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Lung Transplantation in Cystic Fibrosis: Trends and Controversies

Joshua Blatter, MD, MPH, and Stuart Sweet, MD, PhD

This article is not an overview of all facets of lung transplantation in cystic fibrosis (CF), but rather it is intended as a review of current allocation controversies, as well as of trends in diagnostics and management in lung transplant recipients and in patients with end-stage lung disease. Despite changes in donor and recipient selection, long-term survival in pediatric lung transplant has continued to be limited by chronic lung allograft dysfunction (CLAD). Due to, in part, this short survival benefit, transplant continues to be an appropriate option for only a subset of pediatric patients with CF. The feasibility of transplant as a therapeutic option is also affected by the limited pediatric organ supply, which has moreover contributed to controversy over lung allocation. Debates over the allocation of this scarce resource, however, may also help to drive innovation in the field of lung transplant. Longer pretransplant survival—as aided by new lung bypass technologies, for example—could help to alleviate organ shortages, as well as facilitate the transport of organs to suitable pediatric recipients. Improved diagnosis and treatment for CLAD and for antibody-mediated rejection have the potential to extend survival in pediatric lung transplant. Regardless, the relative rarity of transplant could pose future challenges for pediatric lung transplant programs, which require adequate numbers of patients to maintain proper expertise.

Introduction

Over the first several decades of lung transplantation, common criteria for donor and recipient selection have changed. While wait list time and geography were originally used to pair donors and recipients, there is now an increased focus on delivering pediatric organs to pediatric recipients, and a complex scoring system (ie, the Lung Allocation Score or LAS) is now being used for older pediatric patients. While median survival has improved, the most significant survival benefit has been noted in the first year following transplant, with early postoperative survival improved by standardization of surgical technique. Long-term survival, in contrast, continues to be limited by chronic lung allograft dysfunction (CLAD), which occurs in ~50% of patients at 5 years following transplant.1 The limited expectations for graft survival mean that lung transplant is an appropriate option for relatively few pediatric patients with cystic fibrosis (CF).

Moreover, lung transplant can be a realistic option for only a very limited number of patients when so few quality organs are available. A lack of organ supply continues to add to the challenge of lung allocation. The allocation of pediatric lungs has been adapted over time, with pediatric recipients being prioritized for pediatric organs. Due to the lack of supply, extending pretransplant survival is essential. Ex vivo lung perfusion (EVLP), a technology that involves applying therapy to lungs that have been removed from a deceased donor, has the potential to improve the quality of marginal donor lungs, thereby increasing organ supply. Extracorporeal membrane oxygenation (ECMO) and paracorporeal lung assist devices (PLAD), both variations on cardiopulmonary bypass, have been used as bridges to lung transplant and have the potential to sustain patients with end-stage lung disease until suitable donor lungs can be found.2

Over time, improved CF therapeutics will sustain lung function and may make lung transplant less necessary for pediatric patients. Nevertheless, some children with CF continue to present for lung transplant in the pediatric age group. Moreover, if survival was improved, lung transplantation could be of even greater potential utility to more pediatric patients; better strategies to diagnose and treat CLAD, for example, could make lung transplant a more broadly beneficial intervention. Ongoing research directed at identifying discrete phenotypes of chronic rejection may improve both diagnosis and treatment. Antibody-mediated rejection (AMR) likely has a role in CLAD, and clarity regarding diagnosis and treatment may also improve long-term survival in lung transplant. To improve survival in pediatric lung transplantation, we will also need to understand why there is a “high-risk window” in the late teenage years, during which transplanted patients with CF have increased mortality risk.3

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This review does not survey the entire process of lung transplantation in CF, but rather highlights current trends in the management of end-stage lung disease and of lung transplant patients. An understanding of current management in end-stage lung disease can help even nonspecialists decide which patients are appropriate for referral, when it is appropriate to refer them, and to where they might be referred. Lung transplantation profoundly challenges patients with CF and their families, as well as clinicians and researchers. Nevertheless, controversies in transplantation can help to drive innovations in diagnosis and management of disease in lung transplant patients and in patients with end-stage lung disease.

History of Lung Allocation

Contemporary lung allocation involves the estimation of transplant benefit. Transplant benefit is calculated based on expected survival before transplant (pretransplant survival), as well as the quality and duration of posttransplant survival.

The first formal policies governing lung allocation were established in 1990. At that time, allocation depended on ABO compatibility and waiting list time, with organs preferentially being offered to the local service area. In 1999, with increasing concerns regarding wait list mortality, the Organ Procurement and Transplantation Network (OPTN) established a lung allocation subcommittee. The first subcommittee proposal was presented in 2003, and the Lung Allocation Committee proposed a revised lung allocation algorithm in March 2004. The LAS was established for candidates aged 12 years and older, based on anticipated pretransplant and posttransplant survival. Part of this proposal was the preferential allocation of pediatric lungs to pediatric recipients (Table 1). The 12 years of age “breakpoint” was established based on observed differences in diagnosis and survival patterns between younger children and adolescents. In June 2004, the UNOS Board approved this revised lung allocation algorithm, and on May 4, 2005, the lung allocation system went live. The pediatric lung allocation policy was updated in 2010; among the changes made at that time were that donors 0–11 years of age were allowed access to organs across a wider geographic area.

The Complexity of Pediatric Lung Allocation: The Case of SM

The ongoing challenge of pediatric lung allocation is effectively highlighted in the case of SM. SM was a 10-year-old female with CF, living in the Philadelphia area, who was initially listed for transplant at the Children’s Hospital of Philadelphia (CHOP) in December 2011. After she spent an extended time on the wait list, the “height range” for acceptable organs was increased by her doctors in November 2012. This change could have enabled her to have access to adult lungs for lobar transplant. SM was admitted to CHOP in February 2013 and transferred to the pediatric intensive care unit for bilevel positive pressure ventilation in May 2013.

On May 23, 2013, CHOP requested an exception to allow SM to have an LAS and to compete on the waiting list with both adolescents and adults. The following day, SM’s family made a public media appeal regarding her case. On May 29–30, 2013, Secretary of Health and Human Services, Kathleen Sebelius, requested information about pediatric lung allocation and the OPTN responded. Secretary Sebelius subsequently requested a prompt review of the pediatric lung allocation policy. On June 5, 2013, SM’s family filed a lawsuit and the Federal Judge, Michael Baylson, ordered the OPTN to immediately cease the application of the Under 12 Rule in this case. Five days later, the OPTN Executive Committee amended their policy, enacting the Lung Review Board Exception Path, which allowed candidates aged 0–11 to be listed as adolescents. SM had a complicated course, ultimately requiring 2 transplants and a prolonged postoperative hospital stay. On June 12, 2013, SM underwent her first transplant, with a second transplant just 3 days later on June 15, 2013. On August 26, 2013, SM was discharged home. The temporary policy adopted in the SM case, allowing for exceptions to the Under 12 Rule, was made permanent in June 2014.

The Complexity of Allocation

The case of SM highlights some of the key challenges in pediatric lung allocation. At the root of allocation problems is the paucity of organs for pediatric lung transplant candidates aged 0–11 (Table 2). There are relatively few pediatric donors and recipients, compared to adults. Only 2% of wait list individuals are typically under 12 years old, and 2%–5% of individuals are from 12 to 18 years old. Nevertheless, there are also relatively few lung donors compared to donors of other organs. Approximately, 5% of under 12-year-old donors provide lungs, while more than 35% adolescent donors do (Fig. 1). This discrepancy represents a potential opportunity to increase available lungs for children, and improving the donor yield of young donors should be a priority.

More than 90% of adolescent lung donor organs go to adult recipients. This issue persists, despite the preferential allocation of pediatric lungs to pediatric recipients (noted in Table 1). Geography can be limiting, with suitable pediatric recipients not always being available within a safe radius. Allograft-sustaining therapies (such as EVLP, discussed here) may enable the safe transport of organs over longer distances. Expanding geographic allocation of pediatric organs could help to ensure that pediatric organs are preferentially offered to pediatric patients. Discrete age boundaries between early childhood, adolescent, and adult recipients are difficult to justify. There are not sufficient data, however, to

### Table 1. Preferential Allocation of Pediatric Lungs to Pediatric Recipients

<table>
<thead>
<tr>
<th>Priority</th>
<th>Donor age &lt;12 years</th>
<th>Donor age 12–17 years</th>
<th>Donor age 18 years and older</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Recipients &lt;12</td>
<td>Recipients 12–17</td>
<td>Recipients 12 and older</td>
</tr>
<tr>
<td>Second</td>
<td>Recipients 12–17</td>
<td>Recipients &lt;12</td>
<td>Recipients &lt;12</td>
</tr>
<tr>
<td>Third</td>
<td>Recipients 18 and older</td>
<td>Recipients 18 and older</td>
<td>Recipients 18 and older</td>
</tr>
</tbody>
</table>

Candidates <12 years old are prioritized by waiting time, and all others are prioritized by Lung Allocation Score.
### Management Trends and Challenges: CLAD

The initial focus in studies of chronic rejection was bronchiolitis obliterans (BO), gradual destruction of small airways by a presumed immune-mediated process. The diagnosis of BO is complicated by the difficulty in establishing the diagnosis—typically by transbronchial or open lung biopsy—and by the potential for sampling error, with a “clean” biopsy not guaranteeing that all parts of the lung are unaffected by chronic rejection. Therefore, the International Society for Heart and Lung Transplantation (ISHLT) established a clinical diagnosis of bronchiolitis obliterans syndrome (BOS), reflecting irreversible declines in pulmonary function testing (PFT). The definition of BOS has undergone subsequent refinement, with the inclusion of midexpiratory flow rate (FEF25–75) criteria, for example, due to recognition of the potential for earlier detection of airflow limitation.

While BOS was traditionally associated with irreversible airflow obstruction, alternate phenotypes of chronic rejection have become evident. Moreover, while BOS was traditionally identified as a clinical marker of BO, there is now evidence that BOS is not specific for BO and that not all chronic rejection is linked directly to observable pathologic changes. With this expanding concept of “chronic rejection,” the more general term “chronic lung allograft dysfunction” (CLAD) has been adopted to describe sustained declines in lung allograft function.

Instead of obstruction and air trapping, some patients with CLAD develop interstitial infiltrates and restrictive patterns on their PFT, and this clinical phenotype (“restrictive allograft syndrome” or RAS) has been associated with worse prognosis. Phenotypes of chronic rejection are important because they have the potential to determine prognosis, but they may also have implications for treatment. Some patients with CLAD are currently being defined by their response to therapy, as in the proposed “azithromycin-responsive allograft dysfunction” (ARAD), which is a form of CLAD defined by forced expiratory volume in one-second (FEV1) increase following the administration of azithromycin.

Other proven potentially life-prolonging treatments for CLAD are available, thereby reinforcing the importance of phenotypic precision. A retrospective analysis identified a decrease in the rate of FEV1 decline among patients receiving extracorporeal photopheresis (ECP, which involves the irradiation and subsequent reinfusion of white blood cells), and a prospective study showed evidence that a majority of CLAD patients treated with ECP showed FEV1 stabilization. Nevertheless, the optimal timing of ECP is not well established, and it is evident that alternate CLAD phenotypes such as RAS may have differing responses to ECP therapy.

### Management Trends and Challenges: AMR

The traditional definition of “antibody-mediated rejection” (AMR) involved a recipient’s preformed antibodies contributing to a hyperacute response to human leukocyte antigens (HLAs). ABO compatibility testing and cross-matching have helped to make hyperacute rejection relatively rare. Subsequent rejection was primarily identified as cellular, a T-cell mediated process often resulting in perivascular lymphocytic aggregation.

AMR is now more broadly understood as a variety of interactions between preformed or de novo donor-specific antibodies (DSAs) and lung allograft HLAs. This interaction can trigger leukocyte recruitment or complement activation, thereby leading to damage of the lung allograft. An AMR can also develop in response to self-antigens (ie, autoantibodies), such as K-alpha 1 tubulin and collagen V, and the development

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**Table 2. Contrast Between Number of Lung Offers Extended to Potential Recipients, by Age, Sampled Between September 2010 and March 2013**

<table>
<thead>
<tr>
<th>Recipient age (years)</th>
<th>REGs ever active</th>
<th>REGs with at least 1 offer</th>
<th>REGs with 3+ offers or acceptance</th>
<th>REGs with an acceptance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>0–5</td>
<td>54</td>
<td>29 (53.7)</td>
<td>27 (50.0)</td>
<td>26 (48.1)</td>
</tr>
<tr>
<td>6–11</td>
<td>49</td>
<td>34 (69.4)</td>
<td>29 (59.2)</td>
<td>18 (36.7)</td>
</tr>
<tr>
<td>12–17</td>
<td>115</td>
<td>100 (87.0)</td>
<td>88 (76.5)</td>
<td>62 (53.9)</td>
</tr>
<tr>
<td>18+</td>
<td>7,323</td>
<td>6,826 (93.2)</td>
<td>6,262 (85.5)</td>
<td>4,396 (60.0)</td>
</tr>
</tbody>
</table>

Age was determined based on the maximum of age at listing or age at the start of the sampling period. A single patient listed at multiple centers would have multiple REGs. REGs, registrations.
of these antibodies is a risk factor for the development of BOS. A National Institutes of Health (NIH) conference in 2003 developed staging criteria, from latent (stage I) to full humoral rejection (stage IV). Latent humoral response is defined as circulating DSAs in the absence of pathology changes, complement deposition, or graft dysfunction, and it is often left untreated.

Full humoral rejection (marked by DSAs, pathology changes, complement deposition, and graft dysfunction) is treated aggressively, usually with some combination of pulse steroids, intravenous immunoglobulin (IVIG), and plasmapheresis, with consideration for other immunomodulatory agents such as rituximab. Lower grade AMR, however, poses several management challenges. Many laboratories report mean fluorescence intensity (MFI), which represents the amount of antibody bound relative to the amount of antigen on a single bead in a DSA assay. This quantitative measurement cannot be interpreted as a titer level, and the meaning of a high or low MFI is still being debated.

Moreover, it is not clear whether high MFI DSAs should be treated in the absence of complement fixation or associated symptoms. DSAs have been associated with the development of BOS, and overall survival is reduced in patients who develop early DSAs after transplant. In a prospective study of DSA treatment comparing IVIG alone and IVIG plus rituximab, the latter group had significantly improved survival. While current guidelines do not call for preemptive treatment of latent AMR, there may be an ongoing trend toward more aggressive screening and treatment of DSAs.

Patients who have reduced immune recognition of the lung allograft may have improved transplant outcomes. Nevertheless, while minimal immune response can protect against antibody formation and subsequent rejection, a complete

![FIG. 1. Contrast between the percentage of under 12-year-old child donors providing lungs each year, compared to the percentage of adolescent donors.](image1)

![FIG. 2. Patterns of lung transplantation, by Diagnosis Group, in the era following implementation of the Lung Allocation Score. Diagnosis Group A includes obstructive lung diseases (such as chronic obstructive pulmonary disease), Group B includes pulmonary vascular disease, Group C includes cystic fibrosis (and immune deficiency), and Group D includes restrictive lung diseases (such as idiopathic pulmonary fibrosis). In this graph, each “year of transplant” starts in May (eg, 2004 runs from May 4, 2004 to May 3, 2005).](image2)
lack of immune response puts transplant patients at risk for infection. One of the ultimate goals of studying AMR will be to identify mechanisms of immune tolerance, a state in which immunosuppression could be lessened because the lung allograft would no longer be recognized as foreign.

Posttransplant survival, whether improved by earlier detection or treatment of AMR or CLAD, is an exciting opportunity in pediatric lung transplant. Pediatric lung transplant recipients often have relatively little comorbidity compared to adult patients, and interventions have the theoretical potential to extend allograft survival by decades. New therapies are unlikely to be effective, however, if patients receive insufficient care, whether due to nonadherence or to gaps in care associated with transition to adulthood. Transplanted teenagers with CF have significantly increased mortality, and identifying root causes of this “high-risk window” will enable us to capitalize on our improving understanding of lung transplantation.

Trends and Opportunities in Lung Transplant: Bypass Technologies

One approach to issues of organ shortage is extending pretransplant survival. The practice of transplant for pulmonary arterial hypertension, for example, is being changed by increasing availability of medical treatments, and it is likewise possible that new CF therapeutics will enable us to extend the period before transplant.

The unpredictability of waiting list times provides another impetus to extending pretransplant survival. In a patient with end-stage disease whose lungs can no longer provide adequate gas exchange, ECMO can be used to remove and oxygenate venous blood and then return it to either the venous or arterial circulation. ECMO is considered a relative contraindication to lung transplant at some centers, but it has also been evaluated as a possible “bridge” to transplant in patients with end-stage lung disease. In a large retrospective review of patients who underwent pretransplant ECMO, the ECMO patients were noted to have a significantly higher LAS and to spend longer on cardiopulmonary bypass intraoperatively, but their survival was not different than those control patients who were not on pretransplant ECMO. Nevertheless, these patients were sustained on relatively short runs of ECMO (with a median of 91 h).

“Ambulatory ECMO” is a practice in which patients receive intensive physical rehabilitation during their ECMO run; therefore, this bridge period is associated with less deconditioning. Some authors suggest that ambulatory ECMO may be easier to implement in patients with chronic respiratory insufficiency (such as those with CF)—compared to those with purely acute respiratory failure—as they have greater tolerance for dyspnea and require less sedation. Patients on ambulatory ECMO may undergo tracheostomy to ensure airway protection in case of ECMO failure and to allow for an increased pulmonary toilet. The mean wait time to transplant in a series of 4 patients with CF using an ambulatory ECMO bridge was 8.5 days, a relatively short ECMO run. Long-term outcomes from ambulatory ECMO patients will need to be studied, and the feasibility of longer ambulatory ECMO runs may need to be considered. An alternate bridging approach that has shown promise is the use of a PLAD such as the Novalung oxygenator (Novalung GmbH, Heilbronn, Germany). PLAD involve oxygenating blood from the pulmonary artery and returning it to the left atrium, and this technology can be used to wean a patient from ECMO support. Using PLAD, children with ventilatory failure have been able to await suitable lung donors for more than 2 months. PLAD may be simpler than ECMO to implement, but while PLAD can be effective at carbon dioxide removal, they have less utility in improving oxygenation. Both ECMO and PLAD present challenges in terms of vascular access and infection risk.

Nevertheless, rehabilitation while on lung bypass technology—likely easier in children with ECMO than with PLAD—has the potential to improve pretransplant survival as well as posttransplant outcomes. These measures are not feasible in children who become “too sick,” however, and we counsel possible early referral to a pediatric lung failure center at which a variety of approaches, including bypass technologies and lung transplant, can be considered. There are also ethical considerations in starting these technologies in patients who may be lung transplant candidates; when a patient is placed on ECMO, for example, as a bridge to transplant, there is still a possibility that the patient will remain too sick for transplant or that donor lungs will not become available. In
such a case, there is a risk of the lung bypass technology becoming a “bridge to nowhere.” Any clinician discussing lung bypass and transplant with families needs to emphasize that lung transplant may not ultimately be feasible.

Trends and Opportunities in Lung Transplant: EVLP

EVLP involves lung harvesting followed by ex vivo diagnostics and therapeutics. EVLP has the potential to alleviate some organ allocation issues by increasing organ supply and by extending geographic areas for donation. One of the most exciting aspects of EVLP involves the repair of marginal organs, optimizing otherwise unusable lungs. High-dose antibiotics can be added to lung perfusate, and empirical antimicrobials in EVLP have already been shown to significantly reduce bacterial load. EVLP can facilitate ongoing evaluation of lung quality, including ex vivo bronchoscopy and imaging studies. Perfusate also can be used to evacuate pulmonary clots, thereby contributing to ex vivo vascular reconditioning. Short-term outcomes in EVLP have been similar to those in lung transplants without ex vivo treatment, but EVLP may improve lung utilization. While the potential to increase organ supply is promising, the feasibility of EVLP in pediatric patients and long-term outcomes in EVLP organ recipients will need to be explored.

The Future of Pediatric Lung Transplantation for CF

While there will continue to be a need for pediatric lung transplantation in congenital surfactant disorders, for example, it is possible that both CF and pulmonary hypertension will become less common as indications for pediatric lung transplantation over time. If new molecular pharmacotherapies in CF (including potentiators such as ivacaftor) help pediatric patients to sustain lung function, it is possible that patients formerly transplanted during adolescence will have no need for lung transplant until adulthood.

Diminishing numbers of pediatric lung transplants could increase the complexity of an already challenging field. Effective transplant teams are diverse, with staffing needs for physicians, surgeons, nurse coordinators, nutritionists, physical therapists, psychologists, social workers, financial coordinators, child life professionals, and more. An adequate number of transplants are required to sustain such a large team, and it is therefore likely that there will continue to be a limited number of pediatric lung transplant programs in the United States. The number of transplant centers performing 10 or more pediatric lung transplants per year has decreased across the world (Fig. 3). Centers with higher volumes of pediatric lung transplants are noted to have better patient survival statistics than low-volume centers, and pediatric experience additionally contributes to improved lung transplant outcomes in children. More pediatric-specific research on topics such as extending pretransplant survival and designing directed treatments for AMR and CLAD is needed. Given that few pediatric patients will require lung transplant, multicenter trials and collaboration with adult centers will be used to fill our knowledge gaps.

Author Disclosure Statement

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References

19. Hachem RR, Tiriveedhi V, Patterson GA, Aloush A, Tru-  
lock EP, Mohanakumar T. Antibodies to K-alpha 1 tubulin  
and collagen V are associated with chronic rejection after  
 to assess antibody-mediated rejection in solid organ trans-  
the testing and clinical management issues associated with  
HLA and non-HLA antibodies in transplantation. Trans-  
plantation 2013; 95:19–47.  
an antibody specific to major histocompatibility antigens  
detectable by flow cytometry after lung transplant is asso-  
ciated with bronchiolitis obliterans syndrome. Transplan-  
23. Morrell MR, Pilewski JM, Gries CJ, et al. De novo donor-  
specific HLA antibodies are associated with early and high-  
grade bronchiolitis obliterans syndrome and death after lung  
transplantation. J Heart Lung Transplant 2014; 33:  
1288–1294.  
antibodies in lung transplantation: risk factors and impact  
leukocyte antigen antibodies and preemptive antibody-  
directed therapy after lung transplantation. J Heart Lung  
Transplant 2010; 29:973–980.  
26. Gracon AS, Wilkes DS. Lung transplantation: chronic al-  
lograft dysfunction and establishing immune tolerance.  
extracorporeal membrane oxygenation as a bridge to lung  
1070; discussion 70–71.  
ECMO as a bridge to lung transplant in a previously well  
pediatric patient with ARDS. Pediatrics 2014; 134:  
e583–e585.  
29. Hayes D Jr, Galantowicz M, Preston TJ, Lloyd EA, Tobias  
JD, McConnell PI. Tracheostomy in adolescent patients  
brugged to lung transplantation with ambulatory venovenous  
extracorporeal membrane oxygenation. J Artif Organs 2014;  
17:103–105.  
30. Hayes D Jr, Kukreja J, Tobias JD, Ballard HO, Hoopes CW.  
Ambulatory venovenous extracorporeal respiratory support  
as a bridge for cystic fibrosis patients to emergent lung  
lung assist devices as a bridge to recovery or lung trans-  
plantation in neonates and young children. J Thorac Cardi-  
32. Bartosik W, Egan JJ, Wood AE. The Novalung interven-  
tional lung assist as bridge to lung transplantation for self-  
ventilating patients – initial experience. Interact Cardiovasc  
33. Abrams DC, Prager K, Blinderman CD, Burkart KM, Brodie  
D. Ethical dilemmas encountered with the use of extracor-  
poreal membrane oxygenation in adults. Chest 2014; 145:  
876–882.  
34. Andreasson A, Karakamou D, Perry JD, et al. The effect  
of ex vivo lung perfusion on microbial load in human donor  
35. Egan TM, Haithcock JA, Nicrota WA, et al. Ex vivo evalua-  
tion of human lungs for transplant suitability. Ann Thorac  
36. Mulloy DP, Stone ML, Crosby IK, et al. Ex vivo rehabilita-  
tion of non-heart-beating donor lungs in preclinical porcine model: delayed perfusion results in superior lung  
37. Cypel M, Yeung JC, Machuca T, et al. Experience with the  
first 50 ex vivo lung perfusions in clinical transplantation.  
lung transplantation: the effect of center volume and ex- 
39. OPTN/UNOS Executive Committee. Lung Allocation  
Policy Review from the Executive Committee of the Organ  
Procurement and Transplantation Network—United Net- 
work for Organ Sharing, June 10, 2013.  
40. United Network for Organ Sharing (UNOS). Organ Pro- 
cuemen and Transplantation Network (OPTN) data. Ac- 
the International Society for Heart and Lung Transplanta- 
tion: seventeenth official pediatric lung and heart–lung  
transplantation report—2014; focus theme: retransplanta- 

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