial “flaps” containing the

phrenic nerves with entirely freed anterior and posterior margins. This enables donor left and right lungs to be delivered posterior to the recipient's broad pericardial tissue flaps at the time of implantation. Resulting anatomic correctness provides protection in the event that redo-lung transplantation is required in the future.

Minimal preparation prior to institution of cardiopulmonary bypass (CPB) is required with respect to the recipient's heart and great vessels. The superior and inferior vena cava should be encircled with tapes and circumferentially dissected as well as the ascending aorta. The superior vena cava is freed from the right pulmonary artery beneath. Heparin is administered and distal ascending aortic and bicaval cannulation is performed. CPB is initiated and systemic cooling is performed with a target temperature of 28°C. Carbon dioxide is used to flood the field. Venting is not required.

Left and right medial retraction of the pericardial flaps helps expose the extrapericardial course of the hilar structures. The right superior pulmonary vein is circumferentially dissected and is divided far laterally with a reticulating endovascular stapler. This exposes the underlying and more cephalad right pulmonary artery more clearly and then this vessel is divided in similar fashion after adequate intra- and extrapericardial dissection. The right inferior pulmonary vein is similarly transected followed by division of the right main bronchus using a transverse stapler. Left pneumonectomy is performed in an analogous fashion and is facilitated by cardiac decompression provided by CPB.

Recipient cardiectomy is performed in a fashion similar to that used for an isolated heart transplant. The caval tapes are tightened and ascending aorta is clamped and divided proximally at the sinotubular junction. The pulmonary artery is similarly divided and then the right atrium is opened longitudinally. The inferior margin of the right atriotomy is directed into the coronary sinus and the incision is extended along the atrioventricular groove. The superior margin of the right atriotomy is carried through the interatrial septum and along the dome of the left atrium. Both lines of atrial transection are brought together laterally leaving behind only the stump-orifices of the pulmonary veins, the posterior wall of the left atrium, the proximal main pulmonary arteries, and the posterior aspect of the right atrium adjoining the cava. Though the remaining remnants of the left atrium and vein stumps can be left in situ, they are generally excised along with the residual right main pulmonary artery and the majority of the left main pulmonary artery. It is advisable to leave behind a small cuff of left pulmonary artery near the ductal insertion so as to minimize injury to the left recurrent laryngeal nerve. The posterior wall of right atrium can be left in situ as well so as to prevent retraction of the cava and facilitate subsequent donor to recipient caval anastomosis. However, the residual right atrium requires transverse division to allow the right lung to be placed posterior to the phrenic bundle. Hemostasis of the posterior mediastinum should be meticulously obtained. Sites of bleeding can be difficult to localize and can lead to an unnecessary requirement for blood product administration with undesirable sequelae.

The final step for recipient preparation entails dissection and mobilization of the distal trachea. Gentle upward retraction is applied to the left and right bronchial stumps and electrocautery is used to free the carina. The trachea is transected one ring above the carina and the remnants of the bronchial stumps are excised. The distal trachea and surrounding soft tissues should be minimally dissected so as to minimize devascularization and avoid the left vagus nerve, which courses anterior to the esophagus.

Preparation of the donor heart-lung bloc consists of tracheal division one cartilaginous ring above the carina. Contained mucous should be swabbed for appropriate cultures and then aspirated completely with a separate suction device. Accompanying

soft tissue surrounding the remaining distal donor cartilaginous ring and carina should not be excised. The interatrial septum is also inspected through the right atrial-inferior vena caval orifice for the presence of a patent formane ovale. If present the defect is suture closed. The graft is lowered into the chest and the left and right lungs are gently delivered posterior to their respective recipient pericardial flaps. Downward retraction on distal donor aorta adequately exposes the two tracheal ends and allows good visualization for performance of a single layer running anastomosis using a 3-0 or 4-0 polypropylene monofilament suture. The posterior membraneous tissue is approximated first from the inside and from the patient's left to right. The cartilaginous portion of the anastomosis is easily completed thereafter and then the donor heart is wrapped in gauze blankets for absorption of ice-cold saline delivered from a continuous cold line. The inferior vena caval anastomosis is performed using a running monofilament polypropylene suture. The left atrial appendage defect and main pulmonary artery pulmonoplegia site are closed with suture and then the superior caval anastomosis is performed in a fashion analogous to that used for the inferior component. Care should be taken not to purse-string either caval anastomoses by tying the sutures too tightly. Systemic rewarming is commenced and an arterial white blood cell filter included in the cardiopulmonary bypass circuit is engaged. An end-to-end aortic anastomosis is performed in single layer running fashion with a 4-0 monofilament polypropylene suture. Prior to the release of the aortic cross-clamp the trachea is suctioned and gentle ventilation is begun. The aortic root is vented and caval tapes are released. In steep Trendelenburg position the heart is massaged and the cross-clamp is released.

It is not uncommon for the new graft to require 30 to 60 minutes of resuscitation on CPB before optimal function is achieved. Dopamine and or isoproterenol drips are commonly used to achieve an acceptable heart rate if temporary epicardial wires are to be avoided. Every effort is made to minimize the FIO_2 as weaning is commenced and oxygen saturations of 90% are accepted to satisfy this effort. The threshold for utilization of NO in the operative suite or during the immediate post-operative period is low. Coagulopathy is occasionally observed and is particularly problematic during the post-CPB period when volume and product administration is not desirable. Early use of coagulation factor VIIa (Recombinant, NovoSeven) or FEIBA VH anti-inhibitor coagulant complex, vapor heated (AICC) is utilized instead of repeated transfusions of fresh frozen plasma. The operation is concluded by chest tube insertion and the sternal wound is closed in routine fashion.

The most common variation in surgical technique described above pertains to the relationship between the recipient's pericardial flaps and the position of the donor lung hilar structures. Some surgeons advocate excision of the pericardium down to the level of the phrenic nerves with placement of the hilar structures in an anterior position. This technique facilitates brief anterior and medial rotation of the nonventilated lungs after CPB is discontinued so that the posterior mediastinum can be inspected for hemostasis. Absence of pericardial tissue anteriorly reduces kinking of the hilum during brief inspection and promotes hemodynamic stability. We have found this technique to be effective, but tend to prefer correct anatomic positioning of the graft so as to facilitate dissection in the event that reoperative surgery is required.

V. Immediate Postoperative Management

In the immediate postoperative period, excessive fluid administration should be avoided and patients are oxygenated with as low of a fraction of inspired oxygen as allowable so

as to maintain an arterial saturation of approximately 90%. A low threshold for initiating inhaled nitric oxide therapy should be adopted and its use is preferable to markedly increasing oxygen delivery. An abrupt and unexplainable requirement for higher oxygen delivery should prompt a search for an etiology. Graft reperfusion injury is a common cause for initial transplant lung dysfunction and occurs in up to 15% of patients (4). Assuming post-operative stability, standard weaning from the ventilator is performed once hemostasis is confirmed and the patient appears to be emerging from anesthesia satisfactorily. Postoperative sinus node dysfunction is effectively treated with an isoproterenol infusion or with temporary epicardial pacing wires if placed. Pulmonary arterial catheters are rarely used and cardiac performance is assessed by closely following systemic and central venous pressures as well as parameters and physical exam findings associated with end-organ perfusion.

VI. Immunosuppressive Protocol/Infection Prophylaxis

Immunosuppressive regimens for HLT are relatively standardized with minor differences between centers. The recent trend at Stanford University Medical Center has been to avoid induction therapy [rabbit anti-thymocyte globulin (RATG), or daclizumab], a feature once considered as the cornerstone of our immunosuppressive strategy. Instead, for unsensitized patients, we currently rely on steroids alone as the initial immunosuppressive medication. Following administration of protamine, 500 mg of methylprednisolone is administered intravenously. Methyprednisolone is readministered every eight hours (150 mg) for three additional doses. Thereafter, prednisone is administered orally (1 mg/kg) in divided twice daily doses until a taper is begun upon discharge. Steroid administration does not appear to result in a greater incidence of postoperative airway complications (5). Mycophenolate mofetil is initiated on the first postoperative day and a calcineurin inhibitor shortly thereafter assuming renal function permits. Tacrolimus is used preferentially by our institution as it appears to be associated with a lower incidence of obliterative bronchiolitis as compared to cyclosporine (6).

Because many patients undergoing HLT frequently have a history of congenital cardiac lesions requiring prior interventions and blood product transfusion, protocols for highly sensitized patients should be firmly established. In addition to standard steroid therapy and calcineurin and purine systhesis inhibition described above, management strategies for highly sensitized patients typically include intraoperative plasmapheresis and IVIG administration followed by continued serial postoperative plasmapheresis and IVIG therapy. Following transplantation, a retrospective cross-match should be performed to determine the need for RATG (cytotoxic cross-match positive) or daclizumab administration (cytotoxic cross-match negative or pulmonary edema present or expected from RATG). Rituximab is administered as well on postoperative day 7 with a subsequent dose given one week later.

VII. Complications

A. Infection

Infections are not uncommon in the post-HLT recipient and can lead to significant morbidity and mortality. Bacterial infections tend to dominate the early postoperative period and are frequently associated with indwelling catheters, prolonged ventilation, and wound-related issues (7). Prophylaxis against bacterial infection during the

immediate postoperative period and subsequent inpatient hospital course consists of vancomycin, cefepime, and tobramycin (cystic fibrosis patients). In contrast, opportunistic infections (viruses, fungus, protozoa) predominate late after HLT as a result of chronic immunosuppression. Cytomegalovirus (CMV) is the most common opportunistic pathogen and is associated with accelerated coronary graft disease and the syndrome of obliterative bronchiolitis in the post-transplant period (8,9). Seronegative recipients receiving grafts from seropositive donors are at the greatest risk for CMV-associated complications (incidence 90%), while seronegative recipients receiving grafts from seronegative donors are infected far less commonly (incidence 10%). A diagnosis of CMV-infection can be made in several ways: (*i*) seroconversion of anti-CMV immunoglobulin M from negative to positive, (*ii*) positive viral cultures, (*iii*) a four-fold rise in CMV immunoglobulin G antibody titers, or (*iv*) presence of viral inclusion bodies on trans-bronchial biopsy specimens. Patients at high risk for CMV infection should receive prophylaxis consisting of intravenous ganciclovir and CMV g-hyperimmunoglobulin (Cytogam) followed by oral valganciclovir (10). Fortunately, fungal infections are rarer; however they remain the most morbid pathogens encountered in the post-HLT period. Prophylaxis against fungal infections is carried out with aerosolized amphotericin B during the inpatient setting and then is converted to oral itraconazole therapy upon discharge. Combination therapy with sulfamethoxazole and trimethoprim is effective in the prevention of *Pneumocystis carinii* pneumonia (11) and *Toxoplasma gondii*–negative recipients receiving seropositive donors receive a finite course of pyrimethamine and leucovorin. Long-term use of clotrimazole is used to help prevent mucosal *Candida* infections.

B. Acute Rejection

The majority of cases of acute rejection occur during the first year following HLT. Pulmonary grafts are primarily affected and in fact simultaneous rejection involving both the pulmonary and cardiac grafts is exceedingly rare. As a result, myocardial biopsies are rarely performed whereas transbronchial biopsies are routine during the first post-transplant year. Acute rejection should be suspected in those patients manifesting dyspnea, pulmonary infiltrates on chest roentgenogram, fever, and with deteriorations in oxygenation and ventilatory parameters (forced expiratory volume in 1 second) (12). Because acute rejection is associated with subsequent development of obliterative bronchiolitis, any decrease in noninvasive lung function testing should be evaluated with transbronchial biopsy. Treatment consists of pulse-dose steroid therapy (1 g of methylprednisolone intravenously daily for 3 days) followed by an increased oral steroid dose with subsequent taper. Resistant cases are managed with monoclonal (OKT3) or polyclonal (RATG) antilymphocyte therapy.

C. Chronic Rejection

Deterioration in graft function secondary to progressive airway disease, or obliterative bronchiolitis, remains the single most common cause for failure after HLT. In fact, review of the International Society of Heart Lung Transplantation registry indicates that the incidence of BOS approaches 50% in HLT recipients at five year after transplantation. Bronchiolitis obliterans is a syndrome (BOS) that manifests as a persistent cough, progressive and unremitting dyspnea on exertion, and increasing presence of interstitial infiltrates on chest roentgenogram. Risk factors for development of the

syndrome include postoperative CMV infection, prior episodes of acute rejection, and increasing degrees of HLA mismatch (13). The latter risk factor suggests that BOS may be an immunologically mediated process. Redo-lung transplantation is the only treatment option for end-stage BOS. Unfortunately, poor actuarial survival rates of 25% at up to three years post redo-transplantation are realized (14).

Of those HLT recipients surviving one year, very few succumb to graft coronary artery disease. Angiographic surveillance of HLT recipients has demonstrated an incidence of approximately 10% of identifiable coronary artery lesions at five-year post-HLT. This incidence of graft coronary artery disease differs drastically from patients receiving isolated heart transplants in which progressive disease of the epicardial vessels contributes substantially to post-transplant morbidity and mortality (15). This discrepancy is attributed to the "combi-effect," an observation in animal models in which the lungs demonstrate more immunologic activity in comparison to the simultaneously transplanted heart (16).

VIII. Late Results

The most common cause of death after HLT remains BOS. A retrospective review of more than 170 patients undergoing HLT at Stanford University Medical Center between 1981 and 2000 revealed that the prevalence of patients alive at three months post transplant and who were diagnosed with BOS thereafter approached 65%. Overall mortality at five years in these patients neared 70% emphasizing the importance of close postoperative surveillance in these patients so as to identify and suppress the effects of BOS. Overall actuarial survival at five years for these more than 170 patients approached 50%. Although a 50% patient loss at five years post-transplant time prompts a continued effort to refine the procedure and subsequent management strategies, this result must be weighed against the dismal survival expected in similar patient populations with end-stage cardiopulmonary disease not transplanted.

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Lobar Lung Transplantation

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I. Introduction

Lobar lung transplantation is an alternative to cadaveric lung transplantation in which a right and left lower lobe from two separate donors are removed and implanted in a recipient in place of entire right and left lungs (1). There are important differences between lobar and cadaveric lung transplantation in terms of donor selection, operative technique, organ preservation, postoperative recipient management, and ethical issues regarding the use of live organ donors.

II. General Principles and Patient Selection

Candidates for lobar lung transplantation must meet standard criteria for cadaveric lung transplantation and be listed on the UNOS Organ Procurement and Transplantation Network lung transplantation waiting list (2). The decision to proceed with lobar lung transplantation is difficult but should center on the expectation that the recipient would die or become an unsuitable recipient before a cadaveric organ becomes available.

Donors considered for living lobar transplantation must have excellent health, adequate pulmonary reserve, an emotional attachment to the recipient, and be willing to accept the risks of donation without coercion. Current criteria for donation include age between 18 and 60; no history of thoracic procedures on the side to be donated; no active or extensive smoking history; no active lung disease on the side to be donated; no identifiable risk for familial lung disease; no cachexia (BMI < 18 kg/m^2) or obesity (BMI >30 kg/m^2); ABO blood type compatibility with recipient; donor lobe size compatible with recipient hemithorax; normal pulmonary function and arterial blood gas results; no conditions that significantly increase the risk of general anesthesia, surgery, or postoperative recovery; no psychological, ethical issues, or concerns about donor motivation; no pregnancy; no active malignancy; and no active significant infection (HIV, hepatitis, acute CMV). Donors taller than the recipient are favored over donors of the same or lesser height as they have the potential to provide larger lobes. Donors may be related or unrelated to the recipient as long as an emotional attachment exists. A psychosocial interview is conducted to delineate motivation, outcome expectation, family and career obligations, as well as untoward coercion.

Acceptable potential donors then undergo a preliminary screening of blood typing, chest radiography, and spirometry. Transplant serologies (HIV, VDRL, CMV, EBV, and

hepatitis), electrocardiogram, echocardiogram, quantitative ventilation/perfusion scanning, and high-resolution chest computed tomography are then completed if the preliminary screening is found acceptable.

After identification of two suitable donors, the larger is usually selected to undergo right lower lobectomy, while the donor with the more complete fissure on the left is chosen to donate that side. Care must be exercised to ensure that the lower lobe is not oversized, although the optimal method of determining an appropriate size match between donor and recipient remains to be defined. Some groups advocate accepting size mismatches between recipient and donor lobar grafts only if the predicted forced vital capacity (FVC) (calculated from the donor measured FVC and the number of pulmonary segments implanted) of the graft is more than 45% of the expected recipient FVC (3).

III. Operative Technique

The performance of lobar lung transplantation involves three simultaneous operations: two donor lobectomies and the recipient bilateral pneumonectomy and lobar implantation. The operative goals of lobar lung transplantation are to avoid morbidity to the healthy volunteer lobe donor while providing adequate tissue margins for implantation in the recipient (4). The lobar vascular and bronchial anatomy of the right and left lower lobe are the most suitable for lobar transplantation.

A. The Donor Lobectomy

There are important differences in performing a lobectomy for lobar lung transplantation in comparison with that for cancer or infection. The lobe must be removed with an adequate cuff of bronchus and pulmonary artery and vein to allow successful implantation into the recipient, while allowing closure of these structures without compromise to the donor. This requires excellent exposure that allows dissection of hilar structures without excessive manipulation of the graft.

Donor Right Lower Lobectomy

The donors are placed in separate operating rooms and epidural catheters are inserted for postoperative pain control. After induction of anesthesia, fiberoptic bronchoscopy, placement of a double-lumen endotracheal tube, and positioning in the appropriate lateral decubitus position, the donor lung is deflated and the chest entered through a standard fourth or fifth interspace posterolateral thoracotomy. After taking down the inferior pulmonary ligament, dissection commences in the fissure to identify the pulmonary arteries to the right lower and middle lobes. The relationship between the superior segmental artery to the right-lower lobe and middle lobe artery should be visualized. Adequate distance between the middle-lobe artery and superior segmental artery of the lower lobe is required to allow placement of a vascular clamp distal to the middle lobe artery, while preserving a sufficient vascular cuff for the pulmonary arterial anastomosis at implantation.

Next, the pericardium surrounding the inferior pulmonary vein is incised and dissection completed to allow a vascular clamp to be placed on the left atrium. The fissures are then stapled using an endovascular stapler. Five to ten thousand units of heparin and 500 mg of methylprednisolone are administered intravenously, and the lung is reinflated and ventilated for 5 to 10 minutes. The lung is then deflated. A vascular

clamp is placed first on the pulmonary artery and subsequently on the left atrial side of the inferior pulmonary vein, optimizing the length of the venous cuff for pulmonary venous anastomosis. The pulmonary artery is transected at a point that will allow an adequate vascular cuff for anastomosis while leaving enough length to permit repair without compromising the remaining pulmonary arterial branches. The inferior pulmonary vein is transected with a small cuff of left atrium. Care must be taken to confirm that the right middle lobe vein does not drain to the inferior pulmonary vein. The bronchus to the right lower lobe should now be exposed. Dissection around the bronchus is minimized. The right middle lobe bronchus is identified, and the bronchus to the lower lobe is tangentially transected from a point above the superior segmental bronchus of the right lower lobe to a point just inferior to the right middle-lobe bronchus.

The donor lobe is then wrapped in a cold, moist sponge and taken to a separate, sterile table for preservation. The donor pulmonary artery and pulmonary vein/left atrial cuff are then repaired in two layers with a running polypropylene suture. The bronchus is closed with interrupted polypropylene, being careful to avoid narrowing of the bronchus intermedius or infolding of the middle-lobe carina. Resecting a small wedge of cartilage at the orifice of the middle lobe may facilitate closure. The bronchial suture line is covered with a pleural flap to separate the arterial and bronchial suture lines. Two chest tubes are placed in the pleural space and the chest is closed in the standard fashion.

Donor Left Lower Lobectomy

Donor left lower lobectomy is performed in a similar manner. A posterolateral thoracotomy through the fourth or fifth interspace is performed, the lung examined, and the pulmonary ligament incised. Dissection begins in the fissure to define the relationship between the superior segmental artery to the lower lobe and the lingular artery, allowing placement of a vascular clamp proximal to the superior segmental artery of the lower lobe. The pericardium around the inferior pulmonary vein is opened circumferentially, and the fissures are completed with an endovascular stapler.

When the dissection is complete, heparin and methylprednisolone are administered and the lung reinflated and ventilated for 5 to 10 minutes as described for the right side. The lung is subsequently deflated and the pulmonary artery and vein are clamped and transected in the sequence described for the right lung. The lingular bronchus is identified and the bronchus transected between the base of the upper-lobe bronchus and the superior aspect of the superior segmental bronchus of the left lower lobe. The donor lobe is then taken to a separate table for preservation. The pulmonary vessels and bronchus are repaired as described for the right side.

B. Allograft Preservation

In contrast to cadaveric transplantation, in vivo preservation of the live-donor lobe is not possible. After the donor lobe is removed, it is taken to a separate, sterile table for preservation, where it is immersed in cold crystalloid solution. The pulmonary artery and vein are cannulated in an alternating fashion and flushed with 1 to 2 L of cold, pulmonoplegic solution until the pulmonary venous and arterial effluents are clear and the parenchyma is blanched white. During perfusion, the lobe is gently ventilated with room air using an appropriately sized endotracheal tube to obtain an adequate seal. The superior segmental bronchus and superior segmental artery may have to be ventilated and perfused separately. Care should be taken to avoid overpressurizing the lung as well

as the introduction of crystalloid bath or preservative effluent from entering the bronchus. After adequate perfusion and ventilation, donor lobe is placed 75% inflated in sterile bags with cold storage solution and transported to the recipient operating room in an ice-filled cooler.

C. Recipient Pneumonectomy

The recipient operation commences concurrently. The explant is performed in a manner similar to standard bilateral cadaveric lung transplantation. We prefer a transverse thoracosternotomy as well as the use of cardiopulmonary bypass as this allows patient stability and the simultaneous controlled reperfusion of both lobes. Contrary to standard lung transplant pneumonectomy, an effort is made to dissect the pulmonary artery and veins as distally as possible to optimize cuff length for the anastomosis with the donor lobe. When the dissection is complete, cardiopulmonary bypass is initiated and the pulmonary vasculature is divided. The pulmonary veins are divided between stapling devices while the pulmonary artery is doubly ligated and divided. The bronchus is divided with a stapling device at the level of the takeoff of the upper lobe bronchus.

D. Allograft Implantation

The allografts are kept cool within the pleural space during implantation. The bronchial anastomosis is performed with running 4-0 polypropylene suture. Care is taken to limit the amount of peribronchial dissection. The bronchial anastomosis places the donor lobar vein in close approximation to the superior pulmonary vein of the recipient, and the venous anastomosis is performed in a running fashion with 5-0 polypropylene suture. The short length of the donor vein makes anastomosis directly to the left atrium difficult and underscores the importance of leaving an adequate length of recipient pulmonary vein during pneumonectomy. The pulmonary artery anastomosis is performed end to end with 5-0 polypropylene suture. A similar procedure is performed for the second allograft.

After completing the bilateral implantations, controlled reperfusion of the grafts is performed and the preservation perfusate is allowed to egress from the venous anastomosis prior to tying the venous sutures. Ventilation is then begun gently. Continuous nitric oxide starting at 20 ppm and intermittent aerosolized bronchodilator therapy are both administered via the anesthesia circuit. Blood volume is gradually returned allowing increased cardiac ejection and pulmonary blood flow to occur with subsequent weaning from cardiopulmonary bypass. At the completion of implantation, patency of the one pulmonary vein draining each side is confirmed with transesophageal echocardiography and bronchoscopy is performed to ensure an adequate bronchial anastomosis. Four chest tubes are then placed, the clamshell incision closed, and the patient transported directly to the intensive care unit.

IV. Postoperative Management

A. Donor Management

Donor management is similar to that of a standard open lobectomy or sleeve resection. Epidural catheters are used routinely. Two chest tubes are required until air leaks have stopped, output is acceptable, and the remaining lung tissue fills the hemithorax. All donors receive low-dose enoxaparin and sequential compression devices. Oral analgesics are administered upon removal of the chest tubes and are continued for a short time at home.

B. Recipient Management

The perioperative management of the lobar recipient can be quite challenging given the unique lobar physiology, whereby the entire cardiac output is flows through two relatively undersized lobes. Efforts are focused on decreasing atelectasis and optimizing expansion of the lobes, while minimizing the risk of reperfusion injury and pulmonary edema. This is accomplished by keeping the recipient sedated and ventilated with positive end-expiratory pressures of 5- to 10-cm water for at least 48 hours, maintaining the recipient in a relatively hypovolemic state, the use of nitroglycerin infusion, and the use of aerosolized nitric oxide for the first 48 to 72 hours.

Perioperative chest tube management is also unique in the lobar recipient as conventional chest tube suction in the postoperative period can result in impaired deflation mechanics, leading to an acute rise in pulmonary arterial pressure. This problem is exaggerated as the discrepancy between the size of the lobe and the thoracic cavity increases. In an effort to avoid this problem, suction is applied at low levels (10-cm water) to each tube sequentially for 1-hour intervals, in a rotational fashion for the first 24 hours postoperatively. Subsequently, each of the four chest tubes is placed on continuous suction that is gradually increased to 20-cm water over the next 48 hours. Chest tube output can be much greater than that seen after cadaveric implantation and the chest tubes are generally left in place for two to three weeks until outputs are acceptable. Any air leaks typically resolve in this time period as well.

The management of the lobar recipient in regard to immunosuppression, antibiotic therapy and prophylaxis, and long-term follow-up is very similar to cadaveric recipients. All patients receive triple-drug immunosuppression (tacrolimus/cyclosporine, mycophenolate mofetil/azathioprine, and prednisone) without induction therapy. Antibiotic use based on preoperative, intraoperative, and postoperative cultures is common in cystic fibrosis recipients due to the nearly universally presence of pathogenic bacterial and/or fungal species. Prophylaxis for *Pneumocystis carinii* and cytomegalovirus is given to all recipients. In all recipients, pulmonary function testing and chest roentgenography are performed with each clinic visit; however, bronchoscopy is performed only when clinically indicated by symptoms, radiography, or a decrease in spirometric results. Transbronchial biopsy is performed sparingly due to the perceived increased risk of bleeding in the lobar recipient.

V. Results

Worldwide, approximately 250 lobar lung transplants have been performed since its introduction in 1992 (5). The vast majority have been performed at the University of Southern California and Children's Hospital Los Angeles, Los Angeles, California, U.S.A. (6). Other programs also exist in the United States, Japan, South America, and Europe (5,7–10). The primary indication in the United States has been cystic fibrosis (over 80%) while the most common indication in Japan is pulmonary hypertension (6,11). Other indications have included idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, and obliterative bronchiolitis (6,12). Lobar lung transplant recipients continue to be young and critically ill with approximately two-thirds hospital bound and one-fifth on mechanical ventilation preoperatively. Overall recipient survival compares favorably with the International Society for Heart and Lung Transplantation (ISHLT) registry data (13). Causes of early and late death remain similar to cadaveric transplantation and rates of development of obliterative bronchiolitis do not appear to be vastly different from cadaveric

transplantation (6). Pulmonary function after lobar lung transplantation appears comparable to that of bilateral cadaveric lung transplantation (14). There has been no reported perioperative mortality in a lobar lung donor (5,15).

VI. Future Direction

A constant awareness of the risk to the living donors must be maintained with any live-donor organ transplantation program. While the lung allocation score has decreased waiting times and deaths on the lung transplant waiting list, lobar lung transplantation has been and remains beneficial to a small group of individuals who are young, small, or critically ill and would otherwise succumb while awaiting a cadaveric donor (16,17). This technique has also proven very useful in societies with strict cadaveric donor laws such as Japan (11). Although cadaveric transplantation is preferable due to the risk to the donors, living lobar lung transplantation should continue to be utilized under properly selected circumstances.

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Critical Care Management

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I. Introduction

At the time of the arrival of the lung transplant patient at the intensive care unit (ICU), the primary goal of the ICU team is to obtain full information about the patients particular history, the procedure performed, eventual specific problems, and most importantly about the patients current status with regard to circulation and oxygenation (1,2). On the basis of these parameters, further treatment can be planned and important decisions about the timing and length of the weaning process can be taken.

II. Mechanical Ventilation and Weaning from the Respirator

Following lung transplantation, patients require a period of ventilation until they are fully stabilized, and the temporary injury resulting to the lung from the transplant procedure itself is overcome. Not infrequently, the latter leads to an early but transient moderate impairment of gas transfer, presenting as an increase in alveolar-arterial DO_2 and an impairment of CO_2 elimination. Important information can be obtained from the first thoracic X ray that is performed immediately after arrival at the ICU (Table 1). It provides evidence about the water content of the transplanted lung, its expansion status, and the eventual presence of atelectasis or pneumothorax, and also about the position of the diaphragm and the mediastinum. If some form of abnormality is recognized, a proper differential diagnosis has to be made and necessary therapeutic interventions have to be initiated.

During this early period, a protective mode of lung ventilation should be applied. Low tidal volume ventilation ($\leq$6 mL/kg predicted body weight) with limited end-expiratory plateau pressures (<30-cm H_2O) should be utilized, similar to what has been the experience in acute respiratory distress syndrome (ARDS) patients (3).

Once the patient is considered to be stable and respiratory parameters are satisfying with an oxygenation index greater than 300, weaning from mechanical ventilation can be started. A bronchoscopy should be performed prior to extubation to check the bronchial anastomosis and to clear the airways from mucus and postoperative blood and secretions. Ideally, the patient should be extubated within the first 24 hours after operation. However, timing of the weaning and extubation is dependent on the preoperative performance status of the patient, his or her overall condition, and his or her underlying disease. Especially in physically severely limited patients with long disease history, prolonged weaning must be anticipated, and in this situation, early tracheostomy can become necessary to provide increased mobility to the patient and to allow for regular cleaning of the airways. Once the patient is extubated, intensive physiotherapy

Table 1 Differential Diagnosis of Chest X Ray After LuTX

	Less than 24 hr	Greater than 24 hr
Diffuse	Overhydration Reperfusion injury Hyperacute rejection	Overhydration Rejection
Localized	Surgical residual Localized graft injury Hemorrhage Pleural effusion	Pneumonia Pleural effusion
Lobar	Vascular problem Obstructing clot	Vascular problem Mucous plug Pneumonia

has to be started immediately, inhaled bronchodilators should be applied, and frequent clearance of secretions has to be performed together with aggressive mobilization of the patient to prevent the development of atelectases and mucous retention. This is especially important since the transplanted lungs are permanently denervated and any secretions below the anastomosis, unlike in healthy individuals, do not trigger a normal coughing reflex. For these reasons, respiratory therapy and intentional coughing are even more important for these patients. All these physical treatment approaches, however, have to be accompanied by effective pain control to become effective. Nonsteroidal anti-inflammatory drugs should be avoided to protect from further damage to the kidneys, and epidural analgesia (4) should be given a preference in this particular situation.

In contrast to the so far described uneventful postoperative course, some 10% to 20% of the patients will present with some degree of early lung dysfunction, generally summarized under the term reperfusion injury (5–10). Reperfusion injury is characterized by an increase of alveolar-arterial partial pressure gradients, a decrease in compliance, and pulmonary edema following the reperfusion of the graft within a time frame of minutes to several hours. Radiographic findings in this situation can vary from slight diffuse shadowing to complete homogenous whitening of the whole lung. Treatment strategies include the use of positive end expiratory pressure (PEEP) and a strict limitation of volume together with low-dose systemic vasopressor therapy (10). The use of PEEP is particularly essential in this situation to limit excessive fluid transfer through the alveolar-arterial membranes. It is generally accepted that the mechanism of PEEP involves recruitment of lung air volume and likely has little or nothing to do with prevention of fluid transfer across the capillary network. PEEP is felt to redistribute fluid within and outside the alveoli. However, peak inflation pressures should be kept as low as possible to avoid additional damage to the transplanted lung. The use of unnecessary high FIO_2 should be avoided, and FiO_2 should be kept at a level compatible with an adequate oxygen saturation level to avoid oxygen toxicity.

Positioning of the patients with the chest elevated and in single-lung TX recipients in a lateral position with the transplanted lung upward is important in this situation to reduce the blood flow through the transplanted lung.

Some authors have suggested the use of inhaled nitrous oxide (NO) (11) for prevention of reperfusion edema after lung transplantation. NO, in contrast to other vasodilating drugs, such as nitroglycerine or prostaglandin E1, is a selective pulmonary vasodilator that does not affect the systemic circulation. Despite encouraging results

from experimental work, the prophylactic use of NO in the clinical situation did, however, not help to avoid reperfusion injury and primary graft dysfunction (12,13). If reperfusion edema is, however, already established, this usually is paralleled by a significant rise in pulmonary vascular resistance. In this situation, NO can become a valuable addition to the other pharmacological therapy administered.

With all these strategies, the majority of patients with reperfusion injury can be stabilized. However, a small minority remains in whom conventional treatment strategies fail and use of venoarterial extracorporeal membrane oxygenation (ECMO) becomes necessary. More details about the use of ECMO will be given in chapter 28.

III. Special Aspects of Single-Lung Transplantation in Obstructive Lung Disease

Bilateral-lung transplantation usually results in complete normalization of respiratory function. In contrast, lung function improves but does not completely normalize after single-lung transplantation (14) and the particular pattern of remaining residual impairment reflects in part the pathophysiology of the native diseased lung, which participates to a limited extent in ventilation.

Especially in patients with obstructive lung disease and severe hyperinflation, this can cause significant problems in the early postoperative course. If the compliance of the single-lung allograft is for whatever reason temporarily impaired, air trapping in the remaining obstructive lung can lead to progressive overinflation of this lung, resulting in severe mediastinal shift and further compression of the transplanted lung. This problem can become so severe that native and transplanted lung may require separate lung ventilation with different respirator settings (15–17) (Fig. 1). The need for such

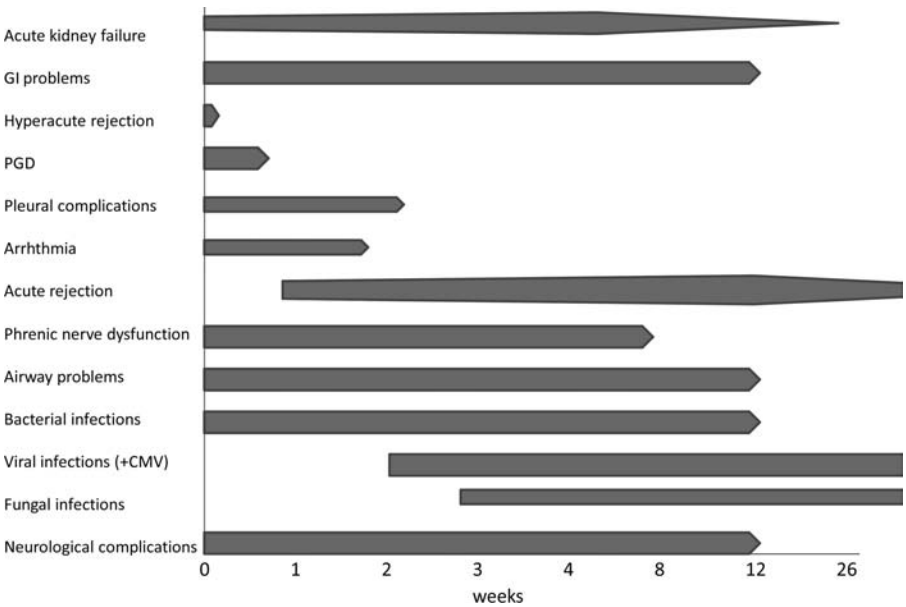

Figure 1 Preferential time of occurrence of postoperative complications after LuTX.

independent lung ventilation in patients undergoing single-lung transplantation for obstructive lung disease is defined by the combination of increased hyperinflation measured on recipients' preoperative lung function tests, a low PaO_2/fraction of inspired oxygen ratio, and a shift of the mediastinum toward the transplanted side, indicating graft dysfunction in the immediate postoperative period (18–21).

IV. Primary Pulmonary Hypertension

One of the highest challenges in postoperative intensive care of lung transplant patients is the treatment of patients transplanted for primary pulmonary hypertension (PPH). These patients have a unique pathophysiology, with the right ventricle significantly dilated and the left ventricle suffering from chronic underfilling and compression by the septum that bulges toward the left. Isolated lung transplantation normalizes the pulmonary vascular resistance, which consequently leads to normalization of the cardiac output. However, this immediate and dramatic change in the pathophysiology also incurs several problems. First, the left ventricle is not used to handling the normal cardiac output that can result in temporary left ventricular failure (22) especially at the time of extubation when the preload of the heart is significantly reduced after termination of PEEP ventilation. This situation can arise in such a dramatic way that patients coming from a completely normal clinical situation start to develop severe lung edema within a few hours. Transesophageal echocardiography (TEE) is necessary to establish the correct differential diagnosis against any other reason of lung edema. Prophylaxis of this condition can be done by fluid restriction, positioning of the chest in upright position at the time of extubation, and by temporary positive inotropic support (dobutamine) of the left ventricle. Once the problem is established, patients usually have to be reintubated and ventilated with high PEEP to reduce the preload of the heart.

The opposite to this problem occurs if fluid restriction is performed too aggressively, which might lead to right ventricular outflow obstruction, resulting from the muscular hypertrophy of the right ventricle. Again, TEE is mandatory to monitor and guide adequate filling of the heart.

All this happens on a background of significantly impaired renal function, and not infrequently, patients with PPH have to be treated with temporary hemofiltration immediately after the transplantation.

V. Management of Renal Function and Temporary Failure

Patients after LuTX are at a high risk for development of kidney dysfunction, at least on a temporary basis. Many of them, especially patients with pulmonary hypertension and CF, come to transplant with significantly reduced renal clearance parameters. Further nephrotoxicity results from the burden to the kidneys during the operation itself, the use of calcineurin inhibitors (CNIs) after transplantation, and the need for a restrictive fluid balance after TX (16–18). The importance of the problem is best demonstrated by the fact that occurrence of post-transplant renal failure is associated with increased mortality and that the one-month postoperative loss of glomerular filtration rate (GFR) was found to be an early marker for long-term renal function (23).

Potential renoprotective strategies after LuTX, therefore, focus on avoidance of peritransplant renal injury, on diligent blood pressure control, and the preferential use of tacrolimus (Tac) after transplantation (24). In addition, induction therapy with antithymocyte globulin (ATG) is a well-established strategy to allow for lower calcineurin

serum levels early after transplantation and is preferentially used in patients with idiopathic pulmonary hypertension (IPH) and cystic fibrosis (CF).

However, many patients with IPH nevertheless do require early temporary hemofiltration to handle fluid balance properly. Weaning from hemofiltration should then be initiated at a later point in time, after successful extubation and complete normalization of the hemodynamic situation.

A. Immunosuppression

The majority of lung transplant recipients receive a triple-drug maintenance regimen including CNIs (cyclosporine or tacrolimus), cell-cycle inhibitors (mycophenolate mofetil, sirolimus, everolimus), and steroids. Recent data from the ISHLT registry show that an increasing percentage of transplanted patients receive Tac instead of cyclosporine A (CsA). A similar trend can be observed for the use of Mycophenolate mofetil (MMF) instead of azathioprine (Aza). Almost all lung transplant patients receive steroids from the beginning of transplantation, and steroid withdrawal is uncommon even five years thereafter. The use of induction therapy with poly- or monoclonal antibodies is controversial and differs between transplant centers. As mentioned before, the potential of induction therapy to allow for a CNI sparing therapy makes this strategy especially interesting in patients with a high risk for renal failure.

Acute rejection occurring in the ICU is usually treated with high-dose IV steroid pulses. A switch from CsA to Tac, in combination with high-dose steroids, is the first treatment step in refractory acute rejection, which is followed by use of antilymphocyte agents and extracorporeal photopheresis (25) if necessary. Further details about immunosuppression will be given in chapter 29.

B. Infectious Prophylaxis

Pulmonary infections are a common problem during the initial postoperative period. Early bacterial infections are related to pneumonia, wound infections, and the use of urinary catheters. Because of the susceptibility to pneumonia, early extubation is highly recommended to avoid ventilator-associated complications.

First-line antibiotic prophylaxis for lung transplant recipients depends on pretransplant identified or potentially suspected microorganisms, which may become pathogenic during the early postoperative course. Routinely, β-lactam antibiotics are used in uninfected recipients. For patients whose underlying disease is of infectious origin, the antibiotic regimen must be adapted according to prior antibiotic sensitivities. Smears are taken intraoperatively from the donor and recipient bronchus, and antibiotic therapy has to be adjusted later on according to the results.

Fungal prophylaxis with IV caspofungin, voriconazole, or liposomal amphotericin is given in high-risk patients, and inhalational amphotericin three times daily has become standard in many departments, usually given until complete healing of the bronchial anastomosis is observed (26).

CMV prophylaxis with IV ganciclovir, together with or without CMV hyperimmune globulin, is started immediately after the transplantation for three weeks. This is subsequently followed by a further oral valganciclovir course for a total of three months, which is extended in high-risk patients for one year or longer (27–30).

Oral trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis jirovecii* (former *Pneumocystis carini*) infections is given lifelong in all heart-lung and lung transplant patients (31).

VI. Specific Early Postoperative Problems and Complications

A wide variety of specific problems and complications may occur early after lung transplantation. Knowledge and anticipation of these issues are important for prevention or treatment, and the time of their appearance after transplantation offers valuable hints for the differential diagnosis (Table 2).

Primary graft dysfunction and *acute rejection* are the most important complications and will be discussed in chapters 26 and 33 in detail.

Hyperacute rejection (32–35), a well-described complication after renal and cardiac transplantation, is less well known in the setting of lung transplantation. It has to be differentiated from primary graft dysfunction and is associated with the presence of antibodies directed against major allograft antigens, usually ABO or human leukocyte antigens (HLA). The severity of this condition requires a prompt diagnosis and an effective management. Unusual as it may be, hyperacute rejection is a life-threatening complication of lung transplantation affecting mainly women, with a very high mortality rate. Therefore, it is important to perform a sensitive panel reactive antibodies (PRA) screening in patients waiting for lung transplantation. A therapeutic option in these rare cases is the use of plasmapheresis to eliminate preformed antibodies together with high dose of steroids.

The data on vascular *anastomotic complications* (36–38) after single- and bilateral-lung transplantation are rare. Pulmonary artery stenosis occurs infrequently and usually becomes relevant especially after single-lung transplantation. Its correct diagnosis can be established by pulmonary angiography only and pronounced stenosis requires reoperation and surgical correction. In contrast, significant stenosis or complete venous occlusion occurs more frequently and usually presents with the radiological picture of severe infiltration restricted to one lobe. The diagnosis is confirmed by CT and TEE. Treatment of this condition requires immediate reoperation, and usually it becomes necessary to resect the lobe involved.

Table 2 Common Complications Following Lung Transplantation

Immediate (first 24 hr)
Mechanical
Pleural, for example, pneumothorax
Hyperacute rejection
Diaphragmatic paralysis
Early (within 2 mo)
Primary graft dysfunction
Acute rejection
Infection
Bronchial dehiscence
Pulmonary embolism
Late (after 2 mo)
Chronic rejection/bronchiolitis obliterans syndrome
Post-transplant lymphoproliferative disorder
Bronchial stenosis
Diaphragmatic hernia
At any stage
Transbronchial biopsy complications

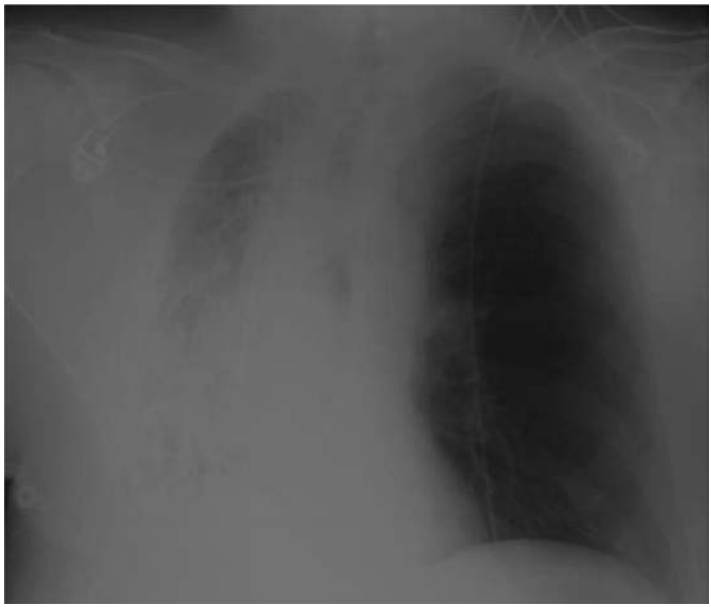

Figure 2 Chest X ray five days after right SLuTX in a patient with lung emphysema. Severe hyperinflation of the native lung with compression of the transplanted side can be observed. Patient was treated with independent lung ventilation for three days.

A significant proportion of lung transplant recipients develop *pleural space complications* (39–47) (Fig. 2). It is important to remember that following a bilateral transplantation through a clamshell incision, the normal anatomic barrier between both pleural cavities is lost, which results in an open communication between both pleural cavities and eventually can result in spread of a problem from one side to the other (Fig. 3).

The range of relevant pleural complications reaches from pneumothorax, which can occur bilaterally, to early hemothorax based on postoperative bleeding and incomplete lung expansion. The latter frequently is the result of pronounced pleural effusions, which eventually can lead to trapping of the lung and formation of a cortex. In such situations, early debridement either videoendoscopically or through open access becomes mandatory. Infection of retained fluids resulting in empyema formation is another potential problem that occurs more frequently in patients transplanted for CF with chronic intrathoracic infections.

Fortunately, *airway problems* (48–53), which were a major limitation to success during the beginning of LuTX, have recently become less common. Early after transplantation, only anastomotic dehiscence is of clinical relevance, whereas anastomotic and distal bronchial stenosis are problems that usually occur at a later point in time.

Airway dehiscence can be suspected when a pneumothorax with a persistent air leak occurs some days after operation. The diagnosis is confirmed by detection of local healing problems of the bronchial mucosa at bronchoscopy and by the finding of small amounts of extra luminal air around the bronchus at CT. An early intervention either in

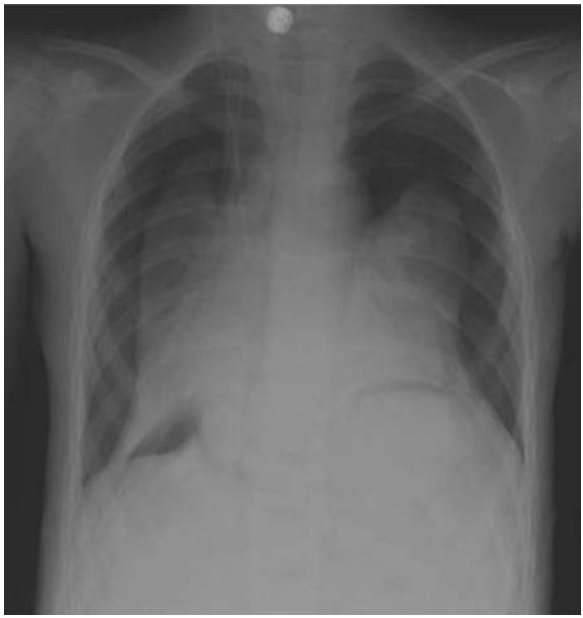

Figure 3 Chest X ray of a nine-year-old patient two weeks after DLuTX showing bilateral pneumothorax after a technical problem during removal of chest tubes.

form of endobronchial stenting or surgical reintervention is mandatory to avoid the development of intrapleural sepsis.

The injury of the phrenic nerve (54–58) is a well-documented complication after cardiac operations, but it is less commonly reported after lung transplantation. Incidence rates vary from 3% to 30%, depending on the methods used for its detection. Phrenic nerve dysfunction may result from different types of injuries during transplantation, such as (*i*) direct injury to the phrenic nerve during the dissection of the mediastinum, (*ii*) stretch on the phrenic nerve during manipulation of the pericardium, and (*iii*) hypothermia of the phrenic nerve during the implantation of the lung. Phrenic nerve dysfunction results in diaphragmatic elevation and paralysis and may lead to all different types of complications that are associated with this condition, including atelectasis, pneumonia, prolonged mechanical ventilation, and prolonged length of stay in the ICU. In such a situation, weaning of the patients from mechanical ventilation frequently has to be performed with noninvasive positive pressure ventilation (NIPPV) (54,59–62) and intensified physiotherapy.

A variety of different *neurological complications* (63–66) can be observed after LuTX, which all can become a significant source of morbidity of the recipients. The relatively high level of immunosuppression that is necessary after LuTX results in a high prevalence of immunosuppressant-related neural toxicity. In addition, opportunistic infections are frequently associated with complications related to the central nervous system. Especially younger patients, who are exposed to higher blood levels of CNIs, tend to develop seizures and posterior reversible encephalopathy syndrome (PRES)

within the first two weeks post-transplant. Early diagnosis of eventual neurological problems, together with a careful search for their potential etiology, is therefore an important task to perform for the ICU team.

Like any other postoperative patient, lung transplant patients are at risk for *pulmonary embolism* (67–70) and *thromboembolic complications*, which has been demonstrated on postmortem studies. Patients are at greatest risk in the first 30 days post transplantation, although complications may still occur at any time postoperatively. Recent studies suggest that this high incidence of thromboembolic complications is due to a hypercoagulable state, which is of an unclear etiology (71). Adequate anticoagulation for this reason is of importance and especially difficult in the setting of a combination with other coagulation disorders.

Finally, *gastrointestinal complications* (72–75) develop in a large number of lung transplant patients and can cause considerable morbidity and mortality post-transplantation. They are associated with the use of steroids, antibiotics, and immunosuppressive drugs. Among them are esophagitis, gastritis, colitis, ileus, reflux, peptic ulcer, gastrointestinal bleeding, cholecystitis, diverticulitis, and antibiotic-associated diarrhea. Acute abdominal surgical interventions have a reported incidence of 4% to 17% (bowel perforation, appendicitis, cholecystitis, pneumatosis intestinalis, colitis, and mechanical ileus).

Gastroparesis due to injury of the vagal nerve (76) or to metabolic/toxic dysfunction is a further serious complication of lung transplantation that can lead to weight loss, gastroesophageal reflux disease, and recurrent aspiration pneumonia early on. Treatment is difficult and is performed first line with erythromycin (77), a motilin agonist, that has been reported to improve gastric emptying and symptoms in patients with gastroparesis (77–80).

In one case report, resolution of gastroparesis has been described with the use of transcutaneous electrical nerve stimulation (TENS).

Finally, *tachyarrhythmia* (81) is another frequent problem after LuTX, with a reported incidence of 30% to 40% early postoperatively (after three to six days). Risk factors are older patient age, underlying diagnosis of IPF, coronary artery disease, enlargement of the left atrium, and use of postoperative vasopressors (1). Mean ICU stay and total hospital stay are both significantly longer in patients who develop atrial arrhythmias, and in hospital death is increased. Most cases, however, can be treated medically, and in only about 10% of patients cardioversion is required.

VII. Summary

Management of the patient after LuTX in the ICU is demanding. Experience with potential problems and complications, however, helps avoid severe consequences in the majority of patients.

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26
Primary Graft Dysfunction

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I. Introduction

Primary graft dysfunction (PGD)—referred to previously as reperfusion edema, reimplantation response, or primary graft failure—is a form of acute lung injury thought due largely to ischemia/reperfusion insults that accompany the lung transplantation processes of organ explantation, storage, and reimplantation. PGD affects 10% to 25% of all lung transplants and is the leading cause of early morbidity and mortality (1–7). Thirty-day mortality rates are up to eightfold higher in patients with severe PGD as compared to those without PGD. In addition, PGD survivors have significantly impaired long-term function (5) and an increased risk of bronchiolitis obliterans syndrome (BOS) (8).

Clinically, PGD typically manifests within the first 72 hours after transplant. While most if not all transplanted lungs will have some degree of injury, the most severe forms of PGD manifest as impaired oxygenation with diffuse pulmonary infiltrates (Fig. 1) and decreased lung compliance in the setting of normal or low left atrial pressures. Diffuse alveolar damage is seen histologically at this time. Clinically, this spectrum of lung injury mirrors the presentation of acute respiratory distress syndrome (ARDS). In 2005, to standardize both clinical and research efforts related to PGD, the International Society for Heart and Lung Transplantation (ISHLT) Working Group on PGD proposed a definition and grading system of PGD analogous to that for acute lung injury/ARDS, based on PaO_2:FiO_2 (P:F) ratio and chest infiltrates assessed at time points up to 72 hours: T (0 – within 6 hours of reperfusion, 24, 48, and 72 hours) (Table 1) (7). These time points for PGD grading were recommended to potentially describe different patterns of lung injury. As such, investigators determining PGD grade at varying time points have reported different outcomes (3,9,10). Since the ISHLT consensus statement on PGD was published, investigators have also suggested expanding the definition of PGD and its grading scheme. For example, Prekker et al. demonstrated that the early trend in P:F can predict 90-day mortality post transplant (11). Other groups have suggested utility of grading PGD at additional early time points (T6 and T12 hours) (12). However, neither trends in P:F nor additional time points have been directly compared to the suggested ISHLT time points for PGD grading as outcome definitions in clinical studies.

II. Epidemiology

Inconsistent definitions of PGD prior to the ISHLT guidelines had led to varied reported incidences of clinically significant PGD (6). In studies using a definition of PGD similar to the definition of ARDS (grade 3 PGD), the reported incidence of PGD ranges from

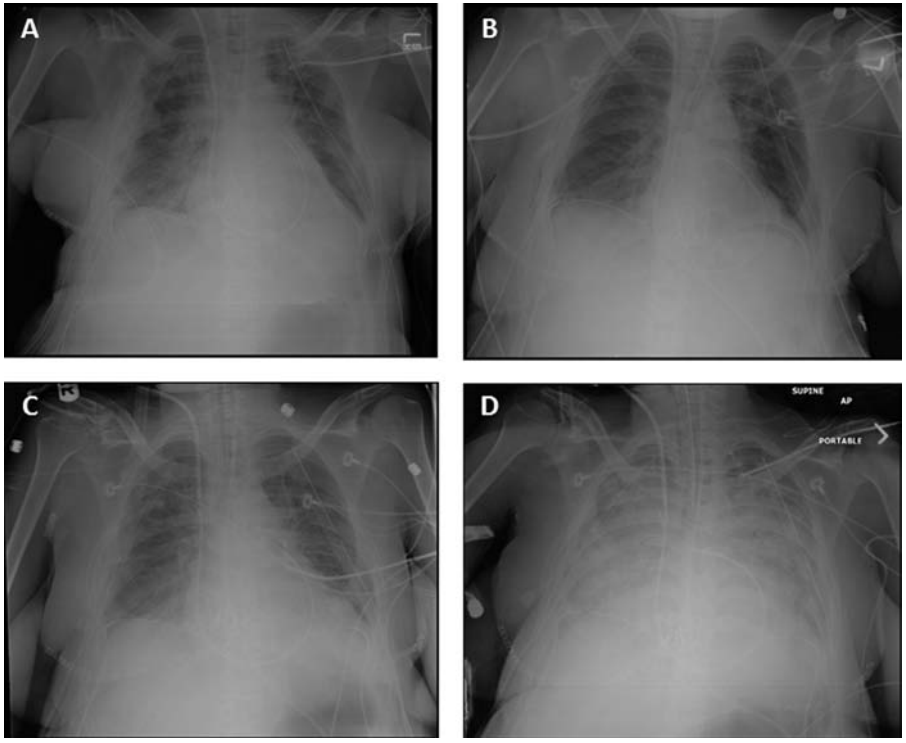

Figure 1 Radiographic progression of PGD after bilateral lung transplant. (**A**) Immediate postoperative chest X ray (CXR); (**B**) postoperative day 1; (**C**) postoperative day 2; and (**D**) postoperative day 3. Note mild diffuse pulmonary interstitial infiltrates forming on day 2, progressing to diffuse alveolar filling pattern on day 3.

Table 1 ISHLT PGD Grading Schema

Grade	PaO_2:FiO_2	Radiographic infiltrates consistent with pulmonary edema
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

Source: Adapted from Ref. 7.

10% to 25%, with 30-day mortality close to 50% (1–3,5,13). When less-stringent definitions of PGD were used, PGD incidence post transplant increased to 50% to 57% with no significant mortality differences between groups (14,15). The ISHLT grading system was validated in 2006 when investigators at the University of Minnesota showed that short- and long-term mortalities, as well as length of hospital stay, were significantly

associated with grade 3 PGD, based on the worst P:F within 48 hours after transplant (16). Although grading criteria were incomplete, the study highlighted the discriminatory ability of PGD grade 3 versus grades 1 and 2 to predict mortality and other outcomes. In 2007, Whitson and colleagues retrospectively reviewed 374 lung transplant procedures and graded PGD over the first 48 hours post-transplant. Survival rates were 51% at 5 years and 11% at 10 years in those patients with grade 3 PGD. BOS-free survival was also lower in the severe PGD group, though only in the bilateral transplant group (17).

An association between PGD and BOS has been hypothesized, but until recently, the studies had yielded conflicting results (18–22). A recent study by Daud et al. provided the most convincing data to date, supporting an association between PGD and increased risk of BOS. In a retrospective cohort of 337 lung transplants, the risk of developing BOS stage 1 was directly related to worsening PGD grade immediately after transplant, independent of acute rejection, lymphocytic bronchiolitis, and community-acquired respiratory infections (8). The reasons for this association are unclear, but some have hypothesized that the injured organ is more immunogenic, called the "injury response hypothesis" (23).

III. Risk Factors for PGD

Because of the impact of PGD on lung transplantation, many investigators have attempted to identify clinical factors for developing PGD after lung transplantation to better identify those patients most at risk. However, as recently reviewed (9,24), these studies are often hindered by small number of patients at single centers, often accumulated over many treatment eras. Factors that have been identified can be generally categorized as donor, recipient, and operative variables (Table 2).

Table 2 Possible PGD Risk Factors

Category	Risk factor for PGD
Donor variables (inherent):	**Age > 45**
	Age < 21
	African-American race
	Female gender
	History of smoking > 10 pack yr
Donor variables (acquired):	Prolonged mechanical ventilation
	Aspiration
	Trauma
	Hemodynamic instability post brain death
Recipient variables:	**Diagnosis of idiopathic pulmonary arterial hypertension**
	Elevated pulmonary arterial pressure at time of surgery
	Diagnosis of diffuse parenchymal lung disease
Operative variables:	Preservation solution and flush technique
	Prolonged ischemic time
	Use of cardiopulmonary bypass
	Blood product transfusion

Bold indicates risk factors most consistently reported in the literature.
Source: Adapted from Ref. 25.

A. Donor Variables

Similar to findings in other solid organ transplant procedures, increased donor age has been associated with increased risk of PGD, particularly in donors greater than 32 to 45 years of age (3,10,26). Younger donor age, donor race, and donor gender have also been identified as potential risk factors for PGD, though these findings have not been validated and mechanisms for such associations remain speculative (3). A positive donor smoking history has also been identified as a possible risk factor for PGD, though not consistently (24,27).

Prolonged mechanical ventilation, aspiration pneumonitis/pneumonia, trauma, and hemodynamic instability following brain death are donor-acquired risk factors that potentially can contribute to the development of PGD (24). Despite possible pathogenic links, studies have not definitively linked such factors to the development PGD. Classic teaching is that donor and operative factors are associated with earlier onset PGD, and recipient characteristics are more important in PGD presenting at later time points. However, in a recent multicenter prospective cohort study examining the risk factors for PGD development at 24 and 72 hours, there were no donor-related risk factors that were independently associated with grade 3 PGD after multivariable analysis (28).

B. Recipient Variables

Several studies have examined recipient-related risk factors for poorer outcomes after lung transplantation (9). However, there still remains no conclusive evidence that recipient age, gender, race, body weight, underlying hepatic or renal impairment, left heart disease, diabetes, and medication use prior to surgery (steroids, inotropes) are directly associated with an increased risk of PGD development (9).

In contrast, there is consistent evidence that elevated pulmonary artery pressures in the lung transplant recipient are associated with increased risk of PGD. Whitson et al. showed that elevated pulmonary artery pressure increased the risk of grade 3 PGD within 48 hours post transplant (10). Other studies have described an association between a recipient diagnosis of pulmonary arterial hypertension (PAH) and PGD (3,15,29). The reason for this association is unclear but may be related to mechanical endothelial shear stress during reperfusion, or alternately, due to shared pathophysiology of PAH and ischemia-reperfusion injury (IRI) (30,31).

Other recipient disease associations with PGD are less consistent. Patients with COPD may have the lowest risk of PGD (3,13,32). Patients with an underlying diffuse parenchymal lung disease may have an increased risk of PGD (9,28).

C. Operative Variables

The type of transplant procedure (single vs. bilateral) has not been shown to be an independent risk factor for PGD development. Confounding by the use of cardiopulmonary bypass (CPB) in bilateral transplant procedures and a higher percentage of PAH patients requiring bilateral transplants does not allow for firm conclusions about bilateral lung transplant and PGD. Independent of indication for CPB use, the association between PGD and CPB is unclear; preoperative PAH is more common in patient groups requiring CPB who then develop PGD, thus confounding the association between CPB and PGD (33). Investigators have demonstrated that in lung transplant recipients without an underlying diagnosis of PAH, the need for CPB during surgery indeed predicted worse early outcomes and death (32). In contrast, others have suggested that CPB use was not

an independent risk factor for PGD and that patients had similar early outcomes when CPB use was not dictated by pulmonary hypertension or other factors (3,34).

Another operative risk factor of interest is blood product transfusion. It has been demonstrated previously that bilateral lung transplant procedures, use of CPB, and recipients with a diagnosis of Eisenmenger syndrome or cystic fibrosis (CF) had a significant demand for more blood products in the first 24 hours after transplant surgery (35). While this study did not directly assess PGD, it raises the issue of transfusion-related lung injury (TRALI) in the setting of lung transplantation and how this may relate to PGD incidence. TRALI can clearly result in an ARDS-like picture similar to PGD (36). Recent multicenter studies have shown an independent association between blood product administration and increased risk for PGD, but the exact relationship between the two processes is not yet clear (28,30). Furthermore, the need for transfusion may be collinear with other PGD risk factors, including PAH and use of CPB; therefore, dissecting the independence of the relationship with PGD is difficult in human studies.

IV. Pathogenesis of PGD

PGD is multifactorial in pathogenesis, implicating all facets of the lung transplant procedure—from pathophysiology related to brain death to organ preservation and reperfusion (Fig. 2). Central to this process is IRI with subsequent generation of reactive oxygen species (ROS) (37). During cold ischemia, anoxia results in ATP depletion and hypoxanthine production, generating the ROS superoxide during reperfusion of the transplanted organ. Additionally, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase on endothelial cells and neutrophils generate ROS during reperfusion (37). These ROS cause direct injury to pulmonary endothelium and epithelium, resulting in the alveolar infiltrates seen clinically in PGD.

A complex proinflammatory cascade resulting from the influx of donor-derived macrophages during lung reperfusion also causes upregulation of chemokines and cytokines, instrumental in recruiting, localizing, and activating recipient T cells and neutrophils. This further perpetuates the injury pattern of PGD (37). The classic complement system is also activated immediately post-transplant, causing increased smooth muscle contraction, increased vascular permeability, and release of cytotoxic granules from various immune cells (38).

This complex series of both immunologic and nonimmunologic events continues to be elucidated. To a degree, the injury pattern can be self-perpetuated. For instance, cellular injury causes platelet activating factor to be released, further activating leukocytes to release cytokines and express cell adhesion molecules and causing platelet aggregation and microvascular thrombi (30,39–41).

In addition, preexisting humoral immunity has been implicated in PGD pathogenesis (42). Recent work has further expanded the understanding of the pathophysiology of PGD to include specific autoimmunity to a newly identified and normally sequestered lung antigen, collagen type V. Using a rodent model, Yoshida et al. showed that IRI unmasks antigenic collagen V (43). This group also recently showed that pretransplant collagen V-specific cellular immunity impacts PGD. In 55 patients awaiting lung transplant, delayed-type hypersensitivity to collagen V was assessed, and P:F ratios were significantly decreased up to 72 hours after transplant in collagen V-reactive versus nonreactive patients (44). Long-term collagen V-specific immune responses have also been linked to the incidence and severity of BOS (45). Similarly implicating long-term

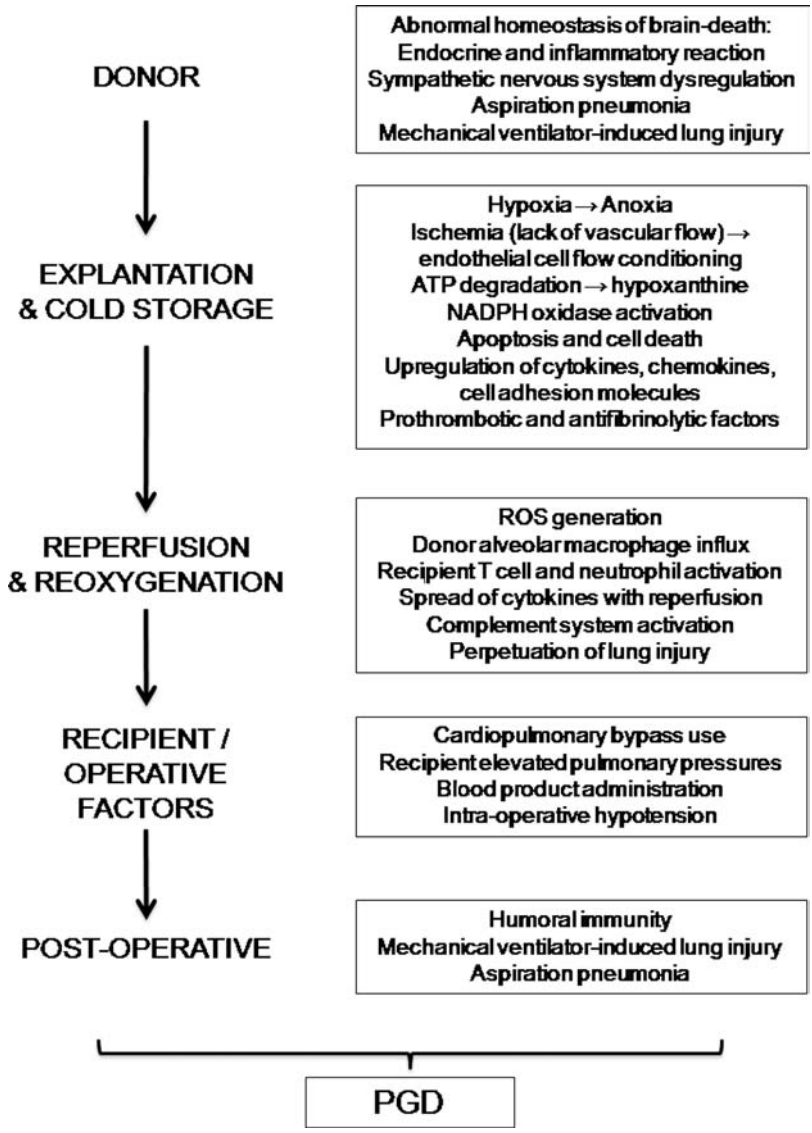

Figure 2 Conceptualization of pathophysiology of PGD. *Abbreviations*: ATP, adenosine triphosphate; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species.

alloimmunity, Bharat et al. also recently showed that five years after transplant, patients with a history of PGD had increased de novo anti-HLA type II alloantibodies (46). The authors hypothesize that through induction of a proinflammatory state post-transplant and increasing donor HLA-II expression, clinically severe PGD promotes the development of donor-specific alloimmunity, therefore mechanistically linking PGD and BOS (46).

V. Prevention and Treatment of PGD

A. Prevention (Table 3)

The majority of the work on preventing PGD has focused on improving lung preservation techniques to prevent significant IRI. Such efforts involve manipulating the volume, temperature, pressure, and components of preservation solutions, and altering inflation and ventilation parameters of the organs during transport (24). Unfortunately, protocols for lung preservation after harvesting are not universally standard, making comparisons difficult (24). There have been only a few randomized, controlled trials examining the prevention of PGD during lung transplantation, highlighted below.

Table 3 Summary of Notable Studies Aimed at PGD Prevention

Author	Design	Intervention	Effect
Meade et al. (47)	RCT: 84 patients	Inhaled NO (iNO): 20 ppm iNO within 10 min of reperfusion	No difference in PGD incidence, time to extubation, ICU LOS, or hospital LOS
Botha et al. (48)	RCT: 20 patients	Inhaled NO: 20 ppm iNO at the onset of ventilation	No difference in PGD incidence, gas exchange, neutrophil sequestration, or BAL inflammatory cytokines
Zamora et al. (49)	Multicenter RCT: 59 patients	Soluble complement receptor-1 inhibitor (sCR1)	50% vs. 19% extubated within 24 hrs in treatment group; duration of MV and length of ICU stay trended lower; no effect on P:F, operative deaths, incidence of infection or rejection, or hospital LOS
Wittwer et al. (50)	RCT: 24 patients	Platelet activating factor antagonist BN52021	Improved oxygenation scores and CXR findings in first 12 hrs
Oto et al. (51)	Observational study: 157 consecutive transplants	Perfadex vs. Euro-collins vs. Papworth preservation solutions	Perfadex trended toward superiority in oxygenation, ICU stay, and 30-day mortality; lower incidence of PGD grades 2 and 3 at 48 hrs in Perfadex group
Schnickel et al. (52)	Observational study: 100 consecutive transplants	Modified reperfusion technique	Incidence of severe PGD was 2%, median time on ventilator 2 days, 30-day survival 97%

Abbreviations: BAL, bronchoalveolar lavage; CXR, chest X ray; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; ppm, parts per million; RCT, randomized controlled trial.
Source: Adapted from Ref. 25.

Given the effects of inhaled nitric oxide (NO) on pulmonary vasodilation, NO has been investigated as a potential agent for the prevention of PGD. NO also affects capillary integrity and prevents leukocyte adhesion and platelet aggregation (53). In a prospective, randomized, blinded clinical trial, Meade et al. prophylactically administered NO to 84 transplant patients in efforts to affect the incidence of PGD (47). There was no difference in PGD incidence when NO was started 10 minutes after reperfusion. A similar trial was conducted more recently by Botha et al., also showing no benefit of NO administered at the onset of reperfusion on PGD grade 3 incidence, gas exchange, neutrophil sequestration, or bronchoalveolar lavage (BAL) concentration of proinflammatory cytokines (48). Other agents investigated in randomized, placebo controlled trials for PGD prevention are summarized in Table 3. While showing some modest improvements in early clinical parameters, these small trials illustrate the multifactorial nature of PGD pathogenesis as well as the difficulty of finding specific targets that have a significant impact on PGD incidence and/or mortality.

While there have been no large, multicentered randomized trials addressing PGD prevention, investigations continue to be conducted with the aim of impacting PGD incidence through refinements of parameters the transplant team can control. In an observational study, Oto et al. compared the three most commonly used organ preservation solutions (Perfadex®, Euro-Collins, and Papworth) used during transportation of the explanted organ(s) in 157 consecutive lung transplants. PGD grade, early oxygenation levels, ICU stay, and 30-day mortality were not significantly different between the three solutions, though Perfadex use trended toward superiority when compared to the other preservation solutions (51). Reperfusion techniques have also been examined as potentially being able to impact PGD (9). Schnickel et al. published their examination of 100 consecutive transplant procedures employing a modified reperfusion technique, involving reperfusion with recipient blood depleted of leukocytes, supplemented with nitroglycerin, adjusted for pH and calcium level, and enriched with glutamate and dextrose. The authors found that the incidence of severe PGD (P:F < 150 with chest X ray infiltrate) was only 2%, and the 30-day survival rate was 97% (52).

The advent of ex vivo conditioning of the lung opens new doors to examining the pathophysiology of PGD as well as developing new treatments (54,55). Although these experiments are in their early stages, there is great potential for diagnostic testing of the organ and delivering targeted pretreatments as needed (56,57). Furthermore, the longer ischemic times afforded by ex vivo conditioning may eventually lead to more selective matching of donors and recipients.

B. Treatment

Treatment of established PGD remains supportive. General treatment strategies are similar to those for patients with ARDS, employing low-stretch ventilation to prevent ventilator-induced lung injury and avoiding excess fluid administration to minimize edema from capillary leak caused by IRI (53). There are no clinical studies systematically evaluating the strategies that have been applied from the ARDS literature to PGD. Postoperative care of lung transplant patients with PGD is therefore still largely individualized by center.

While inhaled NO does not have an established role in prophylaxis against PGD development, it may be beneficial in clinical settings of established PGD. There are several reports and case series that show improved outcomes with NO administration in settings of severe PGD and refractory hypoxia post-transplant (58–60). However, there

are contradictory studies showing no efficacy for inhaled NO in the setting of established PGD (61). Currently, the lack of randomized clinical trials showing survival benefit precludes the widespread recommendation for the use of NO in the treatment of PGD, though its use may be justified in selected cases of severe hypoxemia and/or elevated pulmonary artery pressures. Extrapolating from the use of inhaled NO in studies with ARDS patients, the beneficial effects of NO are primarily on short-term improvements in oxygenation that also appear transient (53).

Extracorporeal membrane oxygenation (ECMO) has been studied in the setting of refractory hypoxia in lung transplant settings, particularly when PGD is seen in combination with hemodynamic instability (13,62,63). Several centers have reported their experience with ECMO institution post-lung transplant, leading to ECMO being regarded as a potentially lifesaving salvage treatment option if instituted early in the course of severe PGD and no later than seven days after transplant (53). However, the identification of the proper patient for this early therapy is difficult. Studies are ongoing examining the optimal use of ECMO (cannulation site, duration, timing of initiation) to improve outcomes and minimize complications.

VI. Conclusions

PGD is the greatest contributor to early mortality after lung transplant and a major risk factor for long-term mortality and BOS. If improvements in both short- and long-term outcomes are to be made, further research into the pathophysiologic mechanisms of PGD is needed. Better understanding of mechanism and pathophysiology will lead to new therapies that may be either applied broadly or to targeted populations. Furthermore, large clinical and laboratory studies using molecular profiling are currently underway at several centers that should yield important insights into PGD pathogenesis and test the ability to predict PGD. Furthermore, the definition of PGD will likely be further refined by this and other work to provide the most accurate outcome measures in clinical research and ensure standardization and applicability of these findings.

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27
Managing Surgical Complications

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I. Introduction

Complications following lung transplantation can occur immediately after surgery or days or weeks later. Clinical suspicion and close follow-up of these patients are the strategies to reduce the morbidity and mortality in those who survive the procedure.

Following the first successful lung transplantation in 1983, the procedure has been the final option for patients for end-stage pulmonary disease failing medical treatment. Improved donor and recipient selection, technical advances, superior immunosuppression strategies, and newer antibiotic regimens have improved the results dramatically. The International Society for Heart and Lung Transplantation (ISHLT) reports that a total of 19,792 lung transplants were performed between January 1995 and June 2007 and the rate of death because of technical complications within the first 30 days following transplantation was 8.3% (1).

The main complications following lung transplantation can be divided into three major groups: (*i*) surgical, (*ii*) immunological, (*iii*) and side effects of immunosuppressive drugs. The main focus of this review is to overview the surgical complications and their management following lung transplant surgery (Table 1).

II. Vascular Anastomotic Complications

Vascular complications following lung transplantation occur as a result of inadequate anastomotic technique. They are relatively uncommon but are associated with a high morbidity and mortality if not corrected immediately (2–11). Anastomotic leaks from the anastomosis are usually corrected during the operation. Pulmonary venous complications usually present in the early postoperative period with unilateral pulmonary edema and respiratory failure. This can be due to anastomotic stenosis and/or thrombosis. External compression of the anastomosis by a clot or pericardial fat or an omentum flap used for coverage of the bronchial anastomosis can also impair venous outflow. In a prospective study, the incidence of pulmonary vein complications in lung transplant recipients studied by transesophageal echocardiography (TEE) within 30 days of operation were 29%. In another prospective study, the incidence of pulmonary venous thrombosis studied with TEE within 48 hours following lung transplantation was 15% (13 of 87 recipients). The mortality among those with a venous complication was 67% compared with 7% with normal pulmonary veins. The other case series also reported a mortality rate between 38% and 100% (8).

Late pulmonary venous abnormalities occurred as a stenosis and thrombosis presenting as pulmonary edema and pleural effusion at 1.9 and 2.3 years after transplantation has been reported. Thus, pulmonary venous occlusion may present early or

Table 1 Surgical Complications After Lung Transplantation

Technical complications
Vascular anastomotic complications
Anastomotic leaks
Pulmonary artery stenosis, kinking
Impaired venous flow due to a narrow atrial anastomosis
Airway complications
Early
Late
Fistula
Stenosis
Formation of granulation tissue
Bronchomalacia
Hemorrhage
Coagulopathy due to use of CPB
Pleural space complications
Hemothorax
Acute hemorrhage requiring early intervention (<12 hr)
Delayed (>24 hr)
Pneumothorax
Pleural effusions
Empyema
Chylothorax
Reperfusion Injury (PGD)
Complications due to approach (Incisions)
Seroma
Lung hernia
Sternal dehiscense (after clamshell incision)
Others
Inguinal lymphocoele (due to cannulation at CPB)
Nerve damage (phrenic nerve)
Oversized lung graft

Abbreviations: CPB, cardiopulmonary bypass; PGD, primary graft dysfunction.

late in the postoperative period (7).TEE is the recommended tool for detecting pulmonary venous anastomotic problems (5–9).

The optimal treatment of pulmonary venous thrombosis after lung transplant remains unclear. Symptomatic pulmonary venous occlusion is associated with a high early postoperative mortality (9–11). Thus, anticoagulation seems warranted for documented thrombi. However, treatment with systemic anticoagulation may lead to perioperative intrathoracic bleeding. Systemic fibrinolytic therapy has also been successfully used to treat a symptomatic occlusive pulmonary venous thrombus (9–11). Surgical revision, preferably using cardiopulmonary bypass, has been recommended to remove the thrombi or to correct the stenosis. However, perioperative mortality is high after revision. Spontaneous resolution of the thrombosis detected by TEE has been observed without specific intervention (9). These clots were associated with only mildly increased venous flow velocity, suggesting that preserved venous flow may increase the likelihood of spontaneous dissolution. Thus, venous occlusion after lung transplantation appears to be often clinically silent yet associated with an increased mortality (5–11).

Persistent pulmonary hypertension and unexplained hypoxemia can occur as a result of stenosis at the pulmonary artery anastomosis. This problem may be detected by a nuclear perfusion scan, which will demonstrate the unsatisfactory flow to a single-lung graft or unequal distribution of flow in a bilateral-lung transplant recipient. TEE is also valuable to detect the stenosis especially on the right side. Pulmonary angiography can be used as a confirmatory test that also help to show the anatomic details. Treatment options include noninvasive approaches like balloon dilatation, stent implantation, and open surgical revision (3,11).

III. Airway Complications

Pulmonary transplantation is unique among all solid organ transplantations, since systemic arterial blood supply is generally not restored during engraftment. For this reason, anastomotic complications have primarily been attributed to ischemia of the donor bronchus (12). Additionally rejection (13), intense immunosuppressive therapy (14), invasive infections (15), or inadequate organ preservation (12) were factors identified as being associated with compromised airway healing. Furthermore, severe reperfusion edema and early rejection episodes have been shown as independent predictors of bronchial complications (16). Recently, refinements in lung preservation and surgical technique, improvements in patient selection, postoperative care, and immunosuppression have reduced the prevalence of airway complications (17). Reflecting these changes, the contemporary rate of anastomotic lesions following lung transplantation has dropped from 80% before 1983 (18) to 2.6–23.8% (16,19). Bronchial ischemia is reported to be a significant risk factor for the development of airway complications (20). The viability of the donor bronchus is initially dependent on retrograde low-pressure collaterals derived from the pulmonary artery as bronchial arterial circulation is lost during the harvest of the donor lungs (13). Several techniques have been proposed to protect the bronchial anastomosis, keeping the donor bronchus as short as possible and wrapping the anastomosis with vascularized pedicles (12), direct revascularization of donor bronchial arteries (21), and double antegrade and retrograde flush perfusion of the donor lungs at the time of harvest (22). On the basis of the favorable results from animal studies, routine use of bronchial anastomotic omentopexy (omentum wrapping) in the early days of lung transplantation was thought to be a key strategy to overcome bronchial healing problems by enhancing the microcirculation of the donor bronchus (17). This technique, although widely used then, has been shown to be no longer essential (23). We, like other transplant centers, also used omentopexy initially, but then abandoned this method. Another strategy aimed at avoiding perioperative steroids, as they were believed to negatively influence the healing process. However, prevention of rejection and potential amelioration of reperfusion injury are useful effects of steroids (24). During acute rejection episodes, microcirculation may be significantly impaired due to increase in pulmonary vascular resistance and decrease in pulmonary collateral blood supply (25).

Recently, severe reperfusion injury and early rejection episodes have been demonstrated to be independent predictors of bronchial complications (16). We and other investigators have demonstrated that the number of acute rejection episodes was not related to the occurrence of bronchial complications (17,20,26).

A strong correlation between the intrabronchial presence of *Aspergillus* and the incidence of airway complications has been reported (27). When bronchial necrosis was

described at the first postoperative bronchoscopy together with *Aspergillus* infection, the incidence of later airway complications was higher than if there was necrosis alone. In our transplant program we start with antifungal therapy early postoperatively using nebulized amphotericin B (2 × 10 mg/day) and per oral itraconazole (2 × 200 mg/day). Our findings support this approach as nearly 85% of the patients did not have fungal membranes at their 6th bronchoscopy. In addition, the rate of severe fungal membranes decreased from 15% to 0.5% (28).

We firmly believe that the surgical technique is paramount for the future successful healing of the bronchial anastomosis. The surgical approach for performing the anastomosis may vary among transplant centers. Telescoping, end-to-end anastomosis with a running suture for the membranous part and interrupted sutures for the cartilaginous part, and end-to-end anastomosis with a single running suture are most often used (17,20,26,27). Some centers have reported changing their anastomotic technique from telescoping to end-to-end single suture, due to a high airway complication rate (27,29). Others have employed telescoping or a modified telescoping technique from the beginning of their program with a low complication rate (20,29). In fact, in most of the studies telescoping has been demonstrated to be an independent risk factor for airway complication (17,19,29). We have not modified our technique since our program was established in 1992. Furthermore, we think that resection of the donor bronchus down to the lobar carina in an oblique plane (Fig. 1), in conjunction with keeping the peribronchial tissue intact, is a critical step while performing the bronchial anastomosis.

In 441 anastomoses performed in our institution, no significant dehiscence was observed (28). In one patient, a small fistula was detected and closed surgically on postoperative day 5. In only 4.9% (10/206) of recipients luminal narrowing was found at the first surveillance bronchoscopy in a consecutive series of 391 bronchial anastomoses

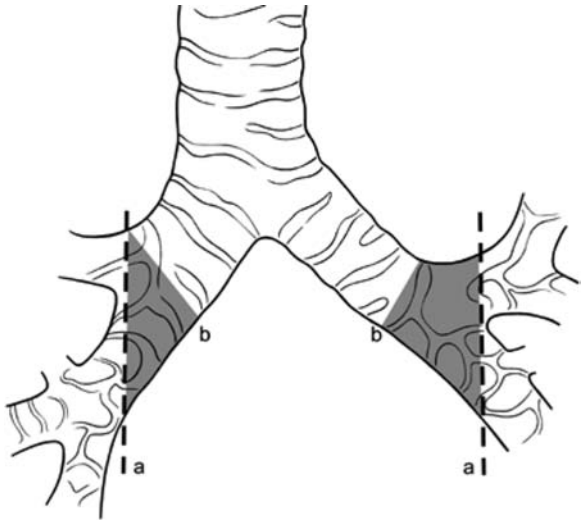

Figure 1 Cut points on the donor bronchus. (**a**) The donor bronchus should be cut back as close to the upper lobe bronchus origin as possible in an oblique plane with special attention to keep peribronchial tissues undisturbed (**b**) if donor bronchus cut at this level there will be a risk zone for bronchial ischemia (*gray zone*).

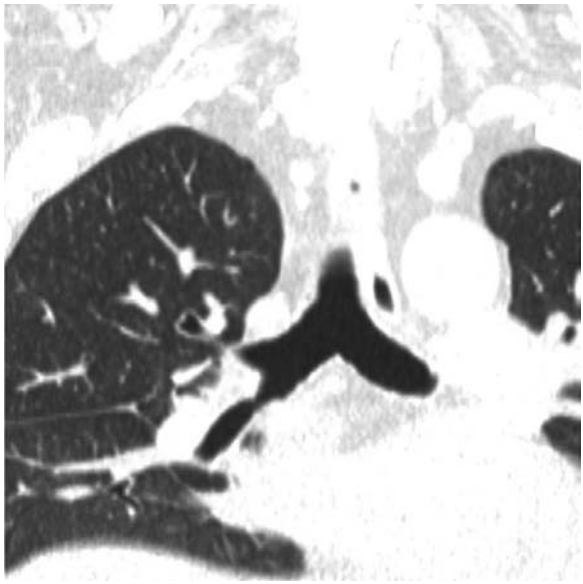

Figure 2 Bronchial stenosis four months after transplant.

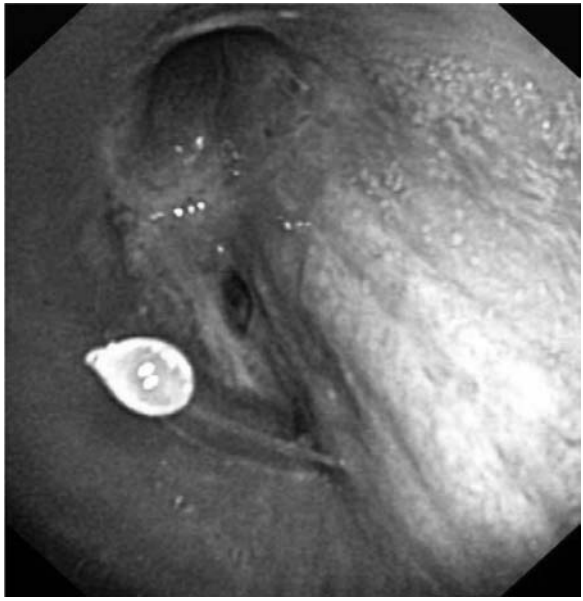

Figure 3 Bronchoscopic view of the patient in Fig. 2 with stenosis of intermediate bronchus.

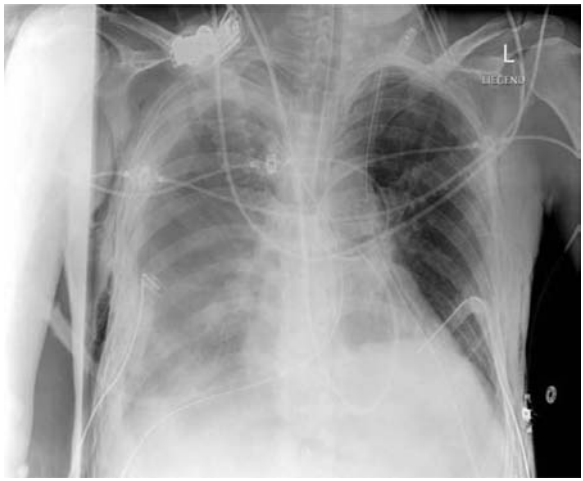

Figure 4 Postoperative hemorrhage (postoperative 6 hours).

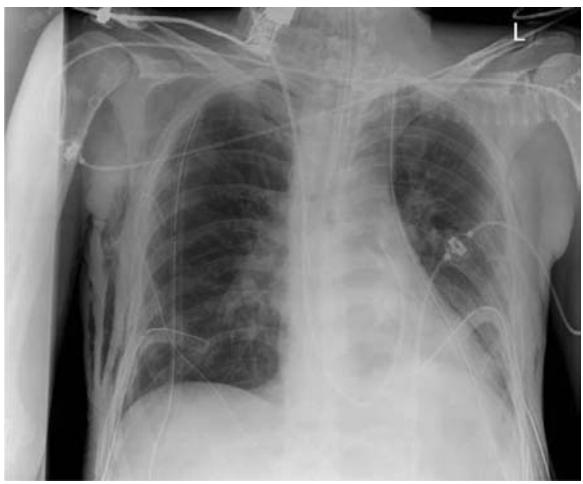

Figure 5 The same patient in Fig. 4 after revision.

(4.6%, 18/391). This rate decreased to 2.3% (9/391) at the sixth bronchoscopy. None of these patients required any intervention, and there was no death related to bronchial anastomotic complications (28).

In our opinion, bronchial anastomotic complications can be avoided by use of a standardized surgical technique that respects the fact that the donor bronchus is poorly vascularized. Prevention of fungal infections with aggressive antifungal treatment may play an important additive role (Figs. 2,3).

IV. Pleural Space Complications

Pleural space complications are common in the early postoperative period after lung transplantation. *Postoperative hemorrhage* requiring reoperation was about 25% in the early experience of some centers that involved heart-lung and en bloc double-lung transplants. The underlying pulmonary disease usually leads to dense pleural adhesions, which can cause hemorrhage during recipient pneumonectomy (Figs. 4,5). Usage of cardiopulmonary bypass in some transplant cases can also increase bleeding because of anticoagulation. However, application of aprotinin has been reported to decrease intraoperative and postoperative bleeding in those who necessitate cardiopulmonary bypass (30,31).

Pneumothorax associated with pneumomediastinum or subcutaneous emphysema may be a sign of bronchial dehiscence. Indeed, when this is present, it is readily treated by chest tube drainage. Size mismatch can also cause pleural space problems. Figs. 6 and 7 show late occurrence of pneumothorax following lung transplantation.

Pleural effusions are extremely common in the early postoperative period after lung transplantation (32–37). It occurs in all transplant recipients, and like pleural fluid following other cardiothoracic surgery is bloody, exudative, and neutrophil predominant. Recently 35% incidence of pleural space problems in living lobar lung transplantation has been reported (34). The most common problem was air

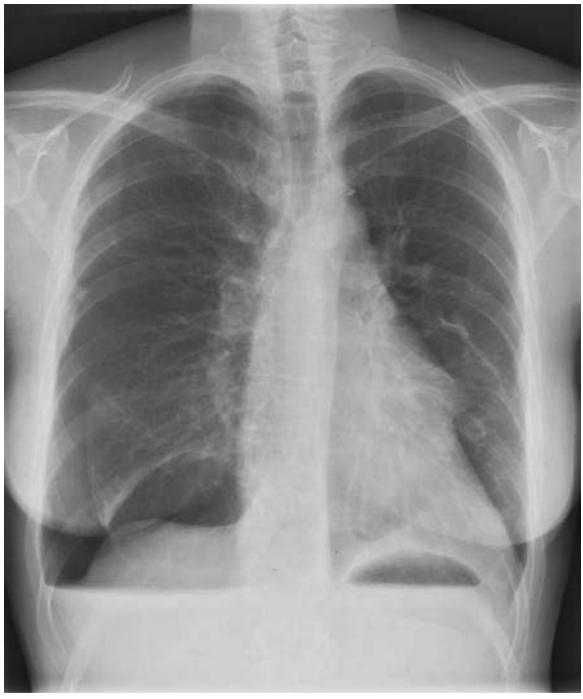

Figure 6 Pneumothorax after four weeks post transplant.

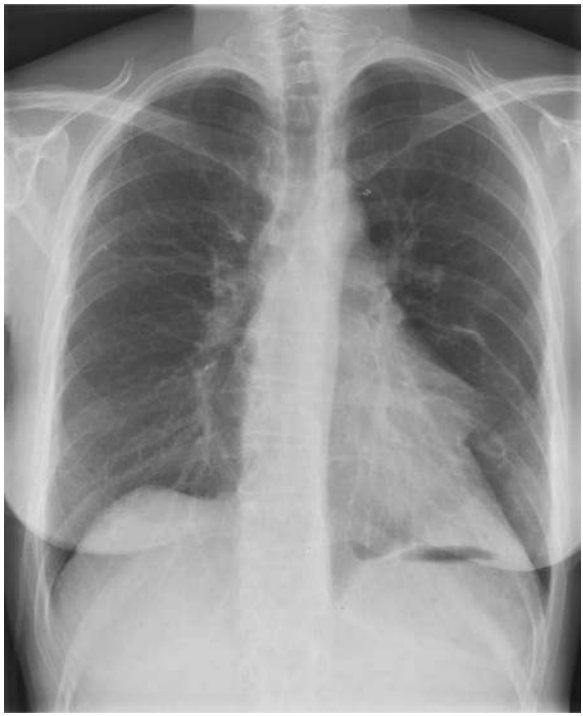

Figure 7 Chest X ray of the same patient in Fig. 6 after chest tube drainage.

leak/bronchopleural fistula, followed by loculated pleural effusion. Empyema was uncommon (2 patients). In four of these patients, computed tomography-guided drainage was used for loculated effusions after chest tube removal. Three patients underwent surgery for persistent air leak and required muscle flap repair. One of these required subsequent omental transfer. Two patients required decortication for empyema (34) (Figs. 8,9).

In another series the incidence of pleural space complications was 22%. Pneumothorax was the most frequent complication, affecting 14 of 30 patients (35). All pneumothoraces resolved spontaneously or with chest tube thoracostomy. One patient required placement of a Clagett window after open lung biopsy and another required thoracotomy and pleural abrasion after transbronchial biopsy.

Empyema affected 7 of 30 patients and occurred exclusively in the double-lung transplant group (38). Sepsis developed in three of the patients with this complication and they subsequently died. A significant proportion of lung transplant recipients will have pleural space complications. The vast majority of these will resolve spontaneously or with conservative procedures. These complications were not related to preoperative diagnosis nor associated with a significant prolongation of hospital stay. Empyema is the only pleural space complication associated with increased patient mortality and, as such, is an important clinical marker for those at risk for sepsis and death.

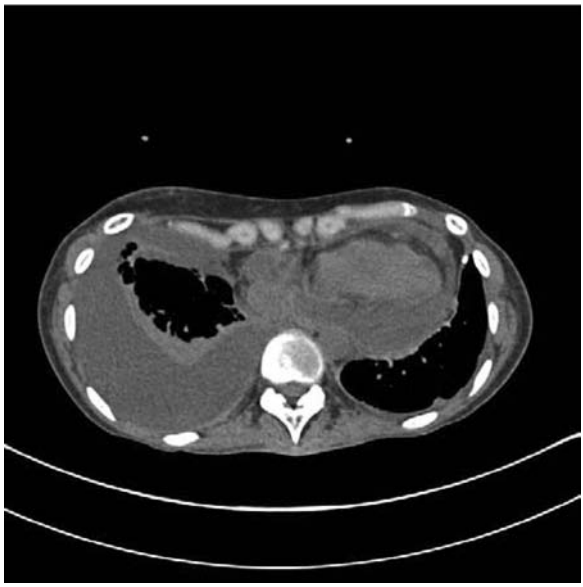

Figure 8 Computed tomogram of a transplanted patient with right pleural effusion.

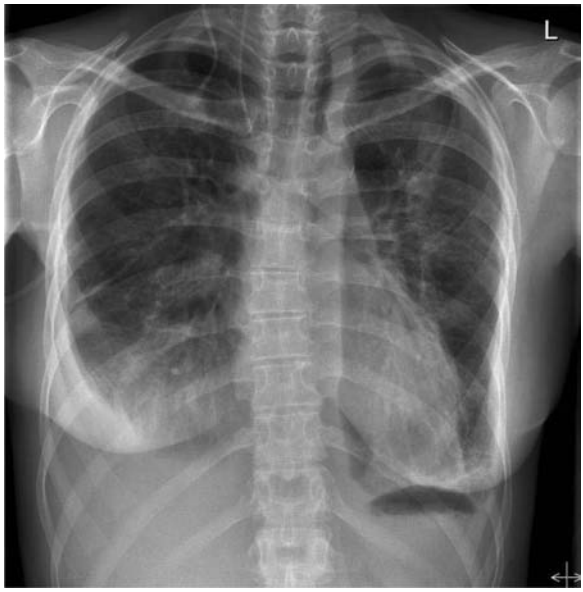

Figure 9 Chest X ray of a patient with right pleural effusion.

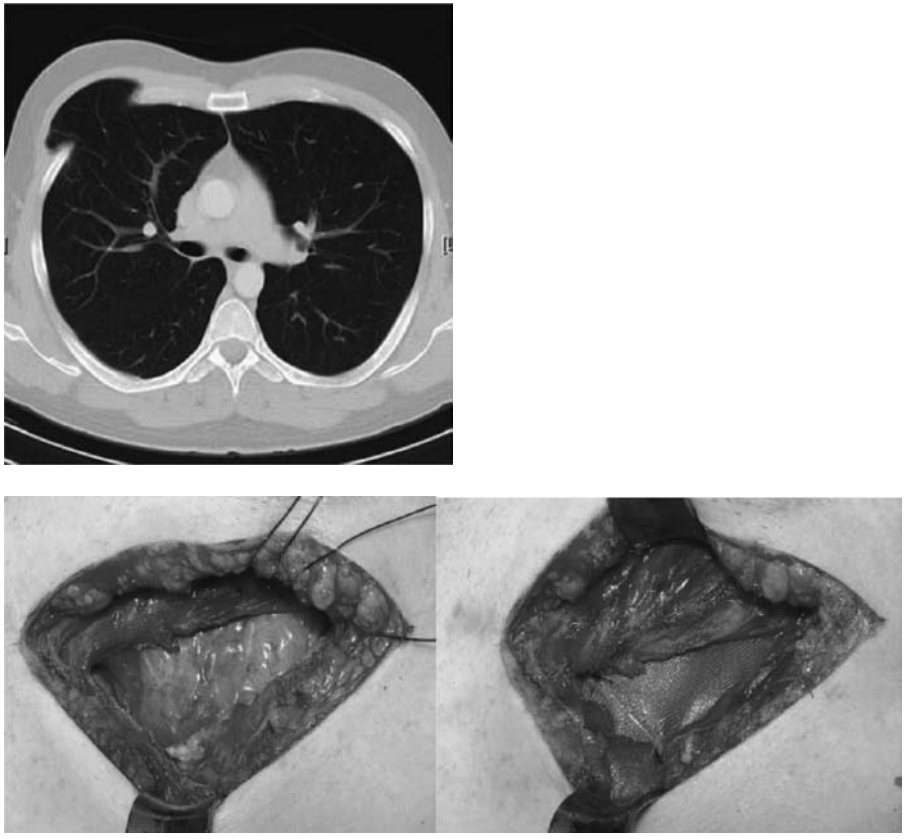

Figure 10 Lung herniation after lung transplant. *Source*: From Ref. 44.

Chylothorax has rarely been reported after lung transplantation. It is most often reported after transplantation for lymphangioleiomyomatosis. Dietary modifications, octreotide infusion, thoracic duct ligation and embolization, surgical pleurodesis, aminocaproic acid, instillation of povidone and pleurovenous shunt are the treatment options for this particular complication (39–43). *Lung herniation* that is defined as a protrusion of the lung parenchyma through a defect of the chest wall is uncommon. Chest pain is the most common symptom. Hernias with persistent pain and entrapped lung usually need reconstruction with a patch to avoid late complications such as recurrent pulmonary infections and hemoptysis because of strangulation (Fig. 10) (44).

V. Phrenic Nerve Damage

Damage to the phrenic nerve, unilaterally or bilaterally, is a well-documented complication of cardiac operations, but less commonly reported after lung transplantation. The incidence of phrenic nerve injury has been reported to be between 3.2% and 29.6% (45–47). Clinically detectable diaphragmatic paralysis is an infrequent

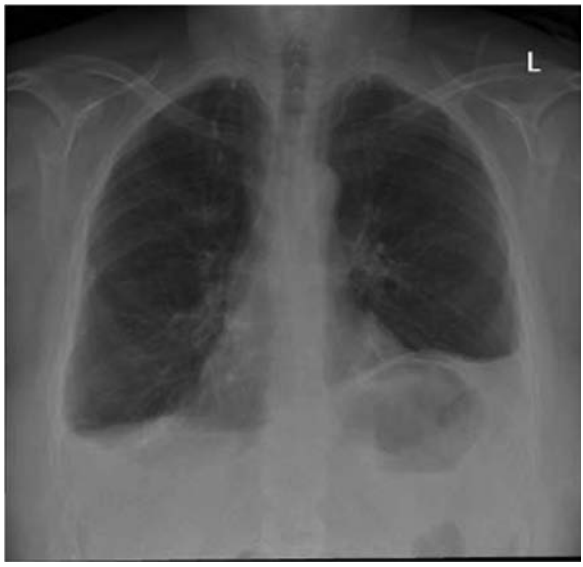

Figure 11 Left phrenic nerve damage following bilateral lung transplantation.

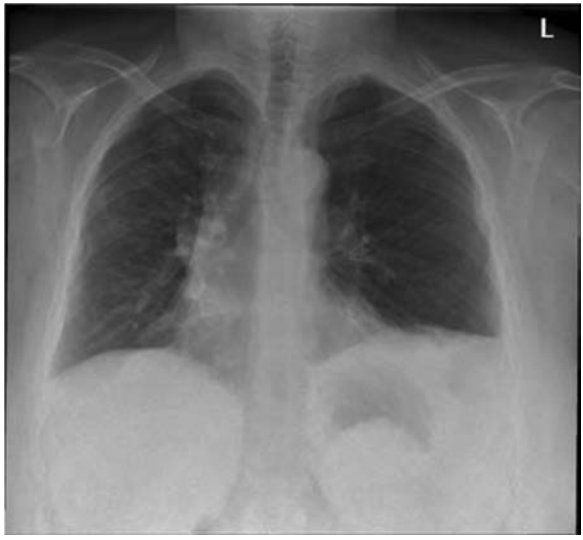

Figure 12 The same patient in Fig. 11 one year after right retransplantation.

complication of lung transplantation and is associated with longer intensive care unit stay and hospitalization, but is not associated with significant adverse outcomes (Figs. 11,12). Phrenic nerve damage is most likely related to difficulty in detecting the nerve caused by adhesions, injury due to dissection, thermal injury by electrocautery, or local

topical hypothermia using ice-slush. Therefore, it is important to take care to avoid injuring the nerve during the operation.

VI. Primary Graft Dysfunction

Primary graft dysfunction (PGD) is a form of acute lung injury that follows the sequence of events inherent in the lung transplantation process, beginning with the brain death of the donor, pulmonary ischemia, preservation of donor tissue, transplantation, and reperfusion of donor tissue in the recipient (48). Early graft dysfunction, ischemia–reperfusion injury, reimplantation response, reimplantation edema, reperfusion edema, noncardiogenic pulmonary edema are some of the synonyms used. PGD typically occurs within 72 hours after lung transplant and is characterized by poor oxygenation, low pulmonary compliance, interstitial/alveolar edema, increased pulmonary vascular resistance, pulmonary infiltrates on chest X ray, and acute alveolar injury, as revealed by diffuse alveolar damage on pathology (49) (Figs. 13 and 14). PGD affects about 10% to 25% of lung transplants and is the leading cause of early post-transplantation morbidity and mortality (49–57). Thirty-day mortality rates are up to eightfold higher in patients with severe PGD as compared with those without PGD.

Pathogenesis for PGD is complex. Reactive oxygen species (ROS) generation during the ischemia/reperfusion process is an important initiative for PGD (48). In addition to direct injury from ROS on pulmonary endothelium and epithelium, inflammatory cascades are initiated, adhesion molecules are upregulated, and procoagulant factors are increased that contribute to lung injury (58–60). The donor-acquired risk factors (61), including prolonged mechanical ventilation, aspiration pneumonitis/pneumonia, trauma, and hemodynamic instability after brain death have not been shown to contribute to the development of PGD, although such risk factors have theoretical bases for an association with PGD. Recipient factors such as age, sex, race, body weight, underlying hepatic or renal impairment, left heart disease, diabetes, or medication use

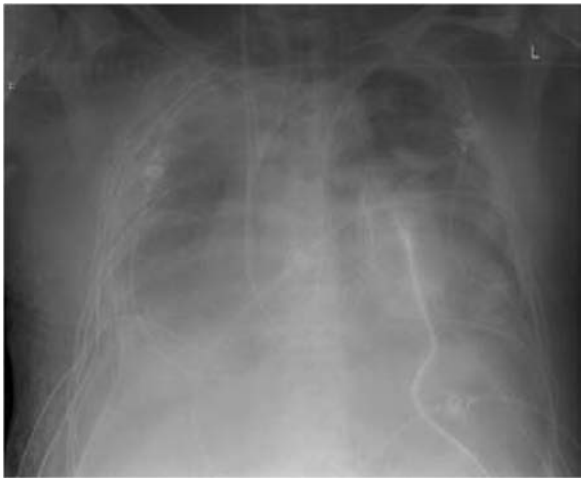

Figure 13 Grade 3 PGD 24 hours after bilateral lung transplant.

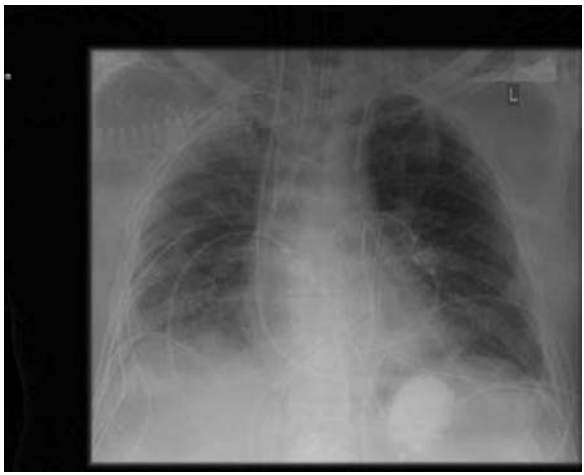

Figure 14 The same patient 48 hours after ECMO.

before surgery (steroids, inotropes) are not directly associated with an increased risk of PGD development (62). Also, a history of prior thoracic surgery or pre-transplant mechanical ventilation has not been shown to directly be associated with PGD. The association between PGD and cardiopulmonary bypass (CPB) is also controversial: in lung transplant recipients without a diagnosis of pulmonary arterial hypertension, the need for CPB predicted worse early outcomes and early death (63), while others have shown that the use of CPB was not an independent risk factor for PGD and that patients had similar early outcomes when CPB was not dictated by pulmonary hypertension or other factors (52,64). Treatment of PGD is mainly supportive. Treatment strategies are low-stretch ventilation for the prevention of barotrauma and avoidance of excessive fluid administration (negative fluid balance) (65), pulmonary vasodilatation (prostaglandin, inhaled NO) (66–68), extracorporeal membrane oxygenation (ECMO) (69–71), surfactant replacement (72,73), and urgent retransplantation. Other experimental therapeutic strategies such as *N*-acetylcysteine administration (74,75), p38, and c-jun kinase inhibitors (76) are promising.

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28
ECMO in Lung Transplantation

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I. Introduction

Extracorporeal membrane oxygenation (ECMO) is a necessary component of a lung transplant program to provide physiologic support for patients that suffer severe primary graft dysfunction (PGD). However, the role of ECMO in the support of lung transplantation has evolved substantially in many programs beyond the traditional, physiologic lung replacement and support for patients with severe PGD. It is now also applied as lung support or replacement for potential lung transplant recipients in a bridge-to-transplant paradigm when failing current ventilator support, as well as for patients during the transplant operation to minimize hypoxia, hypercapnia, and hemodynamic instability without the need for full cardiopulmonary bypass and anticoagulation.

The expanded role of ECMO has been enabled by substantial improvements in the ECMO circuit including the oxygenator, tubing, pumps, and cannulas available. The oxygenators have evolved from the use of silicone membrane or polypropylene microporous oxygenators to the current polymethylpentene (PMP) oxygenators that have the advantages of reduced red blood cell and platelet transfusion requirements, better gas exchange, decreased resistance, lower priming volume, longer functional life, and having been coated with heparin (1). Because of the heparin-coated tubing, much lower systemic heparin is required, which subsequently reduces the bleeding complications. The newer generation of centrifugal pumps requires smaller priming volumes with improved safety characteristics (2). The cannulas developed to facilitate minimally invasive cardiac surgery have been applied to achieve improved percutaneous peripheral access for establishing ECMO. The most recent cannula technology has enabled ambulatory ECMO support.

II. Post-Lung Transplant ECMO

The primary use of ECMO in lung transplantation has been associated with the support of lung allograft recipients who experience PGD. Severe PGD causes or significantly contributes to the majority of early post-transplant deaths. Unless reversible causes could be identified, treatment has been supportive, with optimization of ventilator parameters, inotropic support, and nitric oxide.

We have shifted to a strategy of early institution of veno-venous (V-V) ECMO in the post-transplant period when recipients develop severe pulmonary edema or require FiO_2 greater than 60%. This shift in strategy has occurred because of the greater ease of providing care for these patients and improved outcomes. Following

initiation of V-V ECMO, patients have marked improved hemodynamics, organ function, and less cardiac irritability. The access for V-V cannulation is dependent on the size of the recipient, the available large vein access sites, the urgency of establishing ECMO, and timing related to the transplant procedure. Our preference is to perform peripheral cannulation. This allows bedside decannulation after ECMO weaning and less bleeding complications. In our experience, access has typically occurred using the right femoral vein with a femoral venous catheter (usually 15–19 Fr, dependent on body size) and the left internal jugular vein with either a pediatric arterial cannula or a percutaneous femoral arterial cannula (usually 14–16 Fr). While the right internal jugular is technically easier to cannulate, this is often already used for placement of the pulmonary artery catheter. Occasionally, we have removed the pulmonary artery catheter and accessed this site with subsequent replacement of the pulmonary artery catheter via an alternative site. Cannulas are placed percutaneously using a modified Seldinger technique over a guide-wire following serial dilatations. We position the femoral venous cannula such that the tip of the cannula is at the right atrial/inferior vena cava junction. The internal jugular cannula is placed such that the tip is at the junction of the right atrium and the superior vena cava. We use transesophageal echocardiography to facilitate and optimize placement. The optimal placement of circuit inflow and outflow ports are adjusted further depending on the level of recirculation noted in the system.

When systemic hypoxia or hemodynamic instability during the transplant procedure necessitates urgent placement of ECMO, central cannulation is performed. We preferentially use the body of the right atrium to place a straight venous cannula into the inferior vena cava (IVC) for venous drainage into the ECMO (blue) and the right atrial appendage to place another cannula for the blood to return back from the ECMO (red). This can be converted to peripheral cannulation when stability is achieved so that subsequent bedside decannulation is possible; this would also allow the opportunity for routine closure of the chest in the operating room. Otherwise, a later return to the operating room for decannulation and chest closure is required.

The circuit consists of a hyaluron-based heparin-coated 3/8″ tubing (GISH Biomedical, Inc., California, U.S.) with a hollow fiber membrane made from PMP Jostra Quadrox. We use albumin-coated oxygenators in adults and heparin-coated ones in pediatric patients. ECMO flows are approximately 2.5 to 3.5 L/min in adults and 1.0 to 2.5 L/min in pediatric patients. In patients with hemodynamic instability, addition to the circuit prime of calcium chloride and/or epinephrine is done to prevent further hemodynamic compromise. While the flow rates are a function of the size of the drainage cannula, these flow rates are usually sufficient to maintain adequate systemic oxygenation while using a protective ventilation strategy. The sweep gas flow is adjusted to maintain the pCO_2 around 30 mmHg so as to maximize pulmonary vasodilation.

The pulmonary vascular resistance routinely decreases after ECMO initiation. The pulmonary capillary leak usually resolves more quickly after V-V ECMO and normally resolves within 24 hours. In our previous experience using V-A ECMO, the capillary leak would usually persist for 48 to 72 hours. Repetitive bronchoscopies are often needed to remove edema and secretions to improve pulmonary compliance.

During V-V ECMO support, a protective ventilatory strategy ($FiO_2 < 30\%$, pressure control < 22, PEEP 8, rate < 10) is used including low oxygen, low pressure ventilation. We use nitric oxide to maximize ventilation-perfusion matching and pulmonary vasodilation.

When ECMO is initiated either at the time of transplant or soon thereafter, anticoagulation is not initiated until reasonable hemostasis is achieved. Frequently, recipient coagulopathy must be corrected. When chest tube drainage is acceptable (<50 mL/hr), heparin is initiated targeting an ACT of 150 to 200 seconds. While systemic anticoagulation improves oxygenator life, it is possible to have prolonged ECMO circuit function without anticoagulation.

Weaning from ECMO is done when the patient's lung compliance has returned to acceptable levels, the pulmonary edema has resolved, the chest X ray has demonstrated predominant resolution of the infiltrates, and acceptable gas exchange is achievable with moderate ventilator support. Weaning from V-V ECMO involves discontinuing membrane gas flow and increasing ventilatory parameters as needed. No increase in anticoagulation is required for V-V ECMO weaning. Provided that the patient's other clinical condition is stable, we obtain at least a daily systemic blood gas on acceptable ventilator settings ($FiO_2 \leq 30\%$, pressure support ≤ 24, and PEEP ≤ 8) 30 minutes after discontinuing the sweep gas.

Using this strategy since November 2002, we have supported 27 patients post-lung transplant on V-V ECMO. One patient suffered an irreversible neurologic injury, and the support therefore was terminated. The remaining 26 patients were all successfully weaned after an average length of support of 4 days (range 1.4–7.6 days). Usually, the patients were maintained on an FiO_2 of less than 30%. In this patient cohort, the 30-day and 1-year actuarial survival was 89% and 74 %, respectively (Fig. 1). The majority of short-term mortality was secondary to multiorgan system failure or infectious complications. These results are substantially better than our previous experience using V-A ECMO (3). Data from the Extracorporeal Life Support Organization (ELSO) registry demonstrated a 42% hospital survivorship following ECMO support (4). Other recent single center reports suggest a 30-day and 1-year survival of 56 % to 74% and 40% to 54%, respectively (5,6).

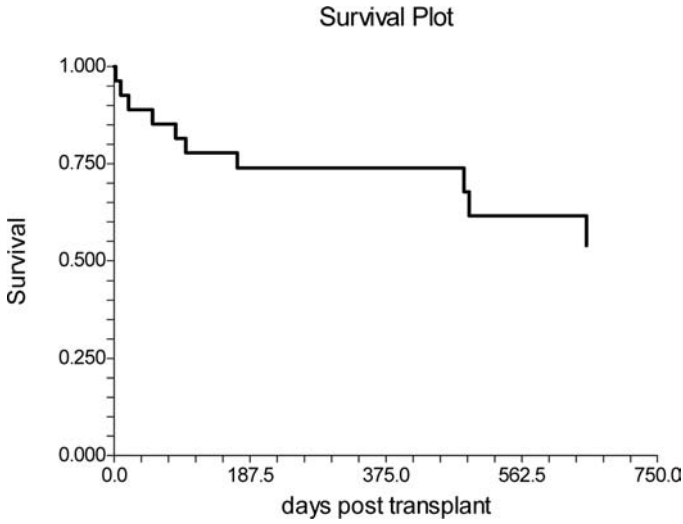

Figure 1 Actuarial survival for patients supported on V-V ECMO following development of PGD 3.

III. ECMO Support During Lung Transplantation

The use of ECMO to support the recipient during the transplant procedure has a number of advantages. In recipients with adequate cardiac function, but very poor respiratory function, V-V ECMO can be used to facilitate the operative procedure. We have increasingly used V-V ECMO in patients who require mechanical ventilation prior to receiving the transplant, particularly those with marked hypercapnia ($pCO_2 > 75$) or with refractory hypoxia, and in those patients who do not tolerate one-lung ventilation. This has greatly decreased the cardiopulmonary instability in these tenuous patients and decreased the stress on our anesthesia colleagues.

Because anticoagulation is not required, extensive dissection can be performed in patients with extensive adhesions related to prior pleurodesis, pulmonary resections, or other thoracic procedures without as much obscuration of the field as it occurs after full systemic heparin required for cardiopulmonary bypass. In these settings, cannulation is performed centrally, using the right atrium for placement of an IVC cannula to drain the deoxygenated blood into the ECMO and using right atrial appendage for placement of a second cannula to return the oxygenated blood from the ECMO. As is our standard practice in all transplants, heparin (100 units/kg) is administered after mobilizing both lungs and following removal of the first lung and preparing the respective bronchus, pulmonary artery, and left atrium for the anastomoses. Additional advantages of using V-V ECMO during the transplant procedure include the ability to utilize protective ventilation and perfusion strategies during the initial allograft perfusion period.

The use of V-A ECMO has its place, particularly in patients with pulmonary hypertension or cardiac instability during the transplant procedure. A disadvantage of this approach, specifically as compared to cardiopulmonary bypass, is the inability to scavenge shed blood from the field into to the ECMO circuit. The use of cell savers can lead to consumption of clotting factors and marked coagulopathy. In one series, the use of V-A ECMO was associated with substantially greater transfusion requirements (7).

IV. ECMO as a Bridge to Transplant

The use of ECMO to support a patient with respiratory failure before the lung transplant has been used increasingly. This increase is associated with greater access to lung allografts, as lung allocation systems evolve from time-waiting based to more need-based algorithms. The use of ECMO as a bridge-to-transplant is not new, first being reported in 1975 (8). Although the patient was successfully weaned, he died 10 days post transplant. In 1993, the Hannover group published three successful cases of lung transplant off ECMO (9). However, the appropriateness of using ECMO as a bridge was controversial, as the estimated one-year survival for transplant off ECMO was only 40% at that time. Additionally, the resources required to successfully bridge the patients have been considerable. This includes prolonged intensive care and hospital stays, substantial transfusion requirements, frequent neuromuscular complications including myopathies and seizures. Patients typically require very prolonged periods of rehabilitation after hospital discharge. A recent report of three young patients bridged off of ECMO (10–28 days of support) from St. Vincent's Hospital highlights the potential success (all survivors) but with substantial complications including two of three experiencing post-transplant seizures (10). Similarly, the Hannover group has reported the use of a pumpless, oxygenator circuit (Novalung) in 12 patients with hypercapnia, but not hypoxia (11). Eight of these patients were one-year survivors.

We have recently bridged four patients to transplant using ECMO. All survived (currently 317–859 days post-transplant) and have achieved full functional capacity. However, the average hospital length-of-stay was 75 days, and all required extensive physical rehabilitation. All experienced a profound diffuse myopathy and required tracheostomy for weaning from the ventilator post transplant. While bleeding complications were not as profound as previously reported in other series, other nonfatal but serious post-transplant complications were relatively frequent.

Strategies to minimize the post-transplant neurologic and myopathic complications are necessary. We currently avoid the use of any muscle relaxants, minimize corticosteroid use, ensure nutritional replacement, and aggressively correct electrolyte abnormalities in this patient population. In these patients, V-V ECMO support is achieved almost universally through peripheral cannulation. We have used the femoral vein for drainage of deoxygenated blood into the ECMO and the internal jugular vein for reinfusion of oxygenated into the patient. There is a growing experience using single cannulation via the right internal jugular vein using a bicaval dual lumen cannula (Avalon Laboratories). This approach has allowed a small number of patients to be extubated and ambulatory may be beneficial since more aggressive rehabilitation can be performed while awaiting transplant.

Given both the difficulties and uncertainties regarding outcomes post-transplantation in these patients requiring ECMO as a bridge to transplantation, the criteria used for selecting appropriate candidates for bridging to transplant have not been well defined. We currently use the following: (*i*) patients with rapidly progressive lung disease who are failing maximal medical therapy; (*ii*) good functional status and preserved physical strength; (*iii*) absence of systemic infection; (*iv*) preserved function of other major organ systems; (*v*) age more than 16 years and less than 55; (*vi*) consistent and reliable social support system; and (*vii*) ability to access the necessary medications and follow-up to be successful post transplant. Patients with lung failure secondary to adult respiratory distress syndrome (ARDS) create a particularly difficult decision algorithm. There have been substantial improvements in the success at bridging either to transplant and to recovery using ECMO support.

V. Conclusion

Advances in ECMO technology have greatly improved the ability to support patients *to*, *through*, and *following* lung transplantation. V-V ECMO, in particular, is an important tool in the armamentarium of any lung transplant program to optimize patient outcomes.

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Maintenance Immunosuppression in Lung Transplantation

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I. Introduction

Sophisticated immunosuppressive regimens and refined surgical technique have ushered in an era in which patients who suffer from end-stage organ disease can now be treated with life-sustaining organ transplantation. The human body is designed to distinguish native tissue from nonnative tissue. Without immunosuppressive medications, the recipient's immune system would quickly reject the transplanted organ, rendering it nonviable.

The lung is the most precarious of transplanted organs. On the one hand, it is accompanied by donor human leukocyte antigen, which necessitates robust immunosuppression. On the other hand, the lung is exposed to a variety of infectious organisms, making immunosuppression a treacherous balance. This chapter will review standard approaches to maintenance immunosuppression in the lung transplantation patient. Dosing regimens given at this institution are provided in the description of each drug. Exact dosing may vary by institution.

II. Maintenance Immunosuppression

A. Corticosteroids

Maintenance therapy for lung transplantation has always included corticosteroids. Efforts have been made to minimize or withdraw steroid use altogether in the lung transplantation population because of the side effects that accompany these drugs. Very few attempts at steroid withdrawal have been successful (1,2). These patients have enjoyed resolution of side effects. For the remaining patients, steroids continue to be included in daily maintenance immunosuppression.

Mechanism of Action

Corticosteroids inhibit both humoral and cell-mediated immunity. The principal effect of corticosteroids is to turn off gene transcription of multiple inflammatory genes (3). The result is a decrease in the inflammatory response through reduced production of cytokines, IL-1, IL-2, IL-6, IFN-γ, and TNF-α (4).

Pharmacodynamics

The most commonly used synthetic glucocorticoids in transplant medicine are prednisone and methylprednisolone. These drugs are highly bioavailable; they are metabolized in the liver to the active metabolite, prednisolone. Elimination is via the urine.

Peak concentration is achieved in two to three hours. In spite of the relatively short half-life of these drugs, pharmacological activity is demonstrated by inhibition of lymphokines that persist for 24 hours (5).

Dosing

The equivalency between oral prednisone to IV methylprednisolone is 5:4. Generally speaking, high-dose methylprednisolone (500–1000 mg) is given in the operating room at the time of transplantation. Maintenance steroids are then commenced on postoperative day 2. The dose is weight based; prednisone is initiated at 0.5 mg/kg and given daily. Maintenance steroids are gradually tapered every two weeks by 5 mg to a goal dose of 5 to 10 mg daily. Dosage adjustments are generally not required with hepatic or renal insufficiency.

Drug Interactions

Corticosteroids are metabolized by the cytochrome P450 enzyme system. See Table 1 for a list of drugs that are metabolized by the cytochrome P450 enzyme system.

Toxicities

Cardiovascular Toxicity

The effect of corticosteroid therapy on systemic blood pressure is not uniform. A few patients who have successfully tolerated steroid withdrawal have enjoyed lower systemic blood pressure (2). Other patients, however, have had no change in blood pressure despite discontinuation of steroids (1). The presence of hypertension pretransplantation is probably the most important indicator of post-transplantation hypertension.

Gastrointestinal Toxicity

Glucocorticoids stimulate gastric acid secretion (6), thereby predisposing lung transplantation patient to gastroesophageal reflux disease, peptic ulcer disease, and stress-related erosion and ulcer disease.

Metabolic Toxicity

Chronic use of glucocorticoids is associated with central adiposity, dyslipidemia, skeletal muscle wasting, insulin resistance, glucose intolerance, and overt diabetes. More than one-third of lung transplantation patients have hyperlipidemia within five years of transplantation and 53% of these patients suffer from diabetes within this period (7). Osteoporosis is caused by glucocorticoid inhibition of osteoblastic activity and increased osteoclastic activity (8).

B. Calcineurin Inhibitors

Calcineurin inhibitors (CNIs) include cyclosporine (CsA) and tacrolimus (TAC). Both CsA and TAC are used as maintenance immunosuppression, but TAC has additional roles in recurrent acute rejection (RAR) and bronchiolitis obliterans syndrome (BOS). According to the 2008 Registry of the ISHLT, greater than 90% of lung transplantation recipients are maintained on a CNI at one and five years post-transplantation, TAC being the most commonly used CNI (7).

Cyclosporine

CsA was revolutionary in the field of organ transplantation because it was the first T-cell-selective drug (9) and effectively induced immunosuppression without the myelosuppression

Table 1 Drugs Metabolized by Cytochrome P450

Drugs that inhibit cytochrome P450 (increase levels of cyclosporine/tacrolimus)	Drugs that induce cytochrome P450 (decrease levels of cyclosporine/tacrolimus)
Calcium channel blockers	Anticonvulsants
Diltiazem	Carbamazepine
Nicardipine	Phenobarbital
Nifedipine	Phenytoin
Verapamil	
Anti-arrhythmics	Antibiotics
Amiodarone	Nafcillin
	Rifabutin
	Rifampin
Macrolide antibiotics	Octreotide
Clarithromycin	
Erythromycin	
Antifungals	Ticlopidine
Fluconazole	
Itraconazole	
Ketoconazole	
Pro-kinetic agents	Orlistat
Cisapride	
Metoclopramide	
H2 antagonists	St. John's wart
Cimetidine	
Proton pump inhibitors	
Lansoprazole	
Rabeprazole	
Antigout drugs	
Allopurinol	
Colchicine	
Bromocriptine	
Danazole	
Methylprednisolone	
Grapefruit juice	

that complicated existing immunosuppressive therapy. In 1983, its success was demonstrated in lung transplantation (10).

Mechanism of Action

CsA binds to a family of cytoplasmic proteins called cyclophilins (11). The CsA-cyclophilin complex inactivates calcineurin. Calcineurin, a protein phosphatase, is critical for transcription of various cytokine genes that are necessary for T-cell activation. CsA, therefore, inhibits proliferation and activation of T lymphocytes (12,13).

Pharmacodynamics

CsA is known for inter- and intraindividual absorption variability. On average, bioavailability is approximately 30% and peak serum levels are reached in 1.5 to 2 hours after oral administration with half-life ranging from 5 to 18 hours (11). The original

commercial preparation, Sandimmune, has poor and unpredictable absorption due to its highly lipophilic nature and dependence on bile for absorption (14). In 1996, the newer, microemulsion formulation, Neoral (Novartis), was introduced and has improved bioavailability, more consistent oral absorption, and more reproducible pharmacokinetic behavior (15). Both preparations continue to be utilized today. It is important to bear in mind, however, that Neoral and Sandimmune cannot be used interchangeably. Any switch between CsA formulations in a particular patient should occur only with vigilant pharmacokinetic monitoring (16).

Dosing

The bioequivalence of IV to oral CsA is 1:3. Typically, CsA administered immediately postoperatively in the IV form at 3 mg/kg/day. When patients are tolerating oral intake, the drug is converted to its oral form at 5 mg/kg/day in divided doses.

Drug Monitoring

CsA has a narrow therapeutic window and variable absorption. As such, monitoring of drug levels is crucial. Trough levels have been shown to correlate poorly with systemic exposure to CsA (17). Therapeutic as well as adverse side effects are primarily dependent on the exposure over time expressed by the area under the curve (AUC) rather than trough levels (18). In lung transplantation patients during the early postoperative period, CsA levels drawn at two or three hours post dose (C2 and C3, respectively) are highly predictive to estimate the exposure to CsA over time. Patients with cystic fibrosis (CF) may have a different pharmacokinetic profile of CsA due to the presence of fat malabsorption associated with CF-related exocrine pancreatic insufficiency, but C2 monitoring is likely most accurate in predicting drug exposure over time for this population as well (12).

Drug Interactions

CsA is metabolized by the cytochrome P450 enzyme system (Table 1). Manipulation of the cytochrome P450 system has been employed to decrease the cost of CsA. For example, cola is known to enhance CsA absorption, and coadministration can reduce the daily dose and cost of CsA (19).

Most statins are substrates of the cytochrome P450 enzyme system. Coadministration of a statin and CsA, and to a lesser extent TAC, will result in a pronounced increase in the statin. Severe rhabdomyolysis has been reported as a result of this interaction (20).

Toxicities

Nephrotoxicity. Renal dysfunction is the most common adverse reaction of CsA, and there are three forms in which it can occur: an acute reversible renal dysfunction, a chronic progressive form, and infrequently, thrombotic microangiopathy that leads to thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (21).

Acute reversible nephrotoxicity is dose related and usually reversible by stopping or reducing the dose of the medication. The mechanism of injury is likely due to vasoconstriction of the afferent arteriole secondary to CsA stimulation of the renin-angiotensin system (22).

Chronic nephrotoxicity, which is manifested by renal insufficiency and arterial hypertension, usually occurs within six months of transplantation. The mechanism of damage is likely repeated episodes of renal ischemia (23). Furthermore, CsA enhances

the expression of transforming growth factor β (TGF-β), which in addition to inhibiting IL-2-stimulated T-cell proliferation also exerts a fibrogenic effect (12). These insults culminate in progressively increasing renal vascular resistance, heavy proteinuria, and tubulointerstitial damage seen on histopathological examination. Although the renal function may stabilize in terms of serum creatinine and GFR, progressive tubulointerstitial injury may still be occurring (24). Several agents have been tested to prevent and minimize chronic CsA nephrotoxicity. The addition of sirolimus has been shown to allow for the reduction of the CsA dose and preservation of renal function (23). Drugs that can potentiate CsA nephrotoxicity are aminoglycosides, amphotericin B and ketoconazole, nonsteroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors (24).

Hypertension. The exact mechanism by which CsA causes systemic hypertension has not yet been definitively described, but in addition to renal vasoconstriction and sodium retention, endothelin activation, nitric oxide reduction, and neurohumoral activation are likely involved (25). Systemic hypertension develops early after initiation of CsA. Standard antihypertensives, such as calcium channel blockers and β-blockers, can be used to control blood pressure in patients receiving CsA. Caution should be used with angiotensin-converting enzymes, however, as this class of medications can potentiate the nephrotoxic effects of CsA.

Hypercholesterolemia. The majority of CsA-treated lung transplant recipients develop hypercholesterolemia. CsA elevates cholesterol by modulating the low-density lipoprotein (LDL) receptor. Pretransplant cholesterol levels have been shown to be an independent predictor of post-transplant hypercholesterolemia (26). In addition to diet, weight loss, and exercise, the vast majority of lung transplantation patients are now treated with statins that, in addition to their lipid-lowering effects, have immunomodulatory properties (27).

Neurotoxicity. Tremor is a common manifestation of CsA neurotoxicity but may improve with time despite continuation of treatment. Other neurotoxic effects of CsA are headaches, seizures, visual abnormalities, akinetic mutism, focal deficits, and reversible posterior leukoencephalopathy (11).

Gingival Hyperplasia. Gingival hyperplasia is a well-known complication of CsA therapy. It can develop rapidly within one to two weeks after initiation of the drug and lead to tooth loss (28). Activation of gingival fibroblasts and collagen production is the presumed mechanism of action. Plaque may be an inciting agent in chronic gingival inflammation, making oral hygiene an important preventative measure. Azithromycin appears to be useful to treat CsA-induced gingival hyperplasia (29). Switching to a different CNI, for example, TAC, will usually lead to resolution.

Hirsutism. CsA is associated with the development of hirsutism. Resolution occurs with discontinuation of the drug (30).

Tacrolimus

TAC (also called FK-506), another CNI, was introduced in liver transplantation as salvage therapy in 1989. In 1994, it was approved by the FDA, and its use has now surpassed that of CsA in lung transplantation.

Mechanism of Action

TAC binds with the cytoplasmic immunophilin, a FK-binding protein 12 (FKBP-12). TAC: FKBP-12 inactivates calcineurin, the enzyme responsible for the production of cytokines

that are necessary for activation of T cells. Although TAC has a similar mechanism of action as CsA, the drugs appear to differ in their effects on patterns of T-cell cytokine expression and possibly some aspects of humoral immunity. Furthermore, lymphocyte sensitivity to the drugs may differ between patients. TAC is more potent in its immunosuppressive properties than CsA but induces TGF-β1 to a lesser extent than CsA, which is the mechanism thought to contribute to the nephrotoxic properties of these agents (31).

Pharmacokinetics

Like CsA, TAC has poor oral absorption, variable bioavailability, and a narrow therapeutic window (12). Oral bioavailability is about 20% to 25%, and food significantly reduces the rate and extent of absorption. Unlike CsA, absorption of TAC is independent of bile (32). A fatty meal (46% fat) will reduce the rate and extent of absorption of TAC by up to 37% (5). It is recommended that patients take the drug on an empty stomach or two hours after a meal.

Dosing

TAC is given intravenously immediately after transplantation at a dose of 0.05 to 0.1 mg/kg over 24 hours. We often use the drug sublingually rather than IV, in doses identical to oral usage. A random dose is then checked in the morning. When a patient is tolerating oral medications, TAC is given on an empty stomach or two hours after food at a dose of 0.03 mg/kg, rounded to the nearest 1 mg twice daily.

Drug Monitoring

Peak concentrations are achieved within one to two hours of oral administration. Although standard technique utilizes trough monitoring, a three-hour post-dose concentration (C3 concentration) has been shown to more accurately reflect systemic exposure to the drug (12).

Drug Interactions

TAC is metabolized in the liver and gastrointestinal mucosa by the cytochrome P450 enzyme system (Table 1).

Toxicities

Nephrotoxicity. As with CsA use, both acute and chronic forms of nephrotoxicity can occur and these events are described in the CsA section. Prospective studies comparing TAC and CsA show no significant difference between the degree of renal dysfunction in lung transplant recipients (33,34). Thrombocytopenic purpura and hemolytic uremic syndrome has been reported in association with TAC use in a lung transplantation recipient (35).

Diabetes. TAC suppresses insulin production at the transcriptional level and appears to be more diabetogenic than CsA in some patients. Factors that increase risk of post-transplant diabetes in the context of TAC use are age, African-American and Hispanic ethnicity, concomitant corticosteroid use, drug dosage, and a family history of diabetes (31). In three separate trials comparing TAC to CsA, there was a trend to a higher incidence of new onset diabetes in patients treated with TAC (33,34,36).

Cardiovascular Toxicity. In normal individuals, neither TAC nor CsA has been shown to affect systemic blood pressure when administered over a short-term period (37), but mild-to-moderate hypertension is present in up to 50% of lung transplant recipients receiving TAC therapy (31). Prospective, randomized trials yield mixed results regarding the effect of CsA versus TAC on systemic blood pressure; some trials

indicate that hypertension is less common with TAC use than it is with CsA use (33,34), while others show equivalent incidence of hypertension with TAC and CsA (36).

Hypercholesterolemia. Prospective trials comparing lung transplantation patients randomized to CsA or TAC showed equivalent need for statin therapy in the two groups (33).

Neurotoxicity. Altered mental status, headache, focal neurological deficits, visual disturbances, and seizures can occur with TAC use (38). Posterior reversible encephalopathy syndrome (PRES) has also been described (39). PRES consists of vasogenic edema in the posterior circulation territories and is reversible with reduction of the dose or discontinuation of the drug but conversion to irreversible edema has been reported. MRI of the brain is the imaging modality of choice for PRES.

Efficacy

TAC Vs. CsA

A prospective trial compared efficacy of CsA versus TAC in 90 lung transplantation patients. Sirolimus was used to treat acute rejection episodes, lymphocytic bronchiolitis, and BOS. Patients treated with CsA were significantly more likely to develop acute rejection or lymphocytic bronchitis. BOS occurred in more patients treated with CsA, but this was not a statistically significant difference (36).

Comparison of TAC-Based Regimens

Retrospective analysis comparing TAC in three different regimens, (*i*) TAC/azathioprine/prednisone (32 patients), (*ii*) TAC/azathioprine/prednisone with daclizumab induction (49 patients), and (*iii*) TAC/mycophenolate mofetil/prednisone with daclizumab induction (28 patients), demonstrated higher freedom from acute rejection at one and three years in the group of patients who received TAC/Mycophenolate mofetil/Prednisone with daclizumab induction (40). Although there was a trend toward higher freedom from BOS with use of this regimen, this difference did not reach statistical significance. Three-year infection rates were similar, demonstrating equivalent safety among these regimens.

RAR and BOS

Several studies indicate that conversion from CsA to TAC is effective in the treatment of RAR and BOS (41–46). The largest of these studies included 110 patients with RAR and 134 patients with BOS (stage 1–3). For patients with RAR, conversion from CsA to TAC yielded a significant decrease in both histologically proven and clinically proven episodes of acute rejection. Steroid pulses were also decreased in this group. Patients with BOS had a marked decrease in FEV1 decline (47).

C. Nucleotide-Blocking Agents

Nucleotide-blocking agents include mycophenolate mofetil (MMF) and azathioprine (AZA).

Mycophenolate Mofetil

Mycophenolic acid (MPA) is a fermentation product of *Penicillium brevicompactum* and related fungi. A synthesized form of MPA, MMF, has improved oral bioavailability compared to MPA. MMF has been shown to be a powerful antifibroproliferative drug at concentrations achieved clinically, supporting a role for MMF in the treatment of obliterative bronchiolitis (48).

Mechanism of Action

MMF inhibits T- and B-cell proliferation by interfering with nucleotide synthesis. MMF is rapidly hydrolyzed in vivo to MPA. MPA is a potent inhibitor of the type II isoform of inosine-5′-monophosphate dehydrogenase (IMPDH). Inhibition of IMPDH depletes de novo guanosine nucleotide synthesis. Activated T and B lymphocytes that express type II isoform of IMPDH are dependent on de novo guanosine nucleotide synthesis to synthesize DNA and to proliferate (49).

Pharmacodynamics

MMF has 94% bioavailability and 99% protein binding (5). After oral administration, MMF is rapidly absorbed and converted to its active form, MPA, in the liver. Further metabolism occurs by glucuronidation of MPA creating the inactive metabolite mycophenolic acid glucuronide (MPAG), which is primarily eliminated in the urine (87%) (50).

Dosing

MMF is available in equivalent IV and oral form. The IV dose is 1 g twice daily and should be transitioned to oral form as soon as the patient is tolerating oral intake. If transitioning from AZA to oral MMF, the initial dose is 250 mg twice daily and increased every three days by 250 mg twice daily to a goal of 1000 mg twice daily. In the event of side effects or if the white blood cell (WBC) count is less than 3.5 cells/mm^3, the dose is decreased by 250 mg twice daily. MMF should be withheld if the WBC count is less than 1.5 cells/mm^3. The dose of MMF should be adjusted in severe renal impairment.

Drug Monitoring

Monitoring of MMF is not routinely performed. There are, however, a number of drugs and circumstances (see sects. “Pharmacodynamics” and “Drug Interactions”) that can alter MPA levels (51). As such, there is good argument in favor of monitoring. Because of the effect of MMF on WBC, a complete blood count (CBC) should be drawn weekly during the first month of treatment, every two weeks for the next two months, and then monthly for nine months.

Drug Interactions

The absorption of MMF is decreased by magnesium, aluminium hydroxide antacids, and cholestyramine. For incompletely understood reasons, CsA will decrease MMF levels by up to 50%, a phenomenon that does not occur with TAC (52). Other protein-bound drugs can displace or be displaced by MMF. These include salicylates, furosemide, and oral contraceptives (50). Acyclovir and probenecid will increase the MMF level.

Toxicities

Gastrointestinal. Nausea, vomiting, diarrhea, and abdominal pain are associated with MMF and are common causes for dose reduction or discontinuation of the drug. Oral ulcerations are also reported as a complication of MMF therapy and likewise resolve with discontinuation the drug. Data indicates that adverse effects of MMF may be more frequent and severe when the drug is started late in the course of transplantation. This may be especially true with diarrhea. It is hypothesized that the higher dose of corticosteroid used early after transplantation confer to the intestinal epithelium some protection against the irritating effect of MMF (53).

Hematologic. Leukopenia and anemia are common consequences of MMF therapy. CBC should be monitored routinely while patients are on MMF.

Infection. MMF increases the risk of CMV disease, likely due to inadequate production of anti-CMV-IgM as a result of the inhibitory effect of MMF on B cells in the early post-transplantation period (54).

Pulmonary. Pulmonary toxicities in association with MMF are reported infrequently. Interstitial pneumonitis that responded to discontinuation of MMF has been reported (55).

Azathioprine

AZA is an antimetabolite that has been used in lung transplantation in combination with steroids since the 1960s. Although MMF is now the more frequently used antimetabolite, the ISHLT reported in 2008 that roughly one-third of maintenance immunosuppressive regimens included AZA at five years after transplantation (7).

Mechanism of Action

AZA inhibits the T- and B-cell cycle by interfering with RNA and DNA production by preventing the synthesis of de novo purine. AZA has no effect on the production of cytokines (12).

Pharmacodynamics

AZA is rapidly, though incompletely, absorbed. It has a bioavailability of 40% with significant intra- and interpatient variation (56). AZA is metabolized to 6 mercaptopurine (6-MP) by glutathione, and then converted to 6-thiouric acid, 6 methyl-MP and 6-thioguanine (6TG) by thiopurine *S*-methyltransferase (TPMT). Approximately 10% of the population possesses polymorphism of TPMT, which causes low enzyme activity and results in acute AZA-induced myelosuppression (57). Although the half-life of 6-MP is measured in minutes, its metabolite, 6TG, has a much longer half-life, possibly as long as 13 days. This ensures adequate immunosuppression with once daily dosing.

Dosing

AZA is available in equivalent IV or PO form and is dosed according to body weight. The starting dose is 2 mg/kg (rounded to the nearest 25-mg dose) and given daily. AZA dose is titrated according to the WBC count; the dose is decreased for a WBC less than 3.5 cells/mm^3 and held if the WBC count becomes less than 1.5 cells/mm^3. AZA's metabolite, 6TG, may accumulate with renal impairment and contribute to potential toxicity.

Drug Interactions

Allopurinol inhibits first pass metabolism of 6-MP by xanthine oxidase, resulting in a fivefold increase of 6-MP levels (58). If administration of allopurinol is necessary, the dose of AZA should be reduced to one-fourth the usual dose and the WBC monitored vigilantly.

AZA has been reported to diminish the anticoagulant effects of warfarin (59). Higher doses of warfarin may be needed to achieve therapeutic international normalized ratio (INR) when administered concomitantly with AZA. If AZA is to be discontinued, caution should be used with patients who are stabilized on Coumadin therapy as bleeding has been reported in this context (60).

Toxicities

Hematologic. Bone marrow suppression, a common complication of AZA therapy, is manifested by leukopenia, thrombocytopenia, and macrocytic anemia. Hematologic effects usually appear 7 to 10 days after initiation of therapy (5), and they

are dose dependent. Exquisite bone marrow sensitivity to AZA may be evidence of TPMT deficiency and warrants evaluation of TPMT genotype. Fatal diffuse alveolar hemorrhage due to AZA-induced thrombocytopenia has been reported in a patient with a homozygous TPMT mutation (61).

Gastrointestinal. Nausea, diarrhea, anorexia, and vomiting are non-dose-dependent adverse effects of AZA and may require discontinuation of the drug. Venoocclusive disease of the liver secondary to AZA has been reported in a lung transplantation patient (62). Severe cholestatic hepatocellular damage secondary to AZA has been reported in clinical contexts other than transplantation. Improvement of liver function was seen after discontinuation of AZA (63).

Efficacy

MMF Vs. AZA

Small studies have suggested superiority of MMF to AZA in preventing acute rejection (64,65). But a more recent, larger analysis indicates equivalency between these two drugs. A randomized, multicenter, international trial compared MMF to AZA in 315 lung transplantation recipients in a CsA-based regimen after receiving anti-thymoglobulin induction (66). At interim analysis, 12-month survival was better in the MMF group versus AZA group (88.1% vs. 79.1%, respectively, $p = 0.038$). But by three years, survival between the two groups was not significantly different. Additionally, the incidence of BOS and biopsy proven acute rejection was not different between the two groups at the one-year interim analysis or at three years. Infection and malignancy rates were likewise similar in both groups. Importantly, there were a significantly greater number of patient withdrawals from the AZA group, primarily for lack of therapeutic response, and this fact may have masked differences between the two groups.

III. Conclusion

Maintenance immunosuppression includes corticosteroids, CNIs, and nucleotide-blocking agents. Careful patient monitoring is necessary in light of the significant side effects involved with the use of these medicines.

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Fungal Infections in Lung Transplant

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I. Introduction

Lung transplantation brings with it a plethora of infectious issues, which are a direct result of an immunocompromised state secondary to a multiprong approach used to disrupt immunity. Lungs are the only organs that are under a constant onslaught of environmental pathogens. Pulmonary fungal infections are not only a cause of major mortality but also of continued morbidity in association with chronic graft loss in lung transplant (LT) recipients.

Up to 15% to 35% of LT recipients (1–3) will acquire fungal infections, and the majority (80%) of these are caused by *Aspergillus* spp. and *Candida* spp. Mortality rates vary from 20% to 60% in invasive disease (4,5); however, overall incidence has been reduced with prophylactic measures. Time-consuming mycological testing, insensitive laboratory tests for diagnosis, paucity of standard guidelines in this field, interaction of antifungals with calcineurin inhibitors (CNIs) and their toxicity compound an already difficult situation. Current studies show a drop in invasive candidiasis (IC) with *Aspergillus* emerging as the primary cause of fungal infections in LT recipients. Recent studies have shown an incidence rate of 2.4% during the first year (5), with majority of cases occurring after the first year (6).

A. *Aspergillus* Spp.

Aspergillus is a widely distributed filamentous organism with septate hyphae whose conidia can be inhaled easily. The most common isolates involved in the disease process are *A. fumigatus*, *A. flavus*, *A. terreus*, and *A. niger.* Development of *Aspergillus* infection is mostly encountered either in first six months or late onset, which is usually more than a year after transplant (6). Alveolar macrophages are the first line of defense against *Aspergillus* conidia, and recent work on in vitro human alveolus model has shown that both Amphotericin-B (Amph-B) and macrophages were required to suppress the growth (7). The actual pathogenesis of this fungus is not clear; however, mycotoxin produced by *A. fumigatus*, gliotoxin, has been shown to suppress functional T-cell responses (8), by possibly causing apoptosis of antigen presenting cells. Multiple risk factors have been confirmed in studies over the years. These risk factors, however, have been deduced from the retrospective studies, and a prospective analysis of the risk factors unique to this population is lacking (Table 1) (1,2,9).

Table 1 Risk Factors Associated with *Aspergillus* Infections

CF
Prior colonization
Immunosuppression
Donor age
Long ischemia time
Concurrent CMV infection
Hypo γ-globulinemia
Suggested association with
Acute rejection
BOS

Clinical Entities

Three distinct *Aspergillus* infectious syndromes exist in LT recipients. They include:

1. *Aspergillus* colonization: The organism has an affinity for structurally abnormal lungs and can be cultured from airways without any symptoms. Three to 20% of pretransplant colonization will progress to invasive aspergillosis (IA) (9), while the early post-transplant colonization increases the risk of IA by 6 to 11 times (10,11). Recent data suggests that *Aspergillus* colonization may be a distinct risk factor for bronchiolitis obliterans syndrome (BOS) (12).
2. Anastomotic or tracheobronchial aspergillosis: During the first three months post transplant, one-third of infections are either bronchial anastomotic or tracheobronchitis. This is a distinct entity compared to pulmonary invasive disease. Cough, dyspnea, wheezing, and hemoptysis are the usual complaints. Diagnosis involves the visualization of pseudomembranous or ulcerative appearance of involved airways, cultures and histopathological evidence of tissue invasion, and/or necrosis (Fig. 1A and B) (13,14). Complications can manifest as necrosis, dehiscence, ulceration, excessive granulation tissue, and

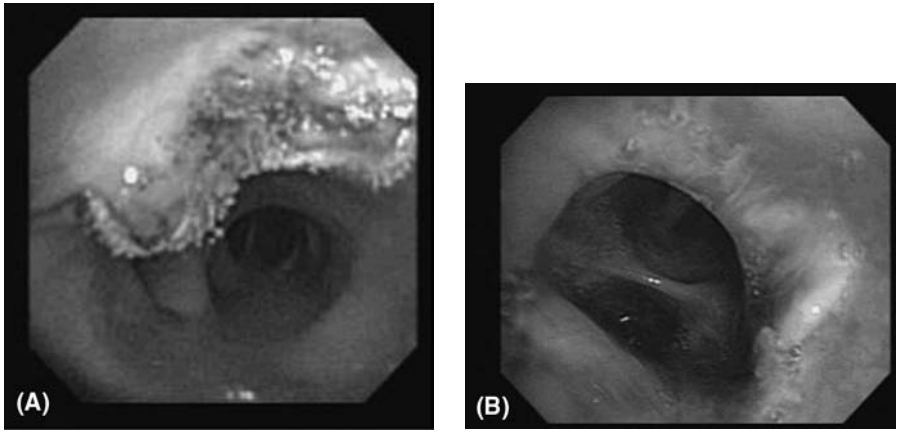

Figure 1 (*See color insert*) (**A**) Bronchoscopic view of right main stem anastomosis with a black fungating mass in a case of *Aspergillus niger* tracheobronchitis. (**B**) Bronchoscopic view of thick blackish plaque adherent to anastomosis in *Aspergillus fumigatus* infection.

subsequent obstruction of anastomotic site, large airways, or pneumonia and are seen in up to 18% of patients (15).

3. Invasive pulmonary aspergillosis (IPA)/disseminated aspergillosis: The onset of IPA has shifted and occurs later than tracheobronchitis as reported in recent studies. Clinical, radiological, and/or histopathological evidence of pulmonary tissue invasion by *Aspergillus* spp. along with corroborating cultures from respiratory sampling are necessary for diagnosis (Fig. 2). The disease is divided into probable and proven categories based on the EORTC criteria. Radiological chest X ray or CT scan findings of nodules, confluent nodules/consolidation, halo sign (considered highly characteristic in neutropenic patients), air crescent sign, and cavitary formation are all nonspecific and lack sensitivity in LT recipients (Fig. 3). Invasive disease in LT recipients has a mortality rate of 60% to 75%. IA may be responsible for up to 9% overall mortality in LT patients (16).

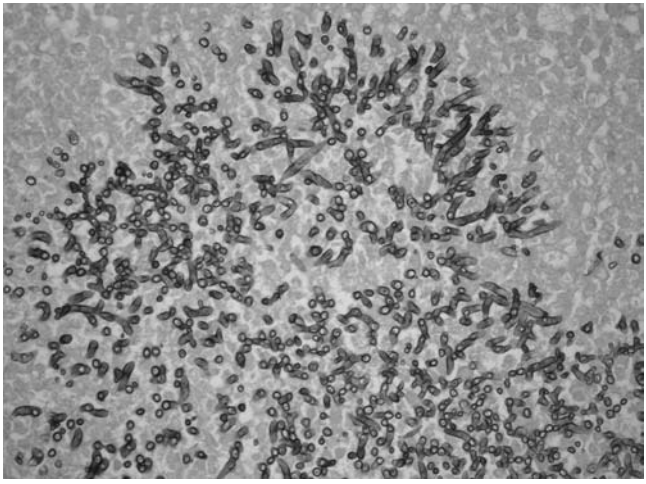

Figure 2 (*See color insert*) Micrograph showing lung parenchymal infiltration by *Aspergillus* (methenamine silver stain, original magnification 100×), note the dichotomously acute angle branching and septate hyphae.

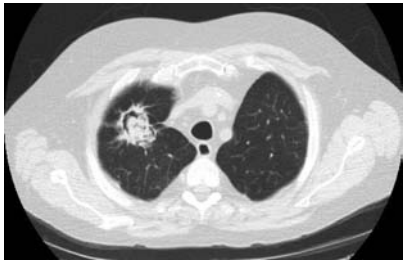

Figure 3 Aspergilloma seen on chest CT imaging in transplanted lung.

Diagnosis

It poses a significant challenge to diagnose invasive mycoses in an immunosuppressed population. Despite multiple testing modalities, lack of high specificity in sampling, and radiological findings, clinical impression plays a key role. The EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study Group) criteria is helpful in diagnosing IA in LT; however, the applicability of the criteria is limited. The diagnosis is primarily made on the basis of the clinical, radiological, microbiological, and histopathology criteria to divide the patients into probable and proven invasive fungal infection (IFI). The diagnosis of possible fungal infection is not applicable in LT. Since these patients are so difficult to diagnose, noninvasive methods of diagnosis are being pursued.

Galactomannan (GM) is a cell wall component of the fungal cell wall and is used in the diagnosis of IA. The serum *Aspergillus* GM antigen test at a GM index value of 0.5 has a sensitivity of 30%, with the specificity of 96.5%. However, the test appears to be more useful when bronchoalveolar lavage (BAL) is used instead of serum. The sensitivity ranges were reported to be 81.8% and specificity of 98.5% with positive and negative predictive values of 51% and 99%, respectively (17). The test can be falsely positive with the administration of pipericillin/tazobactam or in disseminated histoplasmosis and penicillinosis (18). At this time, there is no approved standardized PCR for *Aspergillus.*

It is important to note that a positive test *alone* will not diagnose the infection, and negative result does not rule out the possibility of IA. Therefore, when viewed in the context of clinical syndrome, a positive test supports the diagnosis.

(1→3)-β-D-Glucan (BG) is also a cell wall constituent in many fungi and testing for BG is not specific for IA. Its sensitivity was found lacking (55%) when compared to enzyme immunoassay (EIA) for GM antigenemia (19). It has a more negative predictive value in excluding invasive fungal disease (IFD) (20).

Treatment and Prophylaxis

The drug of choice for the treatment is voriconazole, which has excellent in vitro activity against *Aspergillus* and has shown to improve clinical outcome (21). Voriconazole works by interfering with sterol synthesis. The drug interactions of voriconazole with CNIs and liver toxicity cause certain limitations. Cyclosporine requires dose reduction by 50%, tacrolimus by 66%, and voriconazole is contraindicated for use with sirolimus (22).

However, liposomal Amph-B remains the alternate choice in the case of drug-related adverse effects, contraindications, or other intolerant factors. Other azoles, such as posaconazole, can also be used as a salvage therapy.

The addition of newer and less-toxic agents other than Amph-B in the antifungal armamentarium has paved the way for combination therapy in refractory invasive fungal diseases. In the case of IA, azole and echinocandin combinations have been evaluated in solid organ transplant (SOT) recipients to show significantly lower mortality in patients with *A. fumigatus* infection and renal failure (23).

Antifungal prophylaxis is an unresolved issue in LT recipients. For the prevention of IA, despite limited data, the majority of programs oscillate between giving aerosolized Amph-B or itraconazole. Another study showed that universal antifungal prophylaxis with voriconazole lowered the rate of IA at one year remarkably from 23.7% to 1.5% (11). Questions addressing the length of prophylaxis continue to remain unanswered with programs usually giving universal prophylaxis in first three months. The pendent question regarding preemptive therapy in high-risk LT patients (single LT, prior colonization) with

Table 2 Comparative Data from Studies Showing Use of Inhaled Ampho-B Preparations for *Aspergillus* Prophylaxis

Author	No. of Pts	IA	NNT	95% CI
Reichenspurner	49 AMBd 24 placebo	8% 20%	8.3	(5.2, 32.8)
Drew	49 AMB d 51 ABLC	2% 2%	1250	(30, ∞)
Minari	87 Inh Amph to ITR 101 HC	4.9% 14%	7.2	(5.5, 13.1)
Husain	30 ITR $\pm$ Inh Amph 65 VRC	21% 1.5%	5.4	(4.5, 15.7)

Abbreviations: AMB d, amphotericin B desoxycholate; ABLC, amphotericin B lipid complex; Inh Ampho, inhaled (aerosolized) amphotericin B; ITR, itraconazole; HC, historical controls; VRC, voriconazole; IA, invasive aspergillosis; NNT, number need to treat.

Table 3 Noncomparative Reports of Antifungal Prophylaxis in Lung Transplants

Author	No. of Pts	Agent	Dosage	Duration	Efficacy (%)
Calvo	65	AMB d	0.2 mg/kg/d	120 days	100
Monforte	72	AMB d	6 mg/kg/8 hr	42 days	75
Borro	60	ABLC	50 mg	13wk	98.3
Monforte	27	L-AMB	25 mg	1 yr	97
Shitrit	40	ITR	200 mg b.i.d.	3 mo	95

Abbreviations: AMB d, amphotericin B desoxycholate; ABLC, amphotericin B lipid complex; L-AMB, liposomal amphotericin B; ITR, itraconazole.

voriconazole or echinocandins has been on the horizon as well. Various prophylaxis strategies employed have been depicted in Tables 2 (11,24–26) and 3 (27–31).

B. *Candida* Spp.

Candida spp. is common yeast with pseudohyphae and a frequent colonizer of human skin and mucosal membranes. The most significant and frequently occurring species are *C. albicans* (50%), *C. tropicalis*, *C. glabrata*, *C. krusei*, and *C. parapsilosis*. The rising trend of non-*albicans* spp. is postulated in some studies to be related to the use of fluconazole prophylaxis (32). *Candida* in LT has a diverse spectrum of disease presentation ranging from colonization, mucocutaneous disease to disseminated disease. Tracheobronchitis effecting anastomosis in LT is well documented (33). However, pulmonary invasion is rare even in extremely compromised hosts. Risk factors include chronic glucocorticoid use, broad-spectrum antibiotic use, and malnutrition, but candidemia is highly associated with intravascular catheters, parenteral hyper alimentation, hemodialysis, renal failure, ventilator use, etc. (32,34,35).

Diagnosis is primarily made on culture results; however, other methods such as PNAFISH are increasingly employed. IC usually occurs during the first two months after LT. In one study, tracheobronchitis was found to be the most common infection (38% of all), followed by bloodstream infection (28%). The overall incidence was shown to have

remarkably declined from 20% in mid-1980s to 1.8% in mid-2000s along with decline in mortality to 15% in IC for LT recipients (32).

Fluconazole and echinocandins (caspofungin, anidulafungin, and micofungin) are the most commonly used antifungals. Echinocandins inhibit (1→3)-β-glucan synthesis via inhibition of (1→3)-β-glucan synthase, thereby disrupting the cell wall. Several randomized trials (in immunocompetent patients) have shown echinocandins to be similar in efficacy to Amph-B and superior to fluconazole in others (36).

C. Cryptococcus

Cryptococcus neoformans var. *neoformans* is the environmental yeast most commonly observed in LT recipients. It is capable of causing human disease ranging from mere colonization to meningitis, pneumonias, and disseminated disease. It is the third most common cause of IFD in transplant population. Mostly acquired by respiratory exposure, it can primarily involve respiratory tract or may spread to other organs via hematogenous route, but it also has a propensity for meninges. In SOT recipients, 75% of this population was symptomatic at the time of diagnosis, which deteriorated to progressive disease. In another study of SOT recipients, more than 50% had pulmonary disease with almost one-third either having asymptomatic or incidental pulmonary nodule findings. Cough and chest discomfort with low-grade fever were more common clinical findings (37–41).

It is imperative to establish the presence of extrapulmonary cryptococcal (disseminated disease) in transplant recipients. Lumbar puncture needs to be performed since treatment implications change. Culturing *C. neoformans* from a site (respiratory or extrapulmonary), histopathological tissue evidence, presence of cryptococcal antigen from serum or CSF, and corresponding radiological findings (cavitating nodules and pleural effusions more consistent with progressive disease) help to formulate the diagnosis.

Serum cryptococcal antigen has been found to be positive in all patients with disseminated diseases, while 73% of isolated pulmonary infections had positive serum cryptococcal antigen (42).

Nevertheless, one has to remember that serum cryptococcal antigen can be negative in patients with meningitis only. Thus, when positive, it reflects the disease (43).

Treatment for cryptococcal pulmonary disease involves induction (Amph-B/lipid formulation) followed by maintenance therapy (fluconazole) as suggested by IDSA. In mild cases, oral fluconazole or itraconazole can be used singly as well. On the other hand, combination of Amph-B (usually 0.7 mg/kg/day) and flucytosine (100 mg/kg/day) are the drugs of choice in central nervous system (CNS) involvement. Therapy duration can extend to more than six months depending on the response. There is almost no data regarding chronic suppression with fluconazole in transplant recipients but is usually followed in majority centers (40,44).

II. Non-*Aspergillus* Molds

In the last two decades, other molds like Zygomycetes, *Scedosporium*, *Fusarium*, and *Paecilomyces* are seen more frequently in SOT and account for 25% to 27% of mold infections currently (45).

A. Zygomycetes

In this class of fungi, the most common genera are *Rhizopus*, *Mucor*, *Rhizomucor*, and *Absidia*. They are ubiquitous organisms that appear to have thin-walled, ribbon-like hyphae (Fig. 4A). Zygomycetes have mainly been studied in hematological

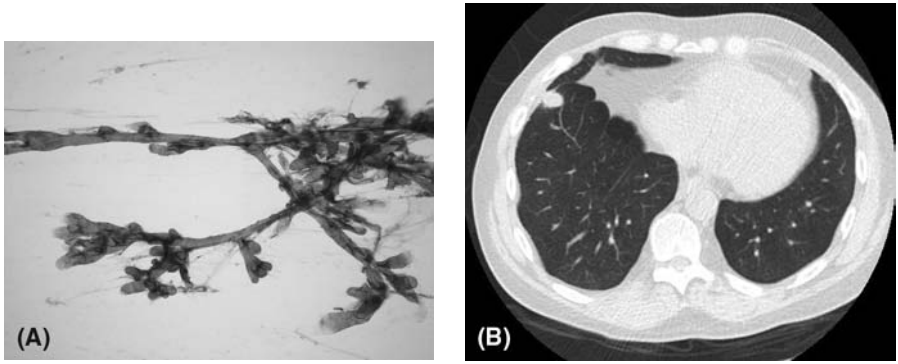

Figure 4 (*See color insert*) **(A)** Micrograph of thin, broad ribbon-like hyphae of mucor with focal bulbous dilatations and irregular branching (original magnification 300×). (**B**) Solitary pulmonary nodule in lung graft on chest CT imaging in a patient with pulmonary mucormycosis.

malignancies and diabetic population, and the risk factors recognized are diabetic ketoacidosis, trauma, iron chelation with deferoxamine, thymoglobulin use, broad-spectrum antibiotics, and neutropenia (46). It is considered a rare complication in LT recipients and mostly associated with augmented immunosuppression.

Zygomycosis has a broad clinical spectrum, and it extends from cutaneous involvement to angioinvasive form. They can infect lungs, sinuses, skin, soft tissue, and CNS. Bronchial anastomotic mucormycosis is a very rare but catastrophic infection.

Zygomycosis is associated with high mortality and morbidity and requires a high level of suspicion to recognize it. In one study, 100% mortality in the disseminated group and 42% in the localized disease group was noted (47). Rapid diagnosis is necessary and requires deep tissue invasive biopsies. Radiological findings are not specific but usually may begin with a focal pulmonary nodule (Fig. 4B) (48). It is difficult to culture and serological testing is unreliable.

The lipid formulation of Amph-B is considered the drug of choice. Posaconazole can be used as salvage therapy. Treatment involves the use of both antifungals and disease control with surgical resection and debridement (49).

B. *Scedosporium* Spp.

There are two main species in this saprophytic mold group, *Scedosporium apiospermum* and *S. prolificans*. *S. apiospermum* is the anamorph for *Pseudallescheria boydii. Scedosporium* spp. are respiratory tract colonizers especially of abnormal airways, seen in cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disease (COPD), and LT. The presentation can vary from colonization to invasive infection. The disease spectrum extends from post-traumatic cellulitis, osteomyelitits, septic arthritis (usually immunocompetent) to pneumonia, meningitis, and ophthalmitis, endocarditis, and brain abscesses (hematological malignancies, organ transplant, and HIV). They account for 20% of non-*Aspergillus* molds (NAM) infection in organ transplant recipients. Fifty three percent of *S. prolificans* infections were associated with fungemia in a study by Husain et al. (50). Histologically, they cannot be differentiated in tissue sections. Caution has to be exercised in identification since it resembles *Aspergillus* and appears

as mats of septate hyphae. The late emergence of this infection in organ transplants has been attributed in some studies to use of antifungal prophylaxis, though without much corroborating data (51).

The bane of these infections, especially *S. prolificans*, is its multidrug-resistant nature, including Amph-B among other antifungals. Voriconazole appears to be the most effective agent as compared to all others for *S. apiospermum* (52). Combination testing with itraconazole and terbinafine has shown synergy in vitro (53). No effective antifungal therapy exists against *S. prolificans*, although a combination of voriconazole and terbinafine has been used.

Lack of effective antifungals, adjunct but disfiguring surgical interventions required for controlling disease, and frequent relapses eventually yield fatal outcomes showing a 58% mortality rate in invasive *Scedosporium* infections (50).

C. *Fusarium* Spp.

Fusarium spp. like others in this group has mostly been studied in bone marrow transplant and hematological malignancies. It is widely distributed in nature, with 12 species, *Fusarium solani* being the most common and the most virulent. The disease manifestation varies from localized sinus tract infection to dissemination. Fusariosis (invasive) has a somewhat similar profile to IA, with features such as angioinvasion and pulmonary cavitations. SOT and hematopoietic stem cell transplant (HSCT) behave differently from LT group since more localized disease with cough, fever, and chest pain was seen in LT recipients. HSCT patients, on the other hand, had more frequent fungemia with very high mortality. Mortality in SOT was approximately 33% (54,55).

Fusarium grows rapidly in culture medium and phialides, macroconidia, septate hyphae, and conidiophores can be seen microscopically. Radiological findings on CT scan in LT patients can show alveolar and interstitial infiltrates, thin-walled cavities, and nodules.

Reducing immunosuppression plays a major role in treatment. *Fusarium* has a poor susceptibility profile to most antifungals. Triazoles (voriconazole, posaconazole, and ravuconazole) have shown good results in treating fusariosis; however, the trend of using combination therapy with Amph-B is favored despite lack of data (15,54–56).

III. Endemic Mycoses

Histoplasmosis (*Histoplasma capsulatum*) is a common but asymptomatic infection in the immunocompetent population. Endemic valleys of Ohio and Mississippi Rivers see a whole host of presentations. Incidence in transplant population is not well known. The dangerous element with this infection is the very wide range of its presentation and a differential diagnosis profile, which involves common diseases like tuberculosis, sarcoidosis, and malignancy.

Pneumonias, cavitary lung disease, nodules, mediastinal lymphadenopathy, fibrosing mediastinitis with superior vena cava (SVC) syndrome, and pericarditis are the multiple ways it can present. Its detection via EIA in blood, urine, or BAL can help in diagnosing it faster. Blood cultures and tissue histopathology/cultures are also a key factor in aggressive management (57,58).

Blastomycosis (*Blastomyces dermatitidis*) is a rare occurrence in transplant recipients, but history and exposure in endemic areas is at times the only key to diagnosis. Presentation is highly variable and its acute form is usually diagnosed initially as community acquired pneumonia. After lung involvement, skin (subcutaneous nodules

with necrosis) and bone/joints are other common extrapulmonary sites. Aggressive culture sampling and tissue histopathological evidence are necessary. Pulmonary disease can be severe and dissemination is more common. Mortality is high in the latter group, up to 40% compared to immunocompetent hosts (59).

Treatment of both histoplasmosis and blastomycosis involves the use of lipid formulations of Amph-B with itraconazole as consolidation therapy depending on the severity of disease. Experience with AIDS population has been used as a guideline for treatment options in transplant recipients with emphasis on more aggressive therapy (60,61). Coccidioidomycosis, caused by a dimorphic fungus (*Coccidioides immitis* and *C. posadasii*), is usually a self-limiting disease, but can cause complications in healthy populations. Data from renal transplant cohorts showed that immunosuppression leads to more disseminated/extra pulmonary disease occurrence (skin and lymph node involvement) (62). Endemic areas such the southwestern United States and South America are more susceptible to disease. Attention to the pretransplant serology in addition to adequate prophylaxis post transplant will likely avoid reactivation. It is suggested to continue lifelong prophylaxis in seropositive individuals (63). Very limited data is available in the context of LT recipients. In SOT recipients, pneumonia with fever and cough may be the most common symptoms. Triazoles (fluconazole and itraconazole) are the drugs of choice. Some studies done in the HIV population showed combinations of Amph-B and triazole to yield good results in disseminated disease (64–66).

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31
Viral Infections

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I. Introduction

Viral infections in lung transplant recipients occur commonly. With the burden of lymphoid tissue present in the organ, lung transplant recipients may receive an increased burden of viruses that are latent in lymphocytes including cytomegalovirus (CMV). In addition, the lung and its epithelium interact directly with the environment increasing its exposure to additional viruses that are transmitted through this route. In this chapter, the epidemiology, risk, and impact of viral infections after lung transplantation will be discussed.

II. Cytomegalovirus

CMV infection has been a topic of active research since the early days of lung transplantation. CMV is a member of the herpesvirus family; infection is often acquired early in childhood, and approximately two-third to three-fourth of adults are seropositive. CMV remains latent after primary infection and can reactivate under the influence of transplant immunosuppression in CMV-seropositive recipients, or it can be acquired de novo from a seropositive donor in the seronegative recipient (or less frequently from transfusions or community exposures).

Internationally accepted definitions have distinguished between CMV infection (which includes asymptomatic viremia) and symptomatic CMV disease (which includes both the flu-like "CMV syndrome" and tissue-invasive CMV disease, in which biopsy of involved tissue shows characteristic CMV inclusions) (1). Of all solid organ recipients, lung transplant recipients appear to be at highest risk of CMV disease, especially CMV pneumonitis. In the early years of lung transplantation, CMV pneumonitis occurred in over 50% of recipients in some series, with devastating and sometimes fatal consequences (2,3). Risk factors include D+/R– (donor-positive, recipient-negative) serostatus (4) and intensified immunosuppression including antilymphocyte therapy (5). In the current era, the incidence of symptomatic CMV disease has significantly decreased with the advent of prophylaxis and quantitative viral load monitoring (6), but it is still a

source of morbidity. In pediatric lung transplant recipients, a first episode of CMV viremia is associated with higher risk for retransplantation or death between days 90 and 365 (7).

CMV prevention programs generally involve prophylaxis, preemptive therapy, or both (3,8–20). "Prophylaxis" refers to administration of antiviral therapy to all patients in a given group. In general, CMV prophylaxis has utilized ganciclovir derivatives (IV and oral ganciclovir, and more recently valganciclovir) and/or immunoglobulin preparations (CMV hyperimmune globulin or unselected intravenous immunoglobulin) (21–24). Acyclovir has much less effect against CMV but does provide prophylaxis against herpes simplex and varicella-zoster virus (VZV). "Preemptive therapy" refers to monitoring with a sensitive early detection test for CMV and only administering antiviral therapy to those who develop a positive test (25–27).

Prophylaxis has altered the CMV landscape considerably (13,15,18). Most studies have demonstrated a significant reduction in CMV events, provided that the duration of prophylaxis is adequate (at least 3 months) (15,28), although "late CMV" can occur. Recent work using valganciclovir has suggested that long-term viral suppression with durations of six months or longer may provide additional benefit, although cost and toxicity must also be considered (15). Because of the risk of CMV occurring after the discontinuation of prophylaxis, some authors have championed the concept of indefinite continued prophylaxis (28).

Diagnosis of CMV infection has been revolutionized by the development of quantitative molecular assays including polymerase chain reaction (PCR) and the hybrid capture CMV DNA assay (29–36). These tests allow for early detection, monitoring during and after an episode, and determinations of viral load that correlate with severity of clinical disease (37). Tissue culture is labor intensive and lengthy; shell-vial centrifugation culture provides a faster answer than tissue culture but lacks sensitivity. The pp65 antigenemia assay is a semi-quantitative assay that reports the number of infected cells per slide and has been used for both preemptive monitoring and diagnosis of clinical syndromes.

BAL fluid obtained during protocol bronchoscopies affords another opportunity to monitor for CMV. Surveillance biopsies may reveal clinically unsuspected CMV pneumonitis (38,39). While viral cultures of BAL fluid do not always predict development of CMV pneumonitis (40), quantitative viral load measurements on BAL fluid may correlate better than blood viral loads with CMV pneumonitis (41–44).

Various measures of CMV-specific immunity constitute an active area of research (45–50) and may become routine tests in the future. These are of particular interest in the D+/R– patient, in whom variable lengths of time are required to develop responses that limit CMV recurrences. In addition, studies of expression of particular genes such as CMV immune evasion genes (51), LIR-1 (52), IL-10 (53), and mixed-genotype CMV infections (54,55) provide additional insight into the mechanisms leading to clinical phenomena such as viral persistence. In the future, CMV prevention strategies may be individualized based on CMV-specific host responses.

Treatment for CMV infection traditionally was IV ganciclovir. However, valganciclovir, an oral drug with bioavailability superior to that of the previous oral ganciclovir formulation, has provided an opportunity for oral therapy of active CMV infection as well as prophylaxis. Use of valganciclovir as a therapy was found to be generally safe and effective in the VICTOR study, which involved mostly kidney transplant recipients and some patients with tissue-invasive disease. Many centers are currently using valganciclovir, particularly for low-to-moderate level viremia with mild

or no symptoms. However, many clinicians still prefer IV ganciclovir when the patient has marked symptoms, a high viral load, or tissue-invasive disease. The VICTOR study also pointed out that two-week courses of therapy are probably too short in many cases, and CMV DNA monitoring should be continued as a guide to length of therapy. Monitoring after the end of therapy is also important to detect recurrences of viremia early. Reduction of immunosuppression can help with resolution of a CMV episode and can also help to prevent recurrences.

Problems with these strategies include the development of neutropenia or neutrophil abnormalities in some patients on longer-term ganciclovir and valganciclovir (56), and also the risk of ganciclovir-resistant CMV, which can be clinically severe (57–59). Antiviral resistance can occur during prolonged or repeated exposure to ganciclovir derivatives, particularly in D+/R– patients with high or rapidly rising viral loads (59,60). Interestingly, in two lung recipients who acquired CMV from a single donor, one developed resistance on therapy whereas the other's CMV remained ganciclovir sensitive (61). Although some have blamed prophylaxis for this complication, ganciclovir-resistant CMV can also occur after preemptive therapy (26). Drugs for treating resistant CMV include foscarnet, combination ganciclovir plus foscarnet, and cidofovir. Both foscarnet and cidofovir are potentially nephrotoxic, and resistance to these drugs can occur as well. The investigational drug maribavir and the rheumatoid arthritis drug leflunomide have been used in some patients with CMV refractory to standard drugs. Adjunctive use of CMV hyperimmune globulin along with antivirals has been recommended in therapy of CMV pneumonitis and other tissue-invasive disease.

One area of intense interest has been the immunologic effects of CMV on the allograft and the possible contribution of CMV to risk for bronchiolitis obliterans syndrome (BOS). CMV infection in the allograft stimulates an immune response that leads to upregulation of certain cytokines that may affect allograft function (20,62–67). Studies have differed in that some have found a significant association of CMV (either serostatus or clinical infection) with risk for BOS development, whereas others have not (6,9,17,68–76). Different definitions of CMV infection, eras (77), treatment of CMV (6,78), immunosuppressive regimens, rejection rates, and other factors may account for these conflicting results. In some studies, other viruses such as HHV-6 appear more significant than CMV in this regard (79). Further studies of the complex relationships between CMV, acute rejection, alloimmunity, and other factors may shed further light on the role of CMV as a trigger for events within the allograft.

III. Other Herpesviruses

Like CMV, the other herpesviruses establish latency after primary infection and may reactivate with immunosuppression after transplantation. Herpes simplex virus (HSV) is prevalent and causes oral and/or genital ulcerative lesions in both immunocompetent and immunocompromised hosts. In the early era of lung transplantation, HSV pneumonitis occurred in a significant proportion (10–20%) of lung and heart-lung transplant recipients with associated deaths (80–82). Since the institution of post-transplant antiviral prophylaxis against CMV or HSV (for CMV D–/R– patients), reports of significant HSV infection after lung transplant have disappeared from the literature.

VZV is another herpesvirus with significant consequences after lung transplantation. In adult lung transplant recipients, reports of primary varicella infection are rare; however, reactivation has been reported with an incidence from 12% to 15% in

retrospective analyses (83–85). The majority of the cases are localized to a single dermatome, occur at least one year post transplant, and approximately 20% to 43% experiencing post-herpetic neuralgias. Disseminated zoster disease is less common, although it may be severe (86). Suspicion of VZV reactivation and early therapy may be beneficial.

Along with CMV discussed above, human herpesviruses 6 and 7 (HHV-6 and HHV-7) are beta-herpesviruses. These newly recognized viruses are ubiquitous with serologic prevalence, indicating prior exposure in greater than 95% of the general population for both viruses. In longitudinal studies, HHV-6 is frequently isolated one to four months following solid organ transplantation. Clinical correlations with infection have included asymptomatic reactivation (87), encephalitis (88), fungal infection (88,89), fever, and death (90). After lung transplantation, detection of both HHV-6 and HHV-7 occurs early in the post-transplant period including during the administration of antiviral prophylaxis against CMV. Lehto et al. reported positive antigenemia for HHV-6 (91%) and HHV-7 (50%) after lung transplantation, while Jacobs et al. showed 66% of recipients developed HHV-6 reactivation within three weeks of transplantation (91,92). Additional studies have evaluated the presence of HHV-6 and/or HHV-7 in bronchoalveolar lavage fluid with an incidence of 20% to 28% for HHV-6 and 12% to 20% for HHV-7 post transplant (76,79,93). However, evaluation for an association between HHV-6 reactivation and the risk of BOS is controversial and requires additional investigation (79,93).

IV. Epstein-Barr Virus

Epstein-Barr virus (EBV), like the other herpesviruses, develops primary infection and then remains latent in the host until immunosuppression and host factors allow reactivation. After transplantation like CMV, risk for EBV infection and reactivation depends on the donor and recipient serostatus. EBV D+/R– lung transplant recipients are at risk for primary EBV infection, while EBV R+ recipients are at risk for EBV reactivation. EBV is related to a spectrum of disorders after transplantation ranging from asymptomatic viremia to infectious mononucleosis to post-transplant lymphoproliferative disease (PTLD) and malignant neoplasia. Risks for PTLD include EBV D+/R– serostatus, younger age at transplant, and relative level of immunosuppression (94,95).

Diagnosis of EBV-related infection relies on clinical suspicion. Common presentations for EBV infection include prolonged fever and malaise. Physical finding may include lymphadenopathy, exudative tonsillitis or pharyngitis, and hepatospenomegaly. In conjunction with physical examination, laboratory testing may reveal elevated transaminases, elevated LDH, and leukopenia with atypical lymphocytes. Serologic testing is generally not useful for diagnosis of acute episodes of EBV infection. However, the detection of EBV DNA in the peripheral blood with molecular assays has gained acceptance to detect the presence of EBV replication. Molecular assays of both peripheral blood and bronchoalveolar lavage fluid have been evaluated to assess the risk for PTLD but require further validation before routinely employed (96,97). PTLD should be suspected with any unexplained lung nodules or lymphadenopathy, especially in patients with active EBV infection, although some PTLD is EBV negative. Further, PTLD can occur in nearly any organ in the body including isolation to the central nervous system. Risk, diagnosis, and management of PTLD are discussed more completely in chapter 36, “Malignancies Following Transplantation.”

V. Parvovirus

Parvovirus B19 is a common community-acquired infection of childhood, characterized by a "slapped-cheek" rash and low-grade fever. In adult women who acquire primary infection, a multifocal arthritis syndrome may ensue, and fetal loss in pregnant women has been described.

In the immunocompromised host, including HIV-positive and solid organ transplant patients, the primary manifestation of parvovirus is severe anemia and sometimes pure red cell aplasia (98–100). In one study, 3 of 54 lung transplant recipients with unexplained anemia were positive for parvovirus on peripheral blood PCR (98). Another prospective study identified markers of parvovirus infection in 24/62 thoracic organ recipients, of whom 19 had hematologic abnormalities and 5 were asymptomatic (99). Since this virus attacks erythroid progenitors, the reticulocyte count is low and bone marrow biopsies show a paucity of cells of the erythrocyte lineage. Sometimes abnormal cells such as giant proerythroblasts are seen. Diagnosis is best made by a PCR on peripheral blood and/or a bone marrow examination.

Therapy for documented parvovirus infection is usually with IVIg; no specific antiviral therapy exists. Repeated doses of IVIg may be necessary to clear the infection, which may persist for several months or more. Reduction of immunosuppression can be helpful.

VI. Hepatitis B Virus

Hepatitis B infection has potential impact after lung transplantation in two major ways: (*i*) when the recipient is hepatitis B surface antigen (HBsAg+) positive and (*ii*) when the donor is HBsAg negative and hepatitis B core antibody positive (HBsAg–, HBcAb+). HBsAg+ thoracic recipients are at risk for worsening of liver disease under the influence of immunosuppression, but modern anti-HBV drugs such as lamivudine and entecavir can reduce this risk. A study from the joint ISHLT/UNOS thoracic registry identified 30 HBsAg+ heart transplant recipients prior to the year 2000; of these, 37% had evidence of active liver inflammation or cirrhosis (101). Shitrit et al. reported on four HBsAg+ lung recipients, of whom two developed high HBV-DNA levels; one had a lamivudine-resistant strain and responded to adefovir; the other responded to lamivudine reinstitution (102). Intensification of antirejection therapy may precipitate HBV reactivation in this setting (103).

Donors who are HBsAg+ are generally not used, except in highly endemic areas. Use of HBsAg–, HBcAb+ ("core-positive") donors, on the other hand, is associated with a low but real risk of HBV transmission in nonhepatic organ transplantation. Successful HBV vaccination prior to transplant and use of post-transplant prophylaxis can further reduce this risk. Shitrit et al. reported on 7 patients who received prophylactic lamivudine for 12 months after lung transplantation from a core-positive donor, none of whom developed clinical HBV (102). Hartwig et al. described 29 lung recipients with core-positive donors, in whom there was no impact on 1-year survival and no clinical HBV disease. All survivors had negative HBV DNA and/or HBcAb at follow-up (104).

Use of HBsAg–, HBcAb+ organs is reasonable given the shortage of donors. Monitoring of HBV-DNA as well as HBV serology post transplant is recommended. Pretransplant vaccination against HBV should be offered to all seronegative lung transplant candidates, although seroconversion may be suboptimal. A strategy consisting of higher-dose HBV vaccine (40 μg at 0–6 months), plus use of booster doses in nonresponders, may be associated with a higher seroconversion rate (53% vs. 7%) (105).

VII. Hepatitis C Virus

The prevalence of hepatitis C virus (HCV) seropositivity among potential lung transplant recipients is 1.9% (106). The impact of HCV seropositivity on morbidity and mortality in lung transplant recipients is unresolved. Although the natural course of HCV infection is prolonged in immunocompetent individuals, HCV-seropositive thoracic organ recipients could potentially develop accelerated disease progression due to higher viral loads with immunosuppression. However, this has not been demonstrated by recent data. A study from the joint UNOS/OPTN lung transplant registry identified 170 HCV-seropositive recipients from 2000 to 2007 and reported no difference in survival rates at one and five years post transplant compared with HCV-negative recipients (107). A smaller single center series demonstrated similar early survival and graft function success in HCV-positive and HCV-negative recipients (106). In addition, although post-transplant viral HCV RNA levels increased markedly, concurrent liver dysfunction was not present in this group of lung transplant recipients.

In a 1999 survey of lung transplant centers, 72% of centers surveyed indicated that they consider HCV-seropositive patients for transplantation using virologic and/or histologic data to determine candidacy (108). Sustained virologic response to antiviral therapy in lung transplant candidates has been reported in small numbers (109). The influence of HCV genotype on the post-transplant course in organ transplantation remains controversial in general without sufficient data in lung transplant recipients at this time. The impact of hepatitis C in lung transplantation remains undetermined, but early evidence indicates that transplantation can be successful in HCV-seropositive candidates.

VIII. Respiratory Viral Infections

The community-acquired respiratory viral infections (CARV) include multiple long-standing viral pathogens such as Orthomyxoviridae (influenza A and B), Paramyxoviridae (respiratory syncytial virus, parainfluenza viruses), picornaviruses (rhinovirus, enteroviruses), and adenoviruses. In addition, emerging respiratory viruses have been increasingly reported in lung transplant recipients and include additional Paramyxoviridae (human metapneumovirus), human coronaviruses (HC0V-229E, NL63, HKU1, and OC43), and a Parvoviridae (human bocavirus) (110–112).

Multiple epidemiologic studies have evaluated for the presence of CARV in lung transplant recipients. Presentation of viral episodes ranged from asymptomatic to vague upper respiratory tract symptoms including rhinorrhea and nasal congestion to lower respiratory tract symptoms including cough, fever, and respiratory failure. Recovery of viral pathogens is limited to 3% to 5% of specimens in asymptomatic lung transplant recipients (113,114). However, in symptomatic lung transplant recipients, viral recovery is more substantial (114–117). In a prospective single-season study, Milstone et al. found that 64% of subjects developed an episode suspicious for CARV with the recovery of a virus in 34% (116). Garbino et al. reported a recovery rate of 55% in a year-long evaluation of bronchoalveolar lavage fluid (114), while Kumar and colleagues reported 66% of subjects with a clinical CARV had virus identified (117). An array of viruses was recovered in these studies including rhinovirus, influenza, parainfluenza, adenovirus, and respiratory syncytial virus.

Viral transmission has been reported from the time of transplant until several years after transplantation. Donor transmission of both influenza and adenovirus appears

in the literature (118,119). After transplantation, viral recovery coincides with the pathogens circulating in the community (117,120). While most studies focus on single episodes, persistent infection with rhinovirus for up to 15 months has been reported by Kaiser et al. (121) in 3 lung transplant recipients.

CARV may have impact beyond the symptoms at the time of acute infection as some epidemiologic studies have linked episodes of CARV with BOS. Retrospective evaluations reported subsequent development of BOS in 32% to 60% of subjects with diagnosis of preceding CARV (119,122–125). However, retrospective studies in pediatric and prospective studies in adult lung transplant recipients reveal conflicting results. Recently reported data in nearly 600 pediatric recipients did not show as association between CARV and BOS at one-year post transplant (120). The prospective single-season study by Milstone et al. found no association between CARV and BOS (116). In contrast, a case-control study of those with and without CARV revealed an association between CARV and subsequent BOS with 18% of the symptomatic subjects developing BOS compared to none of the controls (117). Hopkins and colleagues reported a significant incidence of BOS six months after CARV for RSV infections but not for human metapneumovirus (115). With the improvement of molecular diagnostics for respiratory virus (126) and increased surveillance, future studies including potential mechanisms are required to evaluate the potential interaction between CARV and BOS.

Prevention is the primary method for avoiding CARV and any potential downstream effects. For all viruses, standard precautions including avoidance of sick contacts and appropriate hand hygiene are paramount. In addition, viral-specific precautions include yearly influenza vaccination for all lung transplant recipients and their close contacts (127), prophylaxis against influenza in the event of known exposure, and palivizumab for pediatric patients under two years of age with chronic lung disease. The importance of infection control in the hospitalized patient with CARV cannot be underestimated to prevent spread within the hospital setting. Standard, contact, and droplet precautions should be implemented with suspected CARV and can be narrowed based on the virus identified following local and national guidelines. Treatment after CARV is diagnosed depends on the virus recovered. Influenza therapy is dependent on the susceptibility of the circulating strains and may vary over time. Therefore, treatment should follow national and international guidelines based on the most recent reports. Therapeutic interventions for the RSV have included ribavirin (aerosolized, IV, or oral) with or without concomitant steroid and IV immunoglobulin in several case series (128–131). Other paramyxoviral infections have also been successfully treated with ribavirin with Raza et al. reporting a single case of human metapneumovirus and McCurdy et al. reporting parainfluenza treatment in five subjects (131,132). Adenoviral infections were treated effectively with cidofovir and IV immunoglobulin in three of four pediatric lung transplant recipients identified by Doan and colleagues (133).

IX. Conclusions

Viral infections are important contributors to post-transplant morbidity and mortality, even in the era of monitoring and prophylaxis. Varying presentations of viral infection require clinicians to remain vigilant during the post-transplant management of the lung transplant recipient. The use of pretransplant serology, prevention strategies, infection control measures, monitoring, prophylaxis, and early institution of therapy should be considered as a part of the care in every lung transplant center.

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32
Bacterial Infections After Lung Transplantation

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I. Overview

Infectious complications are the leading cause of morbidity and mortality at all time points following lung transplantation and are the cause of death in at least 50% of lung transplant recipients. Bacterial infections are responsible for the majority of the infectious complications following lung transplantation, with most of these infections occurring in the immediate post-transplant period (two weeks). Upwards of 80% of all infections in lung transplant recipients occur in the lung, mediastinum, and pleural space (1,2). Although infections are a considerable hazard in the lung transplant recipient, chronic rejection characterized histologically by obliterative bronchiolitis remains the major impediment to successful long-term outcomes in lung transplantation. Obliterative bronchiolitis afflicts two-thirds of patients and is the major predisposing factor for cumulative increased infectious risk following lung transplantation. The combined process of increasing immunosuppression to manage obliterative bronchiolitis coupled with markedly impaired lung function and mucus clearance dramatically raises the predisposition to infections in these patients. Infectious complications are the most common cause of death in patients who develop obliterative bronchiolitis. Furthermore, evidence exists that bacterial infections may play a role in the establishment of obliterative bronchiolitis by amplification or persistence of an inflammatory immune response to foreign antigens and providing another form of non-alloimmune lung injury (3,4). In fact, pilot studies of long-term antimicrobial antibiotic therapy have shown preliminary evidence of a positive influence on outcome of obliterative bronchiolitis (5).

Infectious risk following lung transplantation varies according to time from transplant (6,7). The large majority of infectious complications (~70%) occur in the first year following transplant with the majority of these infections clustered in the first month post transplant. In those patients less than one month post transplant, nosocomial drug-resistant pathogens such as vancomycin-resistant *Enterococcus* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) predominate. Sources include both donor and recipient lungs, central or peripheral venous or arterial catheters, urinary catheters, wound infections, and anastamotic leaks. *Clostridium difficile* infection (CDI) is also seen. Between one and six months post transplant is when the risk for the classic opportunistic infections that occur following transplant are seen; however, anastamotic leaks and CDI continue to be prevalent. Routine *Pneumocystis jirovecii* prophylaxis (PCP) with trimethoprim-sulfamethoxazole (TMP/SMX) is widely employed by almost all transplant centers, which does provide some antibacterial protection as well. Despite the use of TMP/SMX, breakthrough infections with *Nocardia* and *Listeria* species are

occasionally seen in this time frame. *Mycobacterium tuberculosis* (MTB) infections do rarely arise during this time period as well. Greater than six months post transplant, community-acquired pathogens causing pneumonia and urinary tract infections are seen. *Nocardia* and *Rhodococcus* infections have also been reported.

Risk is mitigated by a combination of exposures and immunosuppression effect. Lung transplant recipients possess a unique constellation of predisposing risk factors, most specifically for pneumonia. Decreased cough reflex, mucociliary clearance, and lymphatic drainage all contribute to risk of pneumonia (8,9). Hypogammaglobulinemia is another increasingly recognized contributory factor and appears to place patients at significantly higher risk for infection (10).

II. Prevention

A. Vaccination

Solid organ transplant recipients, including lung transplant recipients, are at high risk for invasive pneumococcal disease. Current recommendations are for universal pretransplant pneumococcal polysaccharide immunization among lung transplant candidates with post-transplant revaccination every two to five years. Despite these recommendations, one study found that only 62.4% of those patients referred for lung transplantation had undergone vaccination (11,12). Response rates to pneumococcal vaccines after lung transplant have not been previously studied. Use of the more immunogenic heptavalent protein conjugated vaccine has been considered in combination with the currently used polysaccharide vaccine, although no studies of this method's efficacy have been carried out in the transplant population (12).

Streptococcus pneumoniae infection in one study affected 6.4% of lung transplant recipients at a median of 1.3 years post transplant (13,14). In this study, all patients were receiving TMP/SMX prophylaxis at the time of infection, 71% of the isolates were resistant to TMP/SMX, and 57% were resistant to penicillin. All patients had been recommended to receive the 23 valent polysaccharide pneumococcal vaccine pretransplant, and all isolates were from the 23 valent polysaccharide vaccine-associated serogroups. Vaccination against tetanus and diphtheria has been shown to be generally safe, although no studies have been carried out in the lung transplant population (15). Immunity against diphtheria wanes over time in renal transplant recipients, although a booster generates a sufficient response in most patients (16). Vaccination and booster administration is likely safe and is therefore recommended, although the cost:benefit ratio is likely lower in adult lung transplant recipients in the United States, given that these pathogens are far less prevalent than pneumococcus after lung transplantation (12,17).

Haemophilus ***influenzae*** type B (Hib) vaccination is recommended in pediatric transplant recipients. It is also safe in adult renal transplant recipients and recommended in all solid-organ transplant recipients who are not immune (12,18–20). There is little information on *Neisseria meningitidis* vaccination in solid-organ transplant recipients, although it is logical to offer it in those transplant recipients who are at high risk (college aged, traveler to endemic areas/areas with outbreaks, military recruits, asplenic patients, and those with terminal complement deficiencies) (12).

The immunologic response induced by vaccines has raised concern about the theoretical potential for vaccination to trigger rejection. Most data about risk of rejection comes from heart and kidney transplant patients who have received the influenza vaccine. With the exception of one article that suggests influenza vaccination may be

associated with low-level rejection, all studies indicate that influenza vaccination does not trigger rejection (21–26).

B. Testing for Latent MTB

MTB after lung transplantation can arise from three clinical scenarios: (*i*) reactivation of latent primary MTB in the recipient, (*ii*) reactivation of MTB in the donor lung, or (*iii*) primary MTB in the recipient (27). The reported incidence is between 2.5% and 10% (27–31), depending on regional endemicity. MTB from the donor lung can go unrecognized, and there are reports of fatal MTB in a lung transplant recipient from a donor who was PPD-positive and never treated (32) and from a donor who was not known to be positive (33). Testing and prophylaxis of PPD-positive recipients, examination of recipient explants for evidence of old MTB, and querying lung transplant recipients about post-transplant exposures represent ways to identify at-risk patients. In one review, 50% of patients experience rejection at any time prior to diagnosis of MTB, and almost 40% had rejection episodes within six months of disease onset (34).

C. Peritransplant Prophylaxis

Recipient colonization or infection [especially with resistant gram negatives in the case of patients with cystic fibrosis (CF) or bronchiectasis] or donor infection can lead to peritransplant infection. Broad-spectrum antimicrobials are empirically administered immediately after transplant. Subsequently, peritransplant prophylaxis can be narrowed to cover organisms recovered from donor and recipient culture results. Virtually all donor lungs are at least colonized with microorganisms at the time of procurement. The majority of these organisms recovered at the time of harvesting (i.e., coagulase-negative *Staphylococcus* and diptheroids) would be considered to be low risk for post-transplant infection. However, significant pathogens (e.g., *S. aureus*, *S. pneumoniae, H. influenzae*, and *Pseudomonas aeruginosa*) can lead to early post-transplant pneumonias (35,36). Obtaining samples of the donor lung via fiber-optic bronchoscopy for microbiologic evaluation is a necessary part of management of the post-transplant recipient. As mentioned above, broad-spectrum antimicrobial perioperative coverage is routinely employed. If a potential pathogen is recovered from the donor specimen at our institution, we conservatively treat these patients with a two-week course of directed therapy. Because of the nature of the disease process and the recurrent infections and colonization seen in CF, these patients pose challenges in the immediate post-transplant care. Despite pretransplant colonization with potential pathogens, CF patients are not at greater risk for post-transplant infectious complications (2). Some centers do advocate either pre- or post-transplant sinus surgery in CF patients to eliminate potential infectious reservoirs. The decision to withhold lung transplantation in a CF patient who is colonized with multiply resistant bacteria (i.e., *Burkholderia cepacia*, *P. aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter*, or *Alcaligenes xylosoxidans*) should be decided by the individual transplant center. Transmission risk and death from donor-derived infection are relatively low if proper antimicrobials administered (37,38).

III. Site-Specific Diseases

A. Pneumonia

Pneumonia is the most frequently encountered infection following lung transplantation (39). One study performed over 15 years with 202 patients found that 178 patients got

859 infections with 944 pathogens. Lung infections were the most common (559, 65.1%), with *P. aeruginosa* as the most common pathogen (40). In patients greater than six months post transplant, community-acquired pathogens such as *S. pneumoniae* and *Legionella* species should be considered, as should viral respiratory pathogens such as influenza, parainfluenza, and respiratory syncytial virus. Urinary antigen tests exist for both *S. pneumoniae* and *Legionella pneumophila*. In the case of *Legionella*, urinary testing only diagnoses *L. pneumophila* serotype 1; therefore, infection with other serotypes would need to be diagnosed by culture. *Legionella* can be nosocomially or community acquired (41–43).

Secondary bacterial pneumonia after viral lower respiratory tract infection is an important cause of morbidity and mortality. It is responsible for up to 25% of influenza-associated deaths. *S. pneumoniae*, *S. aureus*, and *H. influenzae* are the prevalent pathogens in normal hosts (44–47). This syndrome should be suspected in those patients who initially improve after a viral illness and then experience a recrudescence of fever or pulmonary symptoms such as cough, purulent sputum, or new pulmonary infiltrates.

Recent work suggests that there may be a relationship between persistent airway colonization with pseudomonads and bronchiolitis obliterans (BO) (48–50). Additionally, bile acid aspiration from gastroesophageal reflux disease (GERD) and pulmonary colonization with *P. aeruginosa* appear to be linked (51), as are GERD and BO (52). The relationship between chronic airway colonization, GERD, and BO is the subject of considerable ongoing research.

B. Bacteremia

In one study, bacteremia affected 9.4% of lung transplant patients, with *Staphylococcal* species being the most predominant pathogens (40). Multidrug resistance was seen in almost 50% of organisms causing bloodstream infections after lungs transplant (at an average of 172 days post transplant), and pulmonary infection was the most common source of drug-resistant gram-negative bacteremia. Mortality at 28 days in those patients with bacteremia was high (25%).

C. Other

Urinary tract infection affected 3.1% of patients in the previously cited study, with the prevalent pathogen being *P. aeruginosa* (40). Cutaneous infections affected 5.5% of patients, with the prevalent pathogens being *Staphylococcal* species (40). CDI affects 7.4% of lung transplant recipients, with the main risk factor being antibiotic exposure. Diarrhea warrants a workup for non-CDI etiologies (especially in patients with a travel history or from regions of high gastrointestinal pathogen endemicity). For patients with CDI, directed therapy with metronidazole or vancomycin should be initiated depending on severity of disease (53,54).

IV. Therapy

Therapy of post-transplant bacterial infections should be influenced by time post transplant and culture results. Obtaining cultures of blood, urine, and sputum as early in the infectious work-up as possible is critical as these are the usual sources. Early removal of central venous catheters, arterial catheters, and urinary catheters is also important. In the first month after transplant, nosocomial pathogens predominate, and empiric therapy should have broad-spectrum coverage. In one study looking at mortality

in the first month post transplant, bacterial etiology accounted for the majority of deaths (primarily attributable to pneumonia and catheter associated bacteremia) (55). Interestingly, multidrug-resistant pathogens such as *Acinetobacter*, which are classically seen during this time period, are increasingly being identified late (greater than six months) in the post-transplant course (56). Mortality is higher in those thoracic transplant recipients infected with nosocomial pathogens (57).

A. Antibiotic Choice

Directed antimicrobial therapy depends on the pathogen causing disease. The emergence of multidrug-resistant pathogens makes this choice particularly challenging, and susceptibility data should always guide therapeutic decisions. MRSA can be treated with vancomycin, linezolid, or daptomycin, although daptomycin should be avoided as therapy for MRSA lung infections. VRE can be treated with daptomycin or linezolid. Gram-negative pathogens producing extended spectrum β-lactamases (ESBLs) or with AmpC mediated resistance (both of which confer resistance to many β-lactam antibiotics) can be treated with carbapenems. *Acinetobacter* isolates are frequently resistant to most antibiotics and are usually treated with carbapenems or colestimethate. Consultation with an infectious diseases specialist is recommended. Table 1 lists increasingly prevalent multidrug resistant pathogens and reasonable empirical antimicrobial coverage. As always, local susceptibility data, culture-specific susceptibility results, and infectious diseases guidance should be employed.

Less prevalent pathogens include *Nocardia* (which affects about 1.9% of lung transplant recipients), *Listeria*, and *Rhodococcus*. For *Nocardia*, treatment with TMP/SMX is classically administered, although given that many patients are on this medication when breakthrough infection occurs, combination or alternative therapy (often with carbapenems, cephalosporins, or fluoroquinolones) should be considered (58,59).

Table 1 Empiric Therapy for Emerging Multidrug-Resistant Pathogens

Pathogen	Common sites of infection	Empiric therapy
Community-acquired MRSA	Skin and soft tissue	Vancomycin
	Pneumonia (often post viral)	Linezolid
	Bacteremia	Daptomycin (not for pneumonia)
ESBL or AmpC organisms	Pneumonia	Carbapenems (note that Ertapenem has no *Pseudomonas* coverage)
	Bacteremia	
	Intra-abdominal	
CDI	Gastrointestinal tract	Metronidazole or Vancomycin (oral) depending on disease severity
S. maltophilia	Lung	TMP/SMX
	Sinuses	
	Skin	
	Bacteremia	
Acinetobacter	Pneumonia	Colestimethate
	Bacteremia	Imipenim-cilastatin
VRE	Bacteremia	Daptomycin
	Pneumonia	Linezolid

Listeria is occasionally a pathogen after solid organ transplantation, and it is usually treated with ampicillin. There is one report in the literature of this infection complicating a lung transplant (60). There is one report of *Rhodococcus* infection after lung transplant in the literature (61). Treatment usually consists of multiple agents and should be guided by susceptibility results and infectious diseases specialist recommendations. There are reports of MTB and nontuberculous mycobacteria complicating lung transplant (29,62). Therapy usually consists of three to four antimycobacterial drugs and should be guided by susceptibility data and infectious diseases specialists. Rifampin, which is frequently a component of theses regiments, interacts with multiple immunosuppressive agents.

V. Minimizing Risk

Nosocomial disease transmission is an important cause of infection, especially with multidrug-resistant organisms. Outbreaks in transplant populations, especially with multidrug-resistant pathogens, have been curtailed with effective infection control strategies involving proper use of contact isolation and hand hygiene (63–65). Such practices should be routinely employed. At the very minimum, aggressive hand hygiene should be routinely utilized in the care of the lung transplant recipient.

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Post-Transplant Lung Pathology

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I. Pathology of Lung Transplant Rejection

The histologic evaluation of lung allograft rejection is performed on formalin-fixed paraffin-embedded tissue obtained by transbronchial biopsy, either scheduled, such as for a surveillance protocol, or when clinically indicated in the symptomatic patient. Features of rejection are patchy, and to improve sensitivity of the biopsy, a consensus statement by the Lung Rejection Study Group (1) recommends that 5 fragments of alveolated lung, each containing bronchioles and more than 100 alveolar spaces, be examined. Importantly, obtaining five appropriate tissue fragments may require greater than five transbronchial biopsies, and this is especially true when looking for features of bronchiolitis obliterans (BO). If the biopsies contain alveolated lung and bronchioles but do not meet the minimum assessable criteria, grading should be done as usual, with a diagnostic comment giving the number of lung fragments and indicating that the findings may not be entirely representative of allograft changes. If no alveolated lung or no airway is present, the type of rejection should be indicated by the appropriate letter, followed by an "X" (see later). Three hematoxylin- and eosin-stained levels should be examined. Special stains for fungus and for fibrosis are done if indicated. An immunohistochemical stain for cytomegalovirus (CMV) is very helpful.

A. Antibody-Mediated Rejection

Antibody-mediated rejection, also called humoral or hyperacute rejection, is a rare phenomenon, with only a few documented case reports in the literature. This entity, characterized by activation of inflammatory, complement, and coagulation cascades due to binding of preformed antibody to endothelium (2), is not included in the standardized classification because of the paucity of cases. In the appropriate clinical setting of progressive respiratory failure within minutes to hours after transplantation, histologic findings of diffuse alveolar damage (DAD), fibrin thrombi, vasculitis, intra-alveolar hemorrhage, and interstitial neutrophilia are suggestive of hyperacute rejection.

B. Acute Cellular Rejection

Release of inflammatory chemokines and upregulation of cellular adhesion molecules because of mononuclear inflammatory cell infiltrate characterize acute cellular rejection. Acute rejection is common around three months post transplant, and most episodes are diagnosed in the window of two to nine months post transplant. There is a broad range, however, of days to years (3), during which acute rejection may occur. Because aspiration and infection may precipitate episodes of acute rejection (4,5), it is important to

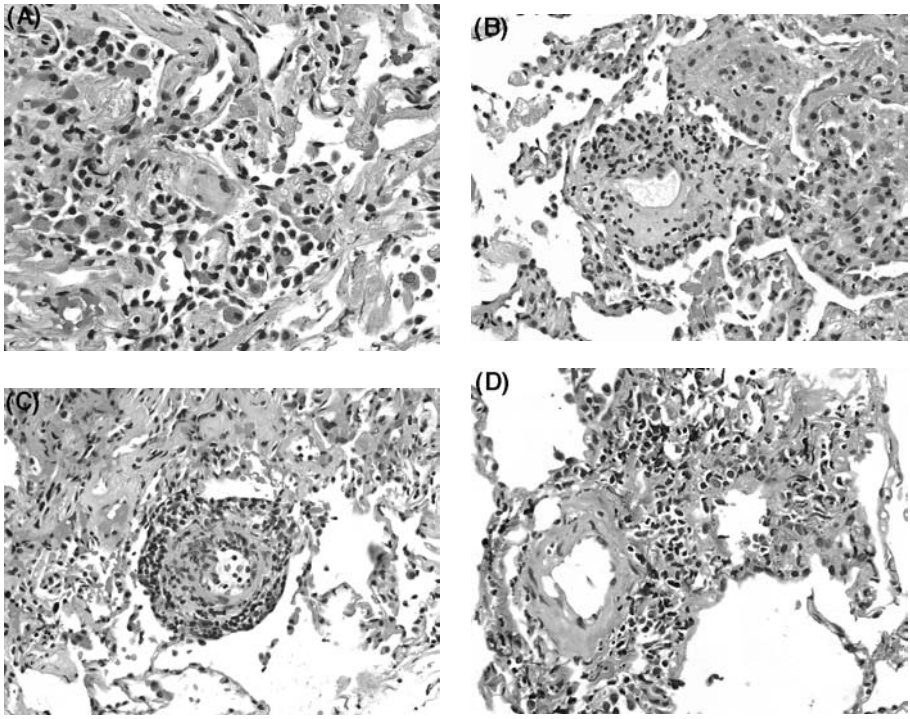

Figure 1 (*See color insert*) Acute cellular rejection, grade A. (**A**) No acute rejection, grade A0: no perivascular infiltrate, but atelectasis and hemosiderin are commonly present in transplant biopsies; (**B**) minimal acute rejection, grade A1: scattered perivascular lymphoplasmacytic infiltrates, two to three cell layers thick; (**C**) mild acute rejection, grade A2: frequent perivascular infiltrates of lymphocytes, plasma cells, macrophages, and eosinophils, more than three cell layers thick and visible at low power; (**D**) moderate acute rejection, grade A3: similar findings as grade A2 plus extension of infiltrates into adjacent alveolar septa. Severe acute rejection, grade A4, is rare (not shown).

note the presence of these entities in the biopsy (see later discussion). However, clinical history and symptoms do not contribute to the histopathologic grading of lung transplant rejection; thus rejection grade is determined entirely on histopathologic findings.

Acute Cellular Rejection, Grade A

Grade A acute cellular rejection is characterized by a perivascular lymphocytic infiltrate. The infiltrate is classified as minimal (grade A1), mild (grade A2), moderate (grade A3), and severe (grade A4). The specific grade is based on the amount and extent of the inflammatory infiltrate (Fig. 1). Eosinophils, plasma cells, and neutrophils are often present in the infiltrate in addition to lymphocytes. The absence of a perivascular infiltrate is stated as grade A0, while inadequacy of the biopsy precluding determination of the presence or absence of perivascular infiltrates is stated as AX. Grade AX indicates lack of alveolated lung tissue or lack of small parenchymal vessels. The presence of a questionable perivascular infiltrate, that is, whether an infiltrate is sufficient to meet the

criteria for acute rejection, would not be categorized as AX, and ideally would be called definitively grade A0 or A1, with an appropriate diagnostic comment or microscopic description as necessary.

Acute Cellular Rejection, Grade B

Grade B acute cellular rejection is characterized by predominantly lymphocytic airway inflammation, and therefore is referred to as lymphocytic bronchiolitis in the rejection classification (1,6). When used alone, however, this term is misleading as it does not adequately convey that a type of acute rejection is present. Because grade B/airway infiltrates are a clinically important type of acute rejection and are a risk factor for the development of chronic rejection (7), they are important to recognize in post-transplant biopsies. Moreover, the 1996 working classification (1) is preferred over the 2007 version (6), as it utilizes a more detailed description of the degree of the inflammatory infiltrate: minimal, grade B1; mild, grade B2; moderate, grade B3; and severe, grade B4 (Fig. 2) than the latter in which low grade (B1R) is equivalent to grades B1 or B2, and

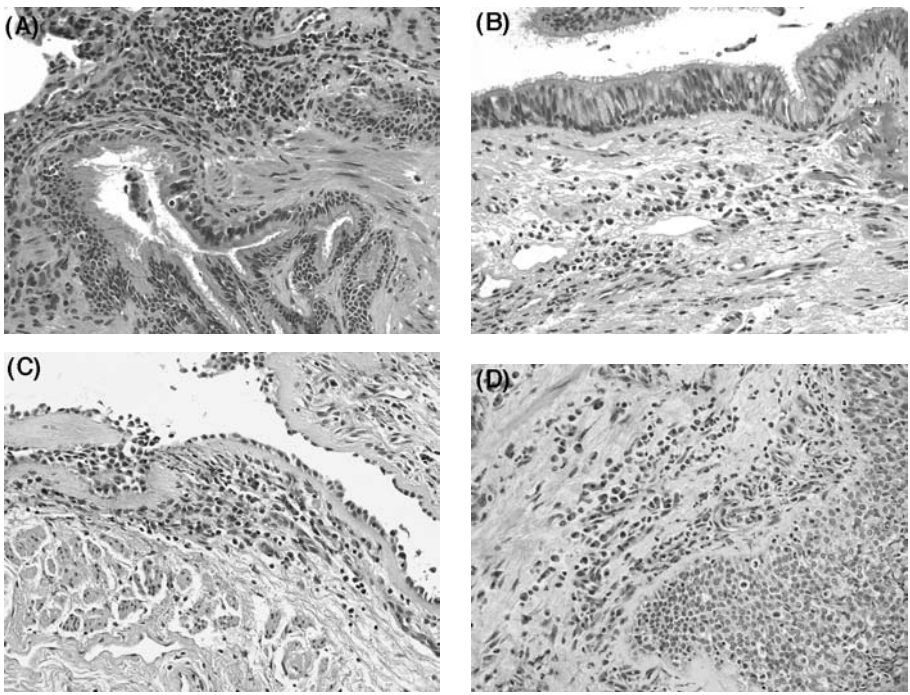

Figure 2 (*See color insert*) Acute cellular rejection, grade B. (**A**) No airway inflammation, grade B0: adjacent bronchial-associated lymphoid tissue (BALT) should not be mistaken for airway rejection; (**B**) minimal airway inflammation, grade B1: scattered mononuclear cells in airway submucosa; (**C**) mild airway inflammation, grade B2: circumferential infiltrate of lymphocytes, plasma cells, and eosinophils in airway submucosa; (**D**) moderate airway inflammation, grade B3: dense band of lymphocytes, plasma cells, and eosinophils in airway submucosa plus transmigration of lymphocytes through epithelium and epithelial cell necrosis. Severe airway inflammation, grade B4, is rare (not shown).

high grade (B2R) is equivalent to grades B3 or B4. The latter grading system does not allow for different treatment algorithms for minimal and mild airway rejection. As with grade A acute rejection, the absence of airway inflammation is stated as grade B0. The absence of any airway in the biopsy is stated as BX. The most important differential diagnosis for an inflammatory infiltrate of the airway is infection (see later); negative cultures and serology support the diagnosis of rejection.

C. Chronic Rejection

The pathogenesis of chronic rejection is not well understood but is thought to be due in part to monocyte/macrophages and their interaction with airway epithelium, which has upregulated expression of major histocompatibility complex (MHC) antigens, co-stimulatory molecules, and adhesion molecules, leading to release of inflammatory and fibroproliferative mediators. Chronic rejection occurs most often more than one year post transplant, but may be seen as early as three weeks, and should be suspected in the appropriate clinical setting of insidious onset of generalized symptoms, including cough and dyspnea, and progressive decline in pulmonary function tests. The most important recognized risk factor for chronic rejection is previous episode(s) of acute rejection (7).

Chronic Airway Rejection, Grade C

BO is the characteristic feature of grade C chronic rejection, although it is difficult to diagnose on transbronchial biopsy. The distribution and severity of the histopathologic findings in BO are patchy, and clinically questionable cases, that is, those without clear bronchiolitis obliterans syndrome (BOS), may require a wedge biopsy for adequate diagnosis. Asymmetric or concentric submucosal fibrosis causing partial or total airway obstruction is diagnostic and denoted as grade C1 (Fig. 3), while the absence of BO is denoted as grade C0 in the 2007 classification (6). Inflammation may or may not be present, and is recognized in the 1996 classification as grade Ca or Cb, respectively (1). Obstructive changes including mucostasis and endogenous lipoid pneumonia may also be present.

Chronic Vascular Rejection, Grade D

Grade D rejection is rare and has not been reported to cause significant allograft dysfunction. It is most often seen in the setting of BO. Histologically, it is characterized by arterial and venous intimal fibrosis with or without inflammatory infiltrates.

II. Other Post-Transplant Pathology

Although transbronchial and sometimes endobronchial biopsies may be taken specifically to rule out additional pathology, biopsies taken for rejection surveillance should also always be evaluated for histopathologic features indicative of infection, aspiration, organizing pneumonia, recurrent disease, and post-transplant lymphoproliferative disorder (PTLD).

A. Infection

Infections of lung allografts can be diagnosed by transbronchial biopsy. Bacterial infections tend to occur in the first month post transplant, while viral and fungal infections occur within the first three to six months. Immunosuppressant therapy also predisposes to a lifelong risk of infectious complications.

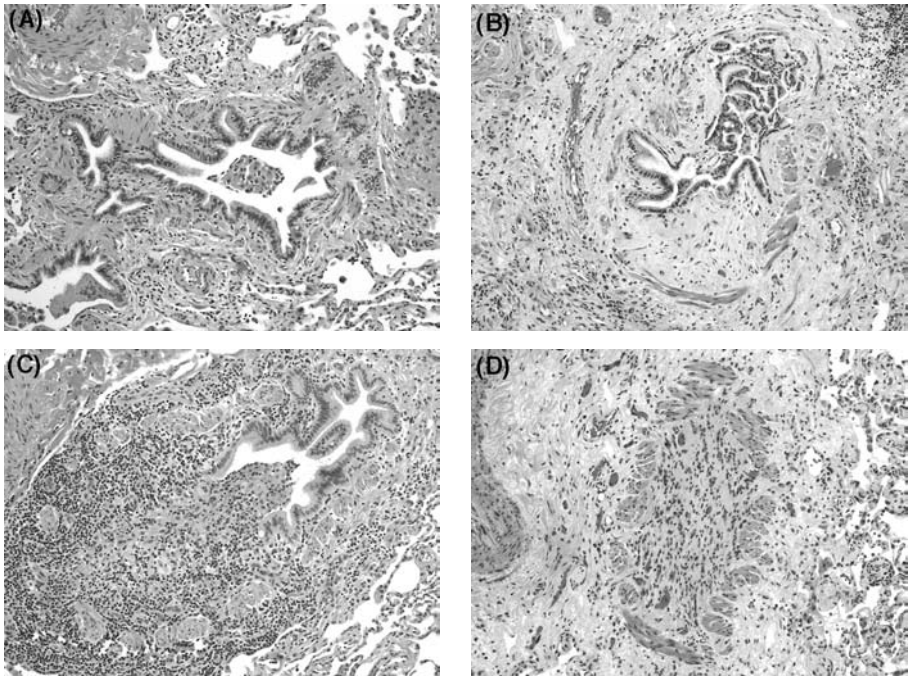

Figure 3 (*See color insert*) Chronic airway rejection, grade C. (**A**) No bronchiolitis obliterans (BO), grade C0; (**B**) subtotal BO without inflammation, grade C1 or grade Cb; (**C**) subtotal BO with active inflammation, grade C1 or grade Ca; (**D**) total BO, grade C1.

Bacterial Infection

The presence of neutrophils in the airway epithelium is suggestive of bacterial infection (Fig. 4A), but the differential diagnosis of grade B acute cellular rejection must also be considered. As with other immunocompromised hosts, gram-negative infections may be present without significant inflammatory response. Most bacteria cannot be identified on biopsy; therefore, bacterial cultures should be sent if there is sufficient clinical suspicion.

Viral Infection

CMV can be readily diagnosed on hematoxylin and eosin sections, but it is recommended to perform immunohistochemistry for CMV antigens to allow for earlier detection and treatment especially in the first post-transplant year (Fig. 4B and C). CMV is characterized by enlarged cells with single large basophilic intranuclear inclusions with a clear halo; multiple small coarse basophilic cytoplasmic inclusions are often present. CMV and other viral infections may also be diagnosed by serologic techniques or culture (5).

Fungal Infection

Fungal infections, including candidiasis, aspergillosis, and mucormycosis, may be diagnosed by the presence of fungal yeasts/hyphae on hematoxylin and eosin stain or

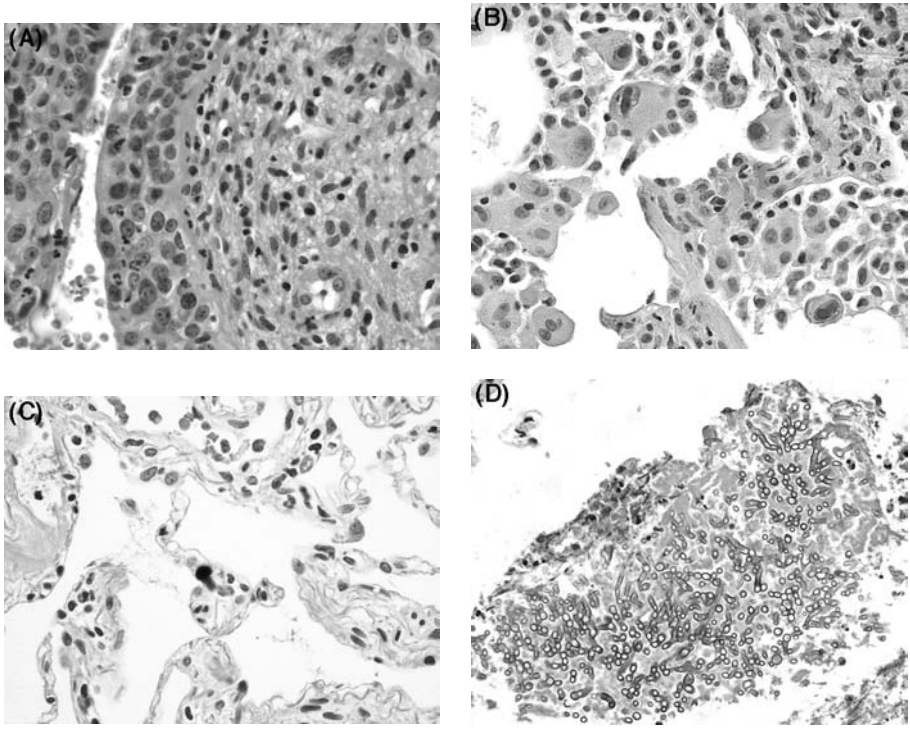

Figure 4 (*See color insert*) Infections. (**A**) Neutrophils in airway epithelium suggestive of bacterial infection; cytomegalovirus is easily recognized on hematoxylin and eosin stain (**B**), but immunohistochemistry for specific antigens (**C**) can allow for earlier detection before cytopathic effect; (**D**) fungal hyphae.

silver stain (Fig. 4D). These fungi can also be seen on frozen section that can be done on wedge biopsies, if clinically indicated. Prophylactic therapy for *Pneumocystis jirovecii* has rendered it rare in lung allografts.

B. Aspiration

Histologic features of aspiration include foamy alveolar macrophages and foreign body giant cell reaction (Fig. 5A), with or without actual foreign material (e.g., gastric content).

C. Organizing Pneumonia

Organizing pneumonia, characterized by a nodular proliferation of young fibroblasts within alveolar spaces (Masson bodies, Fig. 5B), is not cryptogenic in the setting of lung transplantation. Instead, organizing pneumonia is a nonspecific reaction due to resolving lung injury from a variety of causes, including acute rejection and infection.

D. Recurrent Disease

Although rare, lung allograft biopsy may reveal evidence of recurrence of the disease, which initially prompted transplant. Two diseases that can recur in lung allografts

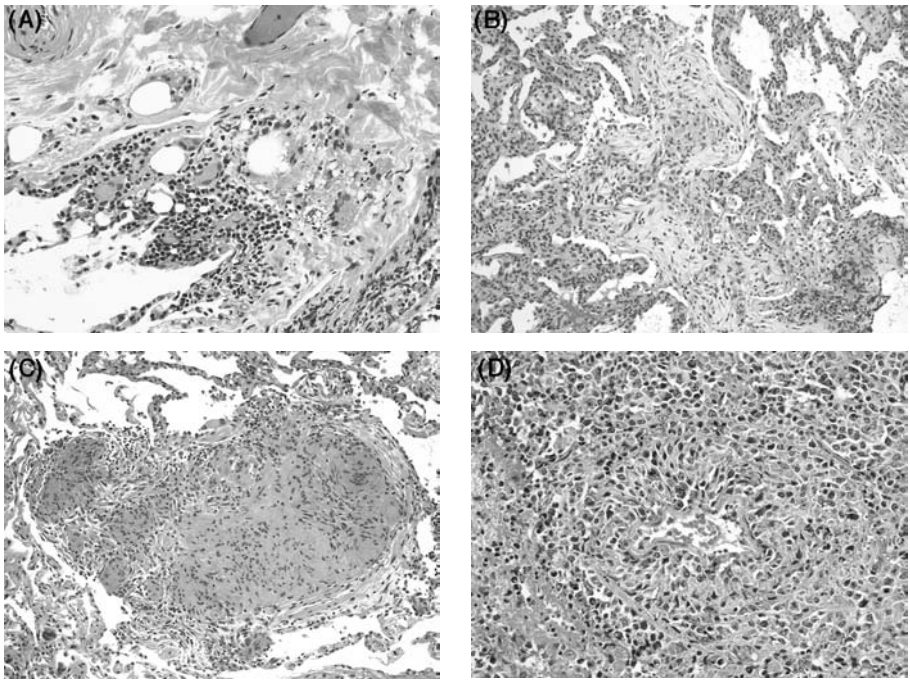

Figure 5 (*See color insert*) Other biopsy histology. (**A**) Microscopic aspiration with foamy alveolar macrophages and multinucleated giant cells; (**B**) alveolar fibroblast proliferation (Masson body) of organizing pneumonia, a nonspecific response to a variety of injuries; (**C**) well-formed nonnecrotizing granulomas of recurrent sarcoidosis; (**D**) high grade lymphoma, posttransplant lymphoproliferative disorder.

include sarcoidosis, characterized by well-formed nonnecrotizing granulomas (Fig. 5C), and lymphangioleiomyomatosis, characterized by nodular interstitial proliferations of smooth muscle.

E. Post-Transplant Lymphoproliferative Disorder

PTLD, a process driven by Epstein-Barr virus, has decreased in incidence due to improved immunosuppression. In lung transplant patients, PTLD often involves the lung allograft, as well as nodal and extranodal sites, and, in adults, is most often characterized by features of high grade lymphoma (8) (Fig. 5D).

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Bronchiolitis Obliterans Syndrome: Clinical Risk Factors and Pathophysiology

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I. Introduction

Although lung transplantation improves survival and provides significant short-term improvements in quality of life for patients with advanced lung diseases, five-year survival following transplantation is limited to 50% with most late deaths due directly or indirectly to the development of bronchiolitis obliterans syndrome (BOS) (1). BOS describes a condition of progressive airflow obstruction associated with chronic airway fibrosis, a pathologic finding known as bronchiolitis obliterans (BO) (Fig. 1). Transplant physicians first recognized this progressive airflow obstruction and associated BO in early lung or heart-lung transplant recipients (1). Unfortunately, transbronchial biopsies, routinely performed to diagnose acute rejection (AR) and infection after lung transplantation, are insensitive for the identification of BO because of the limited sampling of bronchiolar tissue and the disease's heterogeneous nature. The clinical syndrome of BOS was thus developed to identify patients with underlying BO. BOS is diagnosed by a persistent fall from a patient's baseline post-transplant forced expired volume in one second (FEV_1) after the exclusion of other causes of airflow obstruction. Current treatment modalities are generally ineffective in arresting airflow decline, so BOS patients steadily progress toward pulmonary failure and death unless retransplanted.

Although the pathologic mechanisms that lead to BO are poorly understood, a number of clinical risk factors for BOS have been identified. Previous studies suggested that prior AR was the most significant predictor for BOS development, perhaps leading to the premature conclusion that BO occurs solely as a result of alloimmunity. Recent research, however, has emphasized the importance of nonalloimmune factors like primary graft dysfunction (PGD), gastroesophageal reflux, or infections. Additional studies have also suggested that other facets of the immune response such as innate- and autoimmunity appear to contribute to BOS and BO. In this chapter, we will highlight established and emerging clinical risk factors for BOS and the basic pathophysiologic mechanisms that lead to its development.

II. Clinical Risk Factors for BOS

A large number of publications have examined clinical risk factors for BOS, but most studies have been single center, retrospective, and observational. In addition, some previous studies are confounded by variable endpoint definitions (e.g., BOS vs. BO),

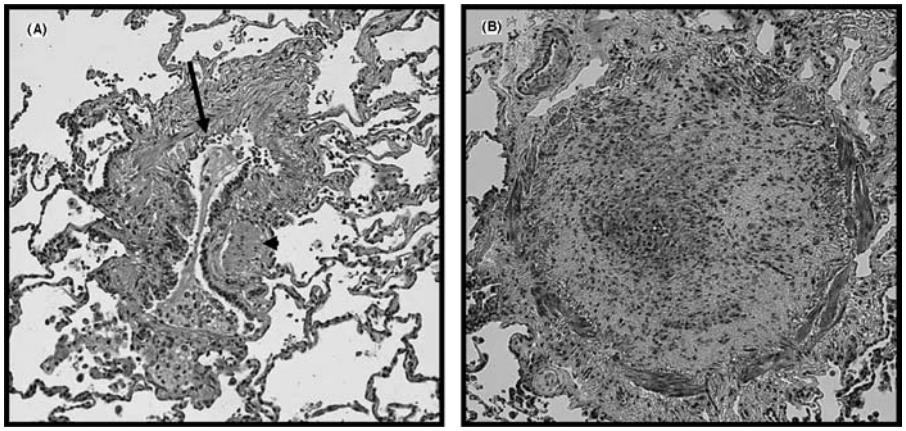

Figure 1 Representative bronchiolitis obliterans lesions. (**A**) Early obliterative lesion with epithelial disruption (*long arrow*) and subepithelial fibrosis (*short arrow*) [hematoxylin and eosin stain, 100×]. (**B**) Advanced lesion with collagen obliteration and cellular infiltration of the airway [Masson trichrome stain, 100×].

inadequate statistical adjustment for the time-dependent onset of BOS, and inconsistent adjustments for other BOS risk factors. Despite these limitations, several consistent risk factors have emerged across studies from multiple centers and constitute the focus of the following sections.

A. Acute Cellular Rejection

Histopathologically, AR describes either perivascular (A-grade) or peribronchiolar (B-grade, lymphocytic bronchiolitis [LB]) mononuclear inflammation on biopsy. Almost all studies that consider BOS risks have found that AR is a significant predictor for BOS (2). Recent data suggests that even a single episode of minimal grade 1 AR increases the risk for BOS (3). Recent attention has also focused on the LB component of AR; interestingly, one study showed that while both A- and B-grade rejections were significant univariate predictors of BOS, only B-grade LB remained significant in multivariate analysis (relative risk, 1.62; 95% confidence interval, 1.31–2.00; $p = 0.001$) (4). Because LB grading is subjective and bronchiolar tissue is often absent on transbronchial biopsy, the relative importance of A- versus B-grade rejection remains uncertain. Nevertheless, the weight of current evidence suggests that the frequency and severity of prior A- or B-grade rejection increases the risk for subsequent BOS.

B. Humoral Rejection

While antibody-mediated rejection is well described in other solid organ transplants, it has only recently received attention in lung transplantation. Complement staining has been used as a marker of humoral rejection, but the utility of this approach remains controversial and has not been consistently replicated (5). In contrast, several studies have demonstrated that preexisting (6) or de novo (7) antibodies directed against human leukocyte antigen (HLA) have demonstrated the risk for BOS. Collectively these results suggest that antibody-mediated rejection occurs after lung transplantation and contributes to the pathogenesis of BOS.

C. Human Leukocyte Antigen Matching

HLA matching generally predicts long-term outcomes in other solid organ transplants (8) and has been studied extensively in lung transplantation (9). Unlike other solid organs, lungs are allocated without regard for HLA matching due to the organs' limited availability and poor tolerance of cold ischemic time. While single-center studies have suggested that HLA mismatches at certain loci might be predictive of BOS, the largest registry study of HLA matching suggested no overall effect of the number of HLA mismatches upon BO (10). Unfortunately, the small number of highly HLA-matched recipients makes even registry studies underpowered, and thus an effect of HLA matching upon BOS development is difficult to exclude entirely.

D. Cytomegalovirus

Cytomegalovirus (CMV), the most prevalent opportunistic infection after lung transplantation, has been implicated in the development of many graft complications. Multiple studies from earlier eras of lung transplantation linked CMV to an increased risk for BOS despite inconsistent diagnostic methodology or treatment protocols (11). In some recent studies, however, CMV is no longer predictive of BOS development (12), probably due to both the institution of ganciclovir prophylaxis (13) and earlier CMV diagnosis and treatment (4). In spite of recent advances, current CMV prophylaxis is not completely protective and most at-risk patients eventually develop CMV infection. The increased risk of BOS development associated with CMV therefore remains controversial, and additional studies with longer-term follow-up are needed.

E. Non-CMV Infections

Community-acquired respiratory viral (CARV) infections have been implicated in the development of BOS. Although early studies were limited to anecdotal or case series, several prospective analyses with serial monitoring for CARV confirm an increase in BOS risk (3). Bacterial respiratory infections may also increase the risk of BOS, although research in this arena is more limited (14–16).

F. Gastroesophageal Reflux Disease

Among transplanted organs, lungs are uniquely exposed to gastroduodenal refluxate; several studies have linked post-transplant gastroesophageal reflux disease (GERD) to an increased risk of BOS. One study suggested that acid reflux severity may predict FEV_1 decline and BOS development (17). Similarly, the presence of bile acids in the bronchoalveolar lavage fluid may increase the risk of early onset BOS (18). Even more compelling is the finding that lung function stabilization or improvement can occur in selected lung transplant recipients with BOS following antireflux fundoplication surgery (19).

G. Single (SLTx) vs. Bilateral Transplant (BLTx)

Although not initially appreciated, several recent studies have confirmed that BLTx offers increased protection against BOS development (20). Since the definition of BOS is based on the relative fall in FEV_1 from a patient's best post-transplant level, this might simply reflect the nature of the clinical definition rather than true differences in the development of BO. Regardless, registry data demonstrates improved long-term survival in BLTx as compared to SLTx, suggesting that the difference in BOS onset might confer enhanced long-term survival (1).

Table 1 Clinical Risk Factors for BOS

Probable risk factors	Possible risk factors	Unlikely risk
• Acute rejection (A-grade)	• HLA mismatch	• Native lung disease
• Lymphocytic bronchiolitis	• Donor traumatic brain injury	• Donor or recipient gender
• Humoral rejection	• Donor extremes of age	• Donor or recipient race
• Single-lung transplant	• Prolonged graft ischemic time	• Nontraumatic donor death
• Primary graft dysfunction	• Organizing pneumonia	• Donor-recipient blood group mismatch
• Gastroesophageal reflux	• Excessive body mass index	
• CMV infections	• Male donor/female recipient	
• Respiratory viral infections	• Bacterial infections -*Chlamydia pneumoniae* -*Pseudomonas aeruginosa*	

H. Primary Graft Dysfunction

PGD is the most common early complication after lung transplantation and presumably occurs as a result of ischemia-reperfusion injury to the lung. Although severe PGD is relatively uncommon, several recent studies reveal a continuous relationship between increasing PGD severity and earlier BOS onset (21).

I. Other Potential Risk Factors

A number of additional clinical factors have been implicated in BOS but not yet confirmed by more rigorous studies (Table 1) (2,22–24). Larger, multicenter studies are necessary to confirm these risks.

III. Pathophysiology of BO

The pathophysiology of BO likely involves a complex interplay of recipient immunity, donor antigen recognition, and environmental stimuli. Our understanding of the process is partially limited by insufficient animal models that do not reliably reproduce all the features of human disease. Although the widely used rodent heterotopic tracheal transplant (HTT) model replicates fibrosis, it uses tracheal tissue instead of bronchioles and lacks environmental interactions, thus limiting its utility as a tool in the study of BO.

A. Antigen Recognition

BO is often preceded by LB suggesting that recipient lymphocyte recognition of alloantigens present in the airways contributes to the development of BO. Similarly, BO has been recorded in allogeneic bone marrow transplant recipients experiencing chronic graft-versus-host disease (25). The importance of alloimmune recognition is further supported by the HTT model in which allogeneic tracheas develop obliteration while their syngeneic counterparts remain unaffected (26), and by the rat orthotopic lung transplant model, in which allogeneic lungs develop LB (27). Alloantigen recognition may proceed through direct allorecognition—when host immune cells recognize allo-HLA on donor lung cells and identify them as foreign—or through indirect allo-recognition—when donor proteins are degraded and presented as foreign antigen by recipient antigen-presenting cells in the context of self-HLA. In the setting of lung

transplantation, both mechanisms may result in the maturation and proliferation of T cells directed against donor antigens.

Despite compelling evidence that allorecognition contributes to the development of BO, it remains uncertain why some patients develop early aggressive disease and others remain BOS-free for many years. Two important recent observations might explain some of these differences. One mechanism implicated in human and murine studies of BO is the development of autoimmunity to self-antigens. Transplant surgery or PGD might expose previously cryptic self-epitopes capable of promoting an autoimmune response. For example, autoreactive T cells to type V collagen and Kα-tubulin, proteins that become exposed from their normal sequestration in the airway basement membrane during injury, have been identified in rodent models of lung rejection and, in the case of type V collagen, can adoptively transfer disease to syngeneic hosts that have undergone transplantation (28,29). More recently, T cells responsive to type V collagen have been associated with an earlier onset of BOS.

Innate immune activation may also play an important role in BO. This is consistent with the central importance of pulmonary innate host defenses given the high burden of environmental stimuli to which the lung allograft is exposed. In support of these ideas, polymorphic variations in innate immune pattern recognition receptors such as Toll-like receptor 4 (TLR4) and its coreceptor CD14 have been shown to modulate the development of post-transplant rejection and BOS (30–32). Further validation for this idea has also been promoted through a novel bone marrow transplant (BMT) model of allogeneic lung injury in which local pulmonary bacterial endotoxin has been shown to potentiate alloimmunity (30).

B. Mechanisms of Injury

Once the recipient immune system has been primed to recognize donor antigens in the lung through either autoimmune or alloimmune mechanisms, a variety of effector mechanisms ensue. Both type 1 and type 2 helper T cells have been identified and might promote cytotoxic T cell-mediated epithelial injury (33) or B cell antibody production (7). Antibodies may directly injure the graft and promote fibrosis (34) or indirectly lead to injury through complement-mediated mechanisms (5). Recent hypotheses have even focused on T helper 17 cells, a distinct T cell population capable of inducing a chronic inflammatory response and the subsequent tissue destruction usually seen in autoimmune diseases (35).

Although not as widely studied, myeloid cells that regulate innate lung host defenses also appear to participate in the initial immune response. Elevations in neutrophils precede the onset of BOS and may represent a distinct clinical syndrome (36). Infectious agents, esophageal reflux, and environmental toxins may all directly activate macrophages and promote antigen presentation or even injure epithelial cells. These cells may, in turn, produce inflammatory cytokines and promote an inflammatory environment that potentiates alloimmune- and autoimmune-mediated graft injury.

C. Fibrosis

In animal models, both syngeneic and allogeneic HTT grafts undergo initial epithelial loss, but only in the allogeneic setting does aberrant repair lead to fibroproliferation. Although the variables that polarize repair in one direction or the other remain unclear, animal models suggest that several factors may favor disregulated repair mechanisms (28). An exhaustive review of the basic mechanisms is outside the scope of this chapter, but several critical points are highlighted below.

Signaling molecules such as platelet-derived growth factor and transforming growth factor-β are elevated in allogeneic HTT grafts above the levels seen in syngeneic grafts, and inhibition of these molecules attenuates fibroblast proliferation and tracheal obliteration in the allogeneic graft (37). The potential importance of these signaling molecules to the fibroproliferative process is emphasized by a small clinical series that correlates platelet-derived growth factor-β with declining lung function (38). Certain CXC-motif chemokines are also elevated in allogeneic grafts; specifically, CXC receptor 2 (CXCR2) likely mediates the vascular supply to the obliterative lesion. CXCR2 ligands were elevated in one cohort of lung transplant patients with BOS, and inhibition of CXCR2 in the HTT model inhibits angiogenesis and vascular proliferation and limits airway obliteration (39).

Perhaps most consistently associated with allogeneic fibrous obliteration are the metalloproteinases, enzymes important in the regulation of fibrosis. Metalloproteinases are elevated in both lung transplant recipients (40) and allogeneic grafts in HTT models (41,42). While modulation of these enzymes has no effect on epithelial recovery in allogeneic grafts, it significantly alters fibroproliferation, specifically through the promotion of myofibroblast proliferation over fibroblast proliferation (41).

IV. Conclusion

BOS and its pathological counterpart BO remain the greatest limitation to the long-term success of human lung transplantation. Several clinical risk factors have been identified for BOS. Cellular and humoral responses directed against donor alloantigens might contribute directly to BO while nonalloimmune factors such as PGD or GERD may promote graft inflammation, potentiate alloimmune injury, and activate autoimmune and innate immune mechanisms of injury. Despite these advances, our understanding of the precise pathophysiology of BO remains quite limited. Fortunately with the recent growth in clinical lung transplantation, large-scale, prospective, multicenter studies are now possible, and intense interest in the basic mechanisms of BO has produced several alternatives to the HTT model that may better replicate features of human disease. Collectively, these factors should accelerate our understanding of clinical BOS and pathological BO leading to the development of more effective prevention and treatment strategies in future years.

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Bronchiolitis Obliterans: Diagnosis and Management

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I. Introduction

Lung transplantation is the final therapeutic option for selected patients with multiple end-stage pulmonary disease entities, yet its long-term success is significantly limited by chronic allograft dysfunction/rejection histologically characterized by obliterative bronchiolitis (OB). Bronchiolitis obliterans syndrome (BOS), the clinical syndrome associated with chronic allograft dysfunction, has a cumulative incidence of 40% to 80% at five years post transplant and accounts for 25% to 30% of the mortality after the first year (1) Unfortunately, therapies for BOS or OB have had limited efficacy and survival curves show little improvement in late mortality for lung transplant recipients over the past six years compared to earlier eras (Fig. 1). As the pathogenesis of OB has been discussed in a prior chapter, this chapter will review diagnosis and treatment strategies for chronic allograft dysfunction.

II. Diagnosis

A. Clinical and Histopathologic Features of Chronic Allograft Dysfunction

OB, the histopathologic hallmark of chronic rejection, is a fibroproliferative small airways disease thought to be preceded by inflammation, epithelial injury, and mucosal ulcerations. Subsequent fibroblast proliferation leads to intraluminal deposition of granulation tissue and obliteration of airway lumens. OB begins at the level of the small airways, making histologic diagnosis challenging to establish by transbronchial biopsy; however the majority of patients with histologic OB also exhibit physiologic changes in lung function. Therefore, clinical criteria of BOS were developed to better identify patients manifesting chronic allograft dysfunction (Fig. 2) (3). BOS is defined by measures of airflow obstruction, that is, a sustained decline in FEV_1 and $FEF_{25–75}$ compared to baseline and staged by severity based on degree of airflow obstruction. Other potential markers of OB have been suggested, including neutrophilic alveolitis, exhaled nitric oxide, soluble CD30 levels and more recently, air trapping on high resolution CT scan; however further studies are needed to determine the role of these and other modalities in diagnosing chronic allograft dysfunction (4,5).

By definition, BOS is a diagnosis of exclusion. Conditions such as acute rejection, infection, native lung hyperinflation, and anastamotic stenosis must be excluded prior to

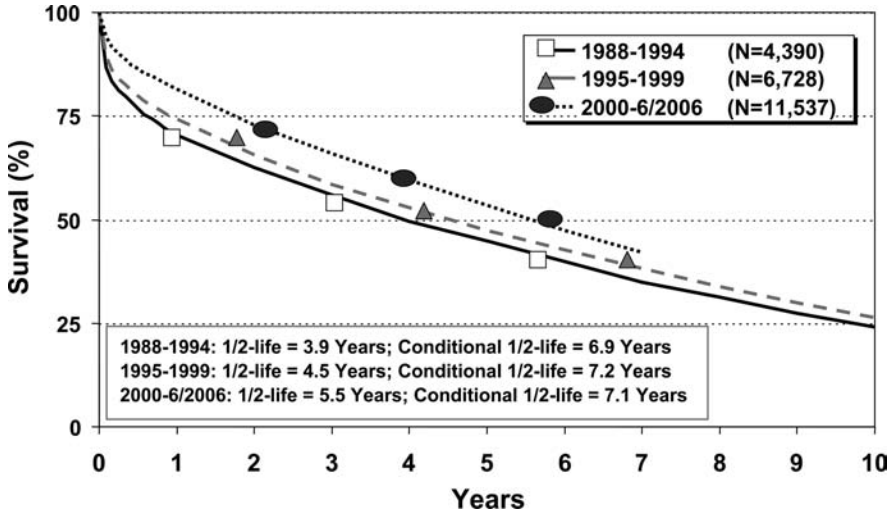

Figure 1 Lung transplant survival by era. Kaplan–Meier survival for adult lung transplant recipients between January 1988 and June 2006. Conditional half-life is defined as time to 50% survival for subset of recipients that were alive one year after transplantation. *Source*: From Ref. 2.

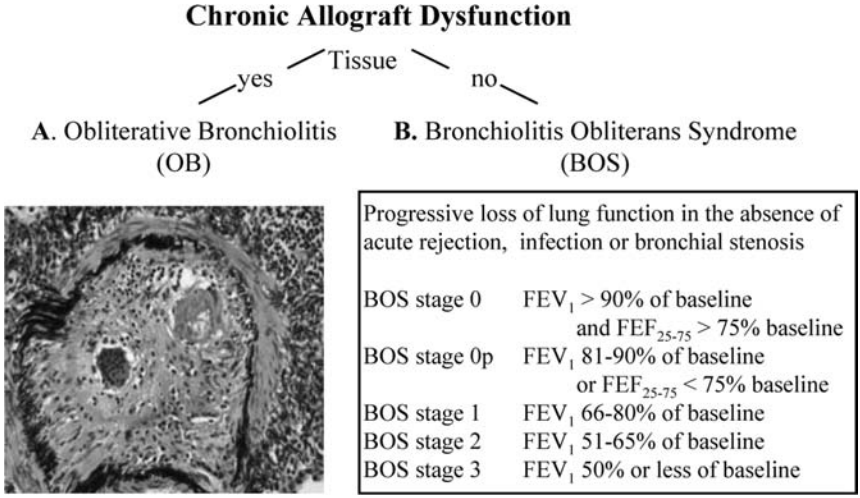

Figure 2 Clinical and histopathologic features of chronic allograft dysfunction (**A**). Histopathology of OB. Obliterated bronchiole with fibrosis and peribronchiolar inflammation. (**B**) Classification of bronchiolitis obliterans syndrome (BOS) severity, 2002 revision based on ISHLT consensus guidelines.

establishing the diagnosis of BOS. However, it is important to recognize that studies correlating BOS to histologic OB are lacking and therefore even in the absence of confounding factors, it is possible that not all patients with clinical BOS necessarily have underlying OB. This is an important distinction since OB, a fibrotic process of the airways, is traditionally considered an irreversible process. Moreover, the recent discoveries of treatments that result in improvement in lung function for select subsets of patients with BOS such as azithromycin and treatment of gastroesophageal reflux (GER) suggests that BOS represents a heterogeneous syndrome that may not be entirely due to irreversible airway fibrosis.

III. Treatment

Despite a strong association between immune-mediated rejection and BOS, immunosuppressive therapies have for the most part not provided beneficial effects with regard to improving lung function after the onset of BOS (Fig. 3). Treatment has focused both on preventive strategies, including known risk factors as well as therapies initiated after the onset of BOS. Unfortunately, the value of many therapies remains unproven because of small sample sizes, use of historical controls, and variable definitions of efficacy in clinical studies. Furthermore, because the rate of decline in FEV_1 may decrease at some timepoint after the onset of BOS (6), it has been difficult to determine whether studies that report a "stabilization" or reduction in the rate of FEV_1 decline represent a positive response to therapy as opposed to simply the natural course of BOS.

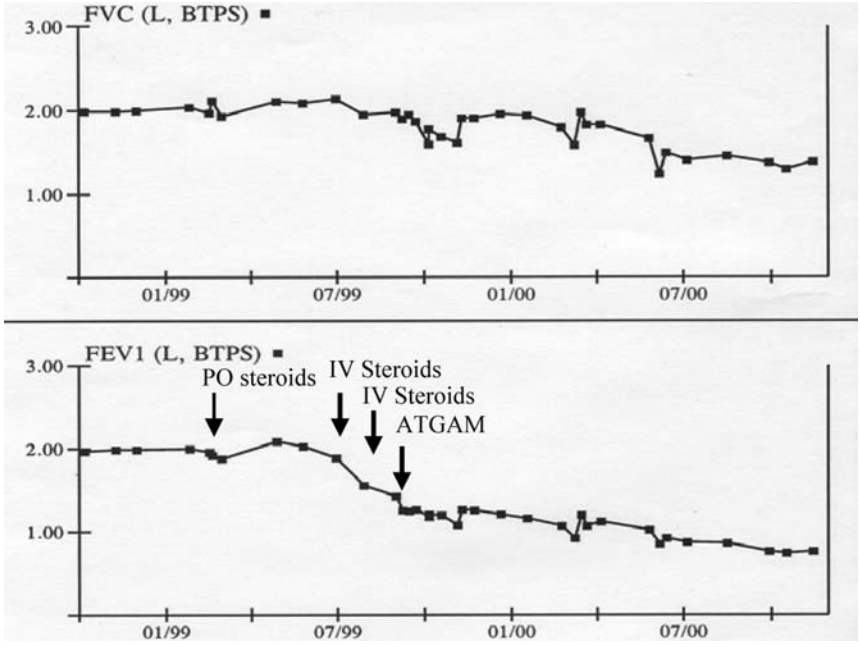

Figure 3 Representative longitudinal spirometry (FEV_1 and FVC) from patient with BOS. Arrows indicate augmentation of immunosuppression at labeled time points.

IV. Risk Factor Modification

A. Acute Cellular Rejection

Several epidemiologic studies document that acute cellular rejection (ACR) grades 1 to 4 is a dominant risk factor for BOS, with earlier development of BOS in patients who have increased severity, persistent or recurrent ACR (7–12). While there is general agreement that moderate to severe rejection (grade A3–A4) should be treated, evaluation and treatment of minimal or mild rejection remains controversial. Studies that favor early detection and treatment of BOS include two studies that reported a worsening in pulmonary function/histologic grade among 41 patients with untreated ACR (13,14). Subsequently, a subgroup analysis from a retrospective study of 228 lung transplant recipients (LTR) showed a reduction in development of BOS 1 in treated A1 rejection compared to untreated A1 rejection (10). Repeat transbronchial biopsies after three to five weeks to assure resolution of ACR is of unproven benefit. Although some studies have not shown a reduction in BOS with surveillance bronchoscopies of *asymptomatic* patients, randomized controlled trials are needed to validate the efficacy of detecting and treating asymptomatic ACR.

B. Anti-HLA Antibodies

While the role of humoral mediated pathways leading to lung rejection remain controversial and difficult to study, recent studies show an increased risk for BOS (HR 3.19, $p < 0.005$) in patients with pre-transplant HLA sensitization and with de novo development of donor specific anti-HLA antibodies post transplant (15–17). Plasmapheresis has been a dominant therapy for antibody removal and in a case series of 35 patients, Appel at al. reported improved freedom from BOS (90% vs. 50%) in presensitized patients who received intravenous immunoglobulin (IVIG) and plasmapheresis compared to those who were not desensitized (18,19). While these and other therapies such as anti-CD20 (rituximab) have been employed for treatment of humoral rejection post transplant, further studies are needed to assess the long-term impact of these strategies in attenuating BOS.

C. Gastroesophageal Reflux in BOS

GER and chronic aspiration are increasingly recognized as a major cause of allograft injury and risk factor for BOS (20–23). Given the widespread prevalence of GER in LTRs (50–75%), several reports have assessed the safety and efficacy of surgical treatment for GER (24,25). In a retrospective single-center series by Cantu et al., 14 patients who received early fundoplication (<90 days post transplant) had improved freedom from BOS and survival at one and three years (100%) when compared to patient with reflux who did not receive fundoplication (60%), delayed fundoplication (47%), or compared to patients who had no history of reflux (62%). In patients with established BOS and pH-probe-confirmed reflux, a retrospective study conducted at the same transplant center stated that fundoplication improved pulmonary function in 16 of 26 patients by a mean FEV_1 of 24% (25), with early stages of BOS most likely to respond. While these early studies show promising results in both prevention and reversal of BOS with early surgical treatment of GER, more rigorous studies are needed to confirm the efficacy of this strategy and to better determine the optimal timing and patient selection criteria to intervene for GER.

D. Cytomegalovirus

Early studies prior to the widespread use of CMV antiviral prophylaxis suggest that CMV seropositive recipients post-transplant{either obtained from the donors (D^+) or by prior infection, in the recipients (R^+)}, and those patients who develop CMV pneumonitis have increased risk of BOS or OB; CMV has been considered a "probable" risk factor for BOS on the basis of these and subsequent studies that showed a decrease in BOS with the use of prophylactic regimens (26–28). Duncan et al. first demonstrated a delay in the onset of BOS among CMV seropositive LTRs (D^+ or R^+) with 90 days of post-transplant ganciclovir compared to acyclovir (29). More recent studies reported a reduction in BOS with prolonged prophylaxis regimens, combined ganciclovir and CMV-IG, and with oral valganciclovir (30–33). While interpretation of these studies is limited by retrospective data, historical controls, variability in patient selection, and choice of anti-viral prophylaxis, some data suggest that the widespread implementation of CMV prophylaxis and treatment is associated with an overall reduction in incidence of BOS comparable to the level of CMV-seronegative (D^-/R^-) LTRs (34,35). As such, current protocols vary from 90 days of prophylaxis with IV ganciclovir in high-risk recipients (D^+/R^-) to indefinite prophylaxis with daily oral valganciclovir in all LTRs. Further randomized controlled studies are needed to determine optimal prophylaxis and treatment regimens for CMV.

V. Selection of Immunosuppressive Agents

A. Induction Regimens

Antilymphocyte agents [antithymocyte globulins (ATG), alemtuzumab] and IL-2 receptor antagonists (IL-2RA) (daclizumab and basiliximab) are commonly used as induction agents in lung transplant recipients. Although prospective studies comparing IL-2RA to ATG have not shown a difference in short-term freedom from BOS (<2 years), long-term retrospective data from 3970 patients in the ISHLT registry between the years 2000 to 2004 favor IL-2RA (36–38). In this study, 57% of patients did not receive induction (NI), 28% were treated with IL-2RA, and 15% were treated with ATG. While two-year freedom from BOS was similar along all groups, freedom from BOS at four years was better with IL-2RA (69%, NI 67%, ATG 58%, $p < 0.04$). Finally, one institution has reported greater freedom from early rejection with use of alemtuzumab (anti-CD52) compared to ATG or daclizumab in a non-randomized trial, but its impact on long-term freedom from BOS is unknown (39).

B. Calcineurin Inhibitors

The majority of maintenance immunosuppressive regimens consist of low-dose prednisone, a calcineurin inhibitor, and an antimetabolite/antiproliferative agent. Although optimal maintenance regimens have not been defined, several studies have assessed the impact of these regimens on BOS. Some studies suggest that tacrolimus may confer increased freedom from BOS compared to cyclosporine (40–42); however, these studies are limited by their open-labeled study design. In one study of 133 LTRs, although mortality was unchanged, fewer patients developed BOS when treated with tacrolimus as compared to cyclosporine (22% vs. 38%, $p < 0.025$) (40). A more recent prospective study of 90 patients showed lower incidence of ACR and a trend toward lower incidence of BOS (stage 0-p, $p < 0.1$ and stage 1 < 0.09) in LTRs treated with tacrolimus as compared to cyclosporine (41). Despite these findings, cyclosporine and tacrolimus are

used nearly equally across programs as primary immunosuppressive therapy. Finally, Iacono et al. demonstrated improved mortality (11% vs. 47%, $p < 0.01$) and freedom from BOS (RR 0.38, $p < 0.01$) in a recent randomized double-blind, placebo-controlled trial of inhaled cyclosporine when added to maintenance immunosuppressive regimens (43). Further multicenter clinical trials of inhaled cyclosporine are ongoing to further define the efficacy of this treatment, which is not yet available for clinical use.

C. Antiproliferative Agents

Although several antiproliferative agents are commonly used in maintenance immunosuppressive regimens for LTRs, long-term freedom from rejection appears to be similar among these agents. Early retrospective studies suggested improved outcomes with mycophenolate mofetil as compared to azathioprine; however, subsequent randomized controlled trials have not shown a difference among agents when initiated de novo after transplant (44–47). In a larger, multicenter randomized trial, McNeil et al. demonstrated similar incidence in freedom from BOS at three years (75% vs. 73%) and no difference in acute rejection at one- or three-year time points between the two agents (47). Recently, Snell et al. compared azathioprine to everolimus in a randomized controlled trial of BOS-free patients; while everolimus group had fewer episodes of acute rejection, and reduced decline in FEV_1 at 12 months, freedom from BOS was no different at 24 months (48). Furthermore, patients in the everolimus group had an increased rate of drug discontinuation (60% at 24 months) and of adverse events including infections and increased creatinine.

VI. Treatment of Established BOS

A. Changes in Maintenance Immune Suppression

Several non-randomized studies have cited stabilization or reduction in decline of FEV_1 with changes in immunosuppressive regimen. Conversion from cyclosporine to tacrolimus in patients with established BOS may be associated with decreased rate of FEV_1 decline based on several retrospective studies (49–51). In the largest of these studies, mean FEV_1 increased slightly (0.34%/mo) for up to 12 months after conversion, although a control group was unavailable for comparison (50). Two small observational studies reported slower rates of decline in FEV_1 in LTRs with established BOS after conversion from azathioprine to MMF, although a concomitant change in calcineurin inhibitor was also made in one of the studies (52,53). In a more recent report, conversion from calcineurin inhibitors to sirolimus + MMF has been associated with stabilization in a subset (3 of 10) of patients with BOS; however, like previously mentioned studies, the lack of control groups limits interpretation of these results (54).

B. Lymphocyte Depletion

Cytolytic and other lymphocyte-depleting strategies have shown variable success with established BOS. The summaries of these experiences are reported later. In several retrospective reports, cytolytic therapy, such as ATG, OTK3, or antilymphocyte globulin, has been associated with a transient slowing in the rate of BOS progression but does not appear to arrest or improve lung function (55–57). Fisher et al. reported an 80% decrease in the mean rate of FEV_1 decline (122–25 mL/mo) in 27 patients who completed 8 to 10 treatments of total lymphoid irradiation; however, 27% of patients did not complete therapy because of adverse effects (58). A similar effect was reported

with the use of extracorporeal photopheresis for BOS in the retrospective 10-year experience at the University Hospital, Zurich, and is consistent with earlier reports of a possible benefit with photopheresis (59,60). More recently, Reams et al. reported stabilization or improvement of BOS grade in 7 of 10 patients treated with the anti-CD52 antibody alemtuzumab (61). Given the potent immunosuppressive effects of many of these options, any potential improvement in BOS must be weighed against the risk of infections and other adverse effects in considering the overall benefit for the patient.

C. Azithromycin

The use of azithromycin is one of few therapies to show an improvement in lung function after onset of BOS. In the sentinel pilot series, Gerhardt et al. demonstrated a mean increase of 17.1% in FEV_1 with azithromycin therapy in five of six LTRs with established BOS (62). Since then, two prospective observational studies have shown improved FEV_1 using azithromycin therapy in 30% to 40% of LTRs with BOS (63–65). Gottlieb et al. reported that patients who responded to treatment within six months had decreased mortality (0 vs. 13 patients, $p < 0.026$) and were protected from long-term disease protection (mean follow-up 1.3 years) (63). Recent studies to predict which patients will respond to therapy suggest that BAL neutrophilia, elevated BAL IL-8, and early onset of BOS (mean 8 months post transplant) are associated with favorable response to azithromycin, with BAL neutrophilia having the strongest correlation (63,66) ($r = 0.79/r = 0.76$). Although these data are promising for select subsets of patients, randomized studies of larger samples are needed to better ascertain the benefit of this therapeutic modality.

D. Retransplantation

Lung retransplantation remains a final option for severe chronic allograft dysfunction at some transplant centers. Despite improvement in recent outcomes, patients undergoing retransplant had 30% higher risk of death compared with patients undergoing initial transplantation, with a mean one-year survival of 62% in a recent cohort study of UNOS registry patients from 2001 to 2006 (67). Several studies document slightly better one-year and five-year survival among patients who are transplanted specifically for BOS, with one-year survival between 66% and 72% and five-year survival between 45% and 60% (67–69). The risk of developing BOS after retransplantation appears to remain higher than in initial transplant although five-year Kaplan–Meier survival estimates are similar between groups (67). Given the inferior outcomes and limited availability of donor organs, the ethics of lung retransplantation remains controversial.

VII. Conclusions

Chronic allograft dysfunction remains a major source of morbidity and mortality after lung transplantation. Although currently there are few well-established therapies for prevention or treatment of BOS, ongoing research continues to advance our understanding of the pathogenesis of chronic allograft dysfunction, which may lead to better treatment strategies. These efforts along with more rigorously designed clinical trials are needed to improve long-term outcomes in lung transplant recipients.

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Malignancy Following Transplantation

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I. Introduction

Lung transplantation (LTx) is now recognized as an effective treatment option for a variety of end-stage lung diseases and is associated with improvements in life expectancy and quality of life. Patients who have undergone solid-organ transplantation (SOT) have a higher prevalence of malignancy than the general population, with estimates suggesting a three- to fourfold increase in the risk of any malignancy and a 100-fold increase in specific malignancies (1,2). The incidence of malignancy may be even higher in LTx recipients (3). The risk of oncogenesis after transplantation is thought to correlate with the overall burden of immunosuppression (1). Developments in surgical techniques, lung preservation, immunosuppression, and management of infections have resulted in a slight improvement in long-term survival, and combined with the recent trend toward transplanting a greater proportion of older recipients, the incidence of post-transplant malignancy is increasing and is expected to be among the leading causes of death in all transplant recipients in the next two decades (1,4). The prevalence of malignancy increases with time post LTx from 3.7% in 1-year survivors and 12.4% in 5-year survivors to 25% in 10-year survivors (4). Beyond the first year, malignancy accounts for 9.3% of deaths. Skin cancers and post-transplantation lymphoproliferative disorders (PTLDs) are the most common malignancies. PTLD is the most common cancer in the first two years after transplantation and in pediatric recipients (1). Skin cancers are the most common malignancy thereafter (4,5). Current candidate selection guidelines consider malignancy within two years an absolute contraindication to LTx, and also recommend excluding patients with malignancy within five years of candidacy (6). There are currently no consensus guidelines for post-transplant cancer screening but general recommendations advise adherence to standard cancer screening guidelines (7). Transplant recipients present an even more complicated picture than the usual cancer patient because of the added burden of immunosuppression and infection risk with treatment as well as difficulties with diagnosis because of atypical presentation. Cancers that develop in transplant recipients are often more aggressive than in the general population, but with new insights into the pathophysiology, available prevention methods, and advances in immunomodulation, the potential to improve the outcome is promising.

II. Post-Transplant Lymphoproliferative Disorders

A. Epidemiology

PTLD accounts for 21% of all post-transplant malignancies compared with only 5% of malignancies in the general population (8). LTx recipients are a subset of patients at special risk for developing PTLD in which the incidence has been estimated at 5% to 20%, the highest in any SOT group (1,9,10). PTLD occurs most commonly in the first year, and is associated with significant morbidity and mortality (7). Epstein-Barr virus (EBV) plays a key role in pathogenesis. More than 90% of tumors are EBV associated, although a recent increase in the number of EBV-negative cases has been reported (11). Overall mortality is in the range of 37% to 50% and varies by age and extent of disease (5). Factors associated with improved survival include younger age at presentation, early onset localized, surgically treatable or allograft-restricted disease, and disease managed with immunosuppression reduction. The worst prognostic indicator is the presence of CNS disease (1).

B. Classification

PTLD comprises a spectrum of subtypes because of abnormal lymphoid proliferation ranging histologically from benign polyclonal hyperplasia to more commonly encountered malignant monoclonal lymphomas (5,7). PTLD has been grouped by the WHO into morphological categories. Early lesions that are usually reactive plasmacytic hyperplasia or infectious mononucleosis like are most often seen in children or young adults and usually occur within the first year post transplantation. Monomorphic PTLD is classified according to lymphoma classification as B-cell lymphomas, diffuse large B-cell lymphoma (immunoblastic, centroblastic, anaplastic), Burkitt's/Burkitt-like lymphoma, plasma cell myeloma, plasmacytoma-like lesions, T-cell lymphomas, peripheral T-cell lymphoma, and lymphoma not otherwise categorized. Other types include polymorphic PTLD, Hodgkin's lymphoma, and Hodgkin's lymphoma-like PTLD. Histologic subclassification also has prognostic value, although this remains imperfect at present (11).

C. Pathogenesis and Risk Factors

The molecular pathogenesis of PTLD is thought to be a result of the combined effects of immunosuppressive agents and infection by oncogenic viruses such as EBV (12). Intensity of immunosuppression and pretransplant seronegative EBV status are the primary risk factors for the development of PTLD. EBV-naive recipients who seroconvert following transplantation are at greatest risk of developing PTLD—the reverse situation is seen in hematopoietic cell transplantation (13). Despite this, the cellular source of EBV is recipient derived in more than 90% of cases as EBV is ubiquitous. Eighty-five percent of adults above 35 years of age are EBV seropositive (13,14). Transplantation at less than 18 years of age and male gender are independent risk factors for PTLD (15). In the presence of disturbed T-cell function, EBV may induce prolonged and unchecked proliferation and transformation of B cells leading to the development of mutations and eventual malignancy (5). The latent membrane protein 1 (LMP1) of EBV-infected cells is thought to play a central role by mimicking members of the family of tumor necrosis factor (TNF) receptors, thereby transmitting growth signals from the cell membrane to the nucleus through cytoplasmic TNF-receptor-associated factors (TRAFs) (16). The EBV load in peripheral blood has been shown to be elevated in patients with PTLD and precedes development of PTLD. Viral loads decrease with treatment (17). EBV infection also appears to play a temporal role in PTLD outcomes. Studies in SOT

recipients show that early polymorphic lymphomas are usually EBV positive and respond well to the reduction of immunosuppression while late-onset monomorphic disease is usually EBV negative, unresponsive to immunosuppression reduction, and associated with a worse prognosis (12,18,19). The pathogenesis for late cases is unclear, but it is known that the increased division of lymphocytes caused by EBV infection yields an increased rate of new mutations and it is possible that one of these mutations may lead to cell replication independent of the presence of EBV. Over time, the EBV virus is lost and the non-EBV-driven cells replicate in an unregulated manner. Impaired immune function due to viral infection may lead to the proliferation of abnormal cells that would otherwise have been eliminated with normal immune surveillance (15). Other investigators have argued that early- and late-developing PTLDs may be separate diseases entirely or that other viruses such as cytomegalovirus (CMV) and polyomavirus could be etiologic agents (1,19–21). Certain types of immunosuppression, including antithymocyte globulin, have been reported to increase the risk of PTLD likely reflecting the profound impact of these agents on intrinsic T-cell activity, but there is conflicting evidence whether other specific medications confer a greater risk independent of their immunosuppressive effects (5). One Italian study found that HIV-infected patients demonstrated a similar pattern of cancer risk as SOT recipients on immunosuppression medication (22). Some studies have found that the incidence of PTLD is increased among those receiving cyclosporine, suggesting a possible direct neoplastic effect (1,23). An apparent protective effect of mycophenolate mofetil (MMF) has been reported and was thought to reflect potentiation of antiviral activity, anti-B-cell activity, or a reduced risk of rejection episodes requiring intensification of immunosuppression therapy (1,23–25). However, a study by Ciancio et al. suggested that the use of MMF with tacrolimus was in fact associated with an increased incidence of PTLD in renal transplant recipients (26). The Collaborative Transplant Study database includes approximately 200,000 SOT recipients followed over 10 years (27). In this database, MMF did not have a protective effect and tacrolimus was associated with a doubled risk of PTLD among kidney (but not liver) transplant recipients. Cyclosporine had no effect compared with azathioprine and steroids. Newer studies suggest that constitutional factors such as cytokine gene polymorphisms may also predispose to PTLD (11). The presence of genetic or epigenetic mutations can lead to the development of PTLD: molecular alterations of *BCL-6*, c-*MYC*, and *p53*, DNA hypermethylation, and aberrant somatic hypermutation have been implicated in PTLD (12).

D. Manifestations

PTLD typically occurs within the first year after transplant and usually involves the allograft and other intrathoracic tissues (7). Early-onset PTLD appears to be more common following LTx than other SOT (28). The mode of presentation of early cases is distinct from late-onset cases and the latter usually have a worse prognosis (5). Patients may present with B symptoms, symptoms localized to anatomic sites of involvement, or with incidental clinical or radiologic findings (23). Presentation varies widely from local nodal involvement to extranodal and disseminated involvement and is not clearly dependent on subtype (29). Similar to nontransplant-related lymphoma, the most common symptoms are nonspecific and include fever, lymphadenopathy, weight loss, abdominal pain, and splenomegaly (15). Rarely, patients present with multiorgan failure (30). In early disease, PTLD involves the thorax in 69% to 89% of cases and usually involves the allograft (7,31). Pulmonary PTLD generally presents as multiple well-circumscribed nodules that may be difficult to diagnose by transbronchial biopsy.

Mediastinal adenopathy is often seen. Isolated pleural effusion is uncommon but may accompany parenchymal disease (29). Endobronchial disease is not common but recognized (31). In contrast, intra-abdominal and disseminated forms of disease predominate in cases presenting beyond the first year and the allograft is less frequently involved (32). Post-transplant lymphomas have increased extranodal involvement, a more aggressive clinical course, a poorer response to conventional therapies, and poorer outcomes in general than lymphoma in the nontransplant population.

E. Diagnosis

Diagnosis is most firmly established by tissue biopsy and excisional biopsies should be obtained to allow for examination of architecture. Fine-needle biopsy may be misleading (15). Histology usually shows sheets of lymphoid cells with varying degrees of polymorphism and atypia. Necrosis is common. Perivascular infiltrates of mixed lymphocytes resembling those seen in acute cellular rejection may be seen at the periphery of nodules and can yield a false diagnosis (5). The lineage of proliferating cells can be assessed by immunohistochemical staining for B- and T-cell markers. Demonstration of the presence of EBV-infected cells is a key diagnostic factor (33). PCR assays for clonal immunoglobulin gene rearrangements are useful in distinguishing between the PTLD subtypes (5).

F. Management

Staging is an important determinant of outcome. In EBV-associated PTLD, quantitative evaluation of viral genomic load can assist with monitoring of therapy. No randomized controlled trials of management have been performed and no single treatment has proven effective for all types of PTLD but reversibility of disease with reduction in immunosuppressive therapy has long been recognized. Conversely, PTLD can manifest a rapidly progressive fatal clinical course if immunosuppression cannot be reduced. The current recommended therapy consists initially of reducing or modifying immunosuppression to permit partial restoration of host cellular immunity directed toward EBV. Patients whose disease is confined to the allograft are most likely to respond to this measure (5). However, loss of graft function secondary to chronic rejection is well recognized in these circumstances, thereby highlighting the delicate balance between risk and benefit associated with immunosuppression reduction (5). The presence of BCL-6 mutations has recently been identified as predicting lack of response to reduction in immunosuppression (23,34). Those with monomorphic proliferations, non-B-cell or EBV-negative lesions or PTLD occurring more than one-year post LTx are also less likely to respond (33). Therapy of PTLD must be tailored to the individual patient. In addition to the modification of immunosuppression, chemotherapy, surgery, radiation therapy, and/or biological modifiers such as rituximab can be used and all may be curative (7,23). When PTLD progresses despite the reduction of immunosuppression, standard lymphoma chemotherapy, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), is generally utilized, although some now consider this a "last resort" as the associated bone marrow suppression is poorly tolerated and the risk of morbidity and mortality is high due to infectious complications (1,5,23). The use of less-toxic immunological agents such as Rituximab, a chimeric human-mouse monoclonal antibody directed against the B-cell marker CD20, has become more common (10). It offers an attractive option for patients with more aggressive disease and those who cannot tolerate a reduction in immunosuppression (5). Multiple case reports have demonstrated complete responses in LTx recipients (35,36). In a report of 274 cardiac

transplant recipients from the Israel Penn International Transplant Tumor Registry (IPITTR), most PTLD patients (42%) were solely treated with immunosuppression reduction. Those in whom immunosuppression was reduced as a component of treatment had better survival than those who did not (32.3% vs. 10.8%; $p < 0.001$) (29). Reports involving kidney transplant recipients suggest that using Sirolimus, an inhibitor of the mammalian target of rapamycin can induce a complete response (1,37). Localized radiotherapy for PTLD has been reported in case studies but no randomized data are available (1,7,14). Although it is often utilized, there is no proven role yet for antiviral therapy in the setting of established PTLD (5). There is a theoretical role for antibody replacement with IV immunoglobulin in PTLD following evidence that loss of antibody against EBV nuclear antigens can lead to subsequent PTLD development (38). Cytokine-based therapies with interferon-α and interleukin-6 antagonist have also been used, though evidence is limited to studies treating less than 15 patients (39,40). The technique of adoptive immunotherapy which involves in vitro expansion and subsequent reinfusion of recipient EBV-specific cytotoxic T-cells also holds promise but further trials are needed (41). Other Herpes viruses have been treated by targeting the virus-specific enzyme thymidine kinase (TK). This is less effective as an antineoplastic therapy in EBV due to viral latency outside of the acute phase and, therefore, the lack of viral TK expression in EBV(+) tumor cells. One proposed strategy involves selective pharmacologic induction of the latent viral TK gene and enzyme in EBV(+) tumor cells using arginine butyrate followed by treatment with ganciclovir, resulting in tumor cell apoptosis (42).

G. Prevention

Much of the work in this area has been done in the pediatric liver transplant population because about 50% of young patients are EBV seronegative at the time of listing (43). EBV antiviral prophylaxis has been reported to reduce the incidence of PTLD (44). Monitoring for EBV in serum has been considered as a means of prevention. A single-institution study compared the rates of PTLD in pediatric liver transplant patients with and without reverse transcription PCR EBV viral-load monitoring and found that without monitoring the incidence of PTLD was 16% (45). In those who were monitored, immunosuppression was reduced if EBV loads exceeded 4000 copies per μg DNA and the PTLD rate decreased to 2% ($p < 0.05$). However, a viral load value truly predictive of PTLD development has yet to be determined. Importantly in this study, all patients with elevated viral loads did not go on to develop PTLD. Lastly, the emergence of EBV-negative PTLD is an entity which is difficult to predict.

III. Skin Malignancy

A. Epidemiology

Nonmelanoma skin malignancies are the most common neoplasm occurring greater than two years post transplant. Squamous cell cancer (SCC) is the most common subtype, with an incidence 65 to 250 times higher than that of the general population varying with sun exposure (1,46,47). Thus, the ratio of basal cell carcinoma to SCC is reversed compared with the general population in which basal cell carcinoma is the most common skin malignancy.

SCC is an aggressive disease in transplant recipients, the mean age of occurrence being 30 to 40 years, compared with 70 years in the general population (1). Half of those

who develop SCC are likely to develop a second skin cancer within 3.5 years. Men have a significantly higher risk for recurrence than women and at least 42% have multiple skin cancers (47). Poor prognosis is associated with older age, the presence of scalp, extracutaneous or multiple tumors, poor histological differentiation, tumor thickness of greater than 5 mm, and invasion of underlying tissue (46).

B. Pathogenesis

As with the general population, greater sun exposure and fair skin type play an important role in skin cancers after transplant. UV-induced *p53* tumor-suppressor gene mutations have been demonstrated in skin cancer tissue from transplanted patients (47). Viruses such as EBV, herpes simplex, herpes zoster, and polyomavirus have been implicated in oncogenesis (48).

C. Management

Given the high frequency of potentially aggressive skin cancers, patients should be educated regarding the dangers of sun exposure and evaluated by a dermatologist pre-transplant and at least yearly following transplantation (15). A randomized, controlled trial of 44 renal transplant recipients found a relative decrease in keratotic skin lesions of 13.4% in those treated with acitretin, an oral second-generation retinoid group, for six months, compared with a 28.2% increase in placebo (49). Larger studies are needed to determine doses, length of therapy, and long-term effects of treatment. Following development of skin cancer, patients should be treated aggressively due to the high risk for metastasis, recurrence, and death. Standard therapies include Mohs micrographic surgery, superficial ablative therapy, cryotherapy, and photodynamic therapy (15). Attenuation of the immunosuppressive regimen is useful for controlling tumor progression. Consensus guidelines for immunosuppression reduction have been developed by the International Transplant Skin Cancer Collaborative and Skin Cancer for Organ Transplant Patients Europe Reduction of Immunosuppression Task Force (50).

IV. Kaposi Sarcoma

Kaposi sarcoma (KS) in SOT occurs mainly in renal transplant recipients with an incidence of up to 6%, which is 500 times higher than that of the general population (15). KS remains recognized but rare in the lung transplant population where the first case was reported in 1997 and involved native lung and trachea in the absence of skin lesions (51). Multiple case reports now describe aggressive symptomatic allograft involvement, HHV8-rich hemorrhagic pleural effusions and endobronchial disease with and without cutaneous lesions (15,51). Reduction of immunosuppression remains the recommended primary intervention. Partial regression and complete remission are well reported following reduction in immunosuppression even in patients with respiratory tract and cutaneous disease (52,53).

V. Lung Cancer

Primary and metastatic carcinomas are rare in the transplanted lung, owing at least in part to careful screening of donors and recipients and the generally younger age of the transplant population. LTx has been performed for treatment of bronchoalveolar carcinoma (22). Although long-term survival has occasionally been achieved, a high

recurrence rate has been documented possibly due to airborne seeding of tumor from a reservoir in the recipient tracheobronchial stump (54). Occasionally malignancy is detected in the explanted lung, which predisposes the recipient to progressive malignancy particularly in the context of higher levels of immunosuppression early post transplant. Good long-term survival has been reported for stage 1 bronchogenic carcinoma in the explanted lung with reduction in immunosuppression, but prognosis for those with more advanced disease is poor and the malignancy can progress in a rapid fashion over a short period of time (55,56). Patients receiving single LTx occasionally develop carcinoma in the residual native lung. In fact, the development of lung cancer has been reported almost exclusively in patients with underlying chronic obstructive pulmonary disease (COPD) (reported incidence 2.0–3.7%) or pulmonary fibrosis (reported incidence 3.4–4.0%), both of which independently predispose to lung cancer (7). Data are conflicting on whether transplantation and the associated immunosuppression confers an increased likelihood of developing lung malignancy or whether the incidence is comparable with that of the general population with similar risk factors such as smoking (57). Treatment is similar to that of patients who are nontransplanted with similar histology, stage, and performance status (58).

VI. Donor Malignancy

In a very small number of cases, malignant tumors have spread from donor lungs to recipients and metastasized. Case reports exist of donors with known glioblastoma multiforme transmitting the tumor to multiple recipients of solid organs including lungs (59). Donor or recipient origin of the tumor can be assessed by molecular diagnostic methods.

VII. Minimization of Risk for Post-transplant Malignancy

Strategies to decrease the incidence and impact of malignancy in transplant recipients are needed. Optimum levels of immunosuppression are critical as over-immunosuppression can increase the risk, but allograft rejection resulting in necessity to augment immunosuppression also increases the cumulative dose. The use of mycophenolate or an mammalian target of rapamycin (MTOR) inhibitor is unproven. Once malignancy occurs, rapid identification is critical. In high-risk transplant recipients, aggressive surveillance (including cystoscopy, colposcopy, and rectal ultrasound) should be employed (1).

VIII. Summary

PTLD and nonmelanoma skin malignancies are the most common malignancies following LTx, but most other malignancies have been reported. Primary therapy is to reduce immunosuppression, and modifications on standard therapy for these malignancies form the mainstay of current recommended treatment.

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Lung Transplantation: Chronic Complications and Management

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I. Introduction

The primary focus of post-transplant management is ensuring that the lung allograft is not rejected and that infectious complications are either prevented or detected at an early stage such that treatment is likely to effectively preserve or restore graft function and not progress to life-threatening illness (1–3). However, many non-allograft complications can occur, especially in the older patient, patients with pretransplant comorbidities, or patients with other organ system dysfunction such as the patient with cystic fibrosis (CF). These complications (Table 1) can become life threatening and, as with the lung allograft, must be prevented or detected at early stages so that treatment can be most effective. Additionally, serious complications can arise from the native lung in single-lung transplant (SLT) recipients. Without attention to such "chronic complications" and their consequences, the allograft may function well, but the patient may do poorly and have their survival curtailed when serious, non-allograft complications occur that are not detected and managed proactively. In addition to medical complications, many transplant recipients develop serious psychosocial and socioeconomic problems that can be difficult to solve. Furthermore, there is a relative paucity of adequately powered clinical trials that can provide robust guidance for dealing with many aspects of lung transplantation, and this is especially the case for chronic complications and comorbidities.

This chapter will review the spectrum of non-allograft chronic complications that can occur following lung transplantation, and it will provide suggested approaches to monitoring for these complications and treating them when they occur.

II. Drug Toxicity and Drug-Drug Interactions

Adverse drug reactions occur frequently in transplant recipients, and long-term administration of some drugs (e.g., prednisone) can cause significant morbidity (Table 2). Because calcineurin inhibitors (CNIs) (cyclosporine or tacrolimus) can cause serious and possibly life-threatening adverse reactions including nonrenal toxicity such as systemic hypertension, hyperlipidemia, hyperkalemia, or seizures (4–6), blood levels of the CNIs must be followed closely to ensure adequate levels for immune suppression and yet avoid excessive levels that can cause renal dysfunction (Tables 3 and 4). Additionally, CNIs may cause significant nonrenal toxicity such as hypertension, hyperlipidemia, hyperkalemia, or seizures. Many potential drug interactions exist for the CNIs (which are metabolized by CYP 3A4 of

Table 1 Chronic Complications of Lung Transplantation

Organ system or type of complication	Specific disorders
Cardiovascular	Systemic hypertension
	Cardiac rhythm disturbances
	Thromboembolism
	Atherosclerotic heart disease
Renal	Chronic renal insufficiency
	Renal failure
Gastrointestinal	Gastroesophageal reflux
	Biliary tract disease
	Bowel disorders (motility disorders, diverticulitis, etc.)
Metabolic/endocrine	Dyslipidemia
	Diabetes
	Excessive weight gain, obesity
	Electrolyte abnormalities
Musculoskeletal	Osteoporosis
	Myopathy
Hematologic	Anemia
	Cytopenia (leukocytes, platelets)
Neurologic	Tremor
	Seizure
	Memory loss
	Neuropathy
Drug toxicity and side effects	Immunosuppressants
	Drug–drug interactions
Malignancy	Post-transplant lymphoproliferative disease
	Primary lung cancer
	Other malignancy
Lung allograft	Acute cellular rejection
	Infection
	Chronic lung allograft dysfunction
	Diaphragmatic dysfunction
	Disease recurrence
Native lung complications	Hyperinflation (emphysema as transplant indication)
	Infection
	Pneumothorax
Pleural disease	Effusion
	Pleural space infection
Chronic infection	Paranasal sinus disease
	Bronchiectatic lung (native or allograft)
Psychosocial problems	Disrupted support system
	Depression
	Medical noncompliance
	Multiple hospitalizations
	Resumption of addictive behaviors
Socioeconomic problems	Inadequate funds to cover medical costs
	Pressure on relationships
	Loss of insurance
	Disability, inability to find gainful employment

Table 2 Complications of Immunosuppressive Drug Therapy

Drug	Potential complications
Corticosteroids	Glucose intolerance
	Diabetes mellitus
	Infection
	Systemic hypertension
	Increased risk of cardiovascular disease
	Dyslipidemia
	Excessive weight gain/obesity/change in physical appearance
	Growth retardation in children
	Osteoporosis
	Avascular necrosis
	Myopathy
	Glaucoma/cataracts
	Skin atrophy
	Psychological change/sleep disturbance
Cyclosporin A	Nephrotoxicity
	Systemic hypertension
	Hyperkalemia, hypomagnesemia
	Seizure, headache, tremor
	Hepatotoxicity
	Gastrointestinal (nausea, vomiting, diarrhea; rarely pancreatitis)
	Hirsutism, pruritis, gingival hypertrophy
	Hemolytic uremic syndrome (rare)
Tacrolimus	Nephrotoxicity
	Systemic hypertension
	Hyperkalemia, hypomagnesemia
	Hyperglycemia, diabetes mellitus
	Prolonged QT interval
	Nausea, vomiting, diarrhea, constipation
	Tremor, headache, insomnia
Mycophenolate	Systemic hypertension
	Hematologic (myelosuppression, leukopenia, neutropenia)
	Gastrointestinal hemorrhage
	Peripheral edema
	Neurologic (confusion, tremor, headache)
	Gastrointestinal (nausea, vomiting, diarrhea, constipation)
	Cough
Azathioprine	Hematologic (leucopenia, thrombocytopenia, megaloblastic anemia)
	Pancreatitis (2–12%)
	Hepatotoxicity (3–13%)
	Gastrointestinal (gastritis, nausea, vomiting)
	Malignancy
Sirolimus	Pulmonary toxicity
	Delayed healing
	Systemic hypertension
	Hematologic (pancytopenia, thrombocytopenia, anemia)
	Hyperlipidemia/hypercholesterolemia
	Hepatotoxicity
	Neurologic (asthenia, headache)
	Arthralgia
	Peripheral edema

Table 3 Risk of Adverse Reactions for Specific Drugs

Drug class	Specific drug	Infusion reactions	Infection	Bone marrow	Renal function	Nervous system	Gastrointestinal	Hepatic	Cardiovascular	Lipid metabolism	Pulmonary toxicity	Wound healing
Calcineurin inhibitors	Cyclosporin A		++	+	++	+	+	+	+ (HTN)	+		
	Tacrolimus		++	+	++	+	+	+	+ (HTN)	+		
Cytotoxic anti-metabolites	Azathioprine		+	+			+	++			+	
	Mycophenolic acid derivatives		+	+		+	+	+			+	
mTOR inhibitor	Sirolimus		+	+				+	+ (HTN)	++		+
Anti-lymphocyte antibodies	Alemtuzumab	+	++	+								
	Antithymocyte globulin	+	++	+			+	+	+			
	Muromonab	+	++	+		+		+	+			
	Rituximab	+	+								+/-	
	Basiliximab	+	+									
	Daclizumab	+	+			+		+	+/-			

Abbreviations: HTN, Systemic hypertension; mTOR, mammalian target of rapamycin.

Table 4 Monitoring for Adverse Reactions to Specific Drugs

Drug class	Specific drug	Recommended precautions and monitoring
Calcineurin inhibitors	Cyclosporin A tacrolimus	• Periodic monitoring of drug levels in peripheral blood • Monitor blood pressure, CBC, renal function, potassium, glucose, and lipids • Monitor for altered blood levels if CYP3A4 inducers or inhibitors are coadministered • Consider dose reduction if progressive renal insufficiency occurs
Antilymphocyte antibodies	Alemtuzumab Antithymocyte globulin Muromonab Rituximab Basiliximab Daclizumab	• Monitor for infusion reactions • Monitor CBC • Monitor renal and liver function • Avoid simultaneous use of antilymphocytic antibodies
Cytotoxic agents	Azathioprine	• Monitor CBC and hepatic function • Dose reduction if coadministered with allopurinol
	Mycophenolic acid derivatives	• Monitor CBC periodically • Monitor for gastrointestinal toxicity and neurotoxicity
MTOR inhibitors	Sirolimus	• Obtain pre-treatment cholesterol and triglyceride levels and monitor on therapy • Monitor blood pressure, creatinine, and renal function • Avoid or limit dosing perioperatively to avoid suppression of wound healing • Evaluate for pulmonary toxicity if respiratory symptoms or signs appear

Abbreviations: CBC, complete blood count; mTOR, mammalian target of rapamycin.

Table 5 Summary of Reported Drug-Drug Interactions

Drug class	Specific drug	Metabolized by CYP 3A4[a]	Imidazole Antifungal agents	Macrolides	Antibacterial agents	Corticosteroids	Antidysrhythmics	Anticonvulsants	Vaccines	NSAIDs	ACE inhibitors	Allopurinol	Coumadin	Statins	Antacids	Grapefruit Juice	Echinacea	Herbal teas, diet supplements
Calcineurin inhibitors	Cyclosporin A	+	++	++	++	+	+	+	+	+	+	+	+	+	+	+	+	+
	Tacrolimus	+	++	++	++	+	+	+	+	+	+				+	+	+	
Antilymphocyte antibodies	Alemtuzumab								+									
	Antithymocyte globulin								+									
	Muromonab																+	
	Rituximab								+			++						
	Basiliximab																+	
	Daclizumab																+	
Cytotoxic antimetabolites	Azathioprine								+		+						+	+
	Mycophenolic acid derivatives				+				+						+		+	
MTOR inhibitor	Sirolimus	+	+	+	+		+	+	+							+	+	+

[a]CYP 3A4-metabolized drugs (competitors; increased levels of other drugs metabolized by CYP 3A4): nefazodone, macrolides, imidazoles, metronidazole, cisapride, cimetidine, chloramphenicol, grapefruit juice, calcium channel-blockers, theophylline.

CYP 3A4 inducers (decreased drug level due to increased activity of CYP 3A4): phenytoin, phenobarbital, modafinil, carbamazepine, quinopristine, rifampin, sulfasalazine, and sulfinpyrazone.

the hepatic cytochrome P-450 system) and other immunosuppressants (Table 5), and, therefore, any medications that are prescribed for a transplant recipient must be given carefully, especially if drug interactions are likely. If mTOR therapy (sirolimus) is given, blood levels also need to be monitored. If mycophenolate toxicity is a consideration (e.g., unexplained refractory diarrhea), mycophenolate blood levels can be obtained, and mycophenolate would be especially implicated as a cause of diarrhea if the levels are above the therapeutic range. Drug-drug interactions must always be considered whenever a change in pharmacologic therapy is considered for the transplant recipient.

Chronic corticosteroid therapy can lead to many complications or exacerbate conditions such as diabetes (7,8). Common complications include weight gain, myopathy, glucose intolerance, diabetes mellitus (DM), cataracts, systemic hypertension, osteoporosis, heightened risk of infectious complications, avascular necrosis, psychological complications, dyslipidemia, and increased risk of cardiovascular complications. The risk of these complications can be reduced by minimizing chronic doses of corticosteroids, especially once patients have successfully made it through the first 6 to 12 months post transplant and have no evidence of allograft dysfunction.

III. Renal Complications

Transplant recipients are at major risk for the development of renal dysfunction, and some degree of renal dysfunction is expected for virtually all patients due to chronic CNI therapy (9,10). Some patients may have some subclinical loss of function prior to transplant, and peri-implantation acute injury may cause extensive renal injury that increases the likelihood of significant chronic dysfunction. Post-transplant systemic hypertension, chronic administration of CNIs and other potentially nephrotoxic drugs, diabetes, hyperlipidemia, and biphosphonate administration can all contribute to impaired renal function. Chronic kidney disease can then, in turn, increase the risk of developing systemic hypertension and anemia.

Acute renal injury due to CNI therapy (which tends to be reversible) appears to be due to direct vasoconstriction of the afferent and efferent renal arterioles that decreases renal blood flow. Chronic CNI renal toxicity is characterized by extensive changes throughout the kidneys that consist of interstitial fibrosis, arteriolar hyalinosis, tubular atrophy, and ischemic glomerular collapse and sclerosis. The available literature does not convincingly show any advantage of CSA versus tacrolimus in avoiding renal dysfunction over time (9). An additional, uncommon form of chronic CNI nephrotoxicity is thrombotic microangiopathy, and this complication can occur with either CSA or tacrolimus and has also been reported with sirolimus in kidney transplant recipients (11).

Renal function and potassium levels should be checked frequently in the first post-transplant months and then at regular intervals thereafter (Table 6). Blood levels of CNIs need to be monitored closely and doses adjusted to ensure an adequate (but not excessive) level that will give the desired degree of immunosuppression but not impair renal function. Other electrolytes that can decline to low values due to renal tubular dysfunction and precipitate various adverse events (e.g., magnesium) or rise to dangerous levels (potassium) also need to be frequently monitored (12–14). When serum creatinine rises irreversibly above 1.5 g/dL (or estimated GFR falls below 50), consideration should be given to referring the patient to a nephrologist who is familiar with transplant issues (Table 7). Additionally, urinalyses should be performed intermittently

Table 6 Screening for Selected Post-Transplant Complications

Complication		Screening	Frequency[a]
Renal dysfunction	GFR >60 mL/min (stage II CKD)	• Cr, BUN, urinalysis, spot urine protein/Cr ratio	Every 6 mo
	GFR 45–60 (stage III b)	• Cr, BUN, urinalysis, spot urine protein/ Cr ratio • Evaluate for drug effect (e.g., CNI level)	Every 3 mo
	GFR 30–45 (stage III a)	• Cr, BUN, urinalysis, spot urine protein/ Cr ratio • Evaluate for drug effect (e.g., CNI level)	Every 2 mo
	GFR 15–30 (stage IV)	• Cr, BUN, urinalysis, spot urine protein/ Cr ratio • Evaluate for drug effect (e.g., CNI level)	Monthly
Electrolyte disorder		Serum electrolytes (K, Mg, other as indicated); May combine this with above	Every 2 mo
Bone marrow suppression		CBC with platelets	Every 2–3 mo
Gastrointestinal		Symptom review	Every 3–6 mo
		Alkaline phosphatase, bilirubin, AST, ALT	
Hyperlipidemia		Lipid panel	Every 6 mo
Osteopenia/osteoporosis		Bone mineral density scan	Every 1–2 yr
Diabetes mellitus		Blood glucose (fasting)	Every 6 mo
		HbA1c	Every 6 mo
Malignancy		Skin examination	Every 3–6 mo
		Bimanual gynecologic exam + PAP test (females)	Annually for age >40 yr
		Mammogram (females)	Yearly post-LTx
		PSA (males)	Annually
		Colonoscopy	One year post-LTx, then every 5 yr if initial exam negative
Cataract		Eye examination	6 months post-LTx, then annually
Psychosocial and socioeconomic problems		Evaluation by transplant coordinator Interview by social worker and/or health psychologist at clinic visits	As needed for a given situation

[a]These are suggested intervals; protocols for specific tests and the frequency with which they are obtained should be determined by individual centers, and some recipients may require more intensive and/or frequent testing for specific situations.

Abbreviations: GFR, glomerular filtration rate; CKD, chronic kidney disease; Cr, creatinine; BUN, blood urea nitrogen; CNI, calcineurin inhibitor; HbA1c, hemoglobin A1c; PSA, prostate-specific antigen; CBC, complete blood count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PAP, Papanicolaou smear.

Table 7 Management of Select Chronic Complications

Problem detected	Intervention	
Renal dysfunction	GFR 45–60 mL/min	• Evaluate and adjust (as able) medications capable of affecting renal function (e.g., CNI) • Check Cr, protein/creatinine ratio (spot urine) every 3 mo
	GFR 30–45 mL/min and/or spot urine protein/creatinine ratio >0.5	• Identify cause • Consider transplant nephrology consultation • Check Cr, protein/creatinine ratio (spot urine) every 3 mo • Follow NKF-KDOQI guidelines • Check intact PTH and calcium-phosphate product every 3 months
	GFR <30 mL/min	• Transplant nephrology consultation • Check Cr, protein/creatinine ratio (spot urine) every month • Follow NKF-KDOQI guidelines • Check intact PTH and calcium-phosphate product monthly
Hyperkalemia	Optimize renal function as able Sodium bicarbonate Optimal diabetes management Kayexalate	
Hypomagnesemia	Supplementation (magnesium + protein) Dietary education	
Systemic hypertension	Avoid excessive salt intake β-Blocker (e.g., metoprolol) Angiotensin receptor blockers Angiotensin converting enzyme inhibitors	
Hyperlipidemia	Statin therapy Fibrate for high triglycerides Check CK, AST, ALT 6 wk after statin therapy initiated	
Anemia	Iron studies, rule out blood loss (e.g., internal bleeding) Iron replacement if low Erythropoietin therapy (e.g., darbopoietin) if normal iron stores	
Leukopenia	Rule out CMV infection Adjust medications as needed (e.g., mycophenolate, azathioprine, trimethoprim sulfa) Consider G-CSF if severe/sustained neutropenia Hematology consultation	

(*Continued*)

Table 7 (*Continued*)

Problem detected	Intervention
Osteopenia/ osteoporosis	Calcium, vitamin D as appropriate Biphosphonate (adjust for renal function) Endocrinology consultation if severe/refractory
GERD	Medical management (behavioral + acid suppression) Consider surgical fundoplication Follow-up evaluation to assess efficacy of therapy (impedance + pH measurement via esophageal probe)

Abbreviations: GFR, glomerular filtration rate; Cr, creatinine; CNI, calcineurin inhibitor; NKF-KDOQI, National Kidney Foundation—Kidney Disease Outcomes Quality Initiative; PTH, parathyroid hormone; HbA1c, hemoglobin A1c; PSA, prostate-specific antigen; CK, creatine kinase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CMV, cytomegalovirus; G-CSF, granulocyte colony-stimulating factor.

to detect albumin and protein loss, which can reflect the presence of ongoing renal injury. Published guidelines for the management of chronic kidney disease may prove useful in establishing surveillance and treatment protocols for recipients who develop post-transplant renal dysfunction (15).

IV. Hematologic Complications

Many of the drugs given for immune suppression, infection prophylaxis, or other indications can significantly depress bone marrow function and cause leukopenia, anemia, and/or thrombocytopenia. Granulocytic cell lines tend to be most susceptible, and neutropenia may complicate therapy by increasing the patient's risk of infection. Additionally, drug combinations such as a CNI plus a cytotoxic agent given for post-transplant immunosuppression may have additive effects, and other drugs (e.g., trimethoprim sulfa or ganciclovir) given for prophylaxis or treatment of infection may contribute to bone marrow suppression and potentiate the hematologic effects of immunosuppressive drug therapies. Intermittent monitoring of bone marrow function via complete blood counts with differential cell count should be performed at regular intervals. Another cause of leukopenia can be cytomegalovirus (CMV) infection and/or the treatment/prophylaxis of CMV with ganciclovir or valganciclovir (16).

V. Metabolic Disturbances and Endocrinologic Disorders

Corticosteroids and other transplant medications can significantly disrupt glucose metabolism and promote obesity. Patients with CF and those who have metabolic syndrome are particularly at risk and have a relatively high pretransplant prevalence of DM, and the risk of developing DM increases significantly after transplantation (17,18). Intensification of corticosteroids for allograft rejection frequently leads to significant hyperglycemia and may require the administration of insulin and monitoring of blood glucose levels. Additionally, the risk of developing diabetes appears to be significantly increased in recipients treated with tacrolimus in contrast to CSA-treated solid-organ transplant recipients (19).

Electrolyte disorders are often encountered following transplantation, especially hyperkalemia as a consequence of the effects of CNI and other drugs on renal function. Hypomagnesemia may also occur, and magnesium supplements may be required. In addition to hyperkalemia and hypomagnesemia, patients with advanced renal dysfunction may develop secondary hyperparathyroidism. Hyperlipidemia is also a common complication of transplantation (discussed below).

Gonadal dysfunction may occur in both males and females with advanced organ dysfunction or following various types of transplantation, potentially causing impotence in males and menstrual irregularities in premenopausal women (20–24). Additionally, hypogonadal function with consequent androgen or estrogen deficiency may predispose patients to the development of osteoporosis (see below) in addition to various other risk factors for osteoporosis that may already be present at the time of transplantation (25). Lastly, CNIs and other immunosuppressive agents (other than prednisone) are pregnancy class C (either studies in animals have revealed adverse effects on the fetus—teratogenic or embryocidal or other—and there are no controlled studies in women or studies in women and animals are not available) or class D (there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk), and pregnancy should be discouraged but monitored very carefully should a patient become pregnant and want to carry the child to term (26).

VI. Musculoskeletal Complications

There is a very high prevalence of osteopenia and osteoporosis in patients with advanced lung disease, and lung transplantation can rapidly accelerate bone loss (27,28). Two factors that are strongly associated with low bone mineral density (BMD) are pretransplant low body mass index and extent of corticosteroid use (28–31). In addition to pretransplant monitoring for osteopenia/osteoporosis, it has been recommended that all recipients should have BMD checked frequently (e.g., 6–12 months post transplant and then yearly) via DEXA scanning and receive antiresorptive and other appropriate therapies if T scores indicate the presence of osteopenia or osteoporosis (32). Treatment should follow currently available guidelines for the treatment of osteopenia/osteoporosis (27), and some investigators have advocated resistance training in addition to pharmacotherapy (33,34).

Other potential complications include myopathy, osteonecrosis, and rhabdomyolysis. Myopathy and avascular necrosis or osteonecrosis are usually related to chronic corticosteroid therapy, and chronic dosing should be kept as low as possible to avoid these and other potential side effects.

VII. Cardiovascular Complications

Cardiovascular complications are quite common and include systemic hypertension, rhythm disturbances (atrial fibrillation is quite common), and hyperlipidemia (35,36). Hypertension has been linked to corticosteroids, CNI administration, and weight gain, and hyperlipidemia has also been linked to chronic administration of immunosuppressive agents. Interestingly, the administration of statins for hyperlipidemia has been linked to improved survival and a decreased risk of developing OB (37). Nearly all long-term survivors will eventually develop systemic hypertension and dyslipidemia, and screening for lipid abnormalities should be performed every 6 to 12 months post transplant as well as routine screening for hypertension.

Cardiac rhythm disturbances can occur early in the postoperative course (35). Agents such as amiodarone can be used to treat supraventricular tachycardia in the short term, and these tachydysrhythmias will often subside in the short term, but electrophysiologic evaluation and ablative interventions may be required. Other agents such as β-blockers or calcium channel blockers may also be useful for acute and chronic therapy of rhythm disturbances as well as systemic hypertension.

The incidence of venous thromboembolism (VTE) in lung transplant recipients has been reported to range from 9% to 29% (38–40). Although venous thromboembolic events tend to occur early post transplant and have been linked to cardiopulmonary bypass as a risk factor (39), these events can occur at later time points.

VIII. Gastrointestinal Disorders

Numerous gastrointestinal complications occur in lung transplant recipients (41,42). Gastroesophageal reflux disease (GERD) is highly prevalent in patients with advanced lung disease prior to transplantation (43), and it has been linked to post-transplant lung function decline and the development of OB/BOS (44,45). Ideally, all candidates and recipients should be screened (pH and impedance measurements) for GERD and receive appropriate medical or surgical therapies as needed to prevent significant reflux (46,47). Pepsin in bronchoalveolar lavage (BAL) fluid has been implicated as a biomarker of gastric aspiration and acute rejection (48), and additional studies are needed to substantiate the utility of this marker in BAL versus other markers associated with reflux, such as bile salts, which have been shown to cause significant alterations in pulmonary surfactant components (49,50).

Recipients with CF are particularly predisposed to GI complications due to disease-related intestinal tract dysfunction (51,52). Patients with CF can develop bezoars, which often form in the early post-transplant period and can inhibit absorption of orally administered drugs (53). CF patients are also at risk for distal intestinal obstruction (52), biliary tract complications (cholecystitis, significant biliary stasis, ascending cholangitis), and intestinal neoplasms (especially colon cancer).

Older recipients are at increased risk for colonic complications such as diverticulitis and intestinal perforation (41,42,54). Colitis caused by *Clostridium difficile* should be ruled out in any patient who develops significant diarrhea. Clinicians must be aware that when *C. difficile* infection causes colitis in patients with CF, diarrhea usually does not occur (55,56).

IX. Neurologic Disorders

Various neurologic complications may occur following transplantation (57–61). Acute neurologic side effects, occasionally severe and life-threatening, may occur as a consequence of CNI soon after transplant. Subacute or chronic neurologic complications of CNI therapy, however, may occur years after transplantation and include peripheral neuropathy, memory loss, seizures, and white matter lesions. Additionally, unusual and/or treatment-resistant infection may occur at any time post transplant.

X. Infection

Extrapulmonary infections or infections involving the residual native lung for SLT recipients may occur many years after transplant and may have very subtle initial

manifestations (62). Such infectious complications are usually due to bacterial and fungal pathogens, although protozoal or nematode infections must also be kept in mind. One potential source of infection in recipients with CF is a subcutaneous indwelling venous infusion device, and removal should be considered post transplant when such devices are no longer needed for administering frequent intravenous therapies.

XI. Malignancy

Transplant recipients are at increased risk for skin cancers, solid tumors (e.g., colon, breast, bladder, and kidney) and post-transplant lymphoproliferative disease (PTLD) (63,64). Additionally, primary lung neoplasms may occur and usually arise in the native lung of SLT recipients who have a significant smoking history (65–67). These neoplasms tend to be relatively advanced when detected, which limits treatment options. The skin should be thoroughly inspected at frequent intervals (e.g., monthly) by the recipient (involvement of a significant other or other support person can help for areas not readily viewed by the patient), and skin inspections should be performed at clinic visits.

PTLD occurs in a substantial number of recipients and is highly linked to Epstein-Barr virus (EBV) infection-induced lymphocyte proliferation (64,68). Lesions can occur in the lung or in various extrapulmonary locations, and diagnosis may be difficult. Reduced immunosuppression, antiviral therapy with ganciclovir/valganciclovir to inhibit EBV DNA replication, and IV immunoglobulin (e.g., IVIG or CMV-IgG) may promote tumor regression. Rituximab has been administered with some success, but refractory disease requires the administration of multiagent chemotherapy.

XII. Native Lung

Single-lung transplantation can be performed for emphysema, interstitial lung disease (ILD), or pulmonary hypertension, and it has occasionally been performed for bronchiectasis. The native lung is prone to infection, especially if it is quite structurally damaged and bronchiectatic. As mentioned above, if primary lung cancer occurs post transplant, these tend to arise in the native lung of SLT recipients. Spontaneous secondary pneumothorax may occur, and some SLT recipients with emphysema will have progressive hyperinflation that encroaches on the transplanted lung and impairs its function (69). Additionally, the native lung in patients with idiopathic pulmonary fibrosis (IPF) is prone to developing infection with opportunistic fungi, particularly *Aspergillus*.

XIII. Primary Disease Recurrence

Patients with various forms of ILD may have their primary lung disease recur in the lung allograft despite their intense immunosuppressive regimen (70), and disease recurrence has been reported for multiple recipients with the transplant indication of sarcoidosis, lymphangioleiomyomatosis, or Langerhans cell histiocytosis. Disease recurrence can lead to progressive allograft dysfunction and loss, although the appearance of granulomas in allografts of recipients with sarcoidosis usually does not have a significant impact on graft function (71). The recurrent granulomatous lesions have been shown to derive from recipient cells (72), and the recurrence can be controlled with augmented immunosuppression, if required. Interestingly, recurrence of usual interstitial pneumonia

has never been reported in the literature. Concern has been raised that recipients with α-1-antitrypsin deficiency may be prone to graft injury and possibly recurrence of emphysema (73), and emphysema recurrence has been reported (74). However, patients generally are not given replacement therapy, and disease recurrence does not appear to be a major issue.

XIV. Psychosocial and Socioeconomic Issues

Lung transplant recipients often have significant psychosocial and economic issues prior to transplant (75–77), and depression rates are quite high among candidates for lung transplantation (78). These problems may continue into the post-transplant period and potentially flare when post-transplant complications occur, and nonadherence to the post-transplant medication regimen and monitoring is more likely to occur in individuals with significant psychological dysfunction and can have disastrous consequences on the outcome (79). Health psychology intervention with a focus on building up coping strategies combined with pharmacologic treatment of depression may provide improved post-transplant psychosocial function and recipients' ability to cope with unexpected post-transplant complications (78).

Anxiety disorders and depression are common problems following transplantation (78,80), but symptoms of depression tend to diminish following transplantation if quality of life improves (78,81). Nonetheless, a significant number of transplant recipients will require ongoing psychosocial support post transplant (75,76,80), and behavioral and psychosocial factors may have a significant effect on post-transplant outcome. Access to care and socioeconomic factors may have a significant impact on post-transplant outcome as has been suggested for heart transplantation (82), but there is relatively little literature that has explored the impact of these factors on lung transplant outcomes. Health psychology experts and social workers who are attuned to the problems faced by patients with end-stage lung disease and lung transplant recipients are essential members of the transplant team.

XV. Patients with Disorders That May Involve Other Organ Systems

CF patients have multiple organ system involvement that requires continued treatment following transplantation. Virtually, all patients with CF have paranasal sinus disease, pancreatic exocrine insufficiency, and gastrointestinal motility dysfunction. Additionally, they may have significant liver disease or osteoporosis, and many have diabetes. Certain other recipient transplant indications also can involve other organs. These include α-1-antitrypsin deficiency (e.g., liver disease) and sarcoidosis (potential involvement of any extrapulmonary organ system). Post-transplant management must include an awareness of extrapulmonary aspects of these disorders, and appropriate interventions for extrapulmonary organ dysfunction should be provided if needed.

XVI. Summary

A myriad of non-allograft complications can make their appearance in the lung transplant recipient. Lung transplant physicians and other personnel need to be aware of these complications and actively monitor and screen their patients to identify early and

provide effective therapy that may prevent serious consequences that can potentially arise as these complications make their appearance. Frequent communication between health care personnel (e.g., transplant coordinators) and transplant recipients may help to identify some of these problems, and clinical evaluations and laboratory testing performed at appropriate intervals may detect complications at early stages when many of these problems are more amenable to therapy and progression to a stage that is refractory to treatment is less likely to occur.

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Quality of Life After Lung Transplantation

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I. Background

Lung transplantation offers the potential to improve both survival and quality of life (QOL) for select patients with advanced lung diseases. Although improvement in health-related quality of life (HRQOL) is generally accepted as an important patient-centered outcome, the current lung allocation system does not include QOL as one of the variables in determining "transplant benefit" and calculation of the lung allocation score (LAS) (1). This omission reflects the general perception in the transplant community that prolonging survival should be the primary objective of transplantation. The absence of methodologically sound studies in the lung transplant literature from which QOL can accurately be quantified reinforces the notion that QOL is an important but secondary objective.

Although the early focus of clinical research in lung transplantation was directed at establishing technical feasibility, measuring physiologic parameters, and achieving acceptable survival outcomes, these measures are inadequate for making an informed decision regarding whether the potential benefits of lung transplantation outweigh the considerable risks and costs for an individual patient. Highlighting the importance of HRQOL data, a study from the Brigham and Women's Hospital showed that more than 50% of patients with advanced heart failure were willing to trade shorter survival for improved health (2). Anecdotally, many lung transplant physicians have reported a similar perception when patients with accelerated chronic rejection in the early post-transplant years express their gratitude for the brief period of "good" QOL they experienced. Clearly, survival alone is an incomplete measurement of transplant benefit. Surrogate markers for "health" are also suboptimal. Whether a patient can walk a certain distance on a six-minute walk test or can achieve an FEV_1 that is 80% vs. 100% of predicted is of less interest to patients than the presence or absence of dyspnea with exertion or the ability to return to work and perform certain activities that interest them. QOL surveys attempt to measure these types of patient-centered concerns. The aim of this chapter is to summarize and explore the issues surrounding QOL after lung transplantation. It will review the studies describing the impact of lung transplantation on QOL measures and highlight the most important factors affecting post-transplant QOL.

II. How is QOL Measured?

Defined variably in the literature, QOL relates to an individual's sense of satisfaction and happiness. It is a general concept that encompasses several important dimensions in a person's life. The World Health Organization defined QOL as "a broad ranging

concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features in the environment" (3). In one of the first tools developed to measure QOL, Flanagan identified five important conceptual categories: (*i*) physical and material well-being; (*ii*) relations with other people; (*iii*) social, community and civic activities; (*iv*) personal development and fulfillment; and (*v*) recreation (4). While lung transplantation can clearly impact all five of these areas, its most quantifiable effects are in the first realm—physical and material well-being. Tools to measure HRQOL specifically focus on this domain.

Two approaches have been developed to assess HRQOL. The first involves the use of generic tools that try to assess the patient's overall state of physical and psychosocial health (5). Examples of generic instruments include the Sickness Impact Profile, Nottingham Health Profile (NHP), Short Form (SF-36), EuroQuol (EQ-5D), and Quality of Well Being questionnaires. These comprehensive tools are useful for assessing the health status across a broad range of patient populations and measuring the impact of certain healthcare interventions. Generic tools, however, are less sensitive for measuring disease-specific symptoms such as dyspnea or cough that may adversely affect a patient's QOL. To better address this issue, validated disease-specific HRQOL instruments are also available. Examples of HRQOL tools used in pulmonary disease include the St. George's Respiratory Questionnaire (SGRQ), the Modified Medical Research Council Dyspnea Index, and the Chronic Respiratory Disease Questionnaire (CRQ). These lung-specific HRQOL measures, although not useful for comparisons between populations with different diseases, have better sensitivity for detecting the impact of medical intervention on disease-related symptoms. Both generic and lung-specific instruments have been used in studies assessing how lung transplantation affects QOL (6).

A primary goal of HRQOL studies in lung transplantation is to determine if post-transplant patients have better QOL than patients with advanced lung disease on the lung transplant waiting list and also to get a sense of how enduring and significant this difference might be. Notably, there have not been randomized controlled trials comparing lung transplantation to medical therapy. Data regarding HRQOL after lung transplantation comes primarily from longitudinal studies that measure QOL in a cohort of patients before and after transplantation, or from cross-sectional studies that compare QOL in a group of patients on the waiting list to a cohort of patients that had undergone transplantation. Both approaches have methodologic flaws that should be considered. One concern is that only lung transplant survivors are surveyed. Thus, the impact of death, which presumably impacts QOL negatively, is not included. This survivor effect may thus favorably bias the data toward lung transplantation as having a benefit on QOL. Cross-sectional sectional studies are flawed because they are comparisons of two different groups of populations. In addition, QOL assessment at a single point in time may not be representative of the true and long-term effects of transplantation (6). In the following sections, important studies on HRQOL in lung transplantation will be reviewed.

III. Does Lung Transplantation Improve QOL?

Several longitudinal studies employing a variety of different measures have demonstrated that lung transplantation improves QOL (7–14). The positive effects of lung transplantation can be immediate. Lanuza et al. showed that in their cohort of 10 lung transplant recipients, within three months of lung transplantation, the patients perceived

significant improvements in strength, overall health status, and QOL (10). TenVergert et al. assessed 24 patients pre transplant and subsequently up to 19 months post transplant with several different HRQOL tools. At four months after transplant, mobility, energy, sleep, activities of daily living dependency level, and dyspnea were all improved and maintained for the following 15 months (14). More recently, a larger cohort of 66 patients at the University of Florida receiving transplants between 1994 and 2001 were followed for a mean of 28 months post transplant (15). Compared to a COPD normative sample, lung transplant recipients reported significantly higher scores on seven of eight SF-36 subscales. However, when compared to the general population, post-transplant scores were still significantly lower across all domains tested (15). Another important observation from this study is that it appears that patients who were farther from transplantation were proportionately more likely to report symptoms of depression, headaches, and breathing difficulties when compared to patients newly transplanted. This suggests that the onset of chronic rejection, or bronchiolitis obliterans syndrome (BOS), is associated with decreased QOL. This association will be discussed in more detail later in this chapter.

Cross-sectional assessments of QOL offer the opportunity to study a larger cohort of surviving transplant recipients with wide ranges of intervals since transplant. This offers insight regarding the relationships between QOL and more chronic issues such as onset of BOS, rejection and infection episodes, and side effects of immunosuppression use. In 2005, the Vienna group published their experience with 108 lung transplant recipients with a mean time since transplant of 42 ± 30 months (16). Forty-seven percent of this cohort was three to five years from transplant. When compared to a normal population using the SF-36, lung transplant patients experienced physical restriction but no deficits in their reported vitality and mental health. Compared to a COPD population, transplant recipients scored significantly better on all aspects of the SGRQ. Declines in SGRQ, however, were strongly associated with onset of BOS grade ≥ 1 (16). Similarly, Kugler et al. showed in a retrospective cross-sectional study of 280 lung transplant recipients using a generic HRQOL questionnaire that the subgroup of patients who were more than five to six years from transplant had significantly reduced measures on five of six subscales of HRQL (physical abilities, relaxation capabilities, positive moods, negative moods, and contact capabilities). The only variable found to be significantly associated with poorer HRQL was the onset of BOS (17). In 2006, Vasiliadis et al. published a small cross-sectional study of 34 transplant candidates on the waiting list and compared them to 71 lung transplant recipients, 18 of whom were five or more years post transplant. On all eight domains of the SF-36, transplant recipients reported higher HRQOL scores than candidates; interestingly, time since transplant was not significantly associated with reduced QOL after adjusting for other variables.

The available evidence indicates that QOL measures are improved for patients who survive lung transplantation. These improvements, however, may not reach normality as seen in the general population.

IV. Does Pre-Transplant Functionality and QOL Affect Post-Transplant Success?

Several studies have tried to answer this important question. If pre-transplant QOL impacts post-transplant survival, a strong argument could be made that QOL should be considered when determining lung allocation. An equally important follow up question

would be: If pre-transplant QOL is a determinant of post-transplant outcome, could interventions prior to transplantation improve the likelihood of post-transplant survival and/or QOL? Finally, it would be useful to know if disease sub-groups have differing degrees of QOL since this may impact the decision regarding appropriateness of transplantation, particularly for diseases such as COPD where the survival benefit associated with transplantation is less certain (18).

Expanding on previous HRQOL studies, Vermeulen et al. recently examined if pre-transplant QOL affects post-transplant survival (8,19–21). In this study, 200 lung transplant recipients completed several HRQL questionnaires every three months as they awaited lung transplantation. The questionnaires completed closest to the date of transplant were used for comparison with post-transplant HRQOL data. After Cox regression analysis, pre-transplant HRQOL scores were not found to be significant predictors of survival after lung transplant (21).

In examining the role of pre-transplant functional status on post-transplant outcome, Martinu et al. prospectively evaluated 376 patients from Duke and Washington University (22). After adjustment for other important covariates, their analysis indicated that pre-transplant distance walked on a six-minute walk test was a strong predictor of post-transplant survival. This finding extended across all disease categories (22). In a large retrospective study from the University of Pennsylvania, Sager et al. showed that poorer functional status as measured by six-minute walk distance (6MWD) pre-transplantation was an independent predictor of reduced post-transplant functional status (23). As has been shown in survivors of ARDS, the level of normal functional status achieved after recovery directly impacts QOL (24,25). Clearly, additional study into the importance of pre-transplant HRQOL and functional status on post-transplant HRQOL and outcomes is needed (15).

Several studies have shown differences in QOL among pre-transplant disease subgroups (16,26,27). Cystic fibrosis (CF) patients, perhaps due to younger age at the time of transplant or longer duration with which CF patients have coped with their disease (often since birth), have higher QOL measures when compared to other disease groups. For example, Burker et al. compared 58 patients with CF to 52 patients with other end-stage lung diseases at the time of evaluation for lung transplantation (26). The CF group was more likely to be working, had lower levels of anxiety, higher levels of social support, and used more functional coping strategies than other patients. These findings suggest that different disease groups may need different types of psychosocial interventions to improve QOL particularly since these interventions pre transplant may positively impact post-transplant QOL (28).

V. Predictors of Long-Term QOL After Lung Transplantation

Only a few studies have looked at the impact of lung transplantation on long-term QOL. Unfortunately, these studies are typically underpowered and have not adequately dealt with the survivorship bias issue. None of them have taken a comprehensive assessment of all five QOL conceptual categories identified by Flanagan (4). As we strive to understand and articulate the long-term experience of lung transplant recipients, data describing the long-term impact on relationships, social functioning, personal development and fulfillment, and recreation in addition to physical and material well-being would be very meaningful. As worldwide experience with lung

transplantation matures, hopefully larger, more robust, multicenter studies will be performed.

Vermuelen et al. in 2007 investigated the role of several variables (age, gender, diagnosis, year of transplantation, time on waiting list, type of transplant, BOS, and pre-transplant HRQOL scores) on the physical and psychological dimensions of QOL in 140 long-term survivors of lung transplantation (29). Interestingly, predictors differed between the physical and psychological dimensions; age, gender, BOS and pre-transplant QOL score seemed to influence the physical dimension more than the psychological, while BOS and pre-transplant depression were the only significant predictors of post-transplant depression. Anxiety was predicted by BOS and age.

Rutherford et al. from the Newcastle group measured HRQOL in lung transplant recipients who had survived for at least 10 years (30). The SF-36 questionnaire was administered to 28 patients; 72% had BOS grade ≥ 1 at the time of assessment. Compared to normative data and a group with chronic illnesses, long-term lung transplant survivors had significantly lower HRQOL in physical domains, although mental health and bodily pain measures were not different. In a prospective study of lung recipients followed for a mean of 4.9 ± 1.2 years, Gerbase et al. aimed to correlate functional outcomes such as FEV_1 and 6MWD with annual assessments of HRQOL using the SGRQ and a visual analog scale (31). The authors showed that recipients of single-lung transplants had significantly lower FEV_1 values and an increased risk for BOS development compared to bilateral lung transplant recipients (31). Notably, 6MWD and SGRQ scores were not different between single- and bilateral-lung transplant recipients at any follow-up period assessed (31). Thus, type of lung transplant procedure may not be an important predictor of long-term post-transplant HRQOL or functional outcome, although, once gain, the selection bias of studying only survivors may have significantly impacted this conclusion.

VI. BOS and QOL

BOS is the leading cause of mortality beyond the first post-transplant year (32,33). Both the severity and timing of onset of BOS (early vs. late) have been shown to have an impact on survival after lung transplant (33,34). As discussed previously, several studies have suggested that the onset of BOS may also reduce long-term HRQOL (9,14,29,35–38). For example, in 2000, van den Berg et al. evaluated HRQOL by performing cross-sectional and longitudinal analysis on a cohort of 116 lung transplant recipients (37). Questionnaires were administered at 4 and 7 months post transplant, and every 6 months afterward for as long as 49 months. Patients with BOS clearly demonstrated poorer HRQOL. In particular, these patients had reduced scores on the dimensions of energy and physical mobility on the Nottingham Health Profile compared to patients without BOS. Pain, sleep, social interaction, and emotional reactions were not affected. On cross-sectional analysis, BOS patients were more likely to report depressive symptoms one and two years after transplant, although longitudinal follow-up did not show a change in depressive symptoms after BOS onset (37). Interestingly, Gerbase et al. recently published a study of 58 long-term survivors of lung transplantation (5.6 ± 2.9 years) showing that despite having similar functional status as measured by the 6MWD, patients with BOS (grade ≥ 2) reported to have a decreased HRQOL. This discordant finding suggests that HRQOL reductions are not simply related to having a poorer functional status, further highlighting the importance of using patient-centered outcomes such as QOL instead of surrogate markers of health in

clinical trials (36). Other factors not specifically assessed by the six-minute walk test that could have had a detrimental impact on perceived HRQOL include peripheral muscle weakness, decreased mobility, dyspnea associated with increased airflow obstruction, side effects related to BOS treatment, and the psychological effect of being diagnosed with a potentially life-threatening condition (29,36,37).

VII. Conclusion

The complex risk-benefit calculation on whether the potential benefits of lung transplantation outweigh the considerable risks for a given patient depends on high-quality data regarding both survival and QOL. Unfortunately, data regarding the utility of lung transplantation, which incorporates the combined effects of both outcomes (quality-adjusted survival), is limited (6,39,40). Nevertheless, lung transplantation appears to improve HRQOL in survivors. Not surprisingly, the long-term QOL benefit is limited by the development of chronic rejection (BOS), the main obstacle to long-term survival. More work in this domain would be useful in determining maximal net transplant benefit, more precise informed consent, and for targeting early intervention in patients considered at risk for compromised QOL.

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Proteomics, Genomics, and Lung Transplantation

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I. Introduction

Current assessment of the immunologic state of the lung allograft and recipient remains limited despite nearly three decades of experience in lung transplantation. Evaluation for cell-mediated rejection relies on transbronchial biopsy, which is invasive and subject to sampling error and inter-reader variability. Detection of chronic rejection relies on findings of airflow obstruction associated with irreversible changes of constrictive bronchiolitis. No standards exist for defining humoral rejection. Evaluation of immunosuppression is based on drug levels, toxicity, and nonspecific assessment of lymphocyte proliferation. Identification and measurement of individual biomarkers have yielded limited success in these settings. Genomic and proteomic techniques offer potential to broadly and noninvasively assess products of deoxyribonucleic acid (DNA) transcription and RNA translation using qualitative and quantitative methods. These techniques may ultimately lead to discovery of pathways and biomarkers associated with the presence or risk for primary allograft dysfunction, acute rejection, chronic rejection, and infection, as well as effect and toxicity of immunosuppressive regimens. In the following section, current genomic and proteomic techniques will be described, and evidence for potential roles in lung transplantation will be reviewed.

II. Genomic and Proteomic Techniques

The development of microarray technology has provided a means for evaluating gene transcription patterns in transplantation and other clinical settings. Translational and post-translational processing leading to protein expression ultimately determines cellular function and phenotype. Proteomics permits further evaluation and identification of biomarkers that may be useful for diagnosis and therapy modification in the field of organ transplantation.

A. Genomics and Microarrays

Microarrays assess the expression of tens of thousands of genes through measurement of fluorescently labeled target hybridization to complementary nucleotide probe sequences. Target samples are usually derived from sample messenger RNA (mRNA), and less commonly from total RNA or micro-RNA. A microarray chip or gene chip consists of a library of complimentary DNA (cDNA) or short oligodeoxynucleotide probes affixed to a slide matrix.

In cDNA chips, a single gene is represented by a cDNA probe several hundred to thousand base pairs (bp) in length. A reference sample is analyzed simultaneously with a test sample. Target cDNA is synthesized from sample mRNA utilizing fluorochrome-labeled nucleotides with a different fluorescence wavelength for test versus reference samples. Gene expression is estimated by comparing fluorescence in the two samples for each individual probe.

In oligodeoxynucleotide chips (oligo chips), a single gene is represented by a group of probes approximately 20 bp in length, corresponding to different segments on the target gene. Sample mRNA is utilized to generate amplified amounts of labeled complimentary RNA (cRNA), which is then hybridized to the chip. Because of this amplification process, very small amounts of mRNA (as little as 5 μg) can be analyzed using oligo chips. Gene expression correlates with fluorescence intensity.

Microarrays delineate upregulation or downregulation of specific genes. This information can then be utilized to detect or predict the presence of a specific disease state such as transplant rejection or to assess response to therapy or to identify specific biomarker candidates for assessment of these conditions (1–5). Because these studies assess thousands of gene transcripts, the identification and validation of specific patterns associated with clinical states require relatively large sample sizes and complex data analysis techniques.

B. Proteomics

Proteomics is the evaluation of all proteins expressed from the genome. While the genome encompasses tens of thousands of genes, variations in gene splicing, protein polymorphisms, and post-translational processing generate a proteome defined by hundreds of thousands of proteins. Unlike DNA or RNA, proteins cannot be assessed using hybridization probes, or amplified using polymerase chain reaction (PCR) techniques. Proteomic analysis is generally based on mass, charge, binding specificity, and peptide sequencing. Protein microarrays utilize probes based on protein-protein interactions.

Two-dimensional gel electrophoresis is based on evaluation of differential migration of proteins on the basis of isoelectric focusing and molecular weight. *Two-dimensional differential in-gel electrophoresis* permits comparison of several differentially labeled samples on a single gel and thus may be useful in comparing patterns of protein expression in the presence and absence of specific disease states such as transplant rejection. These techniques can be used to separate proteins, which can then be further analyzed and identified through *mass spectrometry*. Liquid chromatography is also used to purify or enrich target protein populations before mass spectrometry analysis. Mass spectrometry characterizes proteins based on their mass-to-charge ratio and the mass-to-charge ratio of peptide fragments produced by proteolytic enzymes. Commonly used mass spectrometry technologies are *surface-enhanced laser desorption/ionization time-of-flight* (SELDI-TOF) and *matrix-assisted laser desorption/ionization time-of-flight* (MALDI-TOF). These techniques can be used to identify potential biomarkers associated with specific clinical states. *Protein microarray* chips permit high-throughput analysis of protein expression and function. Protein chips can analyze proteins based on specific binding or biochemical activity. The most common iteration utilizes chips coated with an array of specific antibodies to which an extracted protein mixture is then applied (6–9).

III. Genomic and Proteomic Studies in Lung Transplantation

A. Primary Graft Dysfunction

Primary graft dysfunction (PGD) is the major contributor to early mortality after lung transplantation. Identification of donor or donor lung biomarkers associated with development of PGD could enhance donor lung selection and utilization.

In a study utilizing a rat model of ischemia reperfusion injury, genomic microarray analysis demonstrated that hundreds of genes are upregulated in association with this process. This group included proinflammatory genes, cytokines, matrix metalloproteinases, and chemokines. Interleukin-6 (IL-6) was most markedly upregulated in this model (10).

Andrade et al. utilized real-time PCR (RT-PCR) to evaluate toll-like receptor (TLR) and inflammatory cytokine expression in serial biopsies obtained from human donor lungs after cold ischemic time, warm ischemic time, and reperfusion. With the exception of TLR3, TLR expression correlated positively with interferon gamma (IFN-γ) and IL-10. TLR4 expression correlated with levels of IL-8, a cytokine that has been associated with PGD. Duration of donor intubation correlated with expression of TLR2, TLR5, TLR6, TLR10, IFN-γ, IL-10, IL-1b, IL-8, and heat-shock protein 70 (11).

Two studies have utilized microarrays to assess gene expression in donor lungs. Ray et al. utilized biopsy samples obtained from 50 donor lungs just prior to cold flushing to assess alterations in gene transcription associated with PGD. This study identified 23 upregulated and 42 downregulated transcripts associated with PGD. Upregulated transcripts including nuclear factor κB (NFκB) were associated with stress-activated pathways. Upregulation of metallothionein (MT) gene transcripts was noted in lungs that did not develop PGD. MTs have a potential role in protection against oxidative stress, scavenging free radicals, and promotion of cell proliferation (12).

A second study utilized donor lung biopsy samples obtained just prior to lung implantation (end of cold ischemic time) in a case control assessment comparing patients with severe PGD with matched control patients with good outcomes. Microarrays were used to identify eight upregulated genes associated with PGD and upregulation of four of these eight transcripts was then confirmed by RT-PCR. Upregulation of these four genes (ATPase class VI type 11b, fibroblast growth factor receptor 2, egl nine homolog, and microcephaly autosomal recessive 1) was predictive of poor survival (hazard ratio for death within 30 days after transplant of 1.96). These genes are associated with mechanisms that could reflect acute responses to significant physiologic stress such as ischemic lung injury (13).

These studies demonstrate that genomic microarrays can be used to identify potential biomarkers and pathways that may be associated with PGD. Ultimately, it is possible that this preliminary work utilizing lung biopsy material could lead to the discovery of circulating biomarkers useful for donor lung selection.

IV. Acute and Chronic Rejection After Lung Transplantation

Ideal strategies for detection and prediction of acute or chronic rejection would incorporate sensitive, noninvasive assessment of transcription patterns, or biomarkers in peripheral blood, bronchoalveolar lavage (BAL), or bronchial brushing samples. Preliminary studies suggest that such approaches may ultimately be feasible. To date, most studies have focused on samples obtained through BAL.

Comparison of gene expression profiles obtained from 34 BAL cell samples in the presence (A + B score > 1; $n = 7$) and absence (A + B score $\leq$ 1; $n = 27$) of acute rejection detected 135 genes that were significantly upregulated in the presence of acute rejection (14). A subsequent study comparing BAL samples from 14 subjects without acute rejection on serial samples and 18 subjects with acute rejection identified 56 transcripts that were highly associated with the presence of acute rejection (15). Interestingly, fewer than 50% of transcripts identified as upregulated in the first study were again identified in the second study. In both of these studies, transcripts identified were involved with T-cell function, granulocyte degranulation, and cytotoxic CD8 activity. Gene ontology classification demonstrated that up-regulated transcripts were most commonly associated with biologic process categories of response to biotic stimulus; defense response; and immune response (15).

Gene expression patterns associated with bronchiolitis obliterans syndrome (BOS) have been evaluated in a single study comparing BAL cell samples from 11 patients with BOS and 9 control transplant recipients. Differential expression of 15 genes was observed in the setting of BOS. Overexpression of genes representing inflammatory, fibrotic, and apoptotic pathways was observed in patients with BOS. These genes included IL-1β, CD40 ligand, TNF, TNF ligands, IL-2, Fas ligand, lymphotoxin-α, ribosomal protein L13a, PDGF-BB, and VEGF. Serial evaluation demonstrated that upregulation was temporally associated with development of BOS with subsequent return to baseline levels of transcription despite ongoing BOS (16).

Genomic studies utilizing a murine heterotopic airway model of obliterative bronchiolitis demonstrated upregulation of genes associated with CD-8 T-cell immune function including granzymes, T-cell receptor genes, CD3, and IFN-γ. Later time points after implantation in this model were also associated with underexpression of genes associated with epithelial cell function (17).

Mass spectrometry evaluation of BAL fluid using MALDI-TOF has also demonstrated patterns associated with BOS in two studies. Elevated levels of human neutrophil peptide (HNP) were shown to have a sensitivity of 75% in predicting development of BOS within the subsequent 15 months. Reduced levels of clara cell protein (CCP) have also been associated with BOS and a lowered ratio ($<$0.3) of CCP to lysozyme was 94% specific and 74% sensitive for diagnosis of BOS. This reduced ratio was observed in two-third of samples obtained within 15 months prior to the onset of BOS. CCP may play a role as an anti-inflammatory agent, and low levels of this protein may therefore lead to excessive inflammatory injury. High levels of HNP may be cytotoxic to epithelial cells (18,19).

Bronchial epithelial cell (BEC) gene expression has also been evaluated in lung transplant recipients. Comparison of genomic expression from BEC samples obtained from bronchial brushings demonstrated variable expression of 153 genes (13 upregulated and 140 downregulated) in lung transplant recipients versus healthy nontransplant subjects. Changes in genomic expression in BECs in association with BOS are currently being evaluated (20).

The lung allograft rejection gene expression observational (LARGO) study evaluated the association of peripheral blood mononuclear cell (PBMC) gene expression profiles with acute rejection. Preliminary results from this study identified 259 genes that were differentially expressed in patients with rejection ($\geq$A2) versus those without (A0) (21). A goal of this study was to further assess quantitative expression of a smaller subset of candidate genes using RT-PCR and to determine a correlation of expression

with the presence and absence of rejection. To date, further results have not been reported.

Preliminary studies in lung transplant recipients have demonstrated variation in genomic and proteomic expression patterns in association with the pathologic states of acute and chronic rejection. The majority of these studies have involved small patient populations. It is hoped that further studies may lead to refinement and validation of candidate genomic and proteomic profiles useful for clinical assessment.

V. Genomics and Proteomic Studies in Nonpulmonary Solid-Organ Transplantation

Genomic studies in other solid-organ transplant settings have also demonstrated alterations in genomic transcription associated with acute rejection. Considerable variation exists in the actual genes identified in different studies. The genes identified in different studies are associated with common molecular pathways associated with inflammation, apoptosis, cell cycle regulation, transcription regulation, and immune response (22). Many of these studies have relied on invasive assessment and analysis of biopsy samples. Recent efforts have focused on less-invasive peripheral blood analysis.

An evaluation of peripheral blood lymphocyte (PBL) gene expression in renal allograft recipients demonstrated minimal overlap in gene expression patterns in PBLs in comparison with biopsy specimens. Alteration in expression of 65 genes from PBLs was associated with acute rejection. Fifteen of these genes were selected for validation and quantitative assessment using RT-PCR. This confirmed the upregulation of these genes observed by microarray, although a much greater magnitude of change was detected by RT-PCR (23). SELDI-TOF mass spectrometry has also demonstrated patterns of urinary protein excretion associated with acute rejection (24).

A recent study documented differential expression of 20 microRNAs in association with acute renal allograft rejection. MicroRNAs are short (22 bp) noncoding molecules involved in gene expression regulation. MicroRNAs have not been evaluated in other solid-organ transplant settings and may provide additional avenues for diagnosis or discovery of novel pathways affecting graft function or immune response after transplantation (25).

Evaluation of drug-free tolerant renal transplant patients also demonstrated differential expression of 49 genes in peripheral blood. Quantitative assessment of 33 of these genes using RT-PCR correctly identified the presence of tolerance in a separate validation group with 99% specificity. Nearly a third of the genes identified were regulated by TGF-β. The genes identified were associated with reduction in costimulatory signaling, immune quiescence, apoptosis, and memory T-cell responses (26). Gene expression profiles associated with tolerance have also been identified in liver transplant recipients (27).

Two studies have identified peripheral gene expression profiles associated with acute cardiac rejection (28,29). One of these studies, the cardiac allograft gene expression observational (CARGO) study, utilized microarray and RT-PCR from PBMCs to develop a clinical test to identify acute rejection. This test, based on quantitative RT-PCR measurement of 11 gene transcripts, was able to successfully identify absence (negative predictive value 99.6%) of moderate-to-severe cardiac rejection (ISHLT grade $\geq$3A) (29).

These recent studies suggest the potential to identify proteomic and genomic alterations that reflect allograft pathologic or tolerant states using less-invasive sampling.

VI. Conclusions

Genomic and proteomic studies are recent developments in medical science. They permit high-throughput molecular analysis of transcriptional or translational products, generating large amounts of data with the goal of finding patterns associated with specific clinical states. From this perspective, they represent hypothesis-generating as opposed to hypothesis-driven approaches to research and discovery. Ongoing technical refinement and interpretation of findings utilizing these tools has mandated evolution in the field of bioinformatics as well as molecular science. Ultimate objectives include identification of pathways and biomarkers that can be utilized to monitor, identify, or alter specific clinical states.

There are many potential applications in the field of solid-organ transplantation. To date, studies have largely focused on identifying patterns associated with acute rejection, chronic rejection, or tolerant states. Assessment of solid-organ allografts continues to rely heavily on histologic evaluation of tissue biopsies, but it is hoped that proteomic and genomic techniques could reduce the need for invasive testing. By further refining the assessment of allograft health and the recipient immunologic status, further refinements in the approach to immunosuppressive therapy may be feasible.

In lung transplantation, these techniques have been used to identify patterns associated with PGD as well as acute and chronic rejection utilizing samples obtained from peripheral blood, BAL, and bronchial brushings in addition to tissue biopsy. Preliminary studies demonstrate alterations in gene transcription or protein translation in association with graft pathology but are limited by sample size. Larger studies may ultimately enhance our ability to identify suitable donor organs as well as presence or risks for acute and chronic rejection. Thus, these techniques offer novel approaches and opportunities for improving timely delivery of appropriate and specific therapy and ultimately patient outcomes after lung transplantation.

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Immune Tolerance

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I. Background

The overall success of transplantation is critically limited by the need for lifelong post-transplant immunosuppression. Antirejection drug regimens, which typically include calcineurin inhibitors, steroids, and antiproliferative agents, inhibit recipient immune responses at the cost of diabetes, renal failure, and cancer. In addition, sustained immunosuppression contributes directly to infection. In lung transplant recipients in particular, infection remains the leading cause of early post-transplant mortality.

Donor-specific immune tolerance (DSIT) implies graft acceptance without the need for chronic immunosuppression and is commonly referred to as the "holy grail" of transplantation (1). Though tolerance has occasionally been achieved experimentally, it has only rarely been observed clinically. The precise mechanisms of tolerance remain complex and incompletely understood. In this chapter, we present known mechanisms of tolerance, current tolerance induction strategies, and future directions in the field.

II. Central vs. Peripheral Tolerance

During transplant tolerance, the recipient immune system remains inactive against the transplanted organ, but responsive to other antigens. Tolerance mechanisms can be classified as central or peripheral (2). Central tolerance refers to immunologic nonreactivity mediated within central lymph nodal tissues. The classic mechanism for central tolerance is clonal deletion, in which self-reactive T cells are deleted in the thymus upon exposure to antigen (3). In fact, clonal deletion was the only established mechanism of transplantation tolerance before 1995. Mixed chimerism is a distinct form of central tolerance, which allows deletion of T cells reactive to both donor and recipient (4,5).

Peripheral tolerance, in contrast, refers to modulation of immune function within peripheral lymphoid tissues. A critical breakthrough in defining peripheral tolerance mechanisms came with the independent characterization of the regulatory T cell (Treg) phenotype by Sakaguchi and Groux (6,7). Tregs are a subset of T lymphocytes that upregulate the transcription factor FoxP3 and promote allograft tolerance when appropriately programmed in the spleen and other lymphoid organs (8). Subsequently, other mechanisms of peripheral tolerance, such as T-cell depletion and anergy from costimulatory blockade (9), have been defined.

III. Chimerism

Hematopoietic stem cell transplantation for treatment of cancer was first proposed in the 1950s (10). Experience in bone marrow transplantation has revealed that mixed hematopoietic chimerism can achieve varying degrees of transplant tolerance. Experimentally, in nonmyeloablative mouse models of bone marrow transplantation, successful mixed allogeneic chimerism can result from combined thymic radiation and T-cell depletion (4). Similar results were achieved in experiments utilizing blockade of costimulatory pathways (11).

Recent clinical studies using mixed hematopoietic chimerism have shown encouraging results toward tolerance induction. Patients with renal failure from multiple myeloma who underwent combined bone marrow + HLA-identical kidney transplant have displayed tolerance of the transplanted kidneys with only transient chimerism (12). Subsequent clinical studies also have shown promise. In patients without hematologic malignancy, use of a nonmyeloablative BMT regimen in conjunction with kidney transplant has resulted in renal allograft tolerance without maintenance immunosuppression (13). These recipients were unresponsive to donor-specific antigens in mixed lymphocyte reaction, suggesting a systemic tolerance mechanism (14). Given the suggestion from these data that chimerism may contribute to clinical tolerance, more clinical studies defining the contribution of chimerism to tolerance induction are warranted.

IV. Cellular and Molecular Mediators of Tolerance

A. Regulatory T Cells

Tregs, known years ago as "T suppressor cells," occur in two types—(*i*) *naturally occurring* and (*ii*) *adaptive (or induced)* Tregs (15). Naturally occurring CD4+ Tregs originate in the thymus and constitutively express CD25 (8). Their primary function is to limit autoimmunity, ensuring "self-tolerance." Specifically, mutation of the gene for the Treg nuclear transcription factor forkhead box P3 (Foxp3) leads to uncontrolled lymphocyte proliferation and activity (8). Naturally occurring Tregs can regulate other immune cells directly, via cell surface molecules such as GITR, OX40, CTLA-4, and TGF-β. Alternatively, Tregs can suppress other immune effector cells in paracrine fashion by secreting cytokines including IFN-γ and interleukin-35 (IL-35) (16).

In contrast, adaptive Tregs may arise from either CD4+CD25– or CD4+CD25+ T cells, depending on local conditions in peripheral lymphoid tissues. In the presence of antigenic stimulation and/or the cytokine TGF-β, adaptive Tregs upregulate Foxp3 and most commonly secrete IL-10 or TGF-β to exert immunosuppressive effects in a paracrine fashion (15).

The relative importance of naturally occurring versus adaptive Treg activity during tolerance induction remains unclear. Since naturally occurring Tregs already have a putative role in regulating autoimmunity, and adaptive Treg responses are induced by antigen and can regulate the adaptive immune response, it is speculated that adaptive Tregs play a more important role in clinical transplant tolerance (15). Experimental studies suggest that donor-specific adaptive Tregs can mediate tolerance. In a murine model of bone marrow transplantation, donor-specific Tregs transferred with donor-specific bone marrow inhibited both acute and chronic rejection (17).

Few clinical studies utilizing Tregs exist; initial trials in bone marrow transplantation have utilized both naive and in vitro expanded Tregs in search of graft

tolerance (15). However, successful tolerance induction in solid-organ tolerance by simple addition of Tregs to a solid-organ transplant recipient is far from guaranteed. First, it is unclear whether native or adaptive Tregs act upon memory T cells, which may be resistant to Treg effects (18). In addition, CD4+CD25+ Tregs can be subverted under proinflammatory conditions into IL-17 producing T helper cells that actually mediate rejection (19). Another practical difficulty in studying Tregs clinically lies in their detection within the circulation. First, the Treg marker Foxp3 is expressed intracellularly and is thus difficult to quantitate; in addition, adaptive Tregs lack truly unique cell surface markers (20).

B. Memory T Cells: A Barrier to Transplant Tolerance?

Experimental data in small animal models notwithstanding, achieving tolerance in large animals and humans, has proven to be a formidable challenge. Experimental and clinical studies have implicated memory T-cell activity during rejection, thus impeding tolerance induction (21). For example, memory T cells have been identified as intragraft IFN-γ producers during rejection of human renal allografts (22). Memory T cells may impede tolerance by several mechanisms. First, memory T-cell reactivation can occur when donor antigens similar to previously encountered infectious or environmental pathogens are encountered. Second, memory T-cell activation requires less antigen and costimulation than for naive T cells, and once active, memory cells achieve effector function more rapidly. Finally, memory T cells can reject allografts without secondary lymphoid organs (23). Studies that characterized naive T cell versus T memory cell responses in a murine model of skin allograft rejection also showed that T memory cells recruited more GR-1+ polymorphonuclear cells to the allograft and that anti-GR-1+ antibody returned the rejection to a naive T-cell kinetic (21). Future strategies directed at tolerance induction will clearly have to account for the multiple mechanisms by which memory T cells achieve an active state.

C. Alloreactive T-Cell Depletion

In solid organ transplantation, the *selective* depletion of activated, alloreactive T cells is attractive in concept, but difficult in practice. The FDA-approved anti-T-cell agents ATG and OKT3 target the T cell receptor (TCR) and CD3, respectively, but create a general immunosuppression by depleting all TCR+ and/or CD3+ T cells (24). The anti-CD52 monoclonal antibody alemtuzumab (Campath-1H), which is used as induction therapy and for treatment of graft rejection, has greatest activity against T cells but also transiently depletes monocytes, NK cells and B cells (25). The most selective induction agents are the anti-IL-2 receptor antibodies daclizumab and basiliximab, which prevent IL-2 interaction with CD25. These agents are selective for activated T cells, though so far they are currently used with traditional immunosuppression regimens (26).

Ex vivo alloreactive T-cell depletion may also permit tolerance. Methods of ex vivo depletion include induced apoptosis of proliferating T cells, depletion of T cells expressing activation markers, and phototherapy. In induced apoptosis, dividing cells are labeled with a "suicide" thymidine kinase gene that also confers ganciclovir sensitivity (27). Ganciclovir treatment then selectively kills T cells that have taken up the suicide gene (27). Interestingly, only transient ex vivo depletion can result in a tolerant-like state in a murine model of islet transplantation (28).

D. Extracorporeal Photopheresis

Extracorporeal photopheresis (ECP) was originally developed as a therapy for cutaneous T-cell lymphoma but has gained some acceptance as an alternative immunosuppressive modality in solid-organ and bone marrow transplantation (29). During ECP, peripheral blood is first separated into red and white blood cells; the white cells are then treated with psoralen (UVADEX). UVADEX covalently binds DNA and thereby facilitates cellular apoptosis within 24 to 48 hours of exposure to ultraviolet radiation (30). Antigen-presenting cells that then process apoptotic cells may adopt a "silent" phenotype, thereby promoting tolerance. The mechanism by which antigen-presenting cell (APC) tolerogenesis occurs is unclear but may involve (*i*) downregulation of costimulatory molecules, (*ii*) IL-10 production and IL-12 suppression, and (*iii*) modulation of Treg activity (31,32). Clinical studies are ongoing to define the therapeutic potential of ECP in modulating immune responses and tolerance induction.

E. "Tolerogenic" Dendritic Cells

Dendritic cells (DCs) play a pivotal role in transplant tolerance since they can induce a protolerant, regulatory phenotype in T cells. For example, loading recipient DCs with donor major histocompatibility complex (MHC) molecules induces deletion of donor-reactive T cells and favors graft infiltration with tolerogenic CD4+Foxp3+ T regulatory cells (33). Not surprisingly, "tolerogenic" DCs and their activities have been an area of intense study within transplant tolerance.

An example of a distinct subset of "tolerogenic" DCs is the plasmacytoid DCs (pDCs). Isolated from the lymph nodes of mice tolerant of vascularized cardiac allografts, they express high levels of MHC class II, LFA-1, ICAM-1, and CD40 (34). Importantly, they proved necessary for Treg cell development and tolerance induction, as well as sufficient for Treg cell development and tolerance induction in therapeutic adoptive transfer studies (34). DC subtypes with activities similar to pDCs may play a role in future in vivo and clinical tolerance protocols.

In vitro modulation of DCs has also been attempted to maintain DCs in an immature and therefore tolerogenic state (35,36). Treatment of DCs with rapamycin, steroids, in addition to immune modulatory molecules such as IL-10 and CTLA4Ig, has been investigated (37). These and other experimental studies suggest a functional relationship between tolerogenic DC activity and the Th2 cytokine IL-10. First, DCs treated with IL-10 favor a regulatory phenotype for T and NKT cells (38). In addition, blockade of IL-10 receptors on splenic DCs negates nonresponsiveness and increases IL-12 production (39). Furthermore, DCs isolated from IL-10-deficient mice have enhanced T-cell stimulatory capacity (40). Conditioning of DCs with IL-10 and/or other factors promoting tolerance holds promise for future experimental and clinical protocols.

F. Soluble MHC and Noninherited Maternal Antigens

In solid-organ transplantation, donor MHC molecules are an important trigger for rejection. Therefore, investigators have sought to define the immune responses to both soluble and membrane-bound MHC molecules in hopes of facilitating tolerance. Soluble HLA molecules are continuously released into the circulation by accepted liver, and to a lesser extent, lung, heart, and kidney allografts (41,42). Soluble class I HLA molecule binding to either the CD8 molecule or the TCR can trigger apoptosis of Fas+ CD8 T cells (42). Moreover, immune stimulatory events such as uncontrolled CMV infection can disturb soluble HLA antigen levels (41).

A novel mechanism of MHC-induced tolerance is maternal antigen exposure (43,44). The hypothesis that neonatal exposure to maternal antigens could induce tolerance to the same antigens in adulthood was driven by the observation that, in a retrospective analysis of 205 renal transplant recipients from sibling donors, transplanted kidneys expressing noninherited maternal HLA antigens had dramatically higher graft survival (77% vs. 49% at 10 years) than those expressing noninherited paternal antigens (44,45). Further studies have gone on to demonstrate that maternal antigens initiate fetal tolerance by generation of FoxP3+ (regulatory) T lymphocytes in the presence of TGF-β and IL-2 in "immunologically privileged" fetal lymph nodes (46). These findings suggest that expansion of Tregs induced by exposure to MHC molecules under "tolerogenic" conditions may lead to a degree of tolerance.

G. NK Cells

NK cells are undoubtedly relevant to tolerance since they constitute the third largest lymphocyte population in the peripheral lymphoid system, can kill antigen without previous exposure, and have a broad range of immune effector functions (47,48). The role of NK cells in tolerance is complex since they can promote either tolerance or rejection depending on the local microenvironment (48). Specifically, NK cells can participate in allograft rejection by producing proinflammatory cytokines, promoting DC maturation, and cytolytic activities during rejection, although studies in Rag knockout mice (which are deficient in T and B cells but have functional NK cells) show that NK cells are not *sufficient* to cause rejection (48,49). In contrast, NK cells have been shown to tolerize islet allografts in experimental models including costimulatory blockade (50). It is unclear whether NK cells promote tolerance by eradicating graft-derived donor cells and thereby limiting alloreactive T-cell activation, by killing autologous APCs, or inhibiting T-cell clonal expansion (49). The dichotomous activities of NK cells have led to the hypothesis that in the absence of local inflammation or the presence of other tolerance factors, NK cells may facilitate tolerance by destroying donor APCs and regulating T-cell activity. During conditions favoring transplant rejection, NK cells may amplify T-cell alloresponses and activate APCs (48). The factors that determine whether NK cells adopt a rejecting or tolerant phenotype, the role of NKT cells, and the molecular targets of NK cells are currently being studied. A greatly improved understanding of these mechanisms is needed to translate our knowledge of NK cells into tolerance protocols.

H. Future Directions

Tolerance induction constitutes a broad area of active investigation. Current foci of study include the potentially tolerogenic activities of Toll-like receptors (51), the recently described membrane glycoproteins T-cell immunoglobulin mucin (TIM) proteins (52), and the role of mast cells (53). In addition, the identification of useful biomarkers of tolerance with in vitro tests or gene arrays also has potential for clinical identification and monitoring of tolerance (54–56).

V. Conclusion

Tolerance in solid-organ transplantation remains elusive due to the complexities inherent in balancing processes that mediate allograft rejection and the counteracting tolerance mechanisms. The rarity of true clinical tolerance likely reflects the need for

several tolerogenic processes to function simultaneously, possibly including activation of Foxp3+ Tregs, inhibition of alloreactive T-cell proliferation and activation, and a cytokine milieu and innate immune system phenotype influenced toward tolerance. Development of successful clinical tolerance protocols will ultimately require a complex, multifaceted strategy that achieves these ends. If our understanding of tolerance mechanisms continues to improve, we will not only be able to extend the longevity of transplanted organs and the lives of their recipients, but also undoubtedly illuminate many interconnected aspects of clinical immunology.

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Augmentation of Maintenance Immunosuppression in Lung Transplantation

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I. Introduction

Despite the aggressive maintenance immunosuppression regimens that are currently used in lung transplantation, there remains a high rate of both acute and chronic rejection after lung transplantation. As a result, several strategies have been considered to augment maintenance immunosuppression in this patient population. These strategies include the use of high-dose steroids, addition of induction therapy, conversion of one drug to another (i.e., conversion to mTOR inhibitor), and the addition of other immunomodulating agents (azithromycin, aerosolized cyclosporine). The use of other salvage therapies including total lymphoid irradiation and extracorporeal photopheresis is also discussed.

II. Induction Therapy

Induction therapy is the brief utilization of an immunosuppressive agent in the immediate postoperative period to temper this initial robust alloresponse to the transplanted organ. These agents can be classified into two groups: cytotoxic agents (antithymocyte globulin, muromonab-CD-3, and alemtuzumab) and noncytotoxic agents (daclizumab, basiliximab).

A. Anti-thymoglobulin

Antithymoglobulin (ATG) is a polyclonal antilymphocyte preparation produced in either rabbits (Thymoglobulin) or horses (Atgam) against human thymic cells. Thymoglobulin is given intravenously within 24 hours of transplantation at a dose of 1.5 mg/kg over six hours. Two additional doses are given 24 hours apart, for a total of three doses. Atgam is also administered intravenously with 24 hours of transplantation. The dose is 7.5 to 15 mg/kg/day for three to five days after transplantation.

An early retrospective analysis of ATG revealed no significant decrease in incidence of bronchiolitis obliterans syndrome (BOS) or in survival times as compared with historical controls and a higher incidence of CMV infection in the recipients treated with ATG induction therapy (1). More recently, a prospective and randomized trial comparing Thymoglobulin with no induction agent showed less acute rejection events in the Thymoglobulin group than in the control group. In this study, there was no difference in incidence of infection or malignancy between the two groups (2). In the hope that the lower acute rejection rates would translate into a lower incidence of BOS and therefore

improved survival, this group followed up with a prospective and randomized evaluation of long-term survival in lung transplantation recipients treated with Thymoglobulin induction versus no induction therapy (3). Although there was a lower early acute rejection incidence in the ATG group, there was no difference in long-term survival between the two groups at eight years. According to the 2008 ISHLT registry, the use of polyclonal ATG has gradually declined in favor of monoclonal preparations such as interleukin-2 receptor (IL-2) antagonists and alemtuzumab (Campath-1H) (4).

B. Muromonab-CD3 (OKT3)

Muromonab-CD3 (OKT3) is a mouse monoclonal antibody that has been used clinically as an induction agent and to treat acute rejection since the 1980s. OKT3 binds to the T cell receptor-CD3 complex, which causes a reversible antigenic modulation of the CD3 complex, leading to immunoincompetence and ultimately depletion of T cells. Prior to these immunosuppressive effects, however, the binding of OKT3 to the CD3 receptor complex initially stimulates T cells to produce a massive first-dose cytokine-release syndrome consisting of fever, rigors, nausea, vomiting, diarrhea, and in some severe cases, hemodynamic instability (5). For this reason, patients are commonly premedicated with steroids, antihistamines, and antipyretics prior to OKT3 dosing. In addition to cytokine-release syndrome, pulmonary edema has been noted and aseptic meningitis has been seen in 3% to 5% of patients receiving OKT3 (6,7). OKT3 is given at a dose of 5 mg per day for 7 to 14 days after transplantation.

Although OKT3 is one of the most potent immunosuppressives available, humans can make neutralizing antibodies to OKT3, which limit prolonged use (8). Side effects included mild elevations in pulmonary artery systolic pressure, mild reduction in oxygenation and pyrexia, which were self-limited, easily treated, and resolved within 12 hours (9). This study is representative of some positive results with OKT3, but many experts avoid using the drug because of its side effect profile.

C. Alemtuzumab (Campath-1H)

Alemtuzumab (Campath-1H) is a humanized preparation of monoclonal rat antibodies directed toward the CD52 antigen that is present on virtually all lymphocytes. Campath-1H has been used in the treatment of rheumatoid arthritis, lymphoid malignancies, graft-versus-host disease, and in bone marrow transplantation. It was first used in solid-organ transplant as an induction agent in 1998 (10). Campath-1H is given intravenously in the following regimen day 1: 3 mg; day 2: 10 mg; day 3: 30 mg; followed by 30 mg three times per week for 4 to 12 weeks.

Campath-1H leads to depletion of T cells by way of complement-mediated and direct cellular cytotoxicity (11). The resultant lymphopenia is profound and long lasting; T-cell levels (both CD4 and CD8) may remain significantly depressed for as long as three years (12). Because the target CD52 antigen is also present on B cells, Campath leads to a B-cell lymphopenia as well, although of a shorter time period, typically about three months. Use of Campath in acute rejection has been noted to be an independent risk factor for opportunistic infection in a large study of 547 organ transplant recipients (13). Like OKT3, Campath also causes a cytokine storm reaction with the first dose. This reaction is more modest than that seen with OKT3 and well treated by preemptive parental steroid administration prior to the initial dose. Diffuse alveolar hemorrhage has been reported with the use of Campath (14).

D. Basiliximab/daclizumab

Interleukin-2 (IL-2) binding to T cells is a critical action in the cellular mediated rejection of the transplanted organs. Daclizumab and basiliximab are chimeric murine/human monoclonal antibody preparations that are specific for and bind with high affinity to the α-subunit of the IL-2 receptor, also known as the CD25 antigen, on activated T cells. Thus, these agents inhibit IL-2-mediated proliferation and differentiation of T cells. Basiliximab contains a greater proportion of murine antibody than daclizumab (25% vs. daclizumab's 10%), has a shorter half-life, and a lower receptor saturation than daclizumab (15).

Daclizumab is administered at a dose of 1 mg/kg within 24 hours of transplantation for a total of five doses. These doses are given at intervals of 14 days. Basiliximab, in contrast, is dosed as a single 20-mg daily dose on the day of transplant and on the fourth day post-transplantation. These drugs do not cause the cytokine release syndrome typical of OKT3 and Campath, but severe, noncardiac pulmonary edema was reported in three separate patients two days after renal transplantation who were given basiliximab induction therapy (16).

According to the 2008 ISHLT registry, IL-2 receptor antagonists (IL-2 RA) were associated with a lower percentage of recipients with rejection in the first year after transplantation when compared with either no induction or use of polyclonal ATG therapy. In terms of overall usage of induction agents, the use of IL-2 RA has risen from December 2000 to December 2006. This contrasts with the use of ATG, which has declined during this same time period (4).

III. Comparison of Different Agents

Studies comparing induction agents have yielded mixed results (17–19). In the largest analysis, 3970 adult lung transplantation recipients reported to the ISHLT registry from over 100 international centers were retrospectively reviewed to examine the impact of induction on graft survival and freedom from BOS (20). Of these 3970 adult recipients, 57% were not given induction therapy, 28% were treated with IL-2 RA induction, and the remaining 15% were treated with ATG induction therapy. Twenty-two percent of patients who did not receive induction therapy were treated for rejection early after transplantation, but only 15% and 17% of patients who received an IL-2 RA and ATG induction, respectively, required treatment for early rejection ($p < 0.0005$). At four years, however, there was a slight trend toward a lower incidence of BOS in the IL-2 RA–treated group.

According to the 2008 ISHLT registry, 54% of lung transplant recipients received induction therapy in 2006 (4). The fact that nearly half of all transplant recipients are not given induction is evidence that transplant physicians do not uniformly support an induction therapy strategy. However, induction therapy may minimize high doses of nephrotoxic agents such as cyclosporine in the early postoperative period. Induction therapy may also allow for a recipient with a high risk of rejection to be transplanted successfully.

IV. mTOR Inhibitors

Sirolimus and everolimus are mammalian target of rapamycin (mTOR) inhibitors. Sirolimus is a macrolide antibiotic with potent antifungal properties derived from the actinomycete *Streptomyces hygroscopicus* (21). In 1999, sirolimus was approved for use

in renal transplantation in combination with cyclosporine. Everolimus is a synthetic derivative of sirolimus designed for enhanced bioavailabilty (22).

A. Mechanism of Action

Sirolimus and everolimus exert their immunosuppressive effect by binding to members of a family of intracellular proteins known as the immunophilins, specifically FKBP12. The sirolimus:FKBP12 complex then blocks the mTOR and therefore interrupts interleukin-mediated proliferation of T, NK, and B cells, leading to the arrest in the G1 phase of the cell cycle and culminating in cell death by apoptosis (23,24). The antiproliferative effects of these drugs have also been shown in fibroblasts, vascular smooth muscle cells, various tumor cell lines, hepatocytes, and endothelial cells, thus the therapeutic potential is extensive (25).

B. Pharmacokinetics and Dosing

Sirolimus is highly lipophilic and is ~95% bound to RBC; as such, it has a long half-life of 57 to 62 hours, allowing for once daily dosing. Everolimus has a shorter half-life compared to sirolimus, as such twice daily dosing may be appropriate. There is inter-individual variablitiy in drug exposure, but factors such as age, weight, gender, or the presence of cystic fibrosis do not significantly influence this variability (26).

Sirolimus is available in liquid (1 mg/mL) and in oral (1 mg tabs) form. Because of synergistic effects, the dose of calcineurin inhibitors should be decreased by 1/2 to 2/3 after starting Sirolimus. Typically, sirolimus is initiated at 2 mg daily. Therapeutic trough levels are in the range of 5 to 15 ng/mL drawn 7 days after any change in dosing. Sirolimus is not removed by hemodialysis and dose adjustments are unnecessary in renal dysfunction (15). Everolimus can be initiated at 1.5 mg twice daily. Trough levels between 3 and 12 ng/mL have been shown to be efficacious and clinically tolerated (26).

C. Drug Monitoring and Drug Interactions

In general trough levels are used to guide therapy. The therapeutic ranges for sirolimus and everolimus are 5 to 15 ng/mL and 3 to –12 ng/mL, respectively. CBC should be monitored for evidence of bone marrow suppression. Both drugs are metabolized by the cytochrome p450 enzyme system mandating dose adjustment in the context of hepatic dysfunction and LFTs monitoring. Inhibitors and inducers of the CYP450 enzyme system should be added cautiously to the recipient's regimen (see Table 1). Specifically, coadministration of imidazole anti-fungal drugs should be avoided.

D. Toxicities

Overall, the majority of toxicities associated with the mTOR inhibitors are similar to many of the other immunosuppressive agents. However, the frequency and the severity of these toxicities often limit the use of these drugs in clinical practice. The following are a few of the common toxicities that have been associated with the mTOR inhibitors.

Hematologic

Both drugs cause thrombocytopenia, anemia, and leucopenia. Bone marrow suppression is dose dependent.

Table 1 Immunosuppressive Medications in Lung Transplantation

+Drug	Role in transplantation	Description mechanism of action	Dose*	Monitoring	Interactions	Side Effects	Comments
Anti-thymoglobulin	Induction Refractory acute rejection BOS	Polyclonal antibody that causes nonspecific T-cell depletion	Thymoglobulin: 1.5 mg/kg over 6 hr, then two additional doses given 24 hr apart Atgam: 7.5–15 mg/kg/day X 3–5 days post transplant	Lymphocyte subsets	–	Leukopenia	Use is declining in favor of IL-2 receptor antagonists and campath
Muromonab-CD3 (OKT3)	Induction Refractory acute rejection BOS	Mouse monoclonal antibody that binds to the T cell receptor-CD3 complex, causing depletion of T cells	5 mg/day X 7–14 days after transplant	Lymphocyte subsets	–	Cytokine release storm (fevers, rigors, vomiting, diarrhea, hemodynamic instability)	Patients will develop neutralizing antibodies to OKT3, limiting prolonged use and necessitating use of alternative drug if future augmentation of immunosuppression is needed

Alemtuzumab (Campath-1H)	Induction Refractory acute rejection BOS	Monoclonal rat antibody directed at CD25 on T cells and B cells, causing depletion of these lymphocytes	Day 1: 3 mg Day 2: 10 mg Day 3: 30 mg, then 30 mg three times per wk for 4–12 wk	Lymphocyte subsets	–	Lymphopenia T cells may remain depressed for up to 3 yr B cells may be depressed for several months May cause cytokine release syndrome, but milder than compared to OKT3	
Basiliximab	Induction Refractory acute rejection BOS	Chimeric monoclonal antibody binds with high affinity to CD25 on T cells to inhibit IL-2 mediated T-cell proliferation	20 mg on the day of transplantation and again on post-op day four	N/A	–		25% mouse, 75% human antibody-derived antibody More effective induction agent when compared to ATG
Daclizumab	Induction Refractory acute rejection BOS	Chimeric monoclonal antibody binds with high affinity to CD25 on T cells to inhibit IL-2 mediated proliferation of T cells	1 mg/kg on day of transplant, then every 2 wk for a total of 5 doses	N/A	–		10% mouse, 90% human-derived antibody More effective induction agent when compared to ATG

(*Continued*)

Table 1 Immunosuppressive Medications in Lung Transplantation (*Continued*)

+Drug	Role in transplantation	Description mechanism of action	Dose*	Monitoring	Interactions	Side Effects	Comments
Corticosteroids **-prednisone** **-methyl-prednisolone**	Maintenance Refractory acute rejection BOS	Inhibits humoral and cell-mediated immunity Binds with DNA sequences (+/− nuclear factor-kB) to inhibit production of inflammatory cytokines	At time of transplant: 1 g IV Maintenance dose: 1 mg/kg initially after transplant with taper to a goal of 5–10 mg/day Acute rejection: 500 mg—1 g IV BOS: 40 mg daily for a period of days to wk	N/A	May increase cyclosporine/ tacrolimus levels	Diabetes GERD, PUD Osteoporosis Skeletal muscle wasting Hypertension Hypercholesterolemia	
Cyclosporine	Maintenance	Calcineurin inhibitor Prevents T-cell proliferation by inhibiting the production of interleukins and other cytokines	3 mg /kg/day IV at time of transplantation 5 mg/kg/day PO	Trough levels typically used but levels drawn 2 hr post dose are most accurate	Metabolized by cytochrome P450 enzyme system See chart	Renal dysfunction Hypertension Hypercholesterolemia Gingival hyperplasia Tremor, headache Hirsuitism	High inter- and intraindividual absorption variability Sandimmune (original formula) and Neoral (microemulsion formulation) are not interchangeable

							Cola and high-fat meal will enhance absorption Marked increased levels of statin drugs when coadministered
Tacrolimus	Maintenace Refractory acute rejection (conversion agent) BOS (conversion agent)	Calcineurin inhibitor Prevents T-cell proliferation by inhibiting the production of interleukins and other cytokines	0.05–0.1 mg/kg over 24 hr IV at time of transplantation and until patient can tolerate oral intake 0.03 mg/kg twice daily taken on an empty stomach or 2 hr after eating	Trough levels are typically used but levels drawn 3 hr post dose are more accurate	Metabolized by cytochrome P450 enzyme system See Table 1, Chapter 29	Renal dysfunction Diabetes Hypertension (less than cyclosporine) Hypercholesterolemia Altered mental status Headache Focal neurological deficits	Marked increased levels of statin drugs when coadministered
Mycophenolate mofetil	Maintenance	Nucleotide blocking agent Inhibits T cell proliferation by blocking nucleotide synthesis	Oral form only Starting dose: 250 mg twice daily within 72 hours after transplantation Increase dose by 250 mg twice daily to a goal dose of 1000 mg daily	Monitor WBC Dose adjusted for leucopenia	Levels decreased by: magnesium Aluminum hydroxide Antacids Cholystera-mine Cyclosporine (but not tacrolimus)	Nausea, vomiting Diarrhea Bone marrow suppression Anemia Increased risk of CMV disease	May inactivate protein bound drugs, especially *oral contraceptives*

(*Continued*)

Table 1 Immunosuppressive Medications in Lung Transplantation (*Continued*)

+Drug	Role in transplantation	Description mechanism of action	Dose*	Monitoring	Interactions	Side Effects	Comments
					Levels increased by: Probencid acyclovir		
Azathioprine	Maintenance	Nucleotide blocking agent Inhibits T- and B-cell proliferation by blocking nucleotide synthesis	IV equivalent to PO Starting dose: 2 mg/kg daily	Monitor WBC Dose adjusted for leukopenia	Levels increased by: allopurinol	Nausea, vomiting Diarrhea Bone marrow suppression	Requires TPMT enzyme for metabolism. Individuals with profound initial side effects may be deficient in this enzyme. May diminish the anticoagulant effects of warfarin
Sirolimus	Maintenance Refractory acute rejection	mTOR inhibitor inhibits T-cell proliferation by blocking IL2 stimulation	Due to effects on wound healing Sirolimus is initiated 3 mo post transplantation	Trough level 5–15 ng/mL draw 7 days after any change	Metabolized by cytochrome P450 3A enzyme system	Delayed wound healing Bone marrow suppression Hypercholesterolemia	Due to effects on wound healing sirolimus is initiated 3 mo post transplantation

	BOS Renal insufficiency	T cell is arrested in the G1 phase of cell cycle	Liquid and tablet form Starting dose 2 mg daily		See Chart	Pulmonary toxicity Diarrhea Nausea	Calcineurin inhibitors should be decreased by ½ to ⅔ when coadministered
Everolimus	Maintenance Refractory acute rejection	mTOR inhibitor inhibits T-cell proliferation by blocking IL2 stimulation	Due to effects on wound healing everolimus is initiated 3 mo post transplantation	Trough level 3–12 ng/mL	Metabolized by cytochrome P450 3A enzyme system	Delayed wound healing Bone marrow suppression Hypercholesterolemia	Due to effects on wound healing everolimus is initiated 3 mo post transplantation
	BOS Renal insufficiency	T cell is arrested in the G1 phase of cell cycle	Starting dose 1.5 mg twice daily		See Chart	Pulmonary toxicity Diarrhea Nausea	Calcineurin inhibitors should be decreased by ½ to ⅔ when co-administered

*These are recommended doses and may vary among institutions.

Hypercholesterolemia

Hypercholesterolemia and hypertriglyceridemia are associated with both everolimus and sirolimus use (26).

Pulmonary

Pulmonary toxicity is emerging as a frequent and serious complication of sirolimus and everolimus use (27–30). Toxicity may include lymphocytic alveolitis, lymhocytic interstitial pneumonitis, organizing pneumonia, focal fibrosis, and pulmonary alveolar hemorrhage (31,32). In general, pulmonary toxicity resolves with discontinuation of therapy but can be fatal (33). Interestingly, there have been reports of resolution with conversion from SIR to EVL (34).

Renal Insufficiency

By itself, sirolimus does not cause renal toxicity, but the addition of sirolimus to cyclosporine raises CNI concentration and potentiates the specific nephropathy of calcineurin inhibition (35). However, in one small study, the addition of sirolimus to a CNI containing immunosuppression regimen allowed for the reduction of the CNI dose, preservation of lung function and improvement of renal function (36). The same is likely true for everolimus (22).

Gastrointestinal

Diarrhea and nausea are common with SIR and EVR use.

E. Efficacy

Sirolimus has antiproliferative properties that make it an ideal agent in organ transplantation but this feature, as it impacts fibroblasts, limits its use in the early post-transplantation period. In fact, sirolimus has been associated with early fatal bronchial dehiscence in lung and heart-lung recipients (37,38). For this reason, most authorities advocate holding the use of sirolimus and everolimus until 90 days post transplantation, when the bronchial anastomosis has epithelialized. For patients already maintained on an mTOR inhibitor and for whom surgery is necessary, discontinuation of the drug for at least six weeks postoperatively is recommended.

Everolimus was compared to AZA in a randomized, double-blinded placebo clinical trial of 213 BOS-free patients receiving a CsA-based regimen. At 24 months, patients in the everolimus group had a significantly less incidence of acute rejection, but BOS and mortality rates did not differ (39). Small uncontrolled studies have suggested that sirolimus may provide stabilization of lung function in patients experiencing BOS (40–42).

V. Azithromycin

Azithromycin has been shown to decrease pro-inflammatory cytokines that have been elevated in the bronchoalveolar lavage fluid of patients with chronic rejection (43). Several small retrospective and case controlled studies have shown a stabilization and possible improvement of lung function with azithromycin (250 mg orally given every other day) in a select group of lung transplant recipients with declining pulmonary function (44). A large prospective randomized clinical trial is still needed to confirm the benefit of this agent.

VI. Aerosolized Cyclosporine

Aerosolized cyclosporine is a new delivery method of cyclosporine to enhance the concentration of this calcineurin inhibitor directly in the lung. A recent study from the University of Pittsburgh showed a decreased risk of death and a greater rejection-free survival in patients who received aerosolized cyclosporine in addition to their maintenance immunosuppression (45). Currently, a larger randomized multicenter study is under way to confirm this benefit in lung transplant recipients.

VII. Total Lymphoid Irradiation

Total lymphoid irradiation (46) is radiation delivered to all major lymphatic areas. These fields are the mantle field (low cervical, supraclavicular, infraclavicular, axillary, mediastinal, and hilar nodes, and the thymus), the paraaortic field (paraortic nodes and the spleen), and the inverted-Y field (iliac, inguinal and femoral lymphnodes). Radiation is given fractions such as 0.8 to 1.125 Gray to a prescribed total dose. Treatment regimens may be daily or twice weekly for a period of weeks (47,48). Transient bone marrow suppression occurs in nearly all patients undergoing TLI, and treatment-related infection is a concern.

VIII. Extracorporeal Photopheresis

In extracorporeal photopheresis (ECP) peripheral blood mononuclear cells (PBMCs) are removed from the patient, exposed to a photosensitizing agent, 8-methoxypsoralen (8-MOP), and then treated with ultraviolet A irradiation. The irradiated cells are then reinfused into the patient. One cycle of ECP involves photopheresis on two consecutive days, a cycle is given every four to six weeks. Patients treated with ECP develop a higher percentage of regulatory T cells compared with non-treated patients on conventional immunosuppression therapy (49).

IX. Potential Future Therapies

The goals of future therapy are to decrease the incidence of acute and chronic allograft rejection with the hopes of promoting tolerance to the lung allograft. Immunosuppressive therapies that are currently in the pipeline include new biologics and small molecule inhibitors. Belatacept (LEA29Y) is a costimulatory blockade molecule that is currently in phase III trials in renal transplantation (50). Early studies appear promising but there have been increased reports of post-transplant lymphoproliferative disease with this agent. Future studies will determine whether the benefits outweigh the risks in the solid organ transplant population. Other newer agents including efaluzimab (raptiva) and alefacept (amevive) are biologics that inhibit T cell function by binding to cell surface markers. They are currently in phase I to II trials in renal transplantation. In addition, a JAK3 inhibitor (CP690550) is a tyrosine kinase inhibitor that blocks signal transduction of multiple intracellular cytokines that has shown promise in early studies in renal transplantation.

X. Conclusion

Lung transplantation has remained a potential life-saving therapy for patients with end-stage lung disease since the discovery of cyclosporine in the 1980s. Optimal immunosuppression is the key to graft survival. In many centers, immunosuppression

commences with induction therapy at the time of transplantation. Maintenance therapy, which is also initiated at the time of surgery, includes the combination of corticosteroids, a calcineurin inhibitor, and a nucleotide-blocking agent. Sirolimus and everolimus are newer agents that are effective in maintenance immunosuppression and are alternative choices in specific contexts such as renal insufficiency. Augmentation therapy, which includes high-dose corticosteroids, conversion therapy, total lymphoid irradiation, and extracorporeal photopheresis, is a strategy to treat acute rejection and bronchiolitis obliterans syndrome.

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Artificial Lung: A New Inspiration

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I. Introduction

From assisting an injured or recently transplanted lung to completely replacing the native organ, many obstacles had to be overcome to make the artificial lung a reality. With patients on the lung transplant list far exceeding available donors, the importance of developing a suitable bridge or replacement technology grows more every day. The number of individuals requiring a lung transplant is on the rise. From 1997 to 2007, there has been an 11% increase in the number of candidates on the lung transplant list (1). Additionally, only 18% of the 13,154 lungs from organ donors were transplanted in 2006; 81% were not recovered (1). The reason for this discrepancy was cited as "poor organ function," leading to an even greater disparity between needed and available lungs (1). As such, research has focused not merely on an artificial lung as a replacement organ but rather an artificial lung as a bridge to transplantation (2,3) or recovery, as a support device following transplant, or simply as an adjunct to mechanical ventilation (2,4).

Historically, artificial lung technology began with the development of cardiopulmonary bypass (CPB), driven by the quest to operate on the human heart. The early pioneers in heart surgery—Gibbon, Lillihei, Debakey, and many others—pushed to develop a heart-lung machine that would allow for longer and more complex repairs of the heart. These early heart-lung machines were only capable of a few hours of support at most and would not have been suitable as artificial lungs. Initially, CPB gas exchange took place through a series of different technologies, including rotating disks (5), screen oxygenators (6), and bubble oxygenators (7). These technologies were traumatic to the blood and failed after only hours of use, making them impractical as artificial lungs (8). Although it would seem a logical extension of CPB, the artificial lung era is more closely associated with the development of the silicone membrane lung, which allowed for days of support instead of just hours.

Ironically, it was "the father of renal dialysis" Willem Kolff (who was also a major player in the development of the first artificial heart) who first observed that gas exchange could occur across a man-made (polyethylene) membrane (8). Kolff showed that desaturated blood entering an artificial kidney exited bright red and fully saturated. Although Kolff's attempts at artificial lung design were unsuccessful due to high resistance, high prime volume, and poor gas exchange, they served as an inspiration to Dr. Theodore Kolobow, then in medical school at what is now known as Case Western Reserve University. By wrapping a thin membrane envelope around a spool, a compact yet high

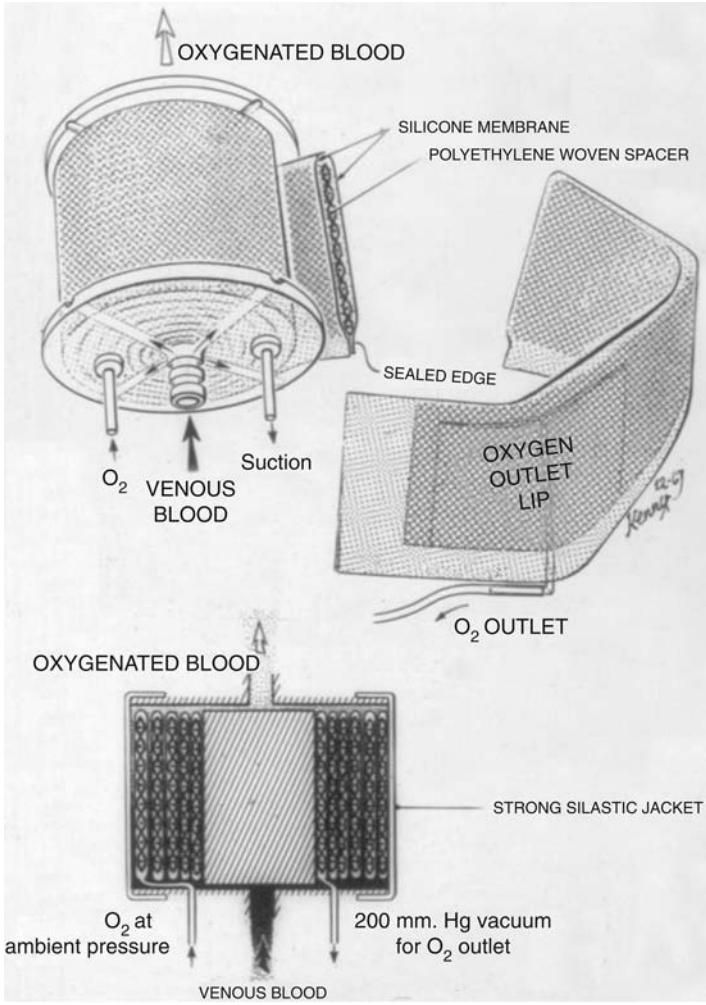

Figure 1 The forerunner of the spiral coiled membrane lung. *Source:* From Ref. 9; Figure 4.

surface area gas exchanger became a reality (Fig. 1). Unlike other early iterations, this gas exchange device proved far less traumatic to the blood since there was no direct contact between the blood phase and the gas phase (10). At the NIH, Dr. Kolobow began the first long-term testing of his spiral coiled membrane lung in sheep (11). This breakthrough design was quickly applied to extracorporeal membrane oxygenation (ECMO).

II. Extracorporeal Membrane Oxygenation

ECMO is the term used to describe prolonged CPB and began in the late 1970s as a modified heart-lung machine with a servo-regulated pump; however, instead of being

designed for hours of support, ECMO can support patients for days to weeks. For the first time, physicians were able to support patients in imminent danger of death from cardiorespiratory failure. ECMO was first applied in an adult with "shock lung" (12) but was popularized by Robert Bartlett in the neonatal population. Initially, when ECMO was applied to a neonatal population thought to have a 90% mortality, an 80% to 90% survival was seen. While results have been, and continue to be, favorable for the use of ECMO in the neonatal population, the use of ECMO in adults has been less clear. From the beginning, unfavorable trial designs and poor outcomes have plagued adult ECMO (13). Recently, a large adult ECMO trial was completed and published (14). The details have been much debated. The CESAR trial in Great Britain compared the standard of care as defined at regional hospitals for acute respiratory distress syndrome (ARDS) to protocol-based care (including ECMO) at a single center (Leicester) with a 16% improvement in six-month survival without disability. Although some will point to the favorable results of this trial as proof of ECMO's role in treating severe respiratory failure, the circumstances required to yield the difference are unlikely to change many practice habits (15).

ECMO is currently an option for patients who have severe potentially reversible disease with a time course of days, not months. ECMO is expensive, resource intensive, requires specialized staff and equipment, and binds the patient to the bed. Thus, the use of ECMO as an "artificial lung" is limited to the acute setting. To broaden the application of technology-augmented gas exchange, a more compact, less complex, ambulatory technology is needed.

III. Intravascular Oxygenator

The intravascular oxygenator (IVOX) was developed by J.D. Mortensen to address the quest for a more compact, less complex gas exchanger that could be inserted into the vena cava. The IVOX consisted of multiple hollow fibers joined together in a potted manifold that communicated with a dual lumen gas conduit at the proximal and distal ends. The fibers were coated in a thin layer of silicone (Siloxone, Applied Membrane Technologies, Minnetonka MN) with covalently bonded heparin as an antithrombogenic coating. Gas would enter and leave the system via conduits outside a small skin incision. Once in proper position, a vacuum pump pulled O_2 through the device fibers (16).

The performance of the IVOX was limited in comparison to the natural lungs (17). Our experience with the IVOX in animal and human studies demonstrated an average of 40 mL/min of CO_2 and O_2 exchange or approximately 25% to 30% of the metabolic demand of the patients implanted with the device (18,19). Under conditions of permissive hypercapnia, up to 50% of CO_2 removal could be accomplished. Unfortunately, IVOX could not be used as a suitable substitute for the native lungs or as a bridge to transplant.

Building on the lessons learned from the in vitro testing of the IVOX, the Hattler catheter incorporates a small pulsating balloon into the middle of a hollow fiber bundle. The use of this balloon allows for convective mixing of the blood, which increases the gas exchange capabilities of the device. Hattler et al., in a 2002 report, tested a variety of balloon sizes and pulsation rates to determine that larger balloon volumes and higher pulsation rates increased both O_2 loading and CO_2 removal in a linear fashion in an in vitro model (20). The in vivo models utilizing healthy calves demonstrated much less-consistent results between balloon sizes. Although work continues with quantification of the gas exchange properties, pilot human trials are discouraging.

IV. Arteriovenous CO_2 Removal

Recent trends in ventilator management dictate limiting inflation pressures and tidal volume, often at the physiologic cost of increasing systemic arterial CO_2 levels. This technique, often referred to as "permissive hypercapnia," has been shown to reduce the incidence of baro/volutrauma, high airway pressures, and to improve survival in ARDS (21–26).

The use of a simple arteriovenous (AV) shunt for extracorporeal gas exchange significantly reduces the complexity of conventional ECMO, yet allows sufficient gas exchange to achieve near total removal of the CO_2 produced. By reducing and eliminating circuit length and components, a number of complications associated with conventional ECMO are eliminated, allowing for less intensive monitoring, lower cost, and improved safety (27). Our group developed a technique of simplified extracorporeal arteriovenous CO_2 removal ($AVCO_2R$) with a new generation low-resistance, commercially available, hollow fiber gas exchanger to provide lung rest in the setting of severe respiratory failure (28). The extremely low resistance of the $AVCO_2R$ gas exchange device (<10 mmHg pressure difference at the rate of 1300 mL/min) allows blood flows of as much as 25% of cardiac output. The cannulae used became the determinants of flow and are small in comparison to what would be required for a typical adult ECMO patient (12F arterial 16F venous). Commercially available kits allow for percutaneous insertion into the common femoral artery and femoral vein as the preferred routes of vascular access. The prime volume of the circuit is small (<250 mL) and allows for crystalloid priming, avoiding the need for blood priming a circuit, which is typically necessary in ECMO.

$AVCO_2R$, however, does not provide substantial O_2 transfer when the arterial PaO_2 level is adequate because inflow to the device is already saturated (>90%) with an O_2 carrying capacity close to maximum. There is a small direct transfer (<10%) and some benefit related to the increased O_2 content of the mixed venous blood reaching the pulmonary precapillary bed, which may result in a slight alteration in the normal vasoconstrictive response to local hypoxia with a resultant reduction in the pulmonary shunt (29).

$AVCO_2R$, termed iLA (interventional lung assist) in Europe, has been widely used with more than 1000 cases performed. Although clinical trials have failed to show a survival benefit in ARDS (25), the iLA has been used as a bridge device to lung transplant supporting 10/12 patients successfully with the longest duration of 38 days (26). Although this approaches the requirements necessary to be termed a true artificial lung, iLA is still frequently an adjunct to the ventilator and native lung function and not a replacement.

V. Paracorporeal Artificial Lung

A long-term support device for the failing lung has lagged behind that of the heart and kidney. Dialysis allows for years of support for those awaiting transplant, and new modern ventricular assist devices (VADs) have become commonplace as a bridge to transplant in heart failure patients, allowing for months of support, ambulation, and even discharge from the confines of a hospital. No such device yet exists for the lungs. ECMO, $AVCO_2R$, and the other lung support devices allow only for a very temporary bridge (days to weeks). A desperate need exists for a month(s)-long bridge to lung transplantation. While the new lung allocation scoring system has decreased the wait list

mortality (30), demand for donor lungs still far exceeds supply. Many obstacles must be overcome for the artificial lung to move from the bench to the bedside. The challenges of design includes developing a pump with hemodynamic and hematological compatibility, defining the proper configuration, placement (both in vessel configuration and placement of the device itself), and durability.

Proper configuration of an artificial lung remains controversial, with different investigators pursuing different paths. Configurations include pulmonary artery to left atrium (PA-LA) (Fig. 2A), pulmonary artery to pulmonary artery (PA-PA) (Fig. 2B), right atrium to pulmonary artery (RA-PA) (Fig. 2C), and a large double lumen veno-venous configuration utilizing a pump (DLVV-pump) (Fig. 2D).

The PA-LA configuration allows for partial support utilizing a pumpless artificial lung, thus allowing for both ambulation and simplicity. Likewise, this configuration creates less stress on the right heart than the PA-PA configuration (31). The pressure gradient between the mean pulmonary artery pressure and the left atrium provides flow through the gas exchanger without the need for a pump. Although simple in design, this configuration has some major drawbacks, including flow that depends on pulmonary vascular resistance (which can change dramatically over a short period of time); a loss of the lung vascular bed as a "filter for clots"; and need for change out of the gas exchanger, which would involve considerable risk of systemic embolus or stroke (bypass of the device in this configuration is not possible).

A PA-PA configuration uses the right heart as a pump; the gas exchanger receives the total right ventricular output. Early on, we found that this configuration creates an excessive amount of right heart strain, resulting in a 50% incidence of right heart failure in adult sheep (32). To combat the right heart strain, an inflow compliance chamber was added to the low resistance MC3 (Ann Arbor, Michigan) prototype (33). By utilizing a standard balloon pump as an augmentation device for the compliance chamber, the PA-PA configuration could allow the artificial lung to be utilized in patients with elevated right heart pressures (pulmonary hypertension). We demonstrated that the modified compliance chamber with balloon pump achieved significant augmentation; however, the pulsatile wave introduced into the delicate pulmonary artery caused severe hemorrhage and death in some animals. This configuration would be a difficult surgery in humans. Sheep have very long main pulmonary arteries (6 cm); this length enables a proximal and distal end-to-side anastomosis. The relatively short human pulmonary artery (2.5–3 cm) would require either dividing the main pulmonary artery with return of the blood postoxygenator to the transected main pulmonary artery, or a graft to the side of the main pulmonary artery diverting all blood flow to the device and back to the right pulmonary artery. Unfortunately, either of these techniques would require CPB for implant and neither are attractive long-term options (34).

A third configuration being explored is the RA-PA. This configuration would require either integration or coupling of the artificial lung to a pump. Functioning in a similar fashion to a right ventricular assist device (RVAD), blood would flow from the right atrium to the device and be pumped into the main pulmonary artery. No CPB would be required for implant and removal, and temporary use of the native circulation would be possible to allow for device change out. Two distinct approaches to this configuration have emerged. In one strategy, the pump and artificial lung become one. Through the use of centrifugal pumps with membrane fibers incorporated into the spinning disk, these all-in-one devices provide forward flow and gas exchange at the same time. They remain in various stages of development (35,36).

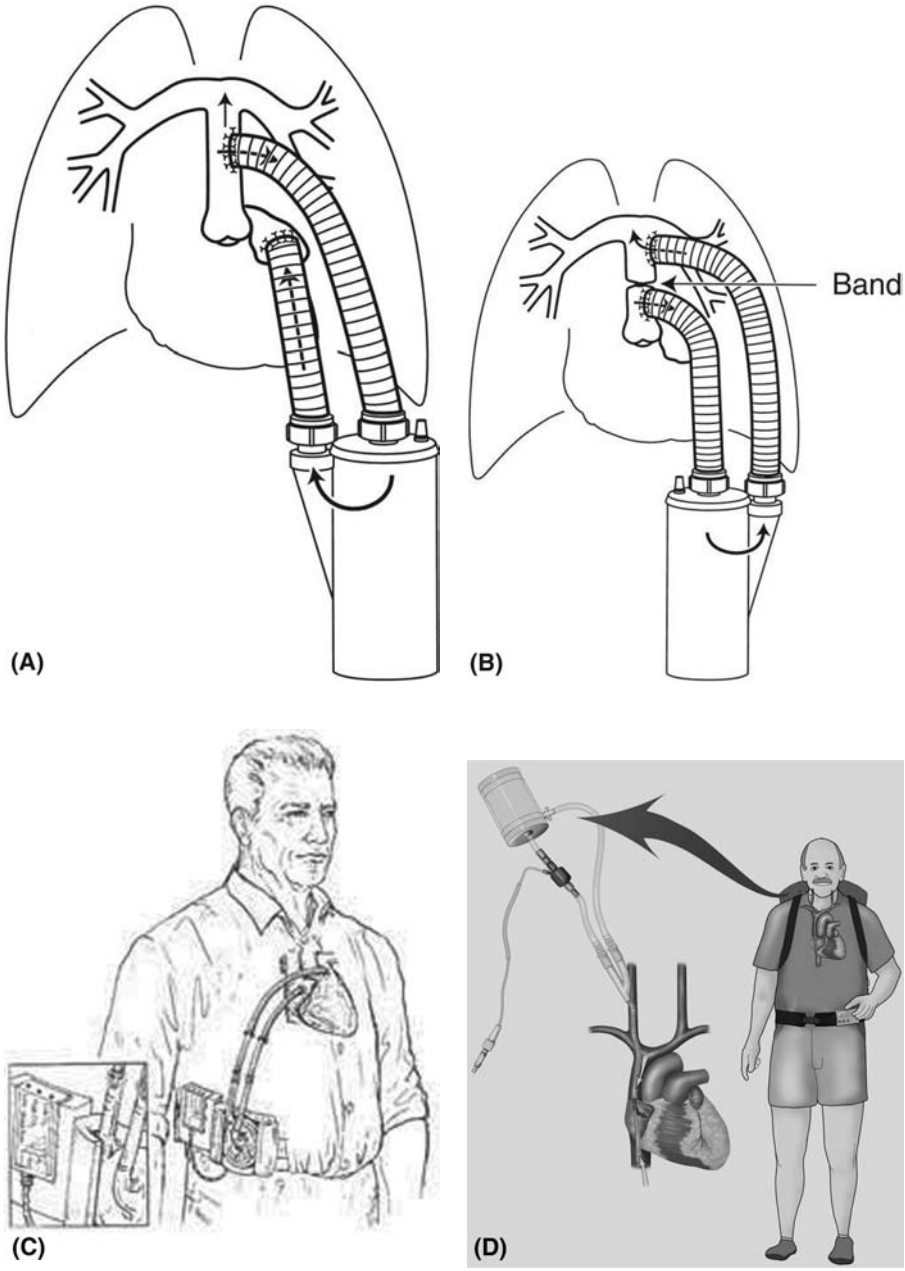

Figure 2 Artificial lung: modes of attachment. (**A**) In parallel configuration: inflow attached to pulmonary artery and outflow attached to left atrium. (**B**) In series configuration: inflow attached to proximal pulmonary artery and outflow attached to distal pulmonary artery (pulmonary artery ligated with band between inflow and outflow cannulae). (**C**) Right artery to left artery with compact pump in an ambulatory configuration. (**D**) (*See color insert*) Artificial lung in a double lumen venovenous configuration. *Source*: From Ref. 3; Figures 2 and 3.

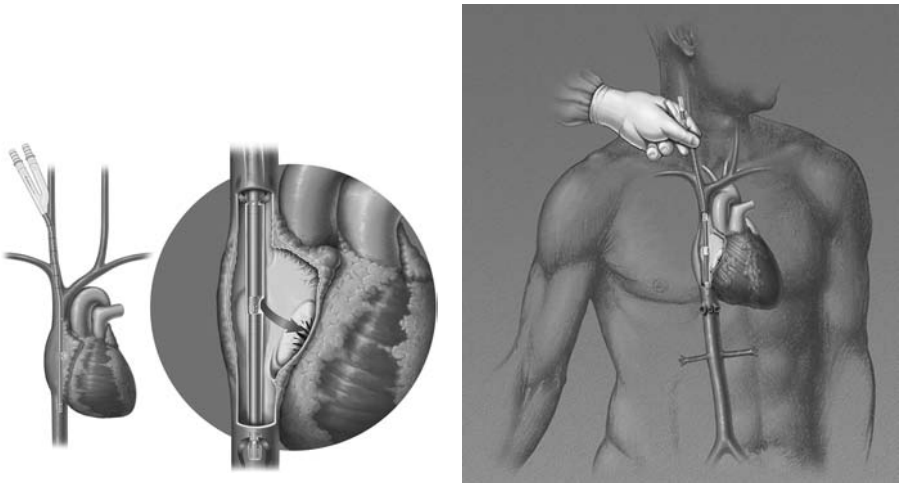

Figure 3 (*See color insert*) Avalon Elite™ (formerly W-Z DLC) is inserted from right jugular vein into superior vena cava (SVC), traversing right atrium (RA) to inferior vena cava (IVC). It drains venous blood from both SVC and IVC and delivers oxygenated blood in RA toward tricuspid valve to achieve minimal to no recirculation and potential total gas exchange. *Source*: From Ref. 37; Figure 1.

Another option for this configuration involves the use of a separate pump and oxygenator coupled together to power the device. Utilizing a pulseless (axial or centrifugal) pump connected to a gas exchanger, pump function and gas exchange function can be separate based on the needs of the patient. The DLVV-pump configuration centers around a newly designed cannula, which evolved from the double lumen cannula used in neonatal and pediatric venovenous ECMO (37). This new cannula, initially called the Wang-Zwische Double Lumen Cannula but currently marketed as the Avalon Elite™ cannula (Fig. 3), replaces the in-series and in-parallel anastomoses with a single cannula. The device consists of two pathways: a drainage pathway and an infusion pathway. The cannula is placed percutaneously or by cut-down through the internal jugular vein; the drainage lumen is open to both the superior vena cava and the inferior vena cava, while the infusion lumen is directed toward the right atrium (37). The blood from systemic circulation flows through the superior vena cava and inferior vena cava into the drainage lumen to the gas exchanger. The blood is oxygenated and returned via the infusion lumen into the right atrium. This oxygenated blood will then be pumped through the native circulation, and thus the native pulmonary bed, receiving the full metabolic and filtering capacities of the native lungs. This configuration eliminates the required major surgery of the other configurations (37). As there are no anastamoses to the pulmonary artery, there is no direct pumping action from the right ventricle. This has twofold consequences. First, the artificial lung must now have a pump device associated with it to ensure blood flow and circulation. Second, the stress on the right ventricle is eliminated and thus avoids any coinciding heart damage and/or strain.

This cannula meets the minimal blood recirculation flow required for total gas exchange (37). Early adult experience with the cannula is promising but as of yet has not been reported in the literature.

Blood surface compatibility in the artificial lung provides a set of unique challenges. With the increased surface area of an artificial lung over a VAD, anticoagulation becomes more difficult. The length of time necessary for a device to be considered a bridge to transplant (6 months or longer) the artificial lungs presents anticoagulation challenges not found in shorter-term modalities such as ECMO. Various events inevitable with long-term devices present many problems, including development of pulmonary hypertension from the constant barrage of small emboli to the lung bed, constant need for anticoagulation, as well as low-level stimulation and complement activation. New fiber technologies such as polymethyl pentane designs, which are commercially available, have reduced the magnitude of anticoagulation required but not eliminated it.

The road to a truly artificial lung with a total or partial gas exchange device still remains filled with challenges. Short-term support can be accomplished currently with new generation hollow fiber oxygenation devices for up to weeks at a time, and the goal of a bridge to transplant gas exchanger is as close now as ever. With true long-term replacements on the horizon, we can truly say we are entering the age of the artificial lung.

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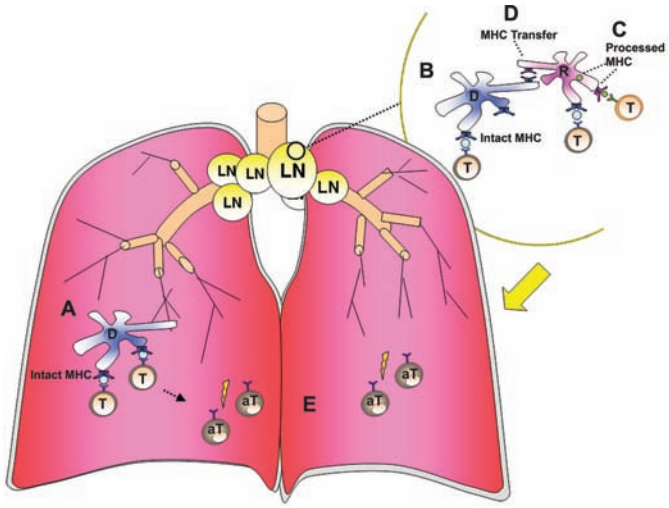

Figure 2.1 Mechanisms of initiating an alloimmune response—lung is a "lymph node with alveoli." After lung transplantation, allorecognition may occur via direct, indirect, or semi-direct antigen presentation to T cells. (**A**,**B**) *Direct allorecognition* occurs when donor dendritic cells (**D**, blue) displaying intact donor MHC:peptide complexes directly present antigen in the lung to naive T cells (T) infiltrating the graft from the blood early after engraftment (**A**) or when donor DCs migrate from the lung allograft to lymph nodes when the lymphatics are restored (**B**). (**C**) *Indirect alloantigen* occurs when recipient dendritic cells (R, pink) in the draining lymph nodes activate naive T cells with complexes of self-MHC and processed donor MHC peptides. (**D**) *Semi-direct pathway* may occur when intact donor MHC molecules are transferred from donor to recipient dendritic cells, and subsequently presented by recipient dendritic cells to naive T cells. (**E**) Activated $CD4^+$ and $CD8^+$ T cells (aT) then return to the lung and induce rejection of the allograft (*see page 9*).

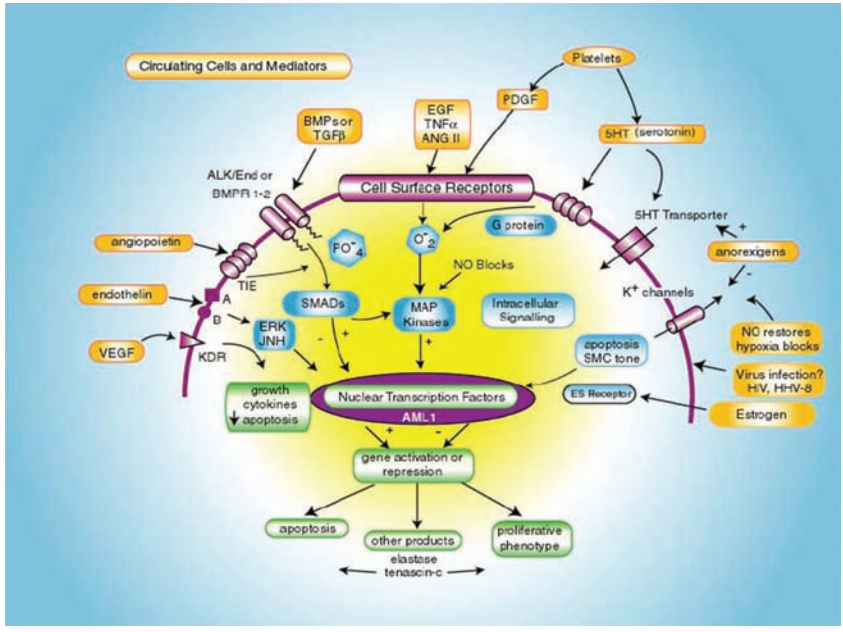

Figure 8.1 The complex pathobiology of pulmonary hypertension. Extracellular mediators and cell surface receptors, ion channels, intracellular signaling, and nuclear responses are illustrated. Many pathways span the extracellular, membrane, cytosolic, and nuclear domains. Intracellular transduction of these pathways is poorly understood. *Source*: Adapted from Ref. 6 (*see page 67*).

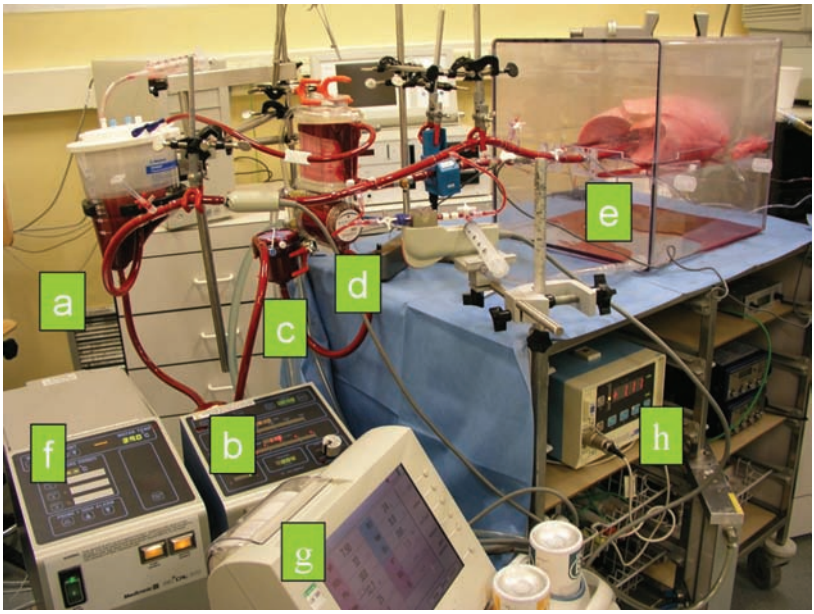

Figure 18.1 Isolated reperfusion circuit for ex vivo assessment of pulmonary grafts. From the hard shell reservoir (**a**) the perfusate is recirculated by a centrifugal pump (**b**) passing a leukocyte filter (**c**) and a membrane oxygenator (**d**) before entering the lung block (**e**). The heater/cooler (**f**) is connected to the membrane gas exchanger. Blood gases and pulmonary artery flow are continuously measured using an inline blood gas analyzer (**G**) and an electromagnetic flow meter (**h**), respectively (*see page 161*).

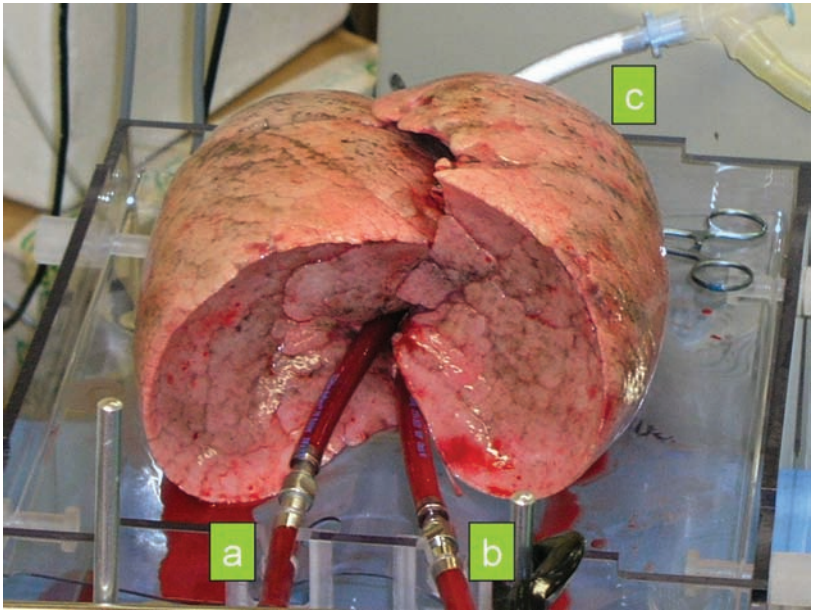

Figure 18.2 The human double lung block is mounted in a plexiglas box for ex vivo perfusion and ventilation. The inflow cannula (**a**) is positioned in the pulmonary artery bringing deoxygenated blood to the lungs and the outflow cannula (**b**) is draining oxygenated blood from the left atrium back to the reservoir. Both lungs are ventilated via an endotracheal tube (**c**) (*see page 162*).

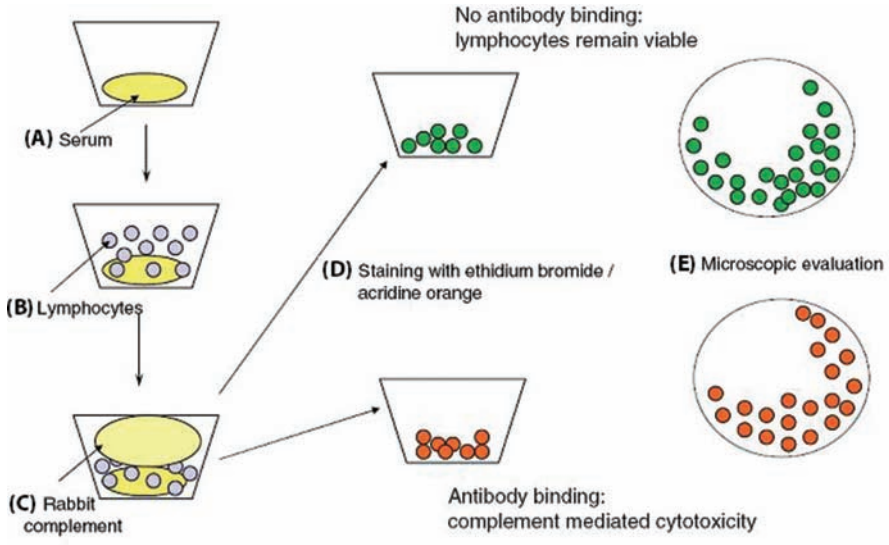

Figure 19.1 Complement-dependent cytotoxicity assay for the detection of anti-HLA antibodies. Recipient serum (**A**) is incubated with (**B**) lymphocytes of known HLA type. Rabbit serum is added as a source of complement after allowing for antibody antigen binding. (**C**) The presence of anti-HLA antibodies results in cell death and is visualized microscopically after the addition of stains (**D**) differentiating viable and dead cells. (**E**) The number of lysed cells expressed as a percentage is the reported panel reactive antibody (PRA). *Source*: From Ref. 13 (*see page 169*).

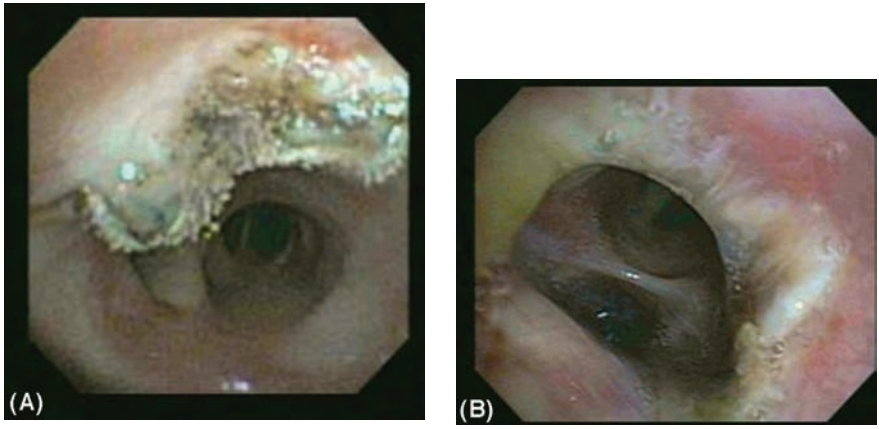

Figure 30.1 (**A**) Bronchoscopic view of right main stem anastomosis with a black fungating mass in a case of *Aspergillus niger* tracheobronchitis. (**B**) Bronchoscopic view of thick blackish plaque adherent to anastomosis in *Aspergillus fumigatus* infection (*see page 286*).

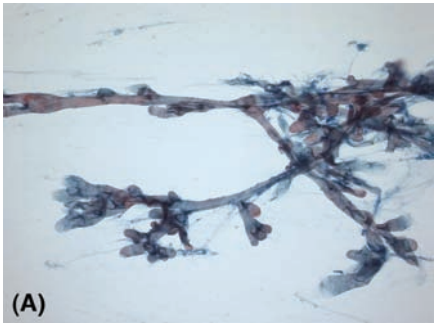

Figure 30.4A Micrograph of thin, broad ribbon-like hyphae of mucor with focal bulbous dilatations and irregular branching (original magnification 300×) (*see page 291*).

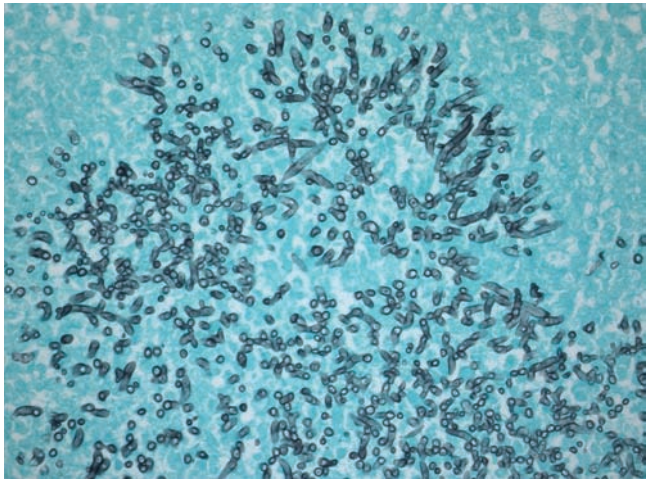

Figure 30.2 Micrograph showing lung parenchymal infiltration by *Aspergillus* (methenamine silver stain, original magnification 100×), note the dichotomously acute angle branching and septate hyphae (*see page 287*).

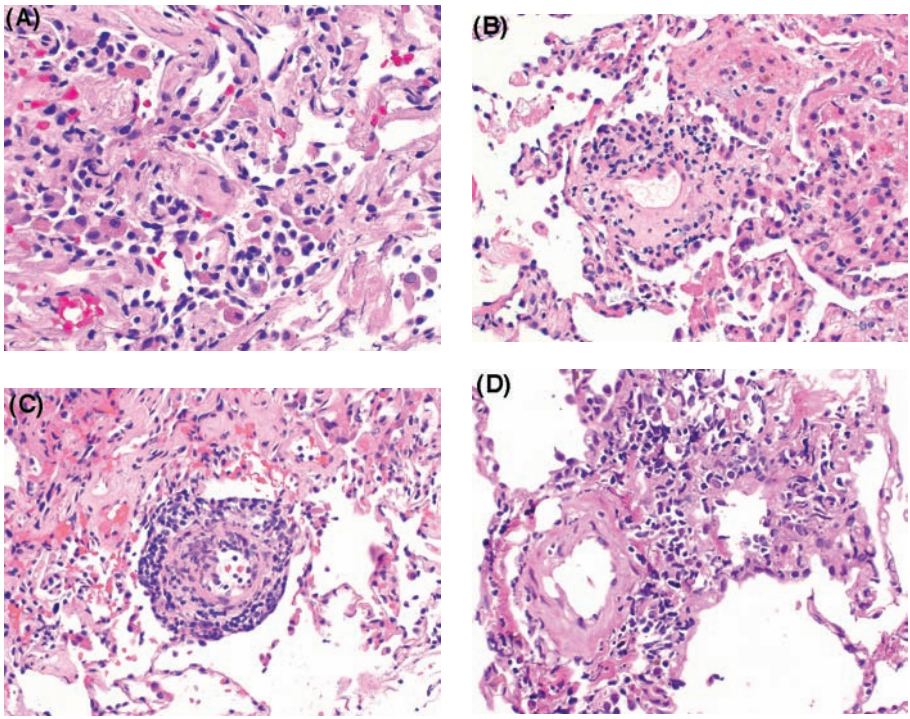

Figure 33.1 Acute cellular rejection, grade A. (**A**) No acute rejection, grade A0: no perivascular infiltrate, but atelectasis and hemosiderin are commonly present in transplant biopsies; (**B**) minimal acute rejection, grade A1: scattered perivascular lymphoplasmacytic infiltrates, two to three cell layers thick; (**C**) mild acute rejection, grade A2: frequent perivascular infiltrates of lymphocytes, plasma cells, macrophages, and eosinophils, more than three cell layers thick and visible at low power; (**D**) moderate acute rejection, grade A3: similar findings as grade A2 plus extension of infiltrates into adjacent alveolar septa. Severe acute rejection, grade A4, is rare (not shown) (*see page 321*).

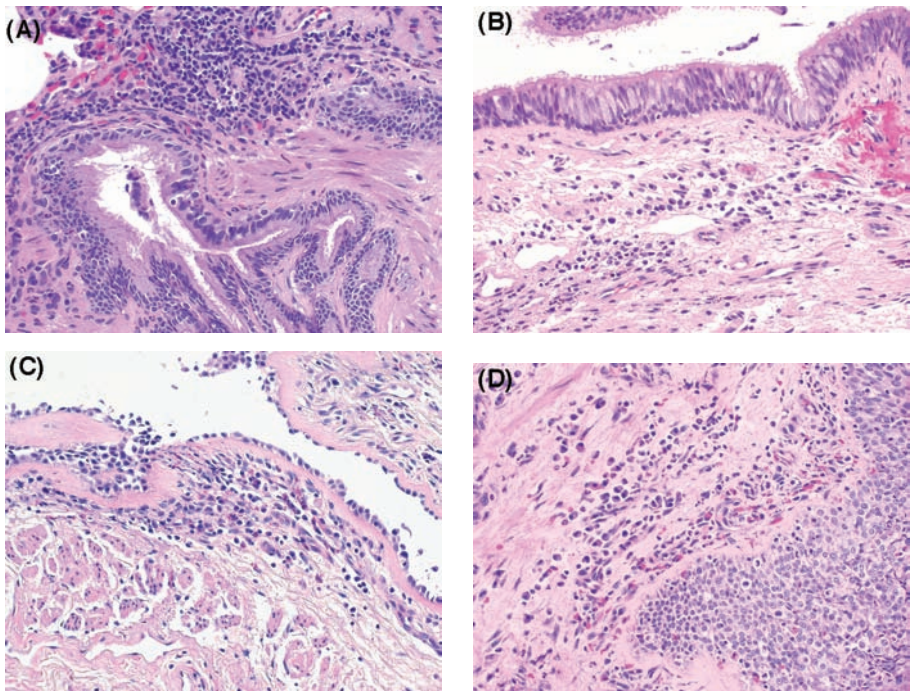

Figure 33.2 Acute cellular rejection, grade B. (**A**) No airway inflammation, grade B0: adjacent bronchial-associated lymphoid tissue (BALT) should not be mistaken for airway rejection; (**B**) minimal airway inflammation, grade B1: scattered mononuclear cells in airway submucosa; (**C**) mild airway inflammation, grade B2: circumferential infiltrate of lymphocytes, plasma cells, and eosinophils in airway submucosa; (**D**) moderate airway inflammation, grade B3: dense band of lymphocytes, plasma cells, and eosinophils in airway submucosa plus transmigration of lymphocytes through epithelium and epithelial cell necrosis. Severe airway inflammation, grade B4, is rare (not shown) (*see page 322*).

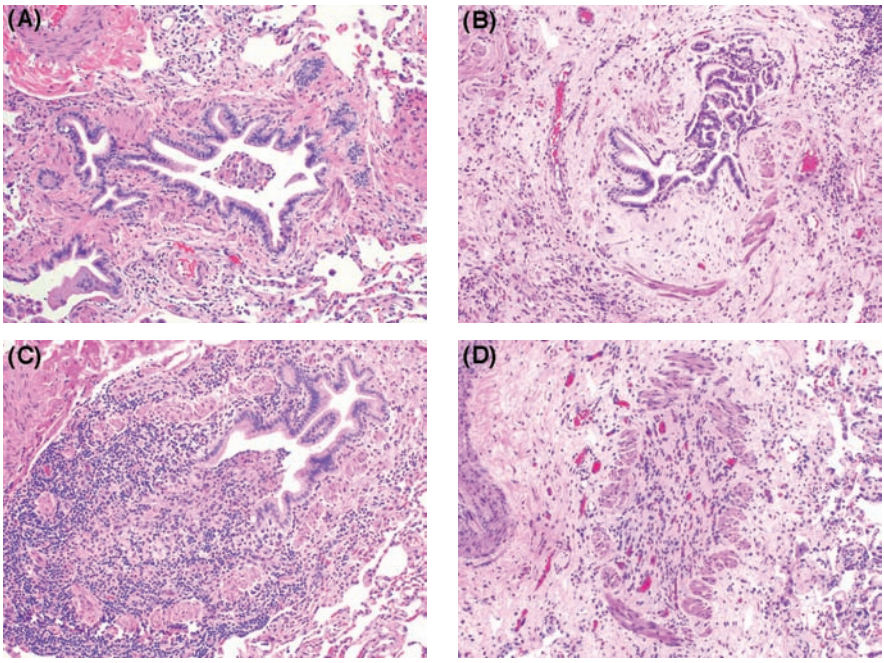

Figure 33.3 Chronic airway rejection, grade C. (**A**) No bronchiolitis obliterans (BO), grade C0; (**B**) subtotal BO without inflammation, grade C1 or grade Cb; (**C**) subtotal BO with active inflammation, grade C1 or grade Ca; (**D**) total BO, grade C1 (*see page 324*).

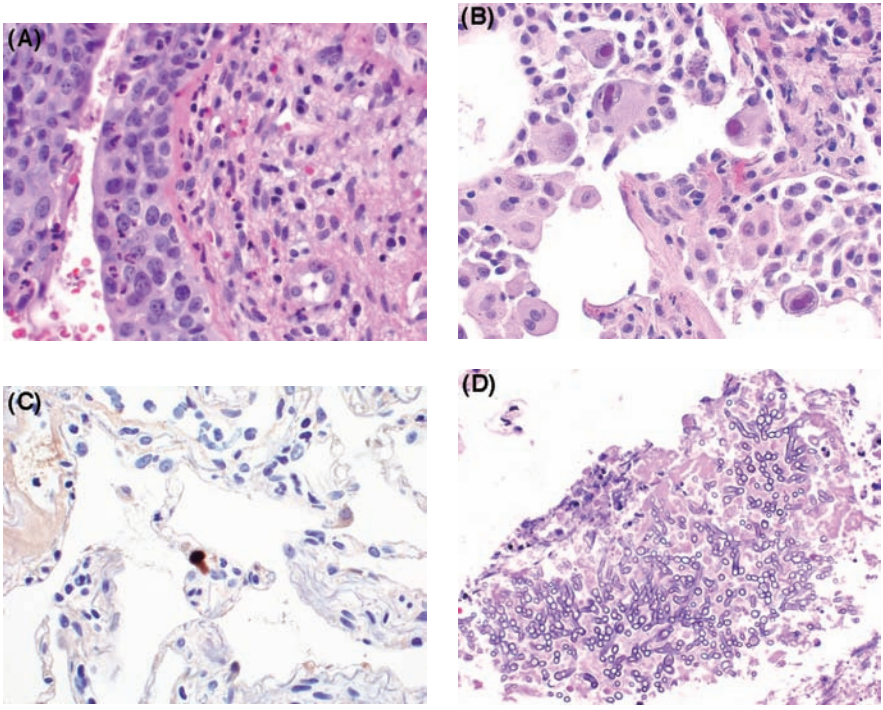

Figure 33.4 Infections. (**A**) Neutrophils in airway epithelium suggestive of bacterial infection; cytomegalovirus is easily recognized on hematoxylin and eosin stain (**B**), but immunohistochemistry for specific antigens (**C**) can allow for earlier detection before cytopathic effect; (**D**) fungal hyphae (*see page 325*).

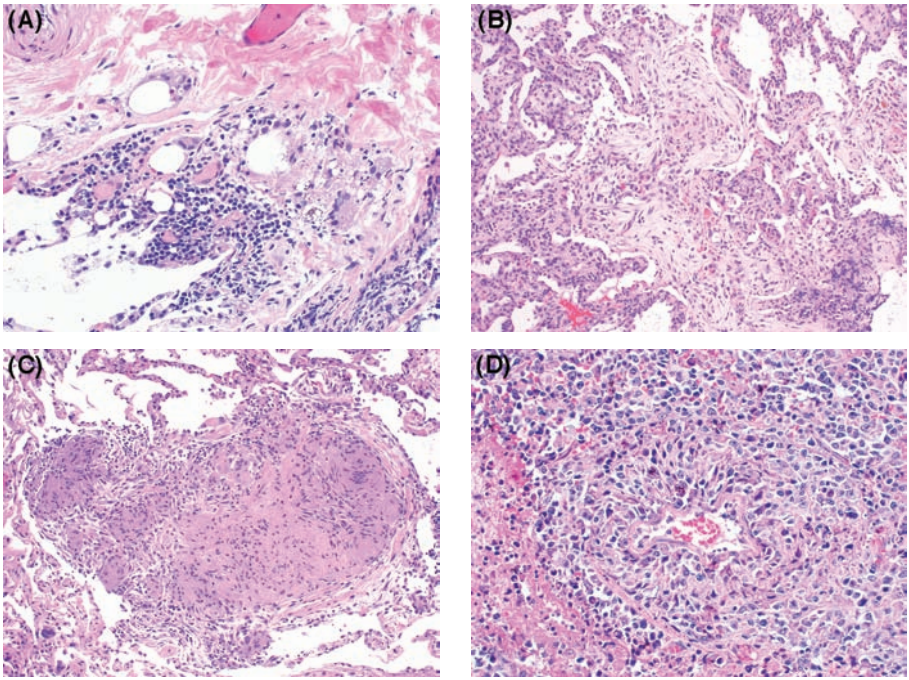

Figure 33.5 Other biopsy histology. (**A**) Microscopic aspiration with foamy alveolar macrophages and multinucleated giant cells; (**B**) alveolar fibroblast proliferation (Masson body) of organizing pneumonia, a nonspecific response to a variety of injuries; (**C**) well-formed nonnecrotizing granulomas of recurrent sarcoidosis; (**D**) high grade lymphoma, posttransplant lymphoproliferative disorder (*see page 326*).

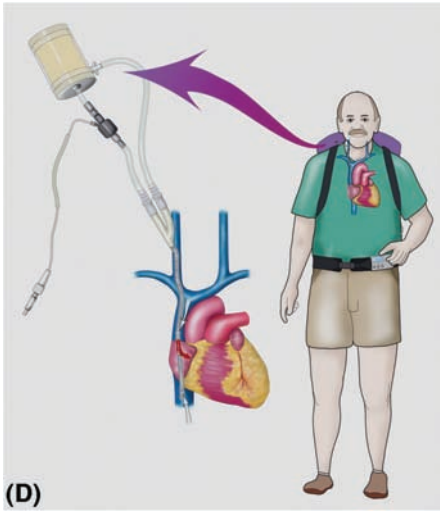

Figure 42.2D Artificial lung in a double lumen venovenous configuration. *Source*: From Ref. 3; Figures 2 and 3. (*see page 418*).

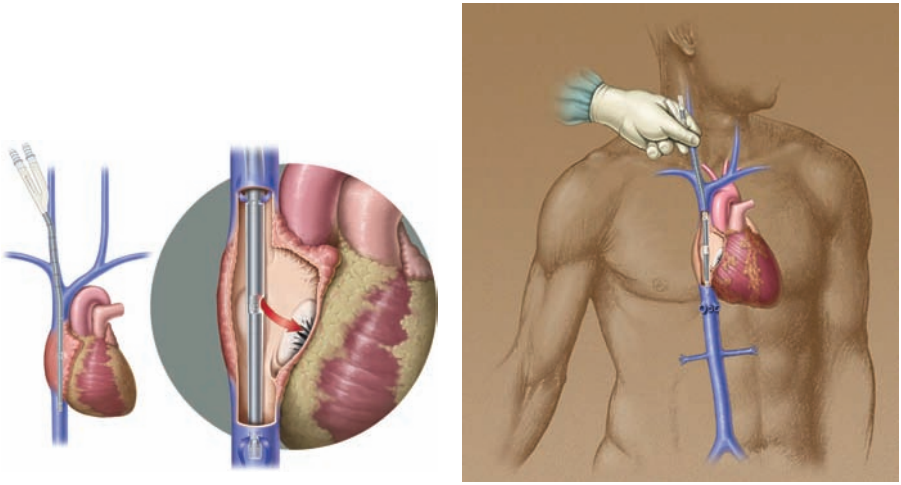

Figure 42.3 Avalon Elite™ (formerly W-Z DLC) is inserted from right jugular vein into superior vena cava (SVC), traversing right atrium (RA) to inferior vena cava (IVC). It drains venous blood from both SVC and IVC and delivers oxygenated blood in RA toward tricuspid valve to achieve minimal to no recirculation and potential total gas exchange. *Source*: From Ref. 37; Figure 1 (*see page 419*).

Lung Transplantation

About the book

Once considered an experimental therapy, lung transplantation is now regarded as a viable treatment option for selected patients with end-stage lung diseases. As more and more of these cases arise, it becomes imperative for those involved in the care of lung transplant patients to have a vast understanding of the multidiscipline process of lung transplantation. This text provides a comprehensive overview of this process covering everything from the history of the lung transplant program to the long term effects of the procedure.

Written by leading experts in the field, this book provides:

- Fundamental background information on the history and immunology of lung transplantation
- A review of the specific advanced lung diseases that may necessitate lung transplantation, including cystic fibrosis and primary pulmonary hypertension
- Important chapters on donor management – specifically looking at donor selection and procurement, as well as lung preservation
- In depth coverage of the procedure – addresses the various types of operations and immediate post-operative care
- Crucial analysis of early and late medical management including chapters on possible infections, Bronchiolitis Obliterans, and overall quality of life

This book is an essential reference for not only pulmonary specialists, but also for all those administering care to patients before or after transplantation.

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