Pediatric Lung Transplantation

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KEYWORDS

• Lung transplantation • Pediatrics • Bronchiolitis obliterans
• Cystic fibrosis • Pulmonary hypertension

HISTORICAL NOTES

Compared with transplantation of other organs, lung transplantation is a young field that continues to grow. Lung transplantation is an important treatment option in children with acquired or congenital lung diseases. The first human lung transplantation was attempted in 1963 by Hardy, as reported in the *New England Journal of Medicine*,[1] but the world's first long-term successful lung transplantation was achieved in Toronto in 1983. Successful heart-lung transplantation and lung transplantation in adults during the early 1980s were followed by the application of lung transplantation in the pediatric population. The first reported pediatric lung transplant occurred in Toronto in 1987 in a 16-year-old boy with familial pulmonary fibrosis,[2] which, along with other early reports of success in children, led to an increased use of this procedure in children.

From 1986 to June 2008, 1278 pediatric lung transplant and 549 heart-lung transplant procedures were reported to the registry of the International Society of Heart & Lung Transplant (ISHLT).[3] The number of lung transplantations performed annually has varied between 20 and 87. In 2007, 93 pediatric lung transplant and 8 heart-lung transplant procedures were reported. To date, this is the highest number of pediatric lung transplants reported in a single year to this registry. According to the 2009 ISHLT Registry report, there are 36 centers worldwide that perform lung transplants in children. These numbers suggest that each center performs 2 to 3 transplants per year on average. In fact, 1 center reported 10 to 19 transplants per year, 3 centers reported 5 to 9 transplants per year, and the remainder performed 4 or fewer procedures annually.

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The overall number of heart-lung transplant procedures has decreased in recent years because of the recognition that isolated lung transplantation or isolated heart transplantation can be used in many conditions once believed to require combined heart-lung transplantation, such as primary pulmonary hypertension (PPH). Even severe right-sided ventricular dysfunction will generally recover when the right ventricle is unloaded after lung transplant. Presently heart-lung transplantation is indicated only in patients with end-stage heart and lung failure or for complex congenital heart and lung disease. Heart-lung transplants are uncommonly performed in North America and are now concentrated in only a few centers. The number of infant lung transplants remains low at less than 10 procedures per year since 1997, with most being performed in the United States. In addition, the number of living donor procedures in pediatric recipients has markedly decreased, with only 3 procedures reported from 2005 to 2007. The numbers of this procedure were highest in 1998 and 1999 when 14 cases were reported per year.[3]

This article describes the current status of pediatric lung transplantation, indications for listing, evaluation of recipient and donor, updates on the operative procedure and graft dysfunction, and the risk factors, outcomes, and future directions.

INDICATIONS FOR LISTING

Lung transplantation in children should be considered in carefully selected patients only. Progressive lung disease or life-threatening pulmonary vascular disease for which there is no further medical therapy are indications for lung transplantation. The indications for transplantation in childhood differ by age group.[4]

A summary of the underlying diagnoses for which lung transplantation may be indicated in children is presented in **Fig. 1**. Most pediatric patients (~60%) receiving a

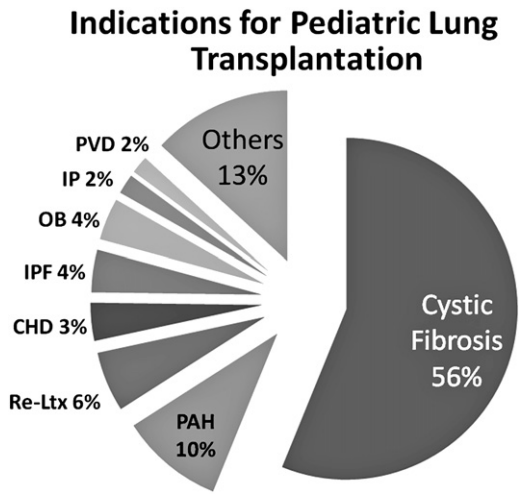

Fig. 1. Indications for pediatric lung transplantation according to the ISHLT Registry data. CHD, congenital heart diseases; IP, interstitial pneumonitis; IPF, idiopathic pulmonary fibrosis; OB, obliterative bronchiolitis (not re-transplant); PAH, pulmonary arterial hypertension; PVD, pulmonary vascular disease; Re-Ltx, repeat lung transplant. (*Data from* Aurora P, Edwards LB, Christie JD, et al. Registry of the international society for heart and lung transplantation: twelfth official pediatric lung and heart/lung transplantation report-2009. J Heart Lung Transplant 2009;28(10):1023–30.)

lung transplant are patients with severe advanced cystic fibrosis (CF) lung disease, although the number of transplants for this indication is decreasing. Other indications within the pediatric age range include pulmonary hypertension, obliterative bronchiolitis (OB; retransplant or nontransplant related), interstitial lung disease, and congenital heart disease. Less common indications in children include Eisenmenger syndrome, pulmonary fibrosis, and bronchiectasis.[3]

Indications for lung transplantation in infants include primary and secondary pulmonary hypertension, congenital heart disease (such as tetralogy of Fallot with absent pulmonary valves), primary pulmonary vascular conditions (pulmonary vein stenosis or alveolar capillary dysplasia), bronchopulmonary dysplasia, and surfactant B deficiency.[5] Infants with other surfactant disorders, such as surfactant protein C deficiency[6] and disorders of the ABCA3 transporter,[7] can also potentially benefit from lung transplantation.

In contrast, most adults are transplanted for chronic obstructive pulmonary disease (COPD) (36%) and idiopathic pulmonary fibrosis (21%), and approximately 16% for CF.[8] According to the American Society of Transplantation consensus statement,[4] regardless of diagnosis, all lung transplant candidates should possess:

1. A clear diagnosis or adequately delineated trajectory of illness despite optimal medical therapy that puts the individual child at risk of dying without a lung transplant
2. An adequate array of family support personnel
3. Adequate access to transplant services and medications after transplantation
4. Adequate evidence of willingness and ability on the part of patient and parent to adhere to the rigorous therapy, daily monitoring, and re-evaluation schedule after transplant.

Contraindications for lung transplantation are similar for adults and children. They include active malignancy, active sepsis, active tuberculosis, severe neuromuscular disease, refractory nonadherence, multiple organ dysfunction, human immunodeficiency virus (HIV), and hepatitis C infection with histologic liver disease. There is also a list of relative contraindications including issues such as chronic airway infection with multiply resistant organisms, mechanical ventilation, and renal insufficiency.[4] This list varies from center to center and will change over time.

In most centers airway colonization with *Burkholderia cepacia* is considered an absolute contraindication, specifically with *Burkholderia cenocepacia* (genomovar III). However, a few centers, such as Toronto, are successfully transplanting CF patients infected with this organism. Several centers reported increased early posttransplant morbidity and mortality due to *B cepacia* in the 1990s[9,10] with genomovar III–positive recipients being at the highest risk.[11,12] However, more recent data show that the risk for poor transplant outcome varies between *Burkholderia* species and this should be taken into account during the assessment of candidates. A recent study in the United States using multivariate Cox survival models to assess hazard ratios of infection with *Burkholderia* species found no significant difference in survival based on *Burkholderia* infection status in CF patients on the waiting list for lung transplantation. However, infection with the nonepidemic strain of *B cenocepacia* resulted in a significantly increased risk of posttransplant mortality compared with uninfected control subjects.[13] It has also been shown that *B cenocepacia* strain E12, which is more common in Canada and the United Kingdom, results in increased mortality in CF patients, with and without lung transplantation.[12,14,15] Patients with *Burkholderia gladioli* were also found to have an increased posttransplant mortality risk, whereas

there was no increased risk for CF patients infected with *Burkholderia multivorans*.[13] This is not to say that poor outcomes have not been reported in patients with *B multivorans*.

The Toronto Group continues to be the center with the largest *B cepacia complex* experience in CF patients in the world and, with the use of a strategy of multiple antibiotic synergy testing, triple antibiotics, and regimens including reduced immunosuppressive drug level targets after transplantation, hopefully it will continue to decrease the post-transplant morbidity and mortality in this high-risk group of lung transplant recipients.

EVALUATION OF RECIPIENT AND DONOR

Evaluation of the Lung Donor

Donors are selected on the basis of medical history, chest radiographs, oxygenation, bronchoscopy findings, and intraoperative evaluation. The ISHLT criteria for ideal lung donors are: age less than 55 years; smoking history of less than 20 pack-years; no chest trauma; duration of mechanical ventilation less than 48 hours; no history of asthma; no history of cancer; negative Gram stain on bronchoalveolar lavage (BAL); arterial partial pressure of oxygen greater than 300 mm Hg on positive end-expiratory pressure of 5 cm H_2O and inspired oxygen 100%; clear chest radiograph; and clear bronchoscopy. It is recognized that few donors meet all these criteria to be defined as ideal and, when these criteria are not met, potential donors are then classified as extended donors.

Several factors may lead to the unsuitability of lungs for transplantation. These include significant pulmonary contusion, pneumonia, pulmonary aspiration, and pulmonary edema.[16] Because many donors sustain severe brain injuries via blunt trauma, chest trauma can lead to pulmonary contusions. Obviously the term ''significant pulmonary contusion'' allows judgment by the transplant surgeon. Fat embolisms can be a complicating factor as reperfusion of the embolized lung may lead to activation of a cascade of inflammation, which can lead to major graft dysfunction early after transplant. A retrograde flush with preservation solution via the pulmonary veins following the initial instillation of preservation solution into the main pulmonary artery can potentially be performed to flush out pulmonary emboli. Protective ventilation strategies are used to recruit collapsed alveoli. Pulmonary edema (neurogenic and other types), often a significant problem in brain-dead donors, can be improved by active fluid management of the multiorgan donor to maintain euvolemia.[16]

The evaluation of donor lungs is standardized. A complete general clinical evaluation of the donor is performed that includes an assessment for blunt trauma, a chest radiograph, and review of the ventilator settings. Flexible bronchoscopy is performed to assess for aspiration and pneumonia, and to acquire a bronchial wash to be sent for microbiology cultures and to evaluate for anatomic abnormalities of the airways. As stated earlier, the ideal donor has a Pao_2/Fio_2 ratio greater than 300 mm Hg and has minimal, if any, lung infiltrates. The lungs, once harvested, are preserved using a standardized protocol using Perfadex cold flush preservation before implantation.

Evaluation of Recipients

The assessment is performed to determine a patient's suitability for lung transplantation and therefore is an in-depth review. There is a standard list of investigations and consultations that needs to be completed.[17] Additional investigations may be added for specific underlying diagnoses or on an individualized basis. For instance, an abdominal ultrasound or a computerized tomography (CT) scan of the sinuses may be added to assess a patient with CF. The assessment includes laboratory tests:

ABO group, hematology and biochemistry, viral serology (HIV, hepatitis B surface antigen/antibody/core antibody, hepatitis C antibody, cytomegalovirus [CMV], Epstein-Barr virus [EBV], varicella, toxoplasma, antibodies to childhood immunizations), urinalysis, sputum cultures including sensitivities/mycobacteria/fungus, tuberculin skin test, measurement of bone mineral density, a chest radiograph, CT scan of chest and neck, quantitative ventilation-perfusion scan, complete pulmonary function tests, 6-minute walk test, electrocardiogram, and cardiac echo. In addition, the assessment should include consultations from the transplant respirologist, transplant surgeon, nurse transplant coordinator, dietician, social worker, pharmacist, anesthetist, psychiatrist, and possibly infectious disease and cardiology consultants.

TRANSPLANT SURGERY

Technically, lung and heart-lung transplant procedures in children are essentially the same as in adults.[18,19] However, there is significantly more frequent use of cardiopulmonary bypass (CPB) in children. Although most adult bilateral lung transplant procedures can be performed as sequential single lung transplants using isolated lung ventilation through a double-lumen endotracheal tube, these tubes are often not available for smaller pediatric sizes, thus most pediatric transplants in younger or smaller children are performed on CPB. In addition, all patients with pulmonary hypertension are usually done on CPB. In the Toronto Program only 44% of transplants are done on CPB, but in the pediatric age group (<18 years), most are done on CPB. The use of CPB is essential in some cases, particularly in pulmonary hypertension and in hemodynamically unstable patients. Disadvantages of using CPB include heparinization with increased risk of bleeding and increased blood product use, coagulopathy, red blood cell trauma, activation of complement, neutrophil activation, and a systemic inflammatory response that may contribute to allograft injury at reperfusion. The use of CPB has been associated with increased risks of bleeding and early graft dysfunction.

Bilateral Lung Transplant

The most common pediatric lung transplant procedure currently performed is the bilateral sequential lung transplant. In this procedure each lung is sequentially implanted separately. The pulmonary artery and veins to that lung are divided. The native lung with the least perfusion is excised first. The bronchial anastomosis is performed first. Usually an end-to-end anastomosis is performed using an absorbable running suture for the membranous wall and interrupted absorbable sutures for the cartilaginous wall (polydioxone suture). Telescoping is done only if the discrepancy is severe. Next, the anastomosis of the main pulmonary artery is completed followed by the atrial anastomosis, which approximates a cuff of donor left atrium surrounding the 2 pulmonary veins to the recipient left atrium. The transplanted lung is then gently reinflated and ventilated. Reperfusion occurs slowly as the pulmonary artery clamp is released gradually over 10-minute period. The procedure is then repeated on the contralateral side. If the donor lungs are larger than required, options include performing lobar transplants (ie, right lower lobe and left lower lobe) or performing a wedge resection using a linear staple. In the Toronto center, 15% of the pediatric transplant patients have received lobar transplants.

Single Lung Transplant

This procedure is most commonly used in the adult population. Single lung transplants are rarely performed in children because most underlying diagnoses indicate bilateral lung transplantation, such as CF or pulmonary hypertension. Single lung

transplantation may occasionally be a consideration in unique situations such as when the patient has had a previous pneumonectomy.

Living Related Donor Lung Transplant

This procedure was initiated in 1993 due to the higher demand than supply for patients waiting for a lung transplant, along with a scarcity of deceased donor organs. A living related donor lung transplant (LDLT) requires 2 living donors to each undergo 1 lower lobectomy. A right lower lobe is removed from 1 donor and a left lower lobe from the other. These lobes are then implanted into the recipient in place of the whole right and left lung, respectively. The most common indication for LDLT in North America is CF, with retransplantation being second.[20] It is well suited for children because the donors must be bigger than the recipients. However, the procedure is limited in younger/smaller children because of the size mismatch between adult donor lobes and the pediatric thorax. The most important surgical difference between LDLT and deceased donor lung transplant (DDLT) is that a single pulmonary vein drains the donor lobe, as a cuff of donor left atrium is not harvested from the living donor (as described earlier), thus there is an end-to-end anastomosis of 1 living donor's pulmonary vein and 1 recipient pulmonary vein for each side.[21]

Donor evaluations and care are provided by physicians who are independent of the pediatric lung transplant team. The advantages of this procedure include a planned operating room time, a shorter ischemic time, and an increase in the pool of donor organs. There is also an increased risk of the donor lung being undersized for the chest cavity.

Published results after 10 years of experience that included 39 pediatric lung transplant recipients found no difference in the actuarial survival between adults and pediatric recipients of LDLT, despite this being a sicker cohort with greater than 50% of the recipients being hospital bound and 18% being ventilator-dependent at the time of the procedure. Infection was the predominant cause of death in this patient group.[22]

Donor outcomes have been published with no reported deaths. However, major complications have included pleural effusion, bronchial stump fistula, bilobectomy, hemorrhage phrenic nerve injury, pulmonary artery thrombosis, bronchial stricture, and persistent air leak. Minor complications include persistent air leak, arrhythmia, and pneumonia.[23,24]

Clearly, deceased donor lung transplantation is the preferred option wherever possible to avoid the risk to 2 healthy donors. However, LDLT is an acceptable alternative when the recipient is not likely to survive long enough to receive deceased donor organs. With the improved lung allocation system (LAS) in the United States, sicker patients are now being appropriately allocated donor organs and the number of LDLTs performed has dropped drastically.

COMPLICATIONS

Posttransplant complications can be categorized into 3 phases: immediate phase, which includes the first few days after transplant; the early phase, which includes the first 3 months; and the late phase, which includes the period after the first 3 months.

Immediate Phase Complications

These include hyperacute rejection, primary graft dysfunction (PGD), ischemia-reperfusion injury, surgical complications, and infections.

Hyperacute rejection

This complication is as a result of circulating preformed recipient serum antibodies that bind to donor tissue antigens and cause complement-mediated graft injury. Endothelial cells lining the blood vessels of the new organ are the principal targets. Preformed antibodies that are generally attributed to prior blood transfusions, a previous transplant, or pregnancy, may be directed at HLA or endothelial antigens. True hyperacute rejection is rare, but when severe, can result in early graft failure. To evaluate the risk for this complication, testing for panel reactive antibodies (PRA) is performed during the assessment process. PRAs include a mix of 60 to 100 different samples that express a wide range of antigens tested with the recipient serum. The percentage of the cell samples to which the serum binds in the panel is reported. Other more sensitive methodologies include flow cytometer and beads coated with purified major histocompatibility complex (MHC) antigens rather than cells. For patients with positive PRAs, a virtual crossmatch can be done before transplant, followed by an actual crossmatch at the time of the transplant using donor leukocytes. If there is a positive actual crossmatch, the recipient is treated with intraoperative and postoperative plasmapheresis and thymoglobulin followed by intravenous immunoglobulins.

Primary graft dysfunction

PGD represents a severe form of acute injury to the allograft with clinical, radiographic, and histologic features similar to those of acute respiratory distress syndrome. PGD is characterized by patchy pulmonary infiltrates, a low ratio of arterial oxygen to the fraction of inspired oxygen, diminished lung compliance, and pathologic findings of diffuse alveolar damage.[25]

PGD is the end result of a series of hits occurring from the time of brain death to lung reperfusion after transplant. Although it is recognized that ischemic reperfusion injury is a major contributor to PGD, it is clearly part of a multifactorial/multihit injury process. Other injuries occurring in the donor before the retrieval process and during lung preservation can contribute to and amplify the manifestations of PGD. Thus it is important that attention be paid to the assessment of donor lungs, effective technique of lung preservation, and careful management of transplanted lungs after reperfusion, to reduce the severity of ischemic reperfusion injury and the incidence of PGD.[26]

Several studies have found that PPH is a recipient risk factor independently associated with the development of PGD.[27–29] This may be because patients with PPH, compared with other causes of pulmonary hypertension, are different in chronicity and degree of right ventricular morphologic changes and have more severe cardiac dysfunction. Secondary pulmonary hypertension has also been implicated as a potential risk factor for PGD, but the strongest and most clearly established recipient risk factor remains the diagnosis of PPH. Other reports showed a link between early PGD and subsequent development of bronchiolitis obliterans syndrome (BOS).[30] It was further suggested that PGD may contribute to nearly half of the short-term mortality after lung transplantation.[31] Survivors of PGD even have increased risk of death extending beyond the first posttransplant year. Christie and colleagues[31] found that the relationship of PGD with mortality among 1-year survivors was remarkable, with a relative increase in the risk of mortality in the next 4 years. Suggested reasons for these finding were a lingering effect after prolonged critical illness or the potential for increased immunogenicity of the allograft as a sequel of earlier severe lung injury.[31]

It is important to continue the search for a better understanding of risk factors and of ways to prevent PGD as it remains not only a major cause of early death after lung transplant but also increases risk of mortality among patients who survive at least 1 year after PGD. Treatment includes supportive care, such as mechanical ventilation,

and pharmacologic interventions, such as PGE_1[32] or nitric oxide,[33] and, in severe cases, extracorporeal membrane oxygenation (ECMO) has been used with success.

Ischemia reperfusion injury

Ischemia-reperfusion induced lung injury continues to be a frequent complication of lung transplantation within the first few days after the procedure. As mentioned earlier, it is a significant contributor to the PGD, which is characterized by nonspecific alveolar damage, lung edema, and hypoxemia occurring within 72 hours after transplant.[26] The clinical spectrum can range from mild hypoxemia associated with a few infiltrates on chest radiograph to a clinical scenario similar to severe respiratory distress syndrome requiring positive-pressure ventilation, pharmacologic therapy, and occasionally even ECMO.[27] Furthermore, it has been recognized that, if this injury is severe, it can lead to an increased risk of acute rejection that could ultimately result in significant graft dysfunction in the long-term.[34] Whether severe ischemia-reperfusion injury increases the risk of chronic rejection remains controversial because some studies have found that there is a relationship[34] and others have not.[35]

Many strategies to prevent lung dysfunction have been studied and used, including optimization of the lung preservation solution,[36,37] and optimizing of volume, pressure, and temperature of the flush solution. In addition, a retrograde flush has been found to have added benefit. Low reperfusion pressure and a protective ventilation strategy during the early reperfusion phase may also decrease lung dysfunction. In established ischemic reperfusion injury, inhaled nitric oxide has been used as it can improve ventilation-perfusion mismatch and decrease pulmonary artery pressures without affecting systemic pressures. Further treatments include supportive care, such as mechanical ventilation, and ECMO in severe cases.[26] Overall, this injury continues to be a significant cause of morbidity and mortality after lung transplantation and further work on its prevention and treatment will decrease its effect on survival and graft function.

Surgical Complications

Surgical complications include postoperative bleeding or airway anastomotic complications, phrenic nerve injury, chylothorax, and wound infection.

Airway complications

Airway complications include dehiscence or stenosis of the airway anastomosis. Pediatric airways are different from adult airways in that they are smaller and have bronchial cartilage that has a higher compliance. However, reports from the mid-1990s in adults showed the rates of airway complications to be between 9% and 15% of the anastomoses at risk, with a related mortality of 2% to 3%,[38,39] and similar rates have been reported in pediatrics.[40] More recently, Meyers and colleagues[41] reported that the frequency of treated airway complications did not differ between adults and children (9% vs 11%). Narrowing at the level of the suture line continues to be seen in a small number of patients. The clinical presentation includes wheezing, along with an obstructive pattern on spirometry and occasionally a biphasic flow volume loop.[4] Airway anastomotic narrowing can be treated with rigid bronchoscopic or balloon dilatation of the affected region. Balloon dilatation can be less traumatic and provide more accurate dilatation of the stenotic segment than rigid bronchoscopy dilatations. Stents are generally avoided in children with potential for airway growth, are difficult to remove, and can cause problems with exuberant granulation tissue growing through the wire mesh. In infants, significant airway malacia can occur, and one option is early tracheostomy to allow weaning from mechanical ventilation over weeks. In one study, independent predictors for airway complications in children

included preoperative *B cepacia*, postoperative fungal lung infection as well as days on mechanical ventilation.[40] Although airway complications can be a significant cause of morbidity, most are successfully treated and patient outcomes are generally not adversely affected.

Infection

The risk of infection continues throughout all posttransplant phases but, because of the higher level of immunosuppression used in the first month after transplant and the use of induction agents in some centers, it is higher early after transplant. Prophylactic antibiotics are generally given in the perioperative period. The choice of antibiotics is initially based on known recipient organisms and can be adjusted once donor bronchial lavage culture results are available. In the absence of known recipient lower respiratory tract organisms, prophylaxis is given according to center-specific lung transplant antibiotic prophylaxis protocols that may include cefuroxime or piperacillin-tazocin.

Early Complications

Complications that occur during the early phase (first 3 months) after transplant include acute rejection, infection, airway complications, and medication side effects.

Acute rejection

Acute cellular rejection, which is T cell mediated, is common in the first year after lung transplantation, especially during the first 3 months. Diagnosing acute rejection in the lung allograft is more difficult than in other solid-organ transplants. The problem is that the presentation of rejection can be similar to that of infection. The histopathologic diagnosis is also not always accurate in the acute rejection of the lung. Often the diagnosis is made on clinical suspicion based on a constellation of symptoms and signs, and confirmed by the response to therapy. Early acute rejection episodes can present with fever, chills, malaise, increased chest tightness, cough, and dyspnea. Physical examination may reveal crackles on auscultation and/or evidence of pleural effusion, with radiograph illustrating interstitial infiltrates with or without a pleural effusion. With later rejection episodes the patient may be asymptomatic, or present with deterioration in pulmonary function tests with a decrease in FEV_1 (forced expiratory volume in the first second of expiration) revealing airflow limitation. In principle, a 10% drop from baseline FEV_1 is considered significant. If the rejection episode is more severe, the patient can present with dyspnea and hypoxia and infiltrates on chest radiograph.

In our and other centers, routine monitoring for acute rejection episodes is performed through daily home spirometry, regular pulmonary function testing, chest radiographs, and routine surveillance transbronchial lung biopsies at 2 and 6 weeks, and 3, 6, 9 and 12 months after transplant. Transbronchial lung biopsies have been the mainstay of lung allograft evaluation. The ISHLT consensus paper[42] continues to advocate for at least 5 biopsy pieces of well-expanded lung parenchyma required for an assessment of acute rejection. The bronchoscopist may need to obtain more than 5 biopsy samples to provide the minimum of adequate tissue for evaluation. Generally, transbronchial biopsies are taken from 2 lobes of 1 lung because rejection may be patchy and multiple biopsies from different lobes increases the chance of picking up rejection. It has been shown that infants and toddlers have a lower incidence of acute rejection compared with older children.[43]

A pathologic diagnosis of acute cellular rejection is based on the presence of perivascular and interstitial mononuclear cell infiltrates in the lung biopsy samples. The distribution of the mononuclear cells, including extension beyond the vascular

adventitia into adjacent alveolar septa, forms the basis of the histologic grade.[42] Acute rejection may be accompanied by subendothelial infiltration and also by lymphocytic bronchitis and bronchiolitis. Grading for acute pulmonary allograft rejection according to the ISHLT classification includes grade 0 to 4, with A0 being no acute rejection, A1 minimal, A2 mild, A3 moderate, and A4 severe acute rejection. The categories of small airways involvement (ie, lymphocytic bronchiolitis) are problematic as these B grades were shown to have significant problems with inter- and intraobserver variability. New recommendations are needed to improve reproducibility. It is unclear to what extent humoral rejection, which is antibody mediated, occurs among lung transplant recipients.

Methylprednisolone pulse at 10 mg/kg/dose daily for 3 days followed by augmented oral prednisone is the treatment of acute cellular rejection. Overall, the response to this treatment, if the diagnosis is correct, is quick, with improvement of symptoms and pulmonary function test results over several days. Treatment options for humoral rejection include plasmapheresis for antibody removal and immunoglobulin infusion.

Infection

With the high-dose triple immunosuppression used, the risk of infection is high. Infections occur in 60% to 90% of recipients. Similar to other ventilated patients, lung transplant recipients are at risk for ventilator-associated infections but also for other lower respiratory tract infections. The clinical dilemma is often whether a presentation with hypoxia, increased white blood cell count, and infiltrates on chest radiograph with or without fever is related to infection or acute allograft rejection. For a definitive diagnosis, a bronchoscopy and BAL, with or without transbronchial biopsies, is performed. If bacterial infection is found, antibiotic treatment is based on the organisms and their sensitivities. Inhaled antibiotics are an alternative or adjunctive strategy to systemic antibiotic treatment, for instance in *Pseudomonas* lung infection. Cotrimoxazole prophylaxis is used to prevent *Pneumocystis jiroveci* pneumonia.

Viral infections

Early-phase respiratory viral infections can have a significant effect on morbidity and mortality. A study evaluating respiratory viral infections within 1 year after lung transplantation in children found that the most frequently documented viral pathogens were adenovirus, rhinovirus, respiratory syncytial virus, and parainfluenza virus, and that respiratory viral infections occurred in 14% of subjects in their cohort with seasonal variation.[44] Subjects with respiratory viral infections during the first hospitalization for transplantation had an increased risk of death or retransplantation within 1 year compared with all subjects and with those who had infections after their initial hospitalization.

Cytomegalovirus

CMV after lung transplantation remains a serious infectious complication, especially in CMV-negative recipients receiving CMV-positive donor lungs (ie, mismatch). Pediatric patients are at increased risk for mismatch because they are more likely to be CMV negative. The incidence of CMV episodes in a recent multicenter retrospective study of pediatric lung transplant recipients was 30%,[45] which is similar to a previous study.[46] CMV infection/disease was found to be associated with increased mortality after pediatric lung transplantation. CMV disease most commonly includes pneumonitis, but can also involve the liver, small bowel, and retina. The use of prophylactic treatment with antiviral drugs such as ganciclovir/valganciclovir has a significant effect on CMV infection and disease.[47] The approach to prophylaxis/treatment varies between centers, as do the means of diagnosis and surveillance. The optimal duration

of prophylaxis is uncertain. Surveillance using quantitative polymerase chain reaction to measure viral load in the blood is most common, and increased risk for CMV infection clearly exists after prophylaxis is stopped, so diligent, regular surveillance for early CMV detection is essential. Preemptive therapy with ganciclovir/valganciclovir may be warranted if significant increases in serum EBV titers occur.

Fungal infections

Antifungal prophylaxis after lung transplantation is used in most pediatric centers. Itraconazole or voriconazole are most commonly used, and nebulized amphotericin B is another option. Fungal infections are common in pediatric lung recipients and a recent retrospective, multicenter study revealed a prevalence of 10.5%[48] and found that pulmonary fungal infections were independently associated with a decreased 12-month posttransplant survival.

Medication side effects

Most pediatric lung transplant recipients remain on triple immunosuppression that typically includes a calcineurin inhibitor (cyclosporine or tacrolimus), an antimetabolite (azathioprine or mycophenolate mofetil) and systemic steroids as maintenance therapy. Complications associated with these medications include hypertension, diabetes (most commonly in recipients with CF), renal dysfunction, and neurologic complications such as seizures, which are typically related to calcineurin inhibitor use. The seizures are believed to be due to cerebral vasoconstriction and the resultant cerebral ischemia. According to the 2009 ISHLT Registry report on lung transplantation, the prevalence of hypertension is 43%, renal dysfunction 10.5%, and diabetes 27% at 1 year, and within 5 years these numbers increase to 69%, 22%, and 33%, respectively.[3]

Late Complications

Complications that occur during the late posttransplant phase include BOS, renal dysfunction, and malignancy.

BOS

Despite the improvements in outcome that have been made in lung transplantation in recent years, progressive airways obstruction and graft dysfunction still develop frequently. Chronic allograft dysfunction is clinically known as BOS, and is defined as a progressive decline in FEV_1 in the absence of other acute events such as rejection or infection. OB is a chronic graft dysfunction process that is histologically characterized by fibroproliferative tissue remodeling with excessive amounts of extracellular matrix deposition resulting in small airway occlusion with sparing of the alveoli and interstitium.[49] The cause of this process remains elusive.

The prevalence of BOS increases with time after transplant. The ISHLT Registry reports a prevalence of 14% within 1 year and approximately 50% within 5 years.[3] The prevalence of BOS in adult lung transplant recipients was 28% by 2.5 years, 51% by 5 years, and 74% by 10 years.[8] There is evidence that infants/toddlers may have a lower risk for the development of OB.[43]

The onset of BOS is insidious, with gradual progressive exertional dyspnea. Patients can also present with a viral-like illness with an acute or subacute cough associated with a wheeze. Treatment with bronchodilators produces no significant response. Auscultation of the lung can be normal or reveal fine crackles with or without a wheeze. The pattern of BOS progression varies. Generally, once established OB/BOS is progressive and results in severe airway obstruction and gradual respiratory failure, but progression may also plateau. Chest radiographs can be normal except for mild

hyperinflation. However, high-resolution CT scans often show a mosaic pattern that is most prominent on expiratory views. This pattern is consistent with variable air trapping in various lung zones/areas. Pulmonary function test results are particularly characterized by an irreversible decrease in FEV_1 and $FEF_{25–75}$ (forced expiratory flow between 25% and 75% of forced vital capacity) due to airway obstruction.

The diagnosis of OB may be made by transbronchial lung biopsies, but, because OB is often patchy in distribution, it can be difficult to diagnose simply by pathology. Because of the low sensitivity and specificity of transbronchial biopsies,[50,51] the BOS clinical criteria were created (**Table 1**).[52] The measurement of exhaled nitric oxide may also be useful for the evaluation of BOS, but currently no published data are available for pediatric lung transplant recipients.

The cause of chronic allograft dysfunction remains unclear, but several risk factors have been noted, including immunologic and nonimmunologic factors. Late or recurrent refractory acute rejection and lymphocytic bronchiolitis seem to be the most convincing factors.[53] Glanville and colleagues[54] found in a large cohort that severity of lymphocytic bronchiolitis detected on transbronchial biopsies was the most significant risk factor for the development of BOS. There is also evidence that CMV may be associated with BOS pathogenesis, and perhaps prolonged antiviral prophylaxis could decrease CMV infection rate and the occurrence of BOS.[55] Other risk factors include the ages of donor and recipient, ischemia reperfusion injury, HLA mismatches, infection, and gastroesophageal reflux with aspiration.

Effective treatment of BOS is extremely limited. Stabilization can sometimes be achieved by changes in immunosuppression, such as switching cyclosporine to tacrolimus.[56] This change has arrested the FEV_1 decline in 50% to 90% of patients with better results if the change was done early. Similar findings were noted with the switch from azathioprine to mycophenolate mofetil. Other medications that have been attempted include pulse steroids, methotrexate,[57] cyclophosphamide,[58] cytolytic therapy,[59] inhaled cyclosporine,[60] total lymphoid irradiation,[61] and photophoresis.[62,63] However, despite this extensive list of potential strategies, treatment success has been fairly limited and improvement of lung function is uncommon, probably because the fibroproliferative process is not reversible. Azithromycin and other macrolides seem to have some role in treatment. In one study, 3 months of treatment with azithromycin were associated with protection from disease progression (as measured by an increase in FEV_1 of 10% or more after 3 months of treatment) and death.[64]

Because children less than 5 years of age are often unable to perform pulmonary function tests (PFTs), making the diagnosis based on the FEV_1 criteria alone can be difficult in this age range. Infant PFT machines exist, but as these measure $FEV_{0·5}$ the classic BOS criteria cannot be used. However, it is recommended that declines

Table 1
Classification of BOS

Stage	Spirometry Result
BOS 0	FEV_1>90% of baseline and $FEF_{25–75}$>75% of baseline
BOS 0-p	FEV_1 81%–90% of baseline or $FEF_{25–75}\leq$ of baseline
BOS 1	FEV_1 66%–80% of baseline
BOS 2	FEV_1 51%–65% of baseline
BOS 3	FEV_1 50% or less of baseline

Abbreviations: $FEF_{25–75}$, mid-expiratory flow rates; FEV_1, forced expiratory volume in 1 second; p, potential.

in lung function be expressed as percent of predicted volumes instead of absolute volumes for BOS scores, because of lung and airway growth.[5,52]

Renal dysfunction

Chronic renal insufficiency is common in pediatric lung transplant recipients, with a prevalence of 10% at 1 year, 23% at 5 years, and 35% at 7 years after transplant.[3] Glomerular filtration rate (GFR) is often used to measure renal function. A single-center study revealed that renal function declined by 33% within 3 months after transplant, and advanced chronic kidney disease occurred in almost half of the patients studied after a median of 23 months.[65] It is clear that many children have a decline in renal function due to the effects of calcineurin inhibitor and other nephrotoxic drugs.

Malignancy

The incidence of malignancies increases with time after transplant with EBV-related posttransplant lymphoproliferative disease (PTLD) being the most common. Among other factors, this is presumably because children are more likely than adults to be naïve to EBV infection before transplant. Therapy for PTLD includes empiric reduction in immunosuppression antiviral drugs, monoclonal antibodies specifically targeting the B-lymphocyte antigen CD20 (eg, rituximab), or chemotherapy, when appropriate.[66,67]

OUTCOME

Survival after lung transplantation is similar in children and adult recipients, and has improved in recent years. Children transplanted between 2002 and 2007 had a 1-year survival of 83% and a 4-year survival of 50%.[3] Outcome seems better in children aged less than 12 years at transplant than in adolescents, but, nevertheless, survival after lung transplantation in general is worse than with other pediatric solid organ transplantation. However, it is evident that equivalent or better outcomes can be achieved in select high-volume experienced centers.

BOS accounts for more than 40% of deaths by 5 years after transplant, whereas early deaths are caused by infectious complications and graft failure.[3] The functional status of most long-term survivors is good, with 84% of 5-year survivors reporting no limitations in activity.

SUMMARY

Lung transplantation remains an accepted therapy for selected pediatric patients with severe end-stage vascular or parenchymal lung disease. Once discharged from the hospital, collaboration between the patients' primary care physicians and the lung transplant team is essential for long-term follow-up. The roles of the primary care physicians include general aspects of pediatric care, from completing immunizations to assessment and management of acute illnesses, such as respiratory infections or fevers. Awareness of complications specific to the immunocompromised organ recipient include consideration of CMV, EBV, or opportunistic infections, the presence of PTLD, or other complications. Live vaccines are contraindicated after transplant, and some antibiotics can significantly alter the blood levels of the immunosuppressive medications. Primary care physicians and the lung transplant team need to work in a partnership with these patients and their families. The transplant team and specialized center continue to follow these patients for posttransplant-specific surveillance of the allograft function and other organ systems.

Lung transplantation in children with otherwise untreatable respiratory failure can result in improved survival and significantly increased quality of life. The challenges

of this treatment include the limited availability of suitable donor organs, the toxicity of immunosuppressive medications needed to prevent rejection, the prevention and treatment of OB, as well as maximizing growth, development, and quality of life of the recipients.

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