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Pediatric lung transplantation

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ABSTRACT

Pediatric lung transplantation is a highly specialized clinical endeavor. Since the late 1980's, there have only been slightly more than 2200 implants reported to the International Society for Heart and Lung transplantation registry. This review will discuss the historical aspects of pediatric lung transplantation. It will familiarize the reader with the current indications for transplant and the referral and listing process. The current state of lung assist devices as a bridge to pediatric lung transplantation is discussed in addition to the technical aspects of the transplant procedure. Finally, posttransplant outcomes, including anticipated morbidity and the role of retransplantation, are clarified.

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Historical perspective

The first clinical attempt to transplant lungs in a pediatric patient was undertaken by Dr. Denton Cooley in 1968. The child survived for 14 hours, and the procedure was actually a heart–lung transplant in a 2-month-old child with a complete atrioventricular septal defect and pulmonary hypertension.[1] Nearly 2 decades later, Cooper reported the first successful isolated pediatric lung transplant at the University of Toronto in 1987.[2] Since 1986, there have been 2229 pediatric lung transplants reported to the registry of the International Society for Heart and Lung Transplantation (ISHLT).[3] Forty-one national and international centers reported pediatric lung transplants. Nineteen were in Europe and 18 were in North America. The remaining 4 were in other geographic locations. Most centers performed between 1 and 4 transplants per year. As of 2014, only 1 center performed more than 10 pediatric lung transplants annually.[3]

Indications for pediatric lung transplantation

In the 19th annual report from the ISHLT registry, there was a focus on defining the diagnostic indications for pediatric lung transplant.[3] Eight categories of indications for pediatric lung transplantation were recognized:

1. Cystic fibrosis
2. Interstitial lung disease (ILD)
3. Interstitial lung disease-other
4. Pulmonary hypertension
5. Pulmonary hypertension-not idiopathic
6. Obliterative bronchiolitis
7. Retransplantion
8. Other

When assessed based on the age of the patient, the most common indication for pediatric lung transplantation is quite different. In patients less than 1 year of age, pulmonary hypertension is the most common indication followed closely by surfactant protein B deficiency. Between 1 and 5 years of age, the most common indication is pulmonary hypertension from all causes (37%). However, it is a less frequent indication for lung transplantation in patients older than 6 years. Cystic fibrosis continues to be the most common indication for lung transplantation in patients between 6 and 10 years of age (50%) and patients between 11 and 17 years of age (67.8%).[3] Although the most common, over time cystic fibrosis continues to decrease in its frequency as an indication for pediatric transplantation because of improving medical therapy.[4]

Contraindications to pediatric lung transplantation include:[5]

- Potential anatomic contraindications
  - o Severe chest wall abnormalities (with the possible exception of scoliosis)[6]
  - o Severe tracheobronchomalacia
  - o Diffuse transpleural systemic to bronchial artery collaterals
  - o Talc pleurodesis
  - o Severe aorta-pulmonary collaterals (i.e., pulmonary atresia/MAPCAs)

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- Severe postpneumonectomy syndrome (with or without spacer)
- Medical contraindications
  - HIV infection
  - Hepatitis C
  - Any active viral infection
  - Burkholderia Cenocepacia (genomovar 3)
- Nonmedical contradindications
  - *Severe* psychosocial and financial issues

Referral and listing for transplant

Once a patient is evaluated and found to be a transplant candidate, the difficulty becomes finding a suitable donor organ in an efficient time frame. This can be a challenging proposition given the size limitations of the pediatric patient. One strategy to address the size limitation of the recipient is lobar transplantation. The first human lobar transplant occurred at Tokyo Medical College in 1966.[7] This landmark achievement led to the application of living lobar transplant in pediatric patients. Japan has accumulated an extensive experience with living donor lobar transplant due to the extreme shortage of donor organs and the relatively recent acceptance of cadaveric donation.[8] The adoption of living donor lobar transplantation was secondary to a prolonged waitlist time (average 800 days) and substantial waitlist mortality (50%). In contemporary studies, nearly 40% of lung transplants in Japan are lobar transplants. The 5-year posttransplant survival is reported to be 72% with this approach.[8] However, due to the difficulty performing lobar transplantation and the potential harm to 3 patients, only 400 living donor lobar transplants have been performed worldwide as of 2011.[9]

Recognizing the limitations with pediatric donor organs, the lung allocation score (LAS) was developed and implemented in the United States in 2000[10] It seeks to allocate organs to those patients who will benefit most from a lung transplantation and thus limit waitlist mortality. This strategy for listing was a stark departure from the historical standard of listing patients based on accrued waitlist time. However, the LAS is only applied to patients 12 years of age and older. There have also been modifications to the listing protocol to account for infants and children who were extremely ill:[11]

1. Pediatric organs are preferentially allocated to pediatric patients.
2. The distance allowed for organ allocation in patients less than 12 years of age is farther than in older patients.
3. The acuity of patients less than 12 years of age is prioritized.

A key question regarding the LAS is whether or not it had the desired impact on organ allocation and reduced waitlist mortality. Lancaster et al. used the United Network for Organ Sharing database to address this question. They reviewed all lung transplants, including pediatric patients, from 1995 to 2014. A comparison of transplant outcomes was conducted by pre- and post-LAS eras. There was a statistically significant decrease in the median waitlist time, death on the waitlist, and an increase in median survival for both adult and pediatric patients after implementation of the LAS.[12]

Besides the LAS, are there other strategies available to reduce waitlist mortality for pediatric patients with end-stage lung disease? In pediatric heart transplantation, for example, the development and clinical application of pediatric-specific ventricular assist devices has had a significant impact on the reduction of heart transplant waitlist mortality.[13] These devices have also been shown to have a favorable impact on posttransplant survival in pediatric patients.[14] However, clinical experience with *"bridging"* pediatric patients to lung transplantation is much less evolved than its cardiac counterpart. In a single institution retrospective analysis, Toprak et al.[15] showed there was no statistically significant difference in either survival to hospital discharge or 1-year posttransplant survival in patients who were maintained on mechanical ventilation or supported with ECMO as a bridge to lung transplant. Their recommendation from this report was that, in suitable patients, these modalities should not be considered a contraindication to lung transplantation. Our European colleagues have reported the use of *ambulatory* ECMO as a bridge to lung transplant with excellent outcomes in adults.[16] In this case series, the device was placed under conscious sedation.

An even less frequently reported modality for bridging pediatric patients to lung transplantation is the paracorporeal lung assist device (pLAD). To our knowledge, there have only been 4 such patients reported in the United States.[17] All 4 had severe pulmonary hypertension. One patient survived to transplant, 1 recovered, and 2 died while awaiting suitable donors. Similar to the St. Louis experience, our experience at Cincinnati Children's Hospital includes 2 small children (< 7 kg) that presented with severe pulmonary hypertension, which we successfully bridged to lung transplantation with a pLAD. One child's pulmonary hypertension was secondary to congenital pulmonary vein stenosis and the other had alveolar capillary dysplasia.

Paracorporeal lung assist device implantation technique

The implantation technique for the pLAD was undertaken utilizing mildly hypothermic (34°C) cardiopulmonary bypass via median sternotomy. A 10 mm Gore-Tex Graft was sewn to a 6 mm EXCOR aortic cannula. The graft was used to implant the device into the main pulmonary artery. For the outflow, an EXCOR atrial cannula was implanted directly into the left atrial appendage after placing 2 opposing purse string stitches and a tie around the appendage near the end of the cannula tip. In this way, no cannula material was exposed in the left atrium and only an end-hole was at the entrance of the appendage. This was done in an attempt to avoid the issues with atrial thrombus and strokes seen by others. A iLA® Membrane Ventilator (Novalung) oxygenator was used in the first patient, and a QUADROX-i oxygenator was used in the second patient and later changed to a Novalung. No pump was used with either system at implantation, although one was eventually spliced into the system of the first patient.

The rational behind this approach was that the resistance within the oxygenator was substantially less than that of the native pulmonary circuit. This would promote preferential flow through the oxygenator and essentially unload the right ventricle potentially allowing for recovery of right ventricular function. The EXCOR cannulas were tunneled from the mediastinum and connected to the device. The chest was closed, and both patients were extubated. Both patients were successfully bridged to bilateral lung transplant via median sternotomy. One patient had an extended hospitalization secondary to persistent renal insufficiency. The second patient died 2 months posttransplant secondary to diffuse RSV pneumonia. Our implantation technique differs from other reported approaches to this operation.[18] We believe cannulation of the left atrial appendage directly for outflow from the device is a simplified yet effective technique both for device implantation and device explantation at the time of transplant.

We gained experience with 2 different oxygenators in these patients. This approach was taken out of necessity because initially the iLA® Membrane Ventilator (Novalung) was not available. Unlike the QUADROX-i oxygenator, Novalung does not contain a heating–cooling component. Therefore, the resistance through the

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