Pediatric Lung Transplantation

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Pediatric lung transplant is a viable option for treatment of end-stage lung disease in children, with > 100 pediatric lung transplants reported to the Registry of the International Society of Heart and Lung Transplantation each year. Long-term success is limited by availability of donor organs, debilitation as a result of chronic disease, impaired mucus clearance resulting from both surgical and pharmacologic interventions, increased risk for infection resulting from immunosuppression, and most importantly late complications, such as chronic lung allograft dysfunction. Opportunities for investigation and innovation remain in all of these domains: (1) Ex vivo lung perfusion is a promising technology with the potential for increasing the lung donor pool, (2) evolving extracorporeal support strategies coupled with effective rehabilitation will effectively bridge critically ill patients to transplant, and most importantly, (3) research efforts intended to increase our understanding of the underlying mechanisms of chronic lung allograft dysfunction will ultimately lead to the development of effective therapies to prevent or treat the variety of chronic lung allograft dysfunction presentations. Key words: lung transplantation; organ donation; cystic fibrosis; pulmonary hypertension. [Respir Care 2017;62(6):776–798. © 2017 Daedalus Enterprises]

Introduction

It has been more than 50 years since the first human lung transplant was performed by Hardy.¹ But it was not until the early 1980s that the combination of calcineurin inhibitors and improved surgical techniques allowed for acceptable survival for lung and heart-lung transplant recipients.^{2,3} The first reports of lung transplant in children

were published in the early 1990s,^{4–6} with registries reporting a steady increase in the number of children receiving lung transplants through the 1990s. From 1986 through June 2013, 2,091 lung and 689 heart-lung transplants in children were reported to the Registry for the International Society for Heart and Lung Transplantation (ISHLT).⁷ Following a steady increase in pediatric lung transplants in the first decade of this millennium, with 125 reported to

Fig. 1. Yearly number of pediatric lung and heart-lung transplants reported to the International Society for Heart and Lung Transplant registry 1984–2014. Data from Reference 7.

the ISHLT registry in 2009, numbers have remained stable since then (Fig. 1).⁷ This review will outline indications, key outcomes and complications, and therapeutic challenges facing pediatric lung transplant candidates and recipients, highlighting areas where effective respiratory therapy and rehabilitation are important.

Most children with end-stage lung disease receive a bilateral lung transplant. Although more common in the early experience, heart-lung transplant is now generally reserved for patients with left-ventricular failure or congenital heart disease not amenable to repair. Roughly 10 heart-lung transplants/y are now reported to the ISHLT registry.⁷ So-called “domino” procedures with a healthy native recipient heart transplanted into a second recipient are now exceedingly rare (Fig. 1). Lung transplant is performed in children much less frequently than heart, liver, and kidney transplants. The reason for this is multifactorial, including lower prevalence of end-stage lung disease in children and improved survival in cystic fibrosis (CF) and pulmonary hypertension.^{8,9} Perhaps not surprisingly,

Fig. 2. Distribution of pediatric lung transplants reported to the International Society for Heart and Lung Transplant registry by age and indication January 2000 to June 2014. CF = cystic fibrosis, CHD = congenital heart disease, ILD = interstitial lung disease. Data from Reference 7.

pediatric lung transplant is a low-volume service in most centers. Among roughly 40 centers reporting pediatric lung transplants, nearly 90% of centers perform < 5 transplants/y. Nearly half of pediatric lung transplants are performed in a small subset of centers.⁷ In the United States, despite allocation policy changes intended to increase allocation to children, compared with adolescents and adults, the mortality rate for pediatric candidates remains higher than for most adults.¹⁰ Efforts to increase access to lung transplant for children through additional allocation policy changes and increased utilization of potential donor lungs remain important.¹¹

Indications and Contraindications to Transplantation

Lung transplantation is indicated in children with untreatable end-stage lung disease or pulmonary vascular disease. Initially, the majority of children receiving lung transplants had CF. However, indications have become considerably broader with growing experience with the procedure, including transplantation of infants with congenital, end-stage lung disease^{12,13} (Fig. 2). Notably, COPD, emphysema, and idiopathic pulmonary fibrosis (the most common diagnoses leading to lung transplant in adults) are virtually absent from pediatric age groups. Pulmonary hypertension (mostly associated with congenital heart disease) and other pulmonary vascular diseases (primarily pulmonary vein stenosis and rarely alveolar capillary dysplasia); disorders of surfactant metabolism, such as surfactant protein B and C deficiencies and ATP-binding cassette A3 (ABCA3) transporter and NKX2.1 mutations; interstitial lung disease; bronchopulmonary dysplasia; and pulmonary hypoplasia make up the diagnoses leading to lung transplant in children younger than 1 y of age.^{13–16}

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Table 1. Contraindications to Pediatric Lung Transplantation

Absolute	Relative
Active malignancy within 2 y*	Pleurodesis
Sepsis	Renal insufficiency
Active tuberculosis	Markedly abnormal body mass index
Severe neuromuscular disease	Mechanical ventilation or ECMO‡
Documented, refractory non-adherence	Scoliosis
Multiple-organ dysfunction†	Poorly controlled diabetes mellitus
Acquired immunodeficiency syndrome	Osteoporosis
Hepatitis C with histologic liver disease	Chronic airway infection with multiply resistant organisms§
Significant psychiatric illness in patient or primary caregiver	Fungal infection/colonization
	Atypical mycobacteria infection/colonization (particularly smear-positive)
	Hepatitis B surface antigen-positive

Data from Reference 17.

* Some centers prefer a disease-free interval of 5 y.

† Consider heart-lung transplant with concomitant left-ventricular insufficiency or irreparable congenital heart disease, liver-lung transplant with concomitant hepatic failure.

‡ Some transplant centers consider venoarterial extracorporeal membrane oxygenation an absolute contraindication.

§ For some transplant centers, infection with *B. cepacia* complex organisms, particularly *B. cenocepacia*, is an absolute contraindication.

ECMO = extracorporeal membrane oxygenation

For infants and for children age 1–5 y, disorders leading to pulmonary hypertension remain the most common indication. In patients 6–11 y of age, CF predominates. CF accounts for nearly three quarters of adolescent lung transplantation.⁷

The main change in transplant diagnoses over the past decade has been the reduction of primary pulmonary hypertension, probably due to improved medical therapies, including prostaglandins (epoprostenol), phosphodiesterase inhibitors (bosentan), and sildenafil.⁷ However, despite a steady increase in the median survival in CF,⁹ the relative percentage of children with CF receiving lung transplants has declined only slightly in recent years.⁷

Absolute contraindications to pediatric lung transplant are driven primarily by conditions that lead to a high risk for a poor post-transplant outcome. These include multi-system organ failure, active malignancy, and systemic infections, such as HIV, active hepatitis C, or tuberculosis (Table 1). Concomitant liver, renal, or heart failure is an absolute contraindication to bilateral lung transplant. Multi-organ transplantation may be considered in selected instances/centers. Because of very poor lung transplant outcomes in patients with CF colonized with *Burkholderia cenocepacia* (formerly BCC, Genomovar III) and a related organism, *Burkholderia gladioli*,^{18–20} colonization with these organisms is generally an absolute contraindication as well. *Mycobacterium abscessus* colonization, particularly in patients with smear-positive sputum, is associated with poor outcomes and may also be considered an absolute contraindication.^{21,22} Relative contraindications include prior pleurodesis, either chemical or surgical, which may lead to longer ischemic time related to bleeding. For some centers, talc pleurodesis is an absolute contraindication.

Multiple arteriovenous collaterals, such as those seen in absent pulmonary artery syndromes, coupled with multiple prior thoracotomies have been associated with poor outcome and are a strong relative contraindication in many centers.^{6,23} Significant allosensitization (related to prior thoracic surgeries or implantation of homograft valves or vessels) is also a relative contraindication because of the risk of hyperacute rejection or subsequent antibody-mediated allograft injury.

Because an effective psychosocial support system and adherence to the prescribed medical regimen are important components of a successful outcome, situations where these are not present can become a strong relative contraindication. To ensure that the child and family are treated fairly, navigating these situations must be an individualized, shared responsibility between the referring and transplant centers. If adherence issues are present, many programs will request that the referring center formulate a contract with the family that outlines adherence requirements and sets an expectation that the contract will be followed for a 3–6-month period before proceeding with transplant evaluation. Significant psychiatric or mental health disorders in either the primary caregiver or the patient may also be considered a strong relative contraindication to transplant.

Finally, cost and logistic issues may play a role in transplant candidacy. In most instances, medical costs are covered by insurance. If insurance is not available, patients will need to raise sufficient funds. Costs will vary by age, level of pre-transplant illness, extent of post-transplant complications, and transplant center contracting. Average costs for bilateral lung transplants in adults exceed \$1 million (United Network for Organ Sharing. <http://transplantliving.org/before-the-transplant/financing-a-transplant/the-costs/>. Accessed May 1, 2017). Costs will be similar for

children and often higher in infants with severe lung disease who remain hospitalized while awaiting transplant. In addition, patients may also be responsible for relocation costs. Because there are relatively few pediatric lung transplant programs, many patients must move to a different city for an average 3–6-month period (waiting time plus 3 months post-transplant).

In general, patients should be referred for lung transplant early enough so that they would survive long enough to receive organs. In the past, the recommendation was to list patients when anticipated survival without transplant was < 2 y. The introduction of the Lung Allocation System made this less relevant for adolescents. The Lung Allocation System was developed and implemented in 2005 by the Organ Procurement and Transplantation Network.²⁴ Based on models of waiting list mortality and post-transplant survival, the Lung Allocation System prioritizes donor lung allocation to maximize the 1-y transplant survival benefit (Lung Allocation System = post-transplant survival $- 2 \times$ waiting list survival, normalized to a 0–100 scale). Diagnosis, age, height/weight, need for oxygen and ventilator support, pulmonary arterial pressures, 6-min walk distance, and lung function are factors in the model. Implementation of the Lung Allocation System has led to decreases in waiting time and waiting list mortality for adolescents and adults.²⁵ The emphasis on waiting list mortality in the algorithm has opened the door for transplant in critically ill patients who previously would not have survived long enough to receive organs, including those requiring mechanical ventilation. Not surprisingly, this group of patients have worse overall survival.²⁶ Because allocation of lungs to children < 12 y old remains based on waiting time within 2 urgency tiers, early referral is more important in this population.²⁷

Beyond these general principles, referral timing is dependent on underlying disease. Patients with surfactant protein B deficiency, alveolar capillary dysplasia, and significant pulmonary vein stenosis often progress rapidly to refractory respiratory failure requiring extracorporeal membrane oxygenation (ECMO) circulatory support. For this reason, prompt referral and transport to the transport center is prudent once the family understands the need for and agrees to lung transplant evaluation.

Timing is less clear in other disease processes. For example, a series of studies in subjects with CF have led to a general recommendation to proceed with lung transplantation once the FEV₁ declines to $< 30\%$ predicted.^{28–30} But even the best of these models can accurately predict mortality $< 50\%$ of the time.²⁹ The challenge for timing lung transplant in children with CF was highlighted by Liou et al³¹ using proportional hazard models developed from the Cystic Fibrosis Foundation and Organ Procurement and Transplantation Network data sets. The authors found that lung transplantation did not provide a survival

benefit to children with CF. Their conclusions were tempered by the fact that data were obtained at the time of listing and not at the time of transplant, often 2–3 y before their actual transplant because of waiting time requirements.¹¹ In contrast, other studies have demonstrated a survival benefit for children with CF.^{32,33} Because lung transplantation remains the only treatment option available to extend life in patients with CF and end-stage lung disease, most centers evaluate and list patients with FEV₁ in the 30s and base the timing of active pursuit of transplant on the clinical picture, including nutritional status, functional status, and frequency of exacerbations.³⁴

For patients with idiopathic pulmonary hypertension or pulmonary vascular disease, a cardiac index of < 2 L/min/m², elevated pulmonary vascular resistance, right-atrial pressures of > 7.4 mm Hg, and right-ventricular end-diastolic pressure of > 10.4 mm Hg despite maximal vasodilator therapy predict poor survival.^{35,36} Referral and evaluation are suggested when it is clear that a patient is approaching these limits. Other risk factors that should prompt consideration for transplant evaluation include von Willebrand factor levels of $> 240\%$, elevated uric acid levels, and plasma levels of brain natriuretic peptide > 180 pg/mL.^{37–39}

The decision of whether and when to transplant patients with Eisenmenger syndrome is challenging. Because of the potential for extended survival (some patients can live for years, if not decades, after diagnosis), indication for transplant includes progressive disease (severe hypoxia, syncope, or a limited functional status). In general, lung transplant is the preferred procedure unless the cardiac lesion is not amenable to repair at the time of transplant.^{40,41}

Patients with other surfactant-processing disorders, such as surfactant protein C deficiency, ABCA3 transporter mutation, or NK2.1x mutation, the presentation and course of disease are variable.⁴² In general, these patients should be referred when they develop progressive respiratory insufficiency unresponsive to medical interventions.

Criteria for transplant evaluation are even less clear in other disease processes. Most pediatric centers consider factors beyond cardiopulmonary function, such as growth and nutrition status, frequency of hospitalizations, and potential for improvement in overall quality of life before deciding when to proceed to lung transplant. Because of this uncertainty, most pediatric lung transplant centers recommend referral well before the patient reaches the tipping point between anticipated waiting list survival and estimated waiting time.¹⁷

Candidate Evaluation and Pre-Transplant Management

Lung transplant evaluation is a multi-disciplinary process, including laboratory and radiographic studies as well as consultation with multiple services (Table 2) intended

Table 2. Recommended Evaluation for Pediatric Lung and Heart-Lung Candidates

Laboratory evaluation
Blood type (ABO)
Complete blood count
Coagulation studies (PT, INR, PTT)
Complete biochemistries, including electrolytes and renal and liver function tests
Lipid profile
Serologies, including cytomegalovirus, Epstein-Barr virus, HIV, hepatitis B and C, measles, varicella, herpes simplex, <i>Toxoplasma gondii</i>
Anti-HLA antibody screen
Arterial blood gas
Autoimmune screen (antinuclear antibody, ANCA, rheumatoid factor, quantitative immunoglobulins)
Thyroid profile
Microbiology
Sputum or deep-throat culture and susceptibility testing
Tuberculin testing
Functional assessment
Pulmonary function testing
6-min walk test
Electrocardiogram
Cardiac catheterization (in select patients)
Imaging
Chest radiograph
Chest CT
Sinus CT (in patients with CF or immunodeficiency)
Echocardiogram
Bone densitometry
Consultations with
Cardiothoracic surgery
Cardiology (in select patients)
Infectious diseases
Social services
Psychology
Nutrition
Physical therapy
Child life

PT = prothrombin time
 INR = international normalized ratio
 PTT = partial thromboplastin time
 HIV = human immunodeficiency virus
 HLA = human leukocyte antigen
 ANCA = anti-neutrophil cytoplasmic antibody
 CT = computed tomography
 CF = cystic fibrosis

to identify comorbidities that would limit post-transplant survival. Determination of candidacy considers both medical and psychosocial components.

Pre-transplant care is often shared with the referring center with the goal of maximizing the patient's chances of surviving the wait for organs and maximizing the post-transplant outcome potential. Typically, this includes maximizing the nutritional status (including placement of a

Fig. 3. Patients' participation in daily physical activity before (Pre) and 1 y after (Post) lung transplantation in comparison with healthy age-matched control subjects. A: Daily step count. B: Time spent in activities requiring > 3 metabolic equivalents (METs). Averages in these groups expressed relative to healthy controls are as follows. A: Pre 34% and Post 58%; B: Pre 13% and Post 44%. Error bars show standard error. Data from References 46 and 47.

gastrostomy tube if needed), minimizing infectious risks (including ensuring that vaccinations are up to date), and ensuring that the patient and family establish or continue routines for adherence to medical therapies.

Although pulmonary rehabilitation is commonly included in the care of lung transplant candidates and recipients, literature to support its efficacy is scant overall and virtually nonexistent in children.⁴³ Several studies in adults have demonstrated that, despite substantial improvements in quality of life over pre-transplant values, patients report persistent limitation of daily physical functioning after transplantation^{44,45} (Fig. 3). These findings are present in patients with improvements in lung function to nearly normal or normal values, suggesting that other factors may be responsible.⁴⁸ Lung transplant candidates are likely to have peripheral muscle dysfunction as a result of inactivity and deconditioning before and during the post-transplant recovery period.⁴⁹⁻⁵⁴ Most patients have impairment in nutrition (particularly those with CF). The use of corticosteroids before and after transplant may contribute to limb muscle atrophy and myopathy.^{55,56} Finally, calcineurin inhibitors may effect muscle structure and function.^{57,58} Thus, it is reasonable to postulate that pulmonary rehabilitation strategies both before and beginning immediately after transplantation may help to mitigate these effects.⁵⁹

Pre-transplant rehabilitation (Table 3) has been shown to improve exercise capacity and quality of life before transplant.⁶¹⁻⁶³ A study of adult subjects demonstrated that each 100-m increase in pre-transplant 6-min walk distance was associated with a 2.6-d decrease in the median length of hospital stay.⁶⁴

Of course, pre-transplant management will vary by disease state. In patients with CF, optimizing airway clearance and managing infection remains a priority. Treatment involves aggressive use of high-frequency chest-wall oscillation devices and/or intermittent percussive ventilation and tailoring of antimicrobial therapy to minimize the infectious burden while avoiding antibiotic resistance. Strategies in patients with pulmonary hypertension and other pulmonary vascular disorders involve maximizing pulmo-

Table 3. Suggested Elements of Exercise Training During Rehabilitation Before Lung Transplantation

Begin with initial evaluation that examines hemodynamic stability, oxygen requirements, bone health, body mass index, medical comorbidities, respiratory mechanics, and overall functional capacity.
Complete patient assessment using psychological, health-related, and generic (eg, SF-36) quality of life measures, shortness-of-breath questionnaires, manual muscle testing, and 6-min walk distance.
Pulmonary rehabilitation should consist of exercise training, including progressive aerobic exercise and upper/lower extremity strengthening, under close supervision and continuous monitoring.
Exercise should begin at low intensity and be progressed gradually to the highest capacity tolerated by the individual, maintaining adequate oxygenation during activity.
Place strong emphasis on patient/caregiver education, as well as psychological, dietary, and occupational therapy support.
Frequent reassessments are necessary because of the progression of the underlying lung disease; close communication with patients' health-care providers outside of pulmonary rehabilitation is essential.

Data from Reference 60.

nary blood flow. Pulmonary vasodilator therapy, diuretics, anticoagulation, and supplemental oxygen may be of benefit, depending on the underlying disease. Patients with refractory pulmonary hypertension may be candidates for atrial septostomy or Pott's shunt procedures.^{65,66} Steroids (either in high monthly dose pulses or daily regimens) and other immunosuppressants may be considered in children with interstitial lung disease.⁶⁷

Most pediatric centers will utilize mechanical ventilation for patients who develop respiratory failure after listing despite the fact that mechanical ventilation is a risk factor for mortality.⁶⁸ Indeed, for infants and toddlers, patient and graft survival were similar for patients requiring mechanical ventilation at the time of transplant.⁶⁹ More recently, extracorporeal support has been used to bridge pediatric and adult patients to transplant, including venovenous ECMO⁷⁰⁻⁷² and pumpless, low-resistance membrane oxygenator devices.⁷³ Such devices have been used successfully in a child as young as 2 y of age.⁷⁴ Because all extracorporeal support devices carry risks for anticoagulant-related complications, their role in long-term bridging to transplant remains to be clearly defined. Pre-transplant rehabilitation is particularly important in patients with respiratory failure requiring ECMO. Lung transplant outcomes in patients receiving transplant from ECMO were significantly better in patients who were able to ambulate than in those who were not.^{75,76} Therefore, it would not be unreasonable to postulate that rehabilitation will be similarly important when using pumpless devices. Identifying the appropriate use of various forms extracorporeal support and striking the appropriate balance of their therapeutic risks against the benefits of reduced ventilator-induced injury and potential for rehabilitation should provide a fertile opportunity for research.

Donor Evaluation

For the most part, pediatric lung transplant recipients receive organs from donation after brain death donors.¹⁰

Evaluation of a potential donor includes arterial blood gases ($P_{O_2}/F_{IO_2} > 300$ preferred), chest radiographs, airway cultures, and airway examination by bronchoscopy. The donor should be free of signs/symptoms of acute viral infection and have negative screens for hepatitis A, B, and C and human immunodeficiency virus.⁷⁷ Opportunities to increase the pool of lungs available for transplant have recently become available through techniques that allow ex vivo assessment and therapy of donor lungs (ex vivo lung perfusion). In addition to assessment and conditioning of brain death donor lungs that have failed to meet standard criteria, ex vivo lung perfusion may facilitate increased use of donation after circulatory death donor organs.⁷⁸ Although ex vivo lung perfusion usage is increasing in adult transplant centers, ex vivo lung perfusion technology has yet to be adapted for use with smaller pediatric donors. Given the ongoing shortage of organs, expansion of ex vivo lung perfusion technology into the pediatric space will be another important opportunity for pediatric lung transplant physicians and surgeons.

Transplant Surgical Procedure

Most procedures in children are performed while they are receiving cardiopulmonary bypass or ECMO. A bilateral anterolateral transsternal "clamshell" incision is made at the fourth intercostal space to optimize visualization and access to both pleural spaces. Recipient pneumonectomies involve first ligating and dividing the pulmonary and arterial and venous vessels and then dissecting out the main bronchus and dividing it with a linear stapling device. The donor lungs typically arrive en bloc with a cuff of the left atrium. They are prepared by dividing and appropriately trimming the left-atrial cuff and main pulmonary artery and trimming each main bronchus to within 2 cartilaginous rings of the upper lobe takeoff. The most common procedure in pediatrics is a bilateral sequential lung transplant with end-to-end rather than telescoping bronchial-to-bronchial anastomoses. This approach is felt to minimize

the potential for stenosis.^{79,80} Pericardial or peribronchial lymphatic tissue from the donor and recipient is used to cover the anastomosis. This approach is intended to improve the blood supply to the vulnerable anastomoses and may also reduce the risk of infection of adjacent vascular structures.^{79,81}

Living-donor lobar lung transplant (using a right lower lobe from one donor and a left lower lobe from a second donor) has virtually disappeared in the United States since the introduction of the Lung Allocation System.⁸² Living-donor lung transplant continues to be utilized in Japan because access to donor organs suitable for children in that country is more difficult.⁸³ Other technical variants to allow the use of larger lungs in infants and small children include downsizing the donor organ with a linear stapling device or lobectomy.⁸⁴

Post-Transplant Management

Immunosuppressive Regimen

Triple-drug immunosuppression and directed antimicrobial therapy is initiated in the immediate post-transplant period. Immunosuppression typically consists of a calcineurin inhibitor (commonly tacrolimus), a cell cycle inhibitor (commonly mycophenolate mofetil), and corticosteroids.⁷ Due to a higher perceived risk for rejection episodes than other solid organ transplant recipients, lung transplant recipients generally receive more intense immunosuppression regimens.⁸⁵ Initial trough level targets for tacrolimus are typically 10–20 mg/mL. Initial dosing for prednisone is typically 0.5–1.0 mg/kg/d, tapering over the course of the first year. Nearly all patients remain on steroids at 1 and 5 y post-transplant. Induction immunotherapy at the time of transplant is used in > 70% of pediatric lung patients. Most receive an interleukin-2 receptor antagonist (ie, basiliximab), and the remainder receive a polyclonal agent (anti-lymphocyte or anti-thymocyte globulin).⁷

Antimicrobial Regimen

Most pediatric lung transplant patients receive intravenous antibiotics for 7–10 d starting immediately after transplant based on their pre-transplant airway colonization and modified based on donor information as well as cultures obtained in the immediate post-transplant period. Prophylaxis for opportunistic infections includes antifungal prophylaxis with voriconazole or a similar agent.⁸⁶ *Pneumocystis jirovecii* (carinii) prophylaxis with trimethoprim/sulfamethoxazole and oral nystatin for *Candida* prophylaxis. Ganciclovir (or acyclovir when donor and recipient are cytomegalovirus-negative) is given as antiviral prophylaxis for cytomegalovirus and herpes simplex virus.

Fig. 4. Maximal isometric quadriceps strength (QF) (A) and 6-min walk distance (6MWD) (B) expressed as percentage of normative reference values specific to the demographic characteristics of participants (percent predicted) in a cohort of subjects that was longitudinally assessed before lung transplantation (Pre), immediately after hospital discharge (Post), and 3 months (3-m post) and 12 months (1-y post) after lung transplantation. One part of the cohort was randomly allocated to receive a supervised exercise training program during the first 3 months following hospital discharge (training); the other group (control) received usual care. Error bars denote standard error. * Statistical significance. Data from Reference 86.

Rehabilitation

There is limited literature to guide decision making regarding rehabilitation during the immediate post-transplant period. However, general principles regarding treatment in postoperative patients admitted to an ICU, including active lower-limb resistance training and early active muscle training, are likely to be of benefit.⁶⁰

There have been 2 controlled studies in adults that assessed the impact of rehabilitation in the first year following hospital discharge. Langer et al⁸⁷ compared 18 subjects who received 12 weeks of high-intensity, symptom-guided, lower-limb endurance and resistance training starting immediately after hospital discharge with 16 subjects receiving standard medical care. Subjects in the treatment group had higher peak work rate during a maximal incremental cardiopulmonary cycle exercise test, longer 6-min walk distance, increased quadriceps strength, and greater participation in daily physical activity compared with controls (Fig. 4). A second study found improved lumbar bone mineral density in 8 adult subjects receiving a supervised 6-month lumbar extension exercise training program beginning 8 weeks after discharge compared with 8 control subjects receiving usual care.⁸⁸

One study involving children found improvements in 6-min walk distance distances at 3 months and at 1 y in pediatric heart and lung transplant recipients who participated in an exercise program 3 times/week after transplant.⁸⁹ The authors acknowledge the limitation of their decision to not include a control group in this study because it was performed in the context of an existing pro-

gram. Optimal strategies for rehabilitation after lung transplantation remain to be identified.

Monitoring

Once discharged from the transplant hospitalization, patients are monitored closely in the out-patient environment. In the author's center, patients are seen twice weekly with laboratory evaluation and spirometry for at least a month post-transplant and then once weekly until the 3-month time point. Patients are provided with home spirometry equipment (typically a handheld spirometer) and pulse oximetry and expected to monitor these daily in the early months post-transplant. Patients return for evaluation and surveillance biopsy every 3 months for the first year and then at 18 months and 2 y. Patients return for evaluation with biopsy based on clinical indications every 6 months thereafter.

Outcomes and Risk Factors

Survival

The most recent ISHLT registry report (for patients transplanted between January 1990 and June 2013) demonstrated survival after pediatric lung transplantation comparable with that in adults. Median survivals were 5.3 and 5.6 y, respectively ($P = .14$).⁷ Although 5-y survival rates for pediatric recipients have demonstrated statistically significant improvement from 42.3% in the early era (1988–1999) to 56.4% in the recent era (2008–2013) when half-life conditional on survival to 1 y is examined, no significant difference is seen when comparing eras. This observation suggests that early mortality improvements are primarily responsible for the era effect. Although survival curves continue to demonstrate the poorest overall survival in adolescents, including curves conditional on survival to 1 y, in contrast to prior reports,⁹⁰ the differences do not reach statistical significance in the most recent report (Fig. 5).⁷

Retransplantation has become a more frequent occurrence since the implementation of the Lung Allocation System,^{25,91} probably as a result of shortened waiting times for children age 12 y and older and improved survival in the recent era.⁹² Nonetheless, a recent registry report suggests caution, with poor (36%) 5-y survival.⁹¹ Appropriate candidate selection for retransplant will remain an important area for investigation.

Causes of Death

Causes of death are time-dependent. The most recent ISHLT report shows that graft failure (including technical failure) is the most common cause of death in the first

30 d, followed by “cardiovascular” and “other.” From 30 d to 1 y, infection is the primary cause of death, followed by graft failure and multiple-organ failure. Beyond 1 y, chronic allograft dysfunction (denoted as bronchiolitis) accounts for roughly 40% of deaths, followed by graft failure and infection.⁷ The distribution of death causes has not changed substantially over the course of time, reinforcing the importance of developing effective therapies for chronic lung allograft dysfunction.

Factors with increased risk for 5-y mortality include earlier transplant era, mechanical ventilation at the time of transplant, and diagnosis of CF.⁷ The significance of mechanical ventilation as a risk factor is less clear in infants.⁶⁹

Adolescence

The observation that outcomes in adolescents are poorer than those in younger children is consistent with prior reports and is observed across all transplanted organs.⁹³ Postulated risks include risk-taking behavior, including non-adherence with medical therapy, leading to an increased incidence of late acute rejection, graft failure, and mortality.^{94,95} Issues related to adherence in adolescence may be magnified during care transitions. Adding a new care environment and often a new insurance provider onto the existing challenges of adolescence may lead to poor medical outcomes.⁹⁶ Successful transition depends on effective communication between the pediatric and adult care providers.^{97,98} Given current adolescent outcomes, it is clear that transition and adherence remain important areas for active study in pediatric transplantation.^{99,100}

Complications

Lung transplant complications occur in 3 general phases. Immediately post-transplant, the primary complications are technical surgical issues and problems arising from the condition of the recipient or the allograft at the time of implantation. In addition to persistent surgical complications, the early phase (1–3 months) is dominated by issues related to the immune response to the allograft, mechanical complications related to the surgical procedure, and adverse effects of immunosuppression (particularly infection). The latter issues continue during in the late phase (beyond 3 months) and also include chronic complications related to the immune response, such as obliterative bronchiolitis and immunosuppression (ie, malignancy).

The depth and breadth of lung allograft rejection is the most important reason that long-term lung transplant outcomes are worse than those of other solid organ transplant recipients. Postulated mechanisms include the lung allograft providing a larger number of antigen-presenting cells that reside in the pulmonary vasculature and lymphatic

Fig. 5. A: Comparison of pediatric lung transplant survival between different age groups. B: Comparison of pediatric lung transplant survival between different age groups conditional on recipient survival to 1 y. Based on data reported to the International Society for Heart and Lung Transplant registry from January 1990 to June 2013. From Reference 7, with permission.

system; the fact that the airways and lung parenchyma are continuously exposed to environmental irritants, toxins, and pathogens; and the fact that the efficacy of the adaptive immune response is enhanced by virtue of the lungs receiving the entire cardiac output.¹⁰¹

Immediate Post-Transplant Phase

Because most pediatric lung transplant procedures are performed during cardiopulmonary bypass or ECMO, bleeding in the thoracic cavity or at the vascular anastomoses is not uncommon, especially in patients who have had prior thoracotomy or pleurodesis.¹⁰² Vascular anasto-

mot complications may become apparent due to hypotension and/or radiographic abnormalities. The left atrial anastomosis or the pulmonary veins may be a site of thrombus formation.¹⁰³ Perfusion scintigraphy and echocardiography immediately post-transplant are often used to evaluate the patency of the vascular anastomoses.

Flexible bronchoscopy may be used in the immediate post-transplant period to assess the integrity of the airway anastomosis and to obtain cultures. Dehiscence at the bronchial anastomoses, although rare since the development of techniques to cover the anastomosis with vascularized tissue, may require an urgent return to the operating room.^{81,104,105}

Hyperacute rejection, caused by preformed recipient antibodies binding to donor human leukocyte antigen (HLA) molecules on the vascular endothelium, is a rare, potentially catastrophic complication that can occur within hours of transplant. Hyperacute rejection leads to vascular damage, obstruction, and severe graft ischemia. Hyperacute rejection is preventable by performing a crossmatch with donor cells and recipient serum before transplant,¹⁰⁶ but because the logistics of organ allocation (including distance between donor and recipient) generally preclude prospective crossmatching, screening the recipient for anti-HLA antibodies and avoiding donors with related antigens (“virtual crossmatching”) is the most commonly used approach to prevent hyperacute rejection. In cases where virtual crossmatch does not effectively predict the true crossmatch, treatment involves early initiation of plasmapheresis.

Primary graft dysfunction is the most common complication seen during the first post-transplant week.^{107,108} Primary graft dysfunction with incidence related to the duration of ischemia before implantation, is thought to be caused by generation of hydroxyl radicals and pro-inflammatory cytokines accumulating during graft ischemia.¹⁰⁹⁻¹¹¹ Primary graft dysfunction effects may range from mild, non-cardiogenic pulmonary edema to fulminant graft failure with diffuse alveolar damage. Primary graft dysfunction is graded on a scale of 1 to 3 daily for the first 72 h post-transplant based on oxygenation index and the presence of diffuse infiltrates on chest imaging.¹⁰⁸ Primary graft dysfunction therapy is primarily supportive and includes fluid restriction and avoidance of barotrauma.¹¹² Severe cases may benefit from ECMO support.^{113,114} Retransplantation for primary graft dysfunction is associated with poor outcomes.¹¹⁵

Early Phase

Immune Complications

Acute Rejection. Acute rejection is the most common form of allograft rejection, affecting a majority of lung transplant recipients. Acute rejection is most commonly seen during the first 3 months (perhaps related to the half-life of donor-derived dendritic cells delivered with the graft) but can be diagnosed even 2–3 y later.¹⁰¹ Younger transplant recipients (< 3 y of age) appear to have a lower risk for acute rejection than older children or adults.^{6,69,116} Acute rejection mimics pulmonary infection with cough, fever, dyspnea, hypoxemia, and tachypnea. Crackles may be evident on chest auscultation. Chest radiograph may show infiltrates, often perihilar, and spirometry may show an obstructive pattern. During the first 3 months post-transplant, evaluation of this clinical picture would typically include bronchoscopy, bronchoalveolar lavage, and transbronchial biopsy to evaluate for both infection and acute rejection. Findings on histology include perivascular

lymphocytic infiltrates with or without airway inflammation and are graded A1 to A4 according to the ISHLT grading system.¹¹⁷⁻¹¹⁹ Because acute rejection may also be asymptomatic, many transplant centers perform surveillance bronchoscopy during the first 12–18 months. The use of surveillance biopsies during the first post-transplant year is supported by data suggesting that a single episode of minimal acute rejection (A1), typically asymptomatic, is an independent risk factor for chronic allograft rejection.^{120,121} However, this finding was not confirmed in a multi-center analysis of pediatric lung transplant recipients.¹²²

Acute rejection grade A2 and above is typically treated with 10 mg/kg intravenous methylprednisolone daily for 3 d and repeat biopsies 2 weeks later. When acute rejection persists on follow-up biopsies, augmented immunosuppression with antithymocyte globulin may be used, especially if the acute rejection grade is increased.

Humoral Rejection. A less common and more recently recognized immunologic complication of lung transplantation is antibody-mediated rejection. Antibody-mediated rejection may appear similar to both infection and acute rejection; patients may have dyspnea, pulmonary infiltrates, and decreased lung function. Specific criteria for diagnosis remain somewhat elusive. The presence of circulating donor-specific HLA antibodies (identified using solid-phase flow cytometry techniques), alveolar capillary complement deposition, and capillaritis in the setting of allograft dysfunction is generally sufficient evidence,¹²³ although a 2012 ISHLT consensus statement includes a much broader set of histologic findings felt to be consistent with antibody-mediated rejection (including all other types of rejection) if in addition donor-specific HLA antibodies are present and capillary complement deposition positivity is present in > 50% of interstitial capillaries.¹²⁴

There is no consensus on treatment of humoral rejection. Pulse steroids, plasmapheresis, intravenous immunoglobulin, and B-cell-directed therapy (cytoxan or rituximab) are used, often in combination.¹²⁵ The proteasome inhibitor bortezomib (which targets plasma cells) and the complement inhibitor eculizumab are also considered in the treatment of antibody-mediated rejection.^{126,127}

Airway Clearance

Airway clearance following lung transplantation can be affected by airway structural changes, direct or indirect effects on respiratory system innervation, and medication adverse effects. Although the native lung has a dual blood supply (pulmonary and bronchial arteries), in most cases, the bronchial arteries are not reconnected following transplant. For this reason, the airway anastomoses are particularly vulnerable to ischemia. Although transplant surgeons try to improve the blood supply by covering the

anastomosis with pericardial or peribronchial lymphatic tissue from the donor and recipient, this area remains particularly vulnerable in the immediate post-transplant period to sloughing and resultant impairment of mucus clearance. Some centers advocate for bronchial artery reanastomosis to reduce this effect. In a single-center study, anastomosis problems were reduced compared with conventional therapy.¹²⁸

Other complications that can occur at the site of the airway anastomoses include dehiscence, which has fortunately has become rare since the development of techniques to cover the anastomosis with vascularized tissue^{81,104,105}; fibrotic strictures; excessive granulation tissue; or airway collapse at the site of the anastomosis. All of these can impair mucus clearance at that level. Despite the smaller size of pediatric airways, airway complications occur at a frequency comparable with that seen in adult lung transplant recipients.^{129,130} Postulated mechanisms to explain the development of anastomotic narrowing include donor airway ischemia, impaired airway healing, and barotrauma in instances where recipients require prolonged mechanical ventilation.¹²⁹ When stenosis of the airway lumen leads to significant air-flow obstruction or recurrent infections, it may be treated with bronchoscopic balloon dilatation or stent placement, although the latter is often fraught with complications, including recurrent granulation tissue, mucus plugging, and inadvertent dislodgement. Metallic expandable stents are generally avoided in children because of the formation of granulation tissue and limited potential for expansion to accommodate growth and significant potential for complication during removal.¹³¹ Silicone rubber stents may be used in children but are more easily dislodged or obstructed with mucus.¹³⁰ More recently, biodegradable stents have been developed that are retained long enough to allow resolution of stenosis but subsequently disappear, allowing for airway growth.¹³²

Other surgical complications include phrenic or recurrent laryngeal nerve injury, leading to diaphragmatic or vocal cord dysfunction, respectively. Both can impair mucus clearance through alteration in pulmonary mechanics. These may resolve over time, but for hemidiaphragm paresis with recurrent pneumonia, plication of the affected diaphragm may be considered.

Mucus clearance can also be impaired as a result of poor cough as a result of multiple factors. The afferent and efferent innervation of the lungs is disrupted at the time of transplant, leading to impairment of the cough reflex. Although it was initially thought that reinnervation does not occur, a 2012 study suggests otherwise.¹³³ Pain in the immediate postoperative period can further impair cough. Finally, injury of the phrenic nerves or recurrent laryngeal nerve may occur during the surgical dissection, causing

diaphragmatic or vocal cord dysfunction. Persistent diaphragm paresis may require plication.

Finally, even well after effective healing of the airway mucosa, there is evidence that lung transplant continues to result in impaired mucociliary clearance.¹³⁴ This may be due in part to diminished ciliary beat frequency^{135,136} or other epithelial abnormalities, perhaps an adverse effect of immunosuppressant drugs. The calcineurin inhibitors and cell cycle inhibitors commonly used in lung transplant recipients have been shown to diminish ciliary beat frequency in animal studies. Although these effects may diminish as calcineurin inhibitor dose is decreased in the months following transplant, one small study has suggested that albuterol may mitigate these effects.¹³⁷

Although many patients benefit from institution of airway clearance measures following transplantation, there have been no studies to identify optimal mucus clearance strategies to be used after lung transplantation. At the author's center, patients with CF are generally counseled to continue airway clearance measures they used before transplant (eg, chest physiotherapy, oscillatory PEP, high-frequency chest-wall oscillation, intermittent percussive ventilation) to manage symptoms with plans to wean as the airways heal post-transplant. Non-CF patients have airway clearance prescribed based on post-transplant symptoms.

Infection. Infection poses a risk for lung transplant recipients immediately after transplant throughout the life of the graft. Nonetheless, the incidence of infection is highest in the first weeks to months after transplant. Contributing factors include the risk of nosocomial infection associated with surgery and ventilator support; immunosuppression (highest in the first few months post-transplant); infections present in the donor at the time of procurement; and disruption of pulmonary lymphatics, leading to impaired trafficking of immune effector cells to regional lymph nodes.¹³⁸ In addition, as noted above, disruption of afferent and efferent lung innervation leading to diminished cough response, airway injury at the time of procurement, interruption of the normal mucociliary ladder at the level of the airway anastomoses add to the risk of infection. Although prophylactic antibiotics are commonly given in the perioperative period, recipient colonization (particularly in patients with CF) and donor infection, including unsuspected viral infection, may lead to early morbidity. Early viral infection is more common and significant in infants and toddlers, perhaps due to immaturity of their immune system.¹² Patients with CF may develop bacteremia due to seeding of the blood or mediastinum with airway flora during explantation. Although in the past, pre-transplant sinus surgery and irrigation was performed because of concern that chronic sinus disease would infect the allograft,^{139,140} a retrospective analysis of sinus surgery in

subjects with CF undergoing transplant did not demonstrate survival benefit.¹⁴¹

Beyond the first week, infections with community and nosocomial bacteria as well as opportunistic pathogens, such as pneumocystis, *Candida*, and cytomegalovirus, become more prevalent. Patients mismatched for cytomegalovirus (ie, donor positive, recipient negative) are at particular risk for cytomegalovirus disease during this early phase.

Cytomegalovirus may present with a viral syndrome including fever and leukopenia or significant pneumonitis and viremia and gastrointestinal tract involvement. Cytomegalovirus pneumonitis may include cough, fever, chills, respiratory distress, crackles, and diffuse interstitial infiltrates. Systemic cytomegalovirus is diagnosed through identification in the bloodstream (typically with polymerase chain reaction). Cytomegalovirus pneumonitis is diagnosed by the positive cytomegalovirus immunohistochemistry on transbronchial biopsy or lung biopsy coupled with clinical findings. Bronchoalveolar lavage (BAL) positive for cytomegalovirus polymerase chain reaction is not uncommon in asymptomatic patients and is felt to be related to viral shedding. Treatment of systemic cytomegalovirus or cytomegalovirus pneumonitis typically involves the use of intravenous ganciclovir for 2–6 weeks. Cytomegalovirus hyperimmune globulin may also be added, particularly in severe cases. After completion of intravenous treatment, oral valganciclovir prophylaxis may be administered for 2–3 months. Although before the availability of ganciclovir, mismatched recipients had a 75% or higher incidence of cytomegalovirus in the first 6 months after transplant,¹⁴² current prophylaxis and treatment strategies have reduced the incidence of cytomegalovirus pneumonitis and limited its significance as a risk factor for chronic rejection.^{143,144}

Similar to cytomegalovirus, effective prophylaxis with trimethoprim/sulfamethoxazole generally prevents the development of *P. jirovecii* (*carinii*) pneumonia. Nonetheless, patients with acute onset of fever, respiratory distress, interstitial infiltrates, and hypoxemia out of proportion to radiographic disease should prompt the consideration of *P. jirovecii* pneumonia. Diagnosis is made by identifying organisms with silver or fluorescent staining of BAL specimens. *P. jirovecii* pneumonia is treated with intravenous trimethoprim/sulfamethoxazole. Although inhaled pentamidine was commonly used as an alternative to trimethoprim/sulfamethoxazole in the past, the availability of prophylaxis alternatives in patients with allergy, such as atovaquone, and the availability of intravenous pentamidine for treatment have reduced the use of inhaled pentamidine.

Respiratory viral infections, as alluded to above, are particularly problematic in young children. Increased exposure from daycare, school, and siblings as well as less well-developed immunity may contribute to this finding.

Adenovirus¹⁴⁵ and paramyxoviruses, including parainfluenza and respiratory syncytial virus, have all been associated with significant lung injury or mortality^{146,147} and are risk factors for the development of chronic allograft dysfunction.¹⁴⁸ For these reasons, viral infections are often aggressively treated with cidofovir and ribavirin as indicated.^{147,149,150}

Finally, infections with fungal organisms and atypical mycobacteria also pose significant risk for post-transplant infection.^{151,152} Many centers use fungal prophylaxis in the immediate post-transplant period.⁸⁶ Currently recommended prophylactic strategies include voriconazole intravenously or orally given for 4–6 months, inhaled amphotericin B liposomal 3 times weekly for 2 months and then once weekly, or daily inhaled amphotericin B standard formulation.¹⁵³

Surgical Complications and Medication Adverse Effects.

There are many non-pulmonary complications that become apparent in the early post-transplant phase. These include gastrointestinal dysmotility and/or gastroparesis, which occurs with an incidence of up to 50%.¹⁵⁴ Supraventricular arrhythmias, including supraventricular tachycardia, atrial flutter, and atrial fibrillation, associated with the left-atrial cuff suture line are not uncommon. Typically, these arrhythmias are not associated with hemodynamic compromise, respond to conventional therapy, and are self-limited.¹⁵⁵ There are a multitude of adverse effects related to the immunosuppression regimen. Calcineurin inhibitors cause hypertension and nephrotoxicity¹⁵⁶ Calcineurin inhibitors are also associated with neurologic symptoms ranging from headache and sleep disturbance to seizures and posterior reversible encephalopathy syndrome.^{157,158} Diabetes, particularly in patients with CF and perhaps precipitated by the use of tacrolimus, is present in > 35% of long survivors of lung transplantation.^{90,159} Cell cycle inhibitors lead to leukopenia, and adverse effects of systemic corticosteroids include hypertension, cataracts, osteoporosis, and insulin resistance.

Late Phase

In addition to the persistence of early-phase complications, including infection, drug toxicity, acute cellular and humoral rejection, and airway anastomotic narrowing, the primary complications appearing in the late phase include post-transplant lymphoproliferative disease and bronchiolitis obliterans, 2 potentially life-threatening complications.

Post-Transplant Lymphoproliferative Disease. The incidence of malignancy after lung transplantation is 5.6% at 1 y and 11.2% at 5 y. The vast majority of malignancies are post-transplant lymphoproliferative disease.⁹⁰ Post-

transplant lymphoproliferative disease is typically an Epstein-Barr virus-driven lymphoma.^{160,161}

Diagnosis of post-transplant lymphoproliferative disease requires a high index of suspicion because presenting symptoms are often vague and mimic other disease processes. Post-transplant lymphoproliferative disease can be asymptomatic or can present with symptoms suggestive of pulmonary infection or with nonspecific symptoms, particularly if involving extrapulmonary organs. Post-transplant lymphoproliferative disease typically involves the allograft during the first year,¹⁶² presenting with one or more round or ovoid pulmonary nodules.¹⁶³ Beyond the first year, extrapulmonary post-transplant lymphoproliferative disease may involve the gastrointestinal tract, the skin, and lymphatic tissue, including the nasopharynx.^{164,165} Screening for post-transplant lymphoproliferative disease involves serial, quantitative polymerase-chain-reaction measurements of Epstein-Barr virus.¹⁶⁶ Although the presence of elevated Epstein-Barr virus as measured by polymerase chain reaction may be treated with reduced immunosuppression,¹⁶⁷ caution with this approach is recommended in children.¹⁶⁸ Alternatively, additional testing with positron emission tomography may be useful as a sensitive and specific test for post-transplant lymphoproliferative disease.¹⁶⁹ Once identified, histologic diagnosis and staging are important components of the diagnostic and prognostic process. Monomorphous post-transplant lymphoproliferative disease has a worse prognosis.¹⁷⁰ In the current era, patients with CD20-positive post-transplant lymphoproliferative disease are treated according to the Children's Oncology Group protocol ANHL 0221 (including Rituximab, an anti-CD20 monoclonal antibody shown to be effective in non-Hodgkin's lymphoma, low-dose cytoxan, and prednisone).¹⁷¹

Chronic Lung Allograft Dysfunction and Obliterative Bronchiolitis. Long-term survival rates in lung transplantation are worse than for other solid organ transplants. Five-year survival in lung transplant recipients is < 60% compared with > 70% in heart and liver and > 80% in kidney transplant recipients.¹⁷²⁻¹⁷⁵ The main reason for this disparity is chronic graft failure, most commonly due to obliterative bronchiolitis or bronchiolitis obliterans syndrome.^{176,177} Obliterative bronchiolitis is the leading cause of death after the first year post-transplant. In children, only 40% of survivors are free of bronchiolitis obliterans at 6 y.⁹⁰ First recognized as a primary cause of death in lung transplant recipients, nearly 30 y ago, the etiology of obliterative bronchiolitis remains elusive, and no uniformly effective treatment options exist.¹⁷⁸

Obliterative bronchiolitis is primarily a histologic diagnosis in the context of irreversible obstructive graft dysfunction. Generally, plain chest imaging is unrevealing in these cases. CT imaging may reveal bronchiectasis and air

Table 4. Classification of Bronchiolitis Obliterans Syndrome

Bronchiolitis Obliterans Syndrome Grade	Pulmonary Function Measurements
0	FEV ₁ > 90% of baseline and FEF _{25-75%} > 75% of baseline
0-p	FEV ₁ = 81-90% of baseline and/or FEF _{25-75%} < 75% of baseline
1	FEV ₁ = 66-80% of baseline
2	FEV ₁ = 51-65% of baseline
3	FEV ₁ ≤ 50% of baseline

Data from Reference 177.
FEF_{25-75%} = forced expiratory flow during the middle half of the FVC maneuver

trapping on high-resolution computed tomography,¹⁷⁹ and ventilation imaging may reveal xenon retention.¹⁸⁰ Fibroproliferative obliteration of small airways, dense eosinophilic sub-mucosal fibrosis in the bronchioles, and partial (concentric or eccentric) or complete luminal occlusion are seen on lung biopsy. Destruction of the airway wall and surrounding smooth muscle may also be present.¹¹⁹ ISHLT pathologic grading schemes originally distinguished between sub-total and total¹¹⁵ and active versus inactive¹¹⁸ forms. However, the current ISHLT grading defines only C0 (no evidence of obliterative bronchiolitis) or C1 (obliterative bronchiolitis present).¹¹⁹ Exclusion of obliterative bronchiolitis by transbronchial biopsy is not possible because obliterative bronchiolitis does not affect all small airways. Diagnosis can even be missed on open lung biopsy. In our experience, obliterative bronchiolitis sometimes presents with alveolar hyperinflation, suggesting the presence of upstream obstruction. For these reasons, a clinical correlate, bronchiolitis obliterans syndrome, was proposed in 1993.^{176,177} A bronchiolitis obliterans syndrome grade of ≥ 1 (reflecting a decline in FEV₁ > 20% from the post-transplant best) is treated as if obliterative bronchiolitis is present (Table 4).

Over the past few years, it has become apparent that the classic obliterative bronchiolitis picture of chronic graft failure is part of a broader spectrum of chronic lung allograft dysfunction, characterized by a loss of lung function (FEV₁) from the best post-transplant baseline.¹⁸¹ It is now known that a subset (approximately 30%) of chronic lung allograft dysfunction patients, typically with BAL neutrophilia, will have improvement in FEV₁ following administration of a macrolide, such as azithromycin.¹⁸² These patients are typically referred to as having "neutrophilic-reversible allograft dysfunction" or "azithromycin-responsive allograft dysfunction." Another subset (approximately 30%) of chronic lung allograft dysfunction patients may develop a restrictive pulmonary function abnormality, denoted "restrictive allograft syndrome"¹⁸³ associated with persistent infiltrates on chest imaging, subpleural thicken-

ing on CT, and pleuroparenchymal fibroelastosis and obliterative bronchiolitis on histopathology. Although uniformly accepted pulmonary function criteria are yet to be established, typically, patients with a persistent decrease in FVC or total lung capacity associated with chronic pulmonary infiltrates are considered to have restrictive allograft syndrome. Patients with restrictive allograft syndrome typically have a shorter survival (6–18 months) compared with 3–5 y for patients with bronchiolitis obliterans syndrome.^{183,184}

Because patients with azithromycin-responsive allograft dysfunction often develop bronchiolitis obliterans syndrome or restrictive allograft syndrome and patients with restrictive allograft syndrome generally have histologic findings consistent with obliterative bronchiolitis/bronchiolitis obliterans syndrome, it is likely that these entities represent different manifestations of a single common pathologic pathway involving aberrant injury/repair mechanisms of the lung parenchyma and supporting vasculature.

There have been many studies seeking to identify risk factors for the development of chronic lung allograft dysfunction. A comprehensive review of single-center studies of obliterative bronchiolitis/bronchiolitis obliterans syndrome found that acute rejection episodes occurring > 3 months post-transplant and lymphocytic bronchitis/bronchiolitis, especially > 6 months post-transplant, were the most consistent risk factors.¹⁸⁵ Although cytomegalovirus was associated with the development of obliterative bronchiolitis/bronchiolitis obliterans syndrome before the wide availability of ganciclovir, it has not been a consistent risk factor in contemporary studies.^{142,143} Single-center analyses have identified anti HLA antibodies^{186,187} as well as α tubulin and collagen V autoantibodies as risk factors^{188,189} Early expression of HLA-G in the allograft is associated with stable graft function.¹⁹⁰ In contrast, the presence of soluble HLA-G in BAL fluid is associated with bronchiolitis obliterans syndrome.¹⁹¹ Airway injury as a result of gastroesophageal reflux is also considered a risk factor. Fundoplication reduced the incidence of obliterative bronchiolitis/bronchiolitis obliterans syndrome in a single-center study.^{192,193} Community-acquired respiratory viruses, including paramyxoviruses, influenza, and adenovirus, have been implicated in obliterative bronchiolitis/bronchiolitis obliterans syndrome.^{194,195}

Another previously described entity is acute fibrinoid-organizing pneumonia. Patients present acute or semi-acute onset of nonobstructive pulmonary function defects and bilateral ground-glass infiltrate associated with interlobular septal thickening, consolidation, or peripheral fibrosis. Histologically, acute fibrinoid-organizing pneumonia is characterized by peribronchiolar and alveolar fibrin deposition with minimal associated inflammation.^{196–198} Given the similarities with restrictive allograft syndrome, it is

suspected that acute fibrinoid-organizing pneumonia may represent a precursor or more fulminant form of restrictive allograft syndrome.¹⁹⁹

Infants and toddlers⁶⁹ and children who have received living related lobar transplantation^{200,201} have a reduced risk of obliterative bronchiolitis/bronchiolitis obliterans syndrome. In contrast, immunosuppression non-adherence is a significant risk factor for obliterative bronchiolitis/bronchiolitis obliterans syndrome.²⁰²

Studies seeking to correlate risk factors to underlying physiologic mechanisms have implicated interleukin-17⁺ T cell-mediated interleukin-8/CXCL-8-induced neutrophilic airway inflammation in azithromycin-responsive allograft dysfunction and lymphocytic bronchitis.^{203,204} Genetic studies have implicated several polymorphisms, primarily affecting the innate immune system, in the development of bronchiolitis obliterans syndrome.^{205–208} Patterns of cytokine, chemokine, and growth factor expression appear to be different in bronchiolitis obliterans syndrome and restrictive allograft syndrome, suggesting differing underlying mechanisms. Restrictive allograft syndrome is associated with distinct expression patterns of alveolar alarmins, increased BAL eosinophils, interleukin-6 and interferon γ -inducible protein 10/chemokine ligand 10, and interferon-inducible T cell α chemokine/CXCL11.^{209,210} In contrast, patients with bronchiolitis obliterans syndrome have increased BAL neutrophils, defensins, tissue inhibitor of metalloproteinase-1 and -2, and total matrix metalloproteinase-2/3/7/8/9.^{211–213} Despite these findings, none of the identified biomarkers are sufficiently specific to provide a clear chronic lung allograft dysfunction diagnosis.¹⁹⁹ Bronchiolitis obliterans syndrome has also been associated with profibrotic cytokines, such as transforming growth factor β ²¹⁴ or platelet-derived growth factor.²¹⁵

Treatment of chronic lung allograft dysfunction is difficult. Approximately 30% of patients presenting with obstructive chronic lung allograft dysfunction respond to azithromycin.²¹⁶ Those who do not respond generally receive altered or augmented immunosuppression as an initial treatment. Changing from cyclosporin A to tacrolimus may be beneficial (although most pediatric centers no longer use cyclosporin A as the primary calcineurin inhibitor).²¹⁷ Agents such as antithymocyte globulin or OKT3 may be effective adjunctive therapy in some patients.²¹⁸ Cyclophosphamide,²¹⁹ methotrexate,²²⁰ and total lymphoid irradiation²²¹ have been beneficial in some patients. More recently, treatment with photopheresis has emerged as an important second-line therapy,^{222–224} although this may be more beneficial when initiated early and in patients with bronchiolitis obliterans syndrome as opposed to restrictive allograft syndrome.^{223–228} Nonetheless, disease progression may occur, often complicated by or worsened by infection.

Retransplantation is generally presented as an option in patients with progressive decline in lung function and no other contraindications, particularly in the Lung Allocation System era of reduced waiting time.²⁵ Nonetheless, this approach must be tempered by data suggesting that adult patients undergoing retransplantation for restrictive allograft syndrome have worse outcome than those with bronchiolitis obliterans syndrome (3-y survival of 34% compared with 68%).²²⁹

Summary

In summary, pediatric lung transplant is a viable option for treatment of end-stage lung disease in children. However, long-term success is limited by limited availability of donor organs, debilitation as a result of chronic disease, complications leading to impaired mucus clearance and increased risk for infection, and, most importantly, chronic lung allograft dysfunction. Opportunities for investigation and innovation remain in all of these domains, including using ex vivo lung perfusion to increase the lung donor pool, using extracorporeal support strategies coupled with effective rehabilitation to effectively bridge patients to transplant, clarifying the benefit of airway clearance techniques in lung transplant recipients, and, most importantly, efforts toward understanding the underlying mechanisms of and developing effective therapies to prevent or treat the many presentations of chronic lung allograft dysfunction.

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Discussion

Berlinski: I'll ask you a politically incorrect question. It takes a lot of time to acquire the expertise to do pediatric lung transplants and you know that there are many centers in the country that probably do one lung transplant per year. Wouldn't it make more sense to have a national approach, to zone the country and designate centers of excellence to do a fair number of transplants so the outcomes might be better? This way the distribution of the donor pool might also be improved.

Sweet: Thank you Ariel, that's a really important question. I think the short answer to that question is of

course. The data when you look at it really support the concept that experience equals outcome in organ transplantation. But if you take a step back from that and ask the question can it be effective? We don't have the infrastructure yet in place to make it effective across the board. So, in addition to saying "OK we are going to designate a handful of centers regionally that are going to be the expert centers for lung transplantation," then we have to break down the barriers to get patients to those centers. Right now those barriers prevent a subset of the patients who don't have the resources or the psychosocial support system from relocating from their home to these transplant centers to wait the 1, 3, or

6 months for organs and then to stay at the transplant center for upwards of 3 months or longer, depending on how their course goes, before they go back to their home environment. I am a complete advocate of that, but it means we'd have to change our reimbursement approach and our approach of supporting families and children through the pre- and post-transplant period so that we don't create inequity in access by doing it.

Panitch: It seems that you have to take that a step further, because after the transplant, unless everyone sends the patients back to your center for follow-up, you'd have to be able to disseminate expertise for good, close

follow-up out into the community. Would you comment on that?

Sweet: The model we use for follow-up has been to bring patients back from wherever they are. In our experience, we have transplanted patients in Australia or the Middle East and other places, and the follow-up can be a challenge. We've tried to develop relationships with local providers and local pulmonologists, but we really rely on bringing patients back to our center for reevaluation intermittently: every 3 months in the first year after transplant, every 6 months afterwards. It's a struggle for me to get the patients who are 5 or 6 y out to come back every 6 months, but I think it's important.

Panitch: But if there are issues that occur in the interim, I would assume you'd want someone local who could at least identify and temporize the situation until the patient can get back to the center.

Sweet: Right. In today's world, phones with video instant access can help with that, but you're right, one of the things that's critical for us when we transplant a patient is to identify the local pulmonologist who's going to be our partner in the immediate identification of problems, stratifying issues, and deciding what expertise is available there. We generally don't want the local pulmonologist doing biopsies, not because they're aren't capable of doing it, but because the infrastructure to actually process the biopsies and read them may not be there. So it is a partnership. You're absolutely right, you can't ignore that component of the process.

Stokes: Stuart, that was a great talk. One of the things we struggle with is the timing of when to refer patients, and my philosophy has always been to refer earlier. If somebody goes to see you and you say come back in a year, that's still good, because the family knows how to get to St Louis and

has been in to see you, but is that a good use of your time to get those patients early, or do you feel like you are getting patients referred appropriately or too soon? Can you speak to that?

Sweet: That's a great point, Dennis. It's been a bit more challenging, and I didn't talk about the Lung Allocation System, but 10-15 years ago, the allocation of lungs in the United States was strictly based on waiting time. So basically, if you wanted to transplant a pediatric lung transplant candidate, you had to get them at least a year or more before they were ready for transplant, or they were likely to die on the waiting list. You had to accumulate enough time on the list to get organ offers. That has changed. In the Lung Allocation System, now patients 12 y and older can get organs relatively quickly, and that has changed the dynamics of referral a little bit. But I agree with you, having us get to know a patient longer before they actually need to be transplanted allows for assimilation of all the information I just provided to you. The family has to fully understand the implications and the outcomes. It gives them the opportunity to engage in rehabilitation; it gives them the opportunity to address any comorbid factors that are going to play a role in their outcome. I'm a big advocate of seeing patients as soon as transplant comes up in the conversation and it's a serious conversation rather than waiting until it's time to relocate to St Louis, because if you wait that long, you miss the opportunity to address those other things.

Panitch: Sometimes patients with chronic lung diseases don't grow very well, and as they approach late adolescence, we have small patients. When size is a factor, what serves the patient better: to refer to the pediatric lung transplant program or to the adult lung transplant program when they're very small people?

Sweet: I would turn the question around and say what does the patient need? The way the allocation system works doesn't discriminate based on size in that window, in the 18–20-y-old patient. You don't lose access dramatically to the adolescent organs; you lose some, but it's not going to be mitigated by being in a pediatric center versus an adult center. Basically, the way the allocation system works is it's not dependent on where you are; it's what your age is. It boils down to what expertise is needed to care for that patient. Ten years ago, I would have said a patient who has chronic lung disease, an 18- or 19-y-old CF patient who's never really been free of their parents and hasn't really developed independence, is probably a bit emotionally behind. And that patient is probably best served in a pediatric center where the care will be a family-centered care model. I would like to think that our adult colleagues, especially our adult CF center colleagues, have begun to recognize the importance of a family-centered approach for patients who aren't fully mature yet. I'd like to think that an adult center would be suitable for them once they hit adulthood, but I think the reality is probably somewhere in between.

Cheifetz: Thank you, Stuart, for a really excellent presentation. I would like to focus on the point of availability of organs for donation and the scarceness of this precious resource. For abdominal organs, one of the approaches, although still somewhat controversial, has been organ donation after cardiac death. Has this approach been considered for lung transplantation? Has it been done? I suspect there are ethical issues and controversies involved, but can you please share your thoughts?

Sweet: The group in Australia has great data¹ on donation after circulatory death. And actually, the outcomes are good. We have just, for better or

for worse, in pediatrics not been able to convince our surgeons to go down that path. The data I showed you from Toronto, if you dig into that paper,² a large number of the organs that they used on their ex vivo lung perfusion circuit were from circulatory death donors. For that there's no ethical barrier, because it's whether the patient is a circulatory death donor, not taking the lungs versus taking the abdominal organs. I completely agree with you, I think it's a huge opportunity for lungs in the United States. I think what we need is the ex vivo lung perfusion technology to become more robust so that people are more comfortable using organs from those donors. The data that are accumulating, particularly in Australia, indicate that with circulatory death donor organs, the outcomes can be as good as or better than with those from brain death. Brain death brings its full set of inflammatory impacts that we probably underrecognize and underappreciate.

Walsh: I have 2 questions. One is about the surgical application of nissen (fundoplication) during transplant. Are you doing that? What's the latest literature to help reduce aspiration?

Sweet: We are not doing fundoplications at the time of transplant. For lots of reasons, but primarily the data that everybody needs a fundoplication are not clear, and the additional time and complications that come with that are not justified by the benefits. The answer is that we're not doing that regularly. The data overall are still very murky as to whether patients benefit from that a priori as opposed to in response to knowledge that there's reflux.

Walsh: And then long-term, do you provide any airway clearance therapies because of their inability sometimes to recognize they need to cough? Is there any type of therapy that we should be recommending for these lung transplant patients?

Sweet: You ask a great question, and that question began to crystallize in my mind as I was looking at these data. The answer right now is that we are not. We tend to wait until we see lots of mucus accumulation in our screening bronchoscopies when we've got recurrent infections. We tend to be more symptom-driven and outcome-driven rather than prophylactic-driven. I think that's an important question that could be answered. If we took a more aggressive approach and if we recognized, as I showed you, that the patients are going to have impairment in their ability to recognize the need to cough, should we be more aggressive, and would that change the long-term outcome? I think that's a really important question.

Walsh: Especially the kids with CF who are used to doing it, can they continue to do those therapies?

Sweet: The reality is that most of those kids are going to be more sensitized to the accumulation of mucus even though they won't have the same sensation in their lungs; they have proximal sensation. Most of those kids are doing mucus clearance even if I don't tell them to specifically.

Stokes: You mentioned azithromycin, but how about inhaled steroids in lung transplant bronchiolitis obliterans?

Sweet: The data supporting the use of that are really thin; nobody has really focused on that. There was a study³ that came out years ago, but it really hasn't caught on in any way, shape, or form. Unfortunately, the approach that's used in bronchiolitis obliterans after bone marrow transplant doesn't translate well to post-lung transplant. And I don't know why; I can't explain it. It may be that the underlying etiology is slightly different, but you would think it would be a common pathway.

Stokes: What do you think is the most sensitive indicator of development; do you use lung function?

Sweet: Yes. At this point that's your best mechanism. The challenge, of course, is in infants and younger children, where we don't do lung function and we're relying more (and I didn't spend time on this) on imaging studies, both high-resolution CT and ventilation perfusion scanning for evidence of air trapping. Those are the other indicators that we use. It's interesting that the literature is now catching up with us in the adult world of using techniques like high-resolution CT to pick up signs of bronchiolitis obliterans.

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