Lung transplant in children

José J. Camargo*, Grupo de Transplante Pulmonar da Santa Casa de Porto Alegre, RS, Brazil

Abstract

Objective: this article presents a review of the main aspects related to lung transplant in children and shows the experience of the first medical team to perform this procedure in Latin America.

Sources: literature review of scientific articles, using the Medline and Lilacs databases.

Summary of the findings: the article was organized into topics. Similarities and differences regarding lung transplant in adults were identified. Specific problems presented by children subjected to transplant are discussed, and special emphasis is given to a specific situation: lung transplant with living related donors.

Conclusions: advances in adult lung transplant for the treatment of parenchymatous or vascular lung diseases have been successfully employed in the pediatric population during the last few years.


Introduction

The first lung transplants for the treatment of children with lung parenchyma disorders or problems related to its vessels were indeed cardiopulmonary transplants, following a current trend in the 1980s, which considered cardiopulmonary transplant to be more appropriate to treat patients with end-stage lung diseases that had or could have some cardiac involvement.

With the advent of unilateral and bilateral lung transplant, which is undoubtedly simpler, and the demonstration that cardiac disorders caused by pulmonary hypertension decreased with the replacement of the diseased lungs, cardiopulmonary transplants became less frequent and were only recommended in those cases of pulmonary hypertension associated with heart defects that could not be surgically corrected and, sporadically, in cases of vascular lung disease with left ventricle failure (usually with previous heart surgery).

Nowadays, bilateral lung transplant is the most widely used in the pediatric population, partly because cystic fibrosis is the most frequent indication for transplants in children, but also because there is some concern with graft growth and with occasional underfunction of the organs donated by extremely small individuals.¹
Other indications for lung transplant include idiopathic pulmonary fibrosis, primary pulmonary hypertension or pulmonary hypertension secondary to congenital heart defects and an array of less frequent parenchyma diseases (Figure 1).

Relative contraindications

Continued use of corticoid (> 0.5 mg/kg/day of prednisone) results in difficult bronchial healing and is a relative contraindication, since the dose of corticoid can usually be reduced way below this limit.

Many transplant centers regard the need for mechanical ventilation as a relative contraindication; however, the experience of centers specialized in transplants in children younger than six months shows that most of them were on mechanical ventilation and that this did not influence the success of the transplant, even in the presence of such cardiorespiratory dysfunction.

The experience of this group revealed that the prompter availability of a donor, given the need for mechanical ventilation, had some impact on the survival rate. Therefore, the use of lobes from living donors has allowed saving the lives of children with remote chances of survival who were waiting for organs from dead donors.

Life expectancy without the transplant is difficult to determine in the pediatric population, but in general, the inclusion of potential candidates in waiting lists follows reasonably safe rules, which vary according to the underlying disease.

Cystic fibrosis

In cystic fibrosis, the rehabilitation programs, especially based on continued physical therapy, adequate antibiotic therapy and proper nutrition, have increased the mean age of cystic fibrosis patients. However, the following criteria have been used to indicate the best time for lung transplant:

- Postbronchodilator FEV₁ of less than 20% predicted for adults, and less than 30% predicted for children and women at any age;
- Resting hypoxemia (PaO₂ of less than 55-60 mmHg);
- hypercapnia (PaCO₂ of less than 50 mmHg);
- relevant secondary pulmonary hypertension (PMAP of less than 35 mmHg or PSAP of less than 45 mmHg);
- hard-to-control weight loss, despite aggressive management (nasoenteral tube, jejunostomy, etc.);
- repeated hospital admissions due to frequent and untreatable infections, suggesting loss of control over the disease.

Cystic fibrosis is the main indication for lung transplant in industrialized countries given the higher prevalence of the disease among Anglo-Saxons. Some exclusion criteria for potential candidates are not a common sense, such as colonization by *Burkholderia cepacia*, for which some services refuse to recommend transplantation alleging high risk, whereas other specialized centers do not see any significant difference in outcome as a result of this agent. An identical situation occurs in relation to the colonization by *Aspergillus*.

Indications

The indications for lung transplant in children are often similar to those observed in adults, including:

- severe respiratory insufficiency;
- lack of response to other forms of clinical or surgical treatments;
- life expectancy shorter than two years, compatible with the length of time on the waiting list;
- no other comorbidities (especially hepatic, renal and CNS);
- psychological and emotional profile compatible with the requirements of a highly complex procedure;
- adequate socioeconomic and family support conditions.
In a different way, the involvement of other organs such as the pancreas and liver may determine an increase in postoperative risk and sometimes requires the transplantation of both lung and liver, an exception procedure that has thrived in several specialized centers.\(^5\)

An important aspect in the preparation for transplantation due to cystic fibrosis is the aggressive treatment against malnutrition, often present at the moment of inclusion in the waiting list. Malnutrition is one of the aggravating factors that adds metabolic difficulties to the losses of chronic infections and to the energy consumption that results from the enhanced respiratory effort. A follow-up with an experienced nutritionist, the prescription of diets extremely rich in proteins and calories and the use of more aggressive methods, such as nasoenteral tube and gastrostomy or jejunostomy (if nasoenteral intubation is not possible), have been currently used with the aim of eliminating this severe condition, which is reason enough for exclusion from the waiting list or could result in failure if transplantation is carried out.

Another relevant aspect is the effective previous control of sinus disease, often expressed in the form of pansinusitis. The colonization by the same bacteria found in the lower airways is inevitable in this population; however, patients with retention of secretions that might be an entry point for pulmonary sepsis in the postoperative period are not allowed to be in the waiting list. Large sinusotomies have locally controlled infection, minimizing the risk of aspiration of gross pus by the upper airways. Sinusotomy, albeit considered a small surgery, requires general anesthesia and the patient usually has difficulty resuming respiratory physical therapy, which could cause serious postsurgical complications. In these cases, an intensive preoperative treatment with multiple antibiotics and rigorous physical therapy are mandatory, with 4 to 6 daily sessions.

As patients with cystic fibrosis are permanently colonized by multiresistant bacteria, invariably *Pseudomonas*, and many times associated with *Staphylococcus*, the use of at least one antibiotic drug should be maintained, preferably one that has not been exposed to the bacterial resistance of these patients so that the risks of postoperative infection can be dealt with to some advantage.

### Pulmonary fibrosis

In pulmonary fibrosis, even though life expectancy is expressed in years from the moment of diagnosis (mean of 6.5 years), there are cases in which the disease develops faster despite the adequate clinical treatment. As the evolution of the disease varies from patient to patient, it is currently recommended that a patient with the confirmed diagnosis of fibrosis be investigated by a lung transplant group.

The following elements indicate the moment of selection for transplantation:

- presence of hypoxemia, aggravated by exercise;
- vital capacity of less than 60% predicted;
- gradual deterioration, despite clinical treatment;
- signs of secondary pulmonary hypertension.

The growing need for oxygen supply and the gradual weight loss are important so that the severity of the situation is known and transplantation can be recommended.

In patients with fibrosis in which the lungs are symmetrically affected (which is usually common), there is a preference for left lung transplant due to the easy spatial adaptation of the new organ, placed in a retracted pleural cavity, to match the reduction in size of the fibrotic organ. Without opposition of the liver, left lung transplantation allows a fast descent of the hemidiaphragm, with total expansion of the newly implanted organ.

The selection of the side is always based on the lowest functional participation of a given lung, established on the initial assessment by means of perfusion scintigraphy (Figure 2).

As expected, the greatest difficulty in carrying out a transplant in children is to have a donor with compatible size. Such difficulty is exacerbated in fibrosis, and is characterized by increased chest retraction caused by parenchyma disease, which allows the use of donors 20% smaller than the recipient.

Approximately one third of transplanted fibrotic patients use extracorporeal membrane oxygenation (ECMO). This necessity is predictable because of previous pulmonary hypertension and because of the need for high doses of oxygen.

Anyway, the need for ECMO is defined in the intraoperative period at the moment of clamping the pulmonary artery for pneumonectomy. Since the use of extracorporeal circulation increases morbidity and mortality, several maneuvers have been suggested in order to avoid them, among which we have the use of nitric oxide, which has proved efficient in many cases from the moment of anesthesia. When, despite the use of nitric oxide, the systolic pressure of the pulmonary artery, after its clamping, exceeds 60 mmHg, the patient should be submitted to ECMO, so as to prevent edema of the native lung, which is inevitable when this pressure is maintained during pneumonectomy and graft implantation. In addition, many patients with this pressure level, acutely established by the clamping of the pulmonary artery, have a hemodynamic imbalance, showing low blood pressure, tachycardia, arrhythmia and desaturation, thus making the use of ECMO imperative.

The availability of modern equipment, which allows blood filtration, with removal of the volume at the end of the procedure, is crucial to mitigate the risks involved in extracorporeal circulation. Comparatively, the patients that use ECMO spend a longer time on mechanical ventilation in the postoperative period, being more slowly weaned than those patients who do not require ECMO.
Pulmonary Hypertension

The life expectancy related to this condition is most difficult to predict, especially because many patients have sudden death due to severe arrhythmia.

The higher morbidity and mortality after transplantation due to primary pulmonary hypertension (PPH) and the fact that the results in the medium and long term are worse than those of other treatable diseases have encouraged the search for alternative clinical solutions to this disease. After defining that the use of anticoagulation increases life expectancy of these patients, important advances have been made in the use of vasodilators, initially calcium blockers and more recently, prostacyclin.

A recent review of primary pulmonary hypertension in children showed that life expectancy in five years is 97% against 35% among those who responded and did not respond to the use of calcium blockers. On the other hand, the continuous use of intravenous prostacyclin, in children in whom calcium blocker had failed, the life expectancy in five years was 92%, compared to 29% for children who did not respond to prostacyclin or who did not have the drug available. The same study revealed that the results obtained from IV prostacyclin were comparable to those obtained through transplantation in a three-year follow-up.

Before the advent of continuous infusion of prostacyclin, 30-40% of the patients with PPH succumbed while they waited for transplantation. This new therapy effectively eliminated this dramatic situation, now regarding transplantation not as an ab initio solution, but as a viable alternative to those patients who do not respond to vasodilators or to those who, after an initial response, failed to respond satisfactorily. There are several case reports that suggest there might be greater success with the treatment of PPH when drugs are used in combination, as is the case of prostacyclin and sildenafil, especially when the patient does not respond specifically to one of them, or when the patient develops tolerance of the drug. To arrive at a final conclusion, further studies have to be carried out. Currently, we can safely affirm that lung transplants are no longer the first therapeutic option for patients with pulmonary hypertension. This option is therefore recommended for those patients who did not respond to vasodilator therapy or for those who failed to respond after some time during the treatment.

The following criteria have been suggested as signs for the inclusion in waiting list for lung transplant:
- class III or IV in NYHA;
- lack of response to the regular use of vasodilators;
- PMAP of greater than 80 mmHg;
- heart rate of less than 2.5 l/seg/m²;
- pressure of atrium D greater than 10 mmHg;
- venous saturation of less than 63%.

Technically speaking, the modern tendency is bilateral sequential transplant, with extracorporeal circulation ab initio, although in unilateral transplant the results may be satisfactory. The preference for bilateral transplant is due to the fact that, if an early graft dysfunction occurs (reperfusion injury, edema due to overhydration, rejection or infection), perfusion will be maintained almost exclusively for the transplanted lung, which will result in severe desaturation by severe shunting. This is due to the rigidity of the vascular network of the native lung, which determines that blood flow predominate in the transplanted lung due to its higher resistance, even in the presence of occasional graft dysfunctions.
Despite the systematic use of prophylactic measures, such as water restriction, elevated decubitus with transplanted lung facing upwards, positive expiratory pressure, inhaled or intravenous vasodilators and deep sedation with or without curarization, inexplicable and fast-developing crises of pulmonary hypertension might also occur, with massive pulmonary edema.

Even though the described difficulties can be effectively managed nowadays, there is a common agreement that, whenever possible, transplantation due to pulmonary hypertension should be bilateral.

Lobar transplant

The pioneering experiment conducted by Starnes attempted to solve the problem with obtaining adequate-sized organs for extremely small recipients. Since pediatric donors are even more rare and as there is a growing demand from critically ill recipients, especially among those with cystic fibrosis, lobar transplant, from family-related donors, has become a daring and, at the same time, intelligent proposal.

The ideal candidate for transplant using living donors is that patient with end-stage lung disease, often with cystic fibrosis, in general, a child or an adolescent with a chest cavity about the size of the lobe of an adult. The recipient can be neither so small that the lobe of an adult cannot fit into the chest cavity, nor so big that a lower lobe of an adult cannot fill the pleural cavity. As the matter only concerns spatial adequacy, some lobar transplants have been performed in adults with a small thorax.

Donors should be blood-related, preferably the parents, so that immunological similarity can be used to the maximum advantage. Such similarity is certainly responsible for the favorable outcome in this group of patients.

When this situation is present, the assessment of the three candidates involved starts with blood typing and determination of size compatibility as to the thorax/lower lobe ratio of each of the potential donors.

In regard to the ABO system, the same criteria used for emergency blood transfusions should be applied, although there should ideally be a perfect compatibility between the recipient and each of the donors.

The second item, that is, size compatibility, is essential because, if organs larger than the recipient’s chest cavity are implanted, severe hemodynamic problems may occur as a result of cardiac compression. On the other hand, the attempt to reduce the volume of lobes to be implanted was not successful since it causes hematomas on the lobe, which tend to expand due to the effect of anticoagulation (essential in ECMO) and certainly compromise the initial function of the implanted lobes.

A slightly smaller lung volume is desirable when the recipient has some pulmonary hyperinflation as a result of the underlying disease.

The thorax/lower lobe ratio of each potential donor can be defined nearly with mathematical accuracy by means of helical tomography for measurement of lung volume, according to the technique developed at our service, which traces a line in the middle of the zone with highest vascular rarefaction observed on CT, thus identifying the scissura, establishing the geographical limits of the lobe, and calculating its volume, which is then compared with the volume of the recipient’s chest cavity (Figure 3).

The assessment of donors is resumed with an extensive clinical and laboratory evaluation with the aim of confirming the good health of each candidate, including a complete functional assessment of the lungs and eliminating potential donors with total pulmonary capacity of less than 85% predicted.

Aside from the serological tests for herpes, CMV, toxoplasmosis, Chagas disease, HIV, among others, the candidates are also submitted to fibrobronchoscopy and pulmonary arteriography corresponding to the side to be used for donation with the intention of ruling out some anatomical anomalies that could impair the use of the lobe.

The technique proposed by Starnes uses the lower lobes (right and left) removed from different donors (usually from father and mother) in order to replace one and the other lung, respectively (Figure 4).

The anatomical similarities of the lower lobe to the corresponding lung greatly facilitate the technique of lobar transplant. Our recent experience with seven pediatric patients who received lower lobes from living donors confirms this observation.
requirements and occasional functional losses, such as reperfusion injury, acute rejection and infection, among others;\textsuperscript{14}

- episodes of acute rejection in the postoperative period are frequent and may be intense despite the kinship, which is attributed to the great immunological competence, characteristic of childhood, especially after the age of three. However, as the management of acute rejection with current drugs has been effective, this behavior does not interfere with the outcome;

- since under these circumstances we have two donors, acute rejections in 30\% of the cases are unilateral or, if bilateral, they are asymmetric, showing that the recipient’s body tends to recognize the transplanted organs as foreign bodies, in a different way and at different times. When rejections affect both lobes at the same time, and with the same intensity, functional involvement may be severe (Figure 5);

- the late detection of bronchiolitis obliterans, which is knowingly a chronic rejection, is quite rare in this group in which donors are obligatorily from the same family. In the experiment conducted by Starnes, the comparison between transplant recipients and dead donors, in terms of survival rate, was widely favorable to the first group. The immunological tolerance enhanced by kinship certainly has a significant participation in late results. While in conventional transplants life expectancy in five years is only 50\%, with blood-related donors, life expectancy rises to 72\%, in five years;

- Starnes et al.\textsuperscript{15,16} compared 14 transplant recipients, with living donors, with 11 recipients with dead donors and found that episodes of acute rejection and pulmonary functional tests (FEV1 and FEV25-75%) were comparable in both groups in one year, but in 24 months, the differences were substantial: the group of living donors had no case of bronchiolitis obliterans (BO) whereas 86\% of the patients who received organs from a dead donor showed some sign of bronchiolitis. The subsequent report of the experience of this group, extended to 53 cases, revealed the persistence of the previously observed differences. The low incidence of BO and infection as the main cause of death in the group of living donors led the authors to consider a slighter immunosuppression scheme and a heavier antibiotic therapy for this group.\textsuperscript{17} The authors regard lung transplant with living donors as the ideal procedure for children;\textsuperscript{15}

- another interesting aspect is the growth of the transplanted organ, keeping up with the pace of the recipient. The presence of growth hormone in pediatric recipients explains why a mature organ, implanted in a developing recipient, sustains growth.\textsuperscript{19} The experiment conducted by Ro et al.\textsuperscript{18} showed that the true growth of the airway detected by computed tomography revealed that implanted lobes grow, following the pace of growth of the recipient’s body.

Figure 4 - a) X-rays of a 12-year-old boy with bronchiolitis obliterans and severe hyperinflation. FEV1: 12\% of expected. b) Radiological control 2.5 years after the transplantation of two lobes (lower lobes from parents). Patient resumed normal life. FEV1: 97\% of expected (during this period the patient grew 13 cm, and the vital capacity increased 290 ml)
Peculiarities of lung transplant in very small children

Despite the predictable difficulties in finding small donors, there are some pioneering experiments with lung transplants in very small children. Recently, the Saint Louis group reported an experiment with 19 transplant recipients aged less than six months. In most cases (13 patients), the disease was parenchymatous, while another six presented vascular lung disease. All of them were submitted to bilateral transplantation, and although surgical mortality was higher (32% or 6/19 patients) than that observed in older children, the late survival rate was comparable to other pediatric groups (44% in a maximum follow-up period of six years).

Bronchial complications and episodes of acute rejection are equally comparable; however, chronic rejection seems to be less frequent in this group, especially, with bronchiolitis obliterans in only two out of 13 survivors (15%), in a three-year follow-up. The residual functional capacity and the pulmonary functional tests have gradually increased, suggesting lung growth concomitant with body growth.

Postoperative outcome

The data collected from the Saint Louis International Lung Transplant Registry showed that children have as good an outcome as that of adults, with a survival rate of 67% in their first year, and 57% in the second year, with slight variations from one center to another. The Saint Louis group did not reveal any difference in risk when compared to children with more or less than three years of age at the time of transplantation.

The necessity of mechanical ventilation before transplantation, the need for high doses of oxygen supplementation, the presence of aortopulmonary collateral vessels and prolonged length of ischemia have been repeatedly cited as elements of surgical risk, with impact on early postoperative death.

Acute rejection is as frequent in children as in adults, although it is seemingly less prevalent in children aged less than three years.

The episodes of rejection are more frequent in the first six months, but may occur at any time.

The incidence of chronic rejection or bronchiolitis obliterans (BO) is high among children. The Saint Louis and Pittsburgh groups, which revealed 24% and 50% of BO in adults, showed this late complication in 27% and 18% of pediatric transplant recipients. On the other hand, the reasons for the high rate of BO after cardiopulmonary transplantation due to cystic fibrosis, described in up to 48% of the cases followed up during three years are not clear, although the malabsorption of cyclosporin in cystic fibrosis and the natural growth factors have been regarded as occasionally responsible for higher rates of chronic rejection.

The level of activity and the quality of life are usually optimal after lung transplantation in children. The pulmonary functional assessment usually reaches an excellent peak in six months. In the experiment by Pittsburg, only two of 26 survivors did not return to normal physical activity, and 21 of 22 survivors in the initial experiment by Saint Louis presented good walking condition.

Complications

Infectious complications are more frequent in pediatric transplants, similarly to what occurs in adults, and are more common in the postoperative period of lung transplantations than in any other solid organ transplant.

For still unclear reasons, some infections, such as that caused by the respiratory syncytial virus, adenovirus and parainfluenza, may lead to severe and sometimes fatal infections.
The previous serology for cytomegalovirus (CMV) is negative in most children, increasing the risk of severe infections when these patients are already immunocompromised and have primary infection by CMV. If a CMV-negative patient receives an organ from a CMV-positive donor, the risk is quite high, especially in the form of pneumonia.

The use of prophylactic ganciclovir and probably the use of CMV hyperimmune immunoglobulin may delay the onset and mitigate the severity of the infection caused by CMV.

Similarly to what occurs in adults, ganciclovir is an efficient drug for CMV infections, especially when they manifest themselves as isolated infections. The association with other agents, especially fungal ones, significantly increases mortality.

Infections caused by *Aspergillus* are problematic in pediatric patients. The sources of contamination include fungal aspiration from contaminated environments, colonization of suture lines, and endogenous airway colonization in patients with cystic fibrosis. The infection may be characterized by tracheobronchitis, pneumonia, aspergillosis or invasive aspergillosis. The prophylactic use of inhaled amphotericin or oral itraconazole may reduce the risks of infection by *Aspergillus*.

In patients with cystic fibrosis, the regular colonization of upper airways by gram-negative bacteria increases the risk of contamination of the graft by these bacteria, especially when there is some kind of injury in the transplanted organ. When the initial outcome is favorable, the rule is that the graft remains sterile, but with the presence of reperfusion injury, acute rejection or viral infections, the risk of bacterial proliferation in the transplanted organ increases a lot, from the germs found in the upper airway.

A similar situation is observed in the late postoperative period of cystic fibrosis, when the sputum test after transplantation is often negative, and remains sterile for several months or years, if evolution occurs normally, but with early recolonization by pseudomonas if there are signs of bronchiolitis obliterans.

Bronchial complications due to the smaller diameter of the upper airways in pediatric patients are slightly less frequent in this population, as expected, and are characterized by cicatricial stenosis or bronchomalacia. Bronchomalacia, albeit less frequent among children, is difficult to control due the occlusive tendency of the small airway, especially in expiration. Repeated dilations and, less frequently, the use of bronchial stents might be necessary.

**Peculiarities of pediatric transplantation**

First of all, a distinction between pediatric patients younger and older than three years has to be drawn. In the experience of Barnes Hospital, children younger than three years have less rejection than others, and no cases of bronchiolitis obliterans by chronic rejection were observed among them.

In general, the incidence of bronchiolitis obliterans has been reported in as much as 50% of pediatric patients, which seems to be paradoxical, given that many centers report less acute rejection in these patients, but apparently other factors favor the occurrence of bronchiolitis obliterans, as the frequent viral infections by CMV, and the difficulties in maintaining a uniform immunosuppression in this age group, in function of the higher speed of hepatic elimination of cyclosporin and tacrolimus in this population, thus requiring higher doses and regular administration.

Most children have not come into contact with the Epstein-Barr (EBV) virus, which results in the enhanced risk of this viral infection if they receive an organ from a test-positive donor, and presumably, a higher probability of developing lymphoproliferative disease in the future. In the experiments carried out by St. Louis and Pittsburgh, the occurrence of lymphoproliferative disease was 9% and 22%, respectively.

The most frequent primary site is the transplanted organ, but other areas, such as the CNS, have been described. An interesting aspect of these experiments is the report that, aside from the primary infection by the Epstein-Barr virus, many children received enhanced immunosuppression with cytolytic agents, which seems to favor this late complication. Likewise, the yet incipient experience with tacrolimus suggests that the incidence of lymphoproliferative disease is more commonly observed with this drug than with cyclosporin.

Transbronchial biopsy, considered an essential tool for the follow-up of adult transplant recipients, is problematic in very small children due to the difficult treatment of such a small airway and to the nonexistence of appropriate clips for the collection of samples. On the other hand, the occurrence of bleeding and pneumothorax is more common among pediatric patients.

Another problem that is characteristic of a pediatric patient is venous access, which is usually overcome with the use of total or partial implantable vascular access. The implantable vascular accesses should be removed after a few months so that they will not become a source of bacterial colonization.

**Specific problems of cystic fibrosis**

Cystic fibrosis, a leading indication for lung transplants in many international centers, is associated with several problems in the postoperative period:

- pancreatic insufficiency and the resulting malabsorption of food causes many patients to have osteoporosis, which tends to worsen with the daily use of prednisone in the postoperative period. Bone marrow compression and pathological fractures may represent serious difficulties in these patients;
predisposition to intestinal constipation, also attributed to pancreatic insufficiency, usually worsens after transplantation as a result of patient’s immobility, sedation with narcotics and reduction of intestinal motility determined by azathioprine. The prophylaxis and early detection of this complication can avoid intestinal perforation and unnecessary and risky surgeries;

the inevitable colonization of the airway of a cystic patient by *P. aeruginosa* and similar germs poses an additional risk to infection of the graft by these bacteria. Some centers, such as that in Toronto, considers the previous colonization by *Burkholderia cepacia* an absolute contraindication for transplantation. Other centers do not go so far as to contraindicate the transplant, but admit that the presence of this agent increases the morbidity and mortality in the early postoperative period. Other microorganisms, such as *Stenotrophomonas maltophilia* (Xanthomonas), *Alcaligenes xylosoxidans* and *Aspergillus fumigatus*, often persist in the respiratory epithelium of the trachea and of the facial sinuses, and represent a great therapeutic challenge in immunocompromised patients;

the tendency of chronification of sinusitis by the germs mentioned above asserts the importance of an appropriate pretransplant preparation, by means of large sinusotomies and an aggressive treatment with antibiotics in the postoperative period. This tendency has been ascribed to the immunological imbalance caused by uncontrollable chronic sinusitis with propensity for chronic rejection, observed in patients transplanted due to cystic fibrosis, since systemic inflammation may alter the P-450 metabolism of immunosuppressants, especially of cyclosporin A;

other problems result from the difficult absorption of the drugs and require different strategies for the treatment of these patients. It is not clear whether cyclosporin and tacrolimus have a different metabolism in cystic fibrosis, but the elimination of prednisone is faster, and many antibiotics, especially aminoglycosides, should be given in higher doses and at shorter intervals than what is recommended for other transplant recipients;

the absorption of cyclosporin, hampered by the initial formulation, significantly improved with the development of Neoral (Sandoz, East Hanover, NJ), a microemulsion that is better absorbed by all patients, including the cystic ones;

presumably due to the great variability in the absorption of cyclosporin, cystic patients are at a greater risk for neurological complications in the postoperative period than other patients.

Follow-up of pediatric transplant recipients in the long term

The pediatric patient, just as the adult one, returns to his/her city of origin after postoperative recovery has been well established, with adequate immunosuppression and preserved pulmonary function.

The family is informed that any clinical change must be reported because it may mean the onset of a remarkable complication, especially of CMV infection, or incipient manifestations of bronchiolitis obliterans. A permanent contact between the pediatrician and the transplantation center is crucial for the successful follow-up of the patient.

Any change in medication should be jointly analyzed, due to the frequent interaction of drugs that could change the immunosuppressive action.

The patient has to return to the transplantation center on a regular basis for periodical follow-ups, transbronchial biopsy and occasional adjustments to immunosuppressant drugs. After six months, it should be possible to define the transplant recipient as a rejector or non-rejector. Based on these elements, the administration of drugs may be occasionally reduced, and an ideal dosage that ensures the prophylaxis of rejections with minimal adverse effects should be attempted.

The routine of physical exercises and nutritional rehabilitation, quite often implemented before the transplant, should be maintained and intensified, with the aim of allowing as normal a lifestyle as possible.

Avoiding exposure to harmful elements, such as tobacco and dust, is very important; however, this concern should not interfere with school activities and other activities that are normal for the patient’s age.

Conclusions

Lung transplant has increasingly established itself as a reliable therapeutic option for those children with end-stage respiratory diseases, with a survival rate similar to that of adults. Cystic fibrosis is the most frequent indication for transplantation in children, followed by vascular lung diseases and idiopathic pulmonary fibrosis. Infectious complications, especially the viral ones, are frequent, and the lymphoproliferative disease is more common in children, probably because many of them are subject to primary infection by the Epstein-Barr virus after transplantation.

Other complications, such as hypertension, hypercholesterolemia, renal dysfunction and airway stenosis, are similar to those described in adults. Children with cystic fibrosis have to cope with some difficulties related to the underlying disease, but life expectancy after transplantation has increased as surgical experience is improved.
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References


Correspondence:
Dr. José Jesus de Camargo
Rua Mostardeiro, 333/516
CEP 90430-000 – Porto Alegre, RS, Brazil
E-mail: jcamargo@plug-in.com.br