Pediatric Lung Transplantation

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Abstract

Children undergoing lung transplantation present a unique constellation of issues that require compulsive management based upon their underlying diagnosis, state of debilitation, post-transplant needs, and immunosuppression. The ventilator management is also somewhat different from a typically ill child. This chapter will focus on those unique aspects of this group of children with an emphasis on complications seen and the management recommended.

Keywords

Lung transplantation • Surfactant abnormalities • Cystic fibrosis • Pulmonary hypertension

Introduction

The first successful pediatric lung transplant was performed at the University of Toronto in 1987. Since that time, lung transplantation in children has slowly become an accepted therapy for end-stage pulmonary disease of varying causes. Included in this chapter are the most common indications for transplant, as well as common post-operative complications and management in infants and children who have received lung transplants.

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Indications

Cystic Fibrosis

Cystic fibrosis remains one of the leading indications for lung transplantation in children. Of the 1,304 pediatric lung transplants performed from 1990 to 2009, 758 (58 %) were in patients with cystic fibrosis [1]. The decision of when to proceed with transplantation is important, since the current median survival time after transplant is 4.6 years [1], and complications related to transplantation are the second leading cause of death in patients with cystic fibrosis [2]. Several studies have looked to provide physicians guidance in this regard. Karem et al. from the Toronto lung transplant program looked at factors that predicted less than 50 % survival in 2 years [3]. They concluded that patients with an FEV_1 of less than 30 % should be considered for lung transplantation. Robinson [4] suggested that referral should be made for children who have an FEV_1 less than 50 % despite aggressive treatment. Others have found that the rate of decline in the FEV_1 may be more predictive of survival than the absolute percentage, and have recommended patients be referred for transplantation when the expected time for their FEV_1 to be less than 20 % of predicted equals the average waiting time for donor lungs [5].

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Surfactant Protein Abnormalities

These include surfactant protein B deficiency, protein C deficiency and ABCA3 mutations. Surfactant protein B deficiency is an autosomal recessive disorder affecting one per million live births [6]. It generally presents as severe respiratory failure in newborns, unresponsive to aggressive therapy [7]. Unlike surfactant protein B deficiency, surfactant protein C and ABCA3 mutations have variable clinical presentations, and some children do not require transplantation. The outcomes following lung transplantation for surfactant deficiencies are similar to those patients undergoing transplantation for other indications [8, 9].

Pulmonary Vascular Disease

Included in this category are patients with idiopathic pulmonary hypertension, Eisenmenger's syndrome, congenital heart disease and other pulmonary vascular diseases. For patients with idiopathic pulmonary hypertension, death typically occurs as a result of progressive right heart failure [10]. Timing of transplant depends on the patient's response to medical therapy, including intravenous prostacyclin therapy, bosentan and sildenafil, and may possibly be postponed for several years [11]. Lung transplantation in this group of patients is available only if left ventricular function is normal. If left ventricular function is poor, heart-lung transplantation may be required. Right heart function is frequently poor in this group of patients, but frequently returns to normal within a short period of time following transplantation [3].

Eisenmenger's syndrome is characterized by pulmonary hypertension secondary to uncorrected congenital heart disease. Unlike in patients with idiopathic pulmonary hypertension, there are no good prognostic indicators as to when to proceed with transplant. Pulmonary vein stenosis and pulmonary veno-occlusive disease are not easily managed with medical therapies. Stenting and dilation of stenotic veins many provide palliation for some time, but it is recommended that these patients be referred for transplant early. The clinical course of patients with pulmonary hypertension following repair of congenital heart disease is similar to that of patients with idiopathic pulmonary hypertension. Again, the decision to perform isolated lung transplant vs. heart-lung transplant depends on the function of the left ventricle.

Respiratory Failure Following Treatment for Malignancy

Lung transplantation is offered to children following treatment for malignancies provided there is a strong certainty that the malignancy has been completely eradicated [12]. Pulmonary toxicity is a potential complication of several chemotherapeutic agents as well as irradiation and bone marrow transplantation [13–15]. The most common causes of respiratory failure following treatment for malignancies include pulmonary fibrosis and bronchiolitis obliterans. The course of pulmonary fibrosis is highly variable, with some patients having complete resolution following removal of the chemotherapeutic agent, and others progressing to severe respiratory failure [15]. Bronchiolitis obliterans (BO) following bone marrow transplantation is nearly always associated with graft vs. host disease [16], with a 65 % mortality rate at 3 years post-diagnosis [17]. While transplantation in this group of patients is considered high risk, it remains a reasonable option with similar results to those with other indications.

Re-transplantation

Lung re-transplantation in children has been associated with lower rates of survival when compared to primary transplantation [18–20]. In some cases, it remains the only viable option for patients who develop graft failure and BO. Since the survival rates are lower and there are a limited number of donor organs available, patient selection is important. In a recent retrospective study of lung re-transplantation, Scully et al. found that patients who were less than a year post-transplant had worse graft survival, and therefore may not be the best candidates for re-transplantation [21]. Patients who were greater than 1 year post-transplant had similar morbidity and mortality to patients undergoing their first transplant. Further research is needed in this area to determine other factors, if any, that may help refine patient selection to maximize outcomes.

Contraindications to Lung Transplantation

Absolute contraindications to lung transplantation include severe dysfunction of other organ systems or severe systemic diseases. This includes, but is not limited to, malignancy, HIV infection, severe neuromuscular disease, multisystem organ failure and active collagen vascular disease [22]. The presence of certain infections prior to transplant are also considered a contraindication, especially colonization with *Burkholderia cenocepacia* [23, 24].

Relative contraindications include medical issues such as severe malnutrition, poorly controlled diabetes, renal insufficiency, prior thoracic surgery and the presence of antibiotic-resistant microorganisms. Social issues such as psychiatric disturbance in the patient or caregiver and a history of poor adherence with medical therapies are also considered as contraindications. These relative contraindications vary by center [25].

Post-operative Treatment

Immediate Post-operative Management

The patient is transferred from the operating room directly into an isolation room in the intensive care unit. Protective isolation is generally practiced although there are no data to support this. Nonetheless, common sense dictates that health care workers should be particularly cautious in preventing transmitted infections. Many of these patients, particularly those with cystic fibrosis will have multi-resistant organisms necessitating isolation precautions anyway. Hemodynamic monitoring is usually with only central venous pressure line and an arterial line. More invasive monitoring lines such as a Swan-Ganz catheter are generally not necessary and are particularly difficult to manage in small children. Fluid management is of great importance, and a negative fluid balance is the goal within the first 48 h post transplant, given that there is evidence that the newly transplanted lungs are susceptible to the development of pulmonary edema. In a retrospective study in adult lung transplant recipients, a central venous pressure of greater than 7 mmHg was found to be associated with a higher hospital mortality rate and longer intensive care unit stays [26]. However, the need to maintain a negative fluid balance needs to be balanced with the fact that over diuresis places the patient at risk for relatively low cardiac output and renal insufficiency. Generally speaking, these patients do not have very much difficulty with hemodynamic instability. The one exception to this is the group of patients with pulmonary hypertension. Right ventricular dysfunction pre-transplant is very common. Although right ventricular afterload is significantly improved post-transplant, some instability is common, usually requiring low to moderate doses of inotropic agents. There is one cautionary note about patients with Eisenmenger's syndrome who undergo lung transplantation and repair of the cardiac defect (usually a ventricular septal defect). These patients may have acquired right ventricular outflow tract obstruction post-transplant because of the severe right ventricular hypertrophy that accompanies this disease. This occurs presumably as a consequence of the dynamic nature of the outflow tract muscle. At the time of transplantation it is advisable to divide some of the muscle bundles present there and postoperatively avoid high dose inotropic agents.

Within the first 24 h following transplant, a lung perfusion scan is obtained to assess pulmonary blood flow and a bronchoscopy is performed to assess the airway anastomosis. Any major discrepancy in the relative amount of blood flow to each lung should trigger further investigation, usually with cardiac catheterization.

Respiratory care focuses on airway clearance. These patients require aggressive postural drainage and frequent removal of secretions. In order to facilitate pulmonary toilet, adequate pain control is also necessary. Most patients are able to be weaned from mechanical ventilation within a few days following transplant. Delays in the ability to wean from ventilatory support should raise suspicion for possible complications, such as graft dysfunction or phrenic nerve injury.

The vast majority of patients undergoing lung transplantation are malnourished to begin with. It is of paramount importance to establish adequate caloric intake post-transplant. This is complicated by poor intestinal motility that frequently occurs following lung transplantation, which may be related to injury to the vagus nerves during the transplant procedure.

Specific complications and their management will be described in more detail in the following sections of this chapter. The most important complications in the early post-operative period include primary graft dysfunction, rejection and infection. Lung protective ventilation strategies are employed to prevent graft dysfunction. Inhaled nitric oxide is frequently used in the postoperative period for prevention of early graft failure, although some studies have questioned the effectiveness of routine use [27]. Empiric antibiotic therapy is generally targeted at organisms that the patient may have been colonized with prior to transplant. If this information is not available, or if the recipient does not have a significant history of infection, broad-spectrum therapy, such as vancomycin and cefepime, is typically employed. As in all ICU patients, the presence of indwelling catheters places these patients at further risk for infection, and the need for these catheters should be reassessed daily and removed when no longer necessary.

Immunosuppression

Current regimes differ amongst centers, but in general consist of a calcineurin inhibitor, corticosteroids and either mycophenolate mofetil or azathioprine [28]. All these drugs put the patients at risk for infections of a variety of sorts. Corticosteroids have been used for decades for immunosuppression. They inhibit the production of cytokines and also inhibit T-cell growth factor [29]. Side effects include hyperglycemia, hypertension, and with prolonged use, possible skin changes. Cell cycle inhibitors, such as azathioprine and mycophenolate mofetil, are also used as maintenance therapy. These drugs lead to decreases in DNA and RNA synthesis within lymphocytes, therefore affecting their proliferation. Possible adverse effects to this class of medications include myelosuppression and nausea.

Calcineurin inhibitors have been widely used for prophylaxis against rejection in organ transplants. Their mechanism of action is to prevent the synthesis of IL-2 and other cytokines produced by activated T cells [30]. Cyclosporine and tacrolimus are perhaps the most widely used in this group. Adverse

effects noted with these medications are renal toxicity, hypertension, hyperglycemia, seizures and posterior reversible encephalopathy syndrome. They also have several important drug interactions, and require close monitoring of serum drug levels. Sirolimus also binds to the FK-binding protein, but instead of inhibiting calcineurin, the complex it forms inhibits the phosphorylation of the p70s6 kinase, which blocks signal transduction from cell surface cytokine receptors, including IL-2, IL-4, IL-15 and IL-10 receptors [31]. Studies have shown a synergistic effect of sirolimus with cyclosporine [31].

Complications of Lung Transplantation

Infection

Bacterial infections remain a common cause of early morbidity and mortality following transplant. The most common of these organisms are gram-negative pathogens such as *Pseudomonas*, *Klebsiella* and *Haemophilus* spp., but gram-positive organisms such as *Staphylococcus aureus* may also cause pneumonia in the postoperative period. In patients with cystic fibrosis, the causative organism will most likely be the same that colonized the airway prior to transplant. A culture of the donor bronchus is taken at the time of implantation of the organ; occasionally this is a source of infection.

Viral infections are also common, with *Cytomegalovirus* (CMV) being the most common. Patients at highest risk of developing severe primary infection are those who are CMV negative and receive lungs from CMV positive donors [32]. Many centers treat these patients with a prolonged 4–12-week course of ganciclovir. All patients positive for CMV pre-transplant and any receiving an organ from a CMV-positive donor should receive prophylaxis with ganciclovir. The duration of treatment and the route of administration are somewhat controversial. In the absence of need for prophylaxis with ganciclovir, many centers now recommend acyclovir for prophylaxis against herpes simplex infections. The presence of CMV infection, or the detection of the virus in serum or BAL specimens, usually responds to a 14–21 day course of IV ganciclovir. Community acquired respiratory viral infections also lead to significant morbidity and mortality in lung transplant recipients. These include RSV, adenovirus, parainfluenza and influenza infections. Adenovirus is of particular importance, as it has been associated with an increased incidence of early graft failure and death [33]. The treatment for most community acquired viral infections is supportive, although some centers use intravenous or inhaled ribavirin in severe cases [34, 35]. Some current recommendations include using acyclovir for prophylaxis against herpes simplex viral infections in patients who do not require prophylaxis with ganciclovir.

Fungal infections can occur as well, with the most common organisms being *Aspergillus* and *Candida* species. The identification of both of these organisms may represent colonization, but due to the potential of invasive disease, treatment should be considered. *Candida albicans* is frequently identified post transplant, and can cause invasive disease [36]. Invasive *Aspergillus* disease has a mortality rate up to 60 % in lung transplant recipients [37]. Risk factors for the development of invasive fungal diseases include colonization with these organisms prior to transplant, especially in patients with cystic fibrosis [38]. Treatment depends on the organism identified and the sensitivity patterns. For *Candida albicans*, treatment with fluconazole is generally effective. For non-albicans species, voriconazole is usually effective. Amphotericin B has been the drug of choice for treatment of invasive *Aspergillus*, although capsofungin is a reasonable alternative. Voriconazole in particular has significant drug interactions with immunosuppressive medications, so careful monitoring is needed.

Graft Complications

Primary Graft Dysfunction

Primary graft dysfunction (PGD) is the leading cause of early mortality after lung transplantation. Also known as early graft dysfunction or severe ischemia-reperfusion injury, it has a reported incidence of between 11 and 25 % [39–41]. PGD generally occurs within the first 24 h after transplantation, with a clinical picture similar to that of acute respiratory distress syndrome (ARDS). In attempts to consistently describe the severity of PGD, a grading system was proposed from the International Society of Heart and Lung Transplantation in 2005. This classification grades the severity of PGD from 0 to 3 based on PaO_2/FiO_2 ratio and the presence or absence of radiographic abnormalities. Absence of infiltrates on chest radiographs (CXR) is rated as grade 0 regardless of PaO_2/FiO_2 ratio. If this ratio is greater than 300, but there are infiltrates on the CXR, it is grade 1. Grade 2 includes PaO_2/FiO_2 between 200 and 300 with CXR abnormalities, and Grade 3 has a PaO_2/FiO_2 ratio less than 200. Any patient on extracorporeal oxygenation is classified as grade 3 [42]. The practical utility of this classification system is marginal in part because of the changing nature of blood gases and chest radiographic findings in the first 48 h post-transplant.

Treatment of PGD includes the use of lung-protective ventilation, maintenance of a negative fluid balance, and pulmonary vasodilator therapy [43]. In severe cases, ECMO has been utilized, with varying results. In adults, there are several case series reporting 1-year survival rates from 26 to 47 % when ECMO has been used post-operatively, predominately for PGD [44–48]. In children, 1-year survival rates range from 28 to 41 % with ECMO for PGD [46, 49], with suggestion that earlier ECMO support may lead to improved

outcomes for this indication [49]. The improved results with earlier implementation of ECMO is likely related to avoidance of barotrauma associated with high ventilator pressures necessary to maintain satisfactory ventilation in the presence of significant lung dysfunction.

Rejection

Patients who are candidates for lung transplantation have extensive pre-transplant testing to assess risk of antibody-mediated rejection. This includes assessment of the Panel Reactive Antibody (PRA) and crossmatch results. The PRA is determined by assessing what percentage of lymphocytes in a stored panel of known HLA types that are recognized by the recipient's antibodies. Patients with a positive PRA are considered high-risk for acute rejection, with decreased survival post-transplant as the PRA increases [50]. Crossmatching is performed by incubating serum from the recipient with leukocytes from the donor to assess real-time antibody binding. Since this is often impractical, a "virtual crossmatch" is often performed instead, by comparing antibodies known to be present in the recipient with donor antigens [50]. Patients with a positive cross-match are treated with IVIG and plasmapheresis.

Antibody-mediated rejection has been recognized as a cause for hyperacute rejection, but is more recently gaining recognition in acute and chronic rejection as well. Hyperacute rejection is due to preexisting antibodies in the recipient that interact with donor antigens. Pathologically, it is identified by the presence of small vessel vasculitis and necrosis and diffuse alveolar damage, with capillary congestion with neutrophils and antibody deposition on endothelial surfaces [51]. The diagnosis of acute and chronic antibody mediated rejection is more difficult, with a lack of consensus as to the pathologic appearance of humoral rejection. The presence of circulating antibodies with or without specific biopsy findings may represent latent or silent rejection, but is of unclear clinical significance [52].

Acute cellular rejection may affect up to 55 % of lung transplant recipients in the first year following transplantation [53], and is defined based on the histologic appearance of lung allograft tissue. While episodes of acute rejection may be symptomatic, presenting with cough, dyspnea, hypoxia and fever, many episodes are diagnosed in asymptomatic patients undergoing routine surveillance. In patients who are able to perform pulmonary function testing, the decline in the FEV1 has been found to have a sensitivity of about 60 % for detecting infection or rejection grade A2 and higher, but can not distinguish between the two [54]. Some studies have demonstrated that the findings of ground-glass opacities, volume loss and pleural effusions on high-resolution chest computed tomography indicate acute rejection, but more recent data indicates a very low sensitivity of 35 % for these findings [55].

Bronchoscopy with transbronchial biopsies remains the most important method by which to diagnosis rejection. The procedure itself is relatively safe, with possible complications including transient hypoxemia, small volume bleeding, pneumothorax and arrhythmia, all occurring at low rates, with no mortality reported [56, 57]. Most biopsies are obtained from the lower lobes, since if rejection is present, the grade has been shown to be worse in the lower lobes as compared to the upper lobes [58].

Bronchoscopy is also performed as surveillance to diagnose asymptomatic rejection in patients post-transplant. Acute rejection has been detected in 6.1–39 % of routine surveillance bronchoscopies [56, 59]. Although varying monitoring strategies are currently in use, there has never been a randomized clinical trial comparing different strategies. With the incidence of acute rejection being the highest in the first year after transplant, many centers perform routine bronchoscopies at 1 month, 3 months, 6 months and then on an annual basis [60].

Treatment of episodes of acute rejection consists of increased immunosuppression. In general, the treatment for acute rejection is pulse-steroids, usually consisting of at least 3 days of high-dose steroids IV followed by an oral taper, which has been proven effective in several studies [61, 62]. Plasmapheresis is the treatment of choice for antibody-mediated rejection. Intravenous immunoglobulin (IVIG) is another common therapy, leading to B cell apoptosis, down regulation of B cell surface antigens, and inhibition of complement activation. Anti-CD20 monoclonal antibodies, such as Rituximab, also deplete B-cells and have been effective in treating presensitized kidney transplant recipients [63–65].

Bronchiolitis obliterans (BO) is thought to be a manifestation of chronic rejection, occurring in about 50 % of patients following lung transplantation [66]. It is a pathologic process characterized by partial or complete obstruction and destruction of distal airways. Several risk factors have been identified in the development of BO following lung transplantation, including recurrent episodes of acute cellular rejection, gastroesophageal reflux disease (GERD), and viral infections. Regardless of the underlying cause of BO, the prognosis is poor. Several studies have found the 3-year survival of patients with BO to be about 51 % [67–69]. Treatment plans for post-transplant BO are variable, but usually includes altering immunosuppression, either by changing agents or adding additional agents. There is evidence that changing from cyclosporine to tacrolimus [70, 71], or adding either mycophenolate mofetil [72] or sirolimus [73] to the current immunosuppressive regime may be helpful. Other therapies, such as extracorporeal photopheresis, have been used with variable results [74, 75]. Still other medications, such as azithromycin, which has anti-inflammatory effects [76] and clotrimazole, which may decrease the proliferation of fibroblasts [64], have not had formal clinical trials to evaluate effectiveness in treating BO. In many cases, re-transplantation is a strong consideration.

Airway Complications

The bronchial anastomosis in lung transplantation is at risk for a variety of complications. This is largely due to the fact that there is no direct blood supply to the bronchus. Normal lungs have a dual blood supply, with the bronchial blood flow arising from the intercostal arteries or directly from the descending aorta. During lung harvest, the bronchial artery circulation is lost, and revascularization may take up to 2–4 weeks [77]. Circulation to the donor's bronchus during this time is dependent on the retrograde filling of bronchial arteries by the pulmonary arteries.

The reported incidence of airway complications varies. Possible airway complications include bronchial dehiscence, bronchial stenosis, granulation tissue formation, bronchial fistulas and tracheo-broncho-malacia. With recent surgical advances in the field, bronchial dehiscence, while once the major source of early morbidity and mortality, has become a relatively rare complication. Bronchial stenosis is the most common airway complication, with a reported incidence ranging from 2 to 32 % [78, 79]. Balloon dilatation using a rigid bronchoscope is typically the treatment of choice. Occasionally stent placement may be necessary. Although the incidence of bronchial anastomotic stenosis is the same for infants as it is for teenagers, small infants have a higher incidence of native tracheo-bronchomalacia in the native airways. This may complicate ventilator weaning.

Vascular and Nerve Complications

Vascular anastomosis complications are also rare. A lung perfusion scan is typically performed within 24 h of transplant to screen for such complications. More common complications include phrenic nerve injury, injury to the recurrent laryngeal nerve and bleeding. Phrenic nerve dysfunction is relatively common, with a reported incidence ranging from 9.3 to 29.6 % [80, 81]. This complication has been found to be more common on the right side, and diaphragmatic dysfunction can be confirmed by fluoroscopy or ultrasound [80, 82].

Other Complications

Atrial flutter has been observed following lung transplantation. This is thought to be secondary to suture lines placed in the left atrium during pulmonary venous anastomosis [83]. Type 1 antiarrhythmic medications have been shown to be effective for treatment if this complication should occur [83].

Impaired gastric motility and GERD are common after lung transplantation [84], and may be exacerbated by iatrogenic vagal nerve injury and the use of calcineurin inhibitors [85, 86]. In addition, an impaired cough reflex following transplantation may increase the risk of aspiration. Some studies have demonstrated improved survival in patients without reflux [87], and prophylactic fundoplication may decrease the incidence of BO in transplant recipients [87–89]. Further studies are needed to determine the long-term benefit of such therapies.

Post-transplant lymphoproliferative disease (PTLD) is another possible complication, occurring in about 10 % of patients, and is associated with primary Epstein-Barr virus infection [90]. Therapy for PTLD includes reduction in immunosuppression, anti-CD20 antibodies, or chemotherapy [25].

Survival

The 5-year survival rate from 1990 to 2008 in pediatric lung transplantation is 48 % [1]. When analyzing the data from 2002 to 2008, the 5-year survival is 52 %, mostly due to improved early survival [1]. Survival is the same for all patients, regardless of pre-transplant diagnosis. The leading cause of death remains to be BO, with infection and graft failure also significant causes. Clearly, better understanding and treatment of BO may improve survival considerably.

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