Pediatric lung transplantation: update 2003

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Lung and heart-lung transplants were first performed successfully in the early 1980s [1,2]. Currently, lung transplantation is considered an appropriate therapy for end-stage pulmonary disease in adults. The most recent annual report of the registry of the International Society for Heart and Lung Transplantation (ISHLT) indicates that through 2001, more than 17,500 lung and heart-lung transplants had been performed worldwide [3]. The experience with pediatric lung transplantation has developed more slowly [4–8]. According to the fifth ISHLT pediatric registry report [9], more than 1200 pediatric lung and heart-lung transplants have been performed worldwide through 2001. This article regarding the current status of pediatric lung transplantation describes indications, outcomes, and complications, with particular emphasis on information useful to the pediatrician and pediatric pulmonologist. The primary sources of data are the most recent ISHLT registry reports [3,9]. Additional information was extracted from the clinical database of the pediatric lung transplant program of St. Louis Children’s Hospital at Washington University (SLCH), which, over the past decade, has accounted for 30% to 50% of total pediatric lung transplants (Fig. 1).

Indications

The indications for pediatric lung transplantation initially paralleled those in adults. Patients with cystic fibrosis (CF), pulmonary hypertension (primary and secondary), and chronic interstitial lung diseases comprised most of the initial pediatric lung transplant recipients. As experience has increased, however, indications have expanded, particularly into the infant population. Roughly 20% of the patients who undergo transplantation at SLCH are younger than 3 years at transplant. Compared with older patients, the indications for infant transplant are somewhat different (Fig. 2). Among the diagnoses in infancy are alveolar...
proteinoses, such as surfactant protein B deficiency, and interstitial diseases of infancy, including surfactant protein C deficiency [10,11].

Contraindications

Not surprisingly, the contraindications for lung transplantation also have changed over time. Conditions that would be made significantly worse or more difficult to treat as a result of immunosuppressive regimen remain absolute contraindications (Box 1). Other conditions, such as colonization with *Aspergillus fumigatus* or *Burkholderia cepacia* (in CF), prior pleurodesis, and systemic steroid dependence, are no longer absolute contraindications in at least some centers. Conditions that would impose increased risk and warrant consideration before embarking on lung transplant are listed in Box 2.

Addressing psychosocial contraindications is a particularly difficult aspect of pediatric transplantation. There must be ample evidence to support a decision to deny a child the opportunity to undergo transplant because the child or the family has had difficulty adhering to a medical regimen or obtaining consistent access to follow-up care. Generally in these situations, the child and family is provided support and given structured opportunity to demonstrate substantive change. Because cadaveric organs remain scarce, however, transplant may not appropriate if, despite these interventions, change does not occur.

Types of lung transplant

**Bilateral sequential lung transplant**

The most common pediatric lung transplant procedure currently performed is the bilateral sequential transplant [12]. This technique involves sequentially
implanting each lung separately. The mainstem bronchus and pulmonary artery are connected via end-to-end anastomoses. The two pulmonary veins from each lung are harvested intact with a patch of donor left atrium. Each left atrial patch is then sewn to the recipient left atrium. In pediatric recipients, this procedure is usually performed using cardiopulmonary bypass.

Heart-lung transplant

Because of technical limitations associated with the mainstem bronchial anastomoses, the initial transplant operation performed for patients with end-stage lung disease was a heart-lung transplant, with the option for the heart of the recipient being given in a “domino” procedure to a patient waiting for a heart transplant [13]. Once techniques were developed that allow successful healing of
the mainstem bronchial anastomoses [14], the frequency of heart-lung transplant, particularly in the United States, decreased significantly. Since 1990, the frequency of pediatric heart-lung transplant procedures has decreased by more than 50% [9]. In the past, heart-lung transplant also may have been considered in patients with cor pulmonale associated with pulmonary hypertension. In general, the right-sided cardiac dysfunction associated with cor pulmonale resolves after lung transplantation. Heart transplant is generally no longer considered in the context of isolated pulmonary hypertension. Currently, heart-lung transplant in pediatric recipients is not indicated unless there is significant left ventricular dysfunction or a congenital cardiac abnormality that is not amenable to repair.

Single lung transplant

Although used more commonly in adults, single lung transplantation has been used sparingly in children. There are two main reasons for this. First, the most common indication for pediatric lung transplant is CF. In this setting, the remaining, chronically infected, native lung would put the transplanted lung at substantial risk for infection. Second, the effectiveness of growth of the transplanted lung remains an open question. Because of the chronic graft dysfunction exhibited by a significant percentage of lung transplant recipients, transplanting as much tissue as possible into a growing child seems appropriate.

Living donor transplant

The scarcity of cadaveric organs and unpredictability of end-stage lung disease led Starnes et al [15] to develop the technique of living donor lobar transplant (LDLT). In this operation, two separate donors each undergo a lower lobectomy to provide a right and left lower lobe that serve as the right and left lungs for the recipient. Size limitations provide practical limits for the population of potential recipients. Adult lobes are generally too large for successful implantation into children younger than 5 years. For adolescents taller than 60 inches, it may be difficult to find donors tall enough to provide adequate lung tissue. Although the outcomes after LDLT have been comparable to cadaveric transplant [16,17], the technical and ethical complexities of this operation (including potential risks to
Box 2. Pediatric lung transplantation: relative contraindications

- Symptomatic osteoporosis
  - Treat aggressively before and after transplant
- Severe musculoskeletal disease
- Corticosteroids
  - Attempt to minimize dose before transplant
- Nutrition
  - Ideally between 70% and 130% of IBW
- Invasive ventilation
  - Risk factor in adults; risk less clear in infants
- Fungal and atypical mycobacterial colonization
  - Consider pretransplant treatment and posttransplant prophylaxis
  - May preclude single lung transplant
- Psychosocial issues
  - Major psychoaffective disorder
  - Poor adherence (must have ability to follow complex medical regimen)
  - Limited access to follow-up care (for financial or geographic reasons)

the donors) have prevented it from being used widely. According to the United Network for Organ Sharing, the only pediatric centers that have performed more than two LDLTs are Children’s Hospital of Los Angeles and SLCH [98].

When to refer for transplant?

Currently, the waiting time for cadaveric organs for an adolescent patient may be 2 years or longer (Table 1). Even in children younger than 5, the waiting time has increased. For this reason, referral to a lung transplant center often must be made before the disease process progresses to the point of significant functional impairment. In CF, the initial recommendations were to refer patients for transplantation when the FEV₁ dropped below 30% predicted [18]. Other studies have attempted to identify additional risk factors for poor prognosis [19–21]. CF lung

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disease, however, remains unpredictable. The author recommends referral to a lung transplant center for evaluation when the FEV$_1$ is persistently below 40% predicted. Similar data are available for pulmonary hypertension, although the use of epoprostenol has prolonged survival in recent years [22,23]. Consultation with a lung transplant center is recommended at the time when epoprostenol is initiated. For other causes of end-stage lung disease, few data are available to predict prognosis. Finally, it is important to understand that once the idea of a lung transplant evaluation is broached, family reluctance and insurance considerations may create extended delays. It is advisable to consult a lung transplant center well before anticipated evaluation. In general, there are limited downsides to an early referral.

**Survival**

The most recent pediatric ISHLT registry report gives an overall survival rate for pediatric lung transplant recipients of 76% at 1 year, 64% at 3 years, and 43% at 5 years (St. Louis Children’s Hospital Lung Transplant Program, unpublished data, 2003). These values are comparable to the adult experience [3] and to the SLCH
experience (Fig. 3). Comparison of subpopulations at SLCH continues to show that patients with lung disease other than CF have better survival than patients with pulmonary vascular disease or CF (Fig. 3). Survival rate of infants is comparable to that of older children (Fig. 4). Outcomes after retransplantation are consistently worse than primary transplants in children (see Fig. 3) and adults [24,25]. The most significant risk factors for poor outcome after lung transplant in adults include repeat transplant, mechanical ventilation at transplant, and diagnosis of congenital heart disease [3]. Similar findings were obtained from an analysis of risk factors at SLCH [26].

The causes of death in pediatric recipients parallel those in adult recipients [3,9]. Early graft dysfunction accounts for most deaths in the first 30 days after transplant. Infection is the primary cause of death for the remainder of the first year. For cadaveric transplant recipients, bronchiolitis obliterans (OB) is the most common cause of death beyond the first year. In contrast, death as a result of OB is much less frequent in LDLT recipients [27].

Complications

The most common complications after lung transplantation fall into three general phases. For the purpose of this discussion, the first few days after transplant
comprise the “immediate phase,” the next several weeks are denoted “early phase,” and beyond 3 months after transplant is called “late phase.”

**Immediate phase complications**

Complications that manifest in the immediate phase fall into four major categories: hyperacute rejection, early graft dysfunction, surgical complications, and infection.

**Hyperacute rejection**

Hyperacute rejection is a rare but important complication that generally arises from prior exposures to foreign tissue antigens. The most common sources of exposure are blood transfusions or (more commonly in adult women) pregnancies. These exposures lead to the presence of antibodies in the recipient’s serum that bind to tissue antigens of the donor and cause complement-mediated graft injury. In the most severe cases, hyperacute rejection can lead to severe vascular inflammation and thrombosis and loss of the graft. The panel reactive antibody test identifies patients who may be at increased risk for hyperacute rejection. For such patients, either prospective or simultaneous cross-match with donor leukocytes is undertaken at the time of transplant. For patients with a positive cross-match, treatment with plasmapheresis in the immediate posttransplant period, often accompanied by cytoxan, is usually successful at controlling hyperacute rejection [28].

Hyperacute rejection is also one of the major hurdles faced in xenotransplantation. Humans have circulating antibodies to tissue antigens of many of the species that would make good organ donors, including pigs and primates. Much of the work in xenotransplantation in the past decade has focused on limiting the complement-mediated injury associated with hyperacute rejection [29].

**Early graft dysfunction**

The ischemic injury that occurs as a result of the process of harvest and reimplantation of the donor lungs may lead to significant early dysfunction of the graft. The response to this injury after transplant varies but generally correlates with the length of ischemic times and, in the author’s experience, with mechanical ventilation at the time of transplant [30]. The role of donor factors (cause of death, presence of subclinical pulmonary injury, time from brain death to organ harvest) and recipient factors (use of cardiopulmonary bypass, presence of chronic infection or inflammation) remains to be elucidated fully. The incidence is estimated to be from 13% to 35% [31].

Patients with early graft dysfunction develop a clinical syndrome consistent with noncardiogenic pulmonary edema, including decreased lung compliance and poor oxygenation. Generally, ischemic times less than 5 hours are well tolerated. Using more recently developed preservation solutions, however, ischemic times as long as 7 hours have been tolerated with little evidence of early graft dysfunction.

In general, supportive therapy (mechanical ventilation and careful fluid management) for early graft dysfunction is successful. Extracorporeal membrane
oxygenation has been used successfully in severe cases [32], although the success
with extracorporeal membrane oxygenation in this context in the SLCH experi-
ence has been limited. Nitric oxide or other drugs that limit the release or effects
of active inflammatory mediators also may be beneficial [33–35].

**Surgical complications**

In addition to postoperative bleeding, the airway and vascular anastomoses are
the source of the major surgical complications that require attention in the
immediate posttransplant period. A nuclear medicine perfusion scan can provide
relatively sensitive assessment of the patency of the pulmonary vascular anasto-
moses. In LDLTs, in which the vascular anastomoses, particularly the pulmonary
venous anastomoses, may be technically difficult, intraoperative transesophageal
echocardiography may be used to verify patency. At SLCH, the bronchial
anastomoses are inspected at bronchoscopy within 24 hours after transplant.
The most common indication for reoperation is persistent bleeding, either from
the vascular anastomoses or the chest cavity. In the series at SLCH, early
reoperation occurred in 11% of cases (unpublished data).

Vocal cord and hemidiaphragm paresis and paralysis are surgical complica-
tions that may become apparent in the immediate posttransplant period. Injury to
the recurrent laryngeal nerve or phrenic nerve at the time of dissection is believed
to be responsible for these findings. The incidence of these complications in the
author’s experience is higher for patients who have had prior thoracic surgery
(either cardiac repair or prior transplant). Most of these injuries resolve in the first
several months after transplant. A few patients with hemidiaphragm paralysis and
persistent respiratory failure or recurrent infection have undergone plication of
the affected hemidiaphragm.

**Infection**

Lung transplant recipients receive immunosuppression medications indefinitely
after receiving a transplant. For this reason, infection is a concern at any time after
transplant. The pulmonary allograft is particularly vulnerable to infection in the
immediate posttransplant period for several reasons, many of which relate to poor
mucus clearance. Ciliary function may be impaired as a result of early graft dys-
function. Tissue integrity can be interrupted as a result of mucosal sloughing just
distal to the mainstem bronchial anastomoses. Cough may be impaired because of
weakness, postoperative pain, and impaired diaphragm function (as a result of
phrenic nerve injury). Patients with poor nutritional status may have low immuno-
globulin levels and decreased immune function. The use of cardiopulmonary
bypass (common in most pediatric centers) may further reduce IgG levels [36,37].
For most patients, the level of immunosuppression is greatest in the first several
months after transplant, particularly in centers that use an induction agent as a
component of the initial therapy.

Prophylactic antibiotics are used perioperatively, chosen based on organisms
known to be harbored by the recipient, and adjusted based on results of cultures
obtained from the donor. Antibiotics include ganciclovir when the donor or
recipient has evidence of cytomegalovirus (CMV) infection and antifungal agents if fungus is present. Despite appropriate prophylaxis, recipients with significant pretransplant pulmonary infection, most commonly patients with CF, may have seeding of their bloodstream with bacterial organisms and toxins during lung explantation. In the SLCH series, a few patients have developed bacteremia and, rarely, septic shock. Because of the poor outcomes in these instances, the author considers evidence of sepsis or systemic inflammatory response syndrome a relative contraindication to lung transplant.

Acute viral infection present in the donor or recipient at the time of transplant can lead to catastrophe, particularly in infants and small children who may have a limited repertoire of antiviral antibodies. In particular, parainfluenza and adenovirus have been reported as major causes of morbidity in pediatric lung transplant recipients [38–40].

**Early phase complications**

Problems that arise during the first several weeks after transplant continue to include infection and complications related to the surgical procedure. The primary immunologic complication during this period is acute rejection. Noninfectious complications related to side effects of immunosuppression also begin to appear.

**Acute rejection**

Acute cellular rejection, manifested histologically by perivascular lymphocytic cuffing in the small vessels of the graft, is a common complication in the first weeks to months after transplant (Fig. 5). Acute rejection may be asymptomatic; however, patients with significant acute rejection may present with symptoms of infection.

Fig. 5. Acute rejection frequency. Frequency of acute cellular rejection (grade A2 or more) in the Saint Louis Children’s Hospital population. (From Saint Louis Children’s Hospital Program 2002; with permission.)
with fever, dyspnea, and hypoxia. Chest radiograph may show perihilar infiltrates or bilateral pleural effusions. Spirometry shows diminished FEV₁ and FVC, often with an obstructive pattern. It may be difficult to distinguish between rejection and infection on clinical grounds alone. In such cases, appropriate evaluation includes bronchoscopy, bronchoalveolar lavage, and transbronchial biopsy. Biopsy specimens are assigned a histologic grade A0 (none) to A4 (severe) using a standardized grading system [41]. Acute rejection grade A2 and above is usually treated with high-dose steroids (methylprednisolone 10 mg/kg intravenously, daily, for 3 days). Most patients promptly respond to steroid therapy with clinical improvement and return of FEV₁ and FVC to baseline. Despite this, acute rejection episodes are significant risk factors for late complications. If rejection persists (usually on the basis of repeat transbronchial biopsy 2 weeks after completion of therapy), patients receive treatment with a mono- or polyclonal T-cell antibody preparation (ie, antithymocyte globulin, or OKT3).

As indicated in Fig. 5, the incidence of acute rejection is highest in the first several months after transplant and is seen much less frequently beyond 1 year after transplant. Infants tend to have a lower frequency of acute rejection than older children (Fig. 5) [26].

**Infection**

Because of life-long immunosuppression, infection remains a significant concern throughout the posttransplant course. CMV infections, especially in CMV-negative recipients who received lungs from a CMV-positive donor, and bacterial lower respiratory tract infections are of particular importance during that time. Prophylaxis for opportunistic infections, including *Pneumocystis carinii* and candidiasis, is usually initiated in the first two weeks after transplant.

**Cytomegalovirus.** Pediatric patients are more likely to be CMV negative and are thus at higher risk. The development of ganciclovir has decreased dramatically the incidence and morbidity of CMV-related infections [42]. CMV remains a potential source of significant morbidity and, rarely, mortality in pediatric lung transplantation [43].

CMV may be localized to the lung and cause pneumonitis. Diagnosis is based on positive immunohistochemistry in lung tissue. In general, a bronchoalveolar lavage culture that is positive for CMV is not specific for significant disease. CMV pneumonitis presents with fever, respiratory distress, hypoxia, and interstitial infiltrates. CMV also can involve the gastrointestinal tract. Fever, abdominal pain, and elevated serum transaminases are commonly observed in this instance. Finally, CMV can be a systemic illness with virema.

The approach to prophylaxis and treatment of CMV continues to vary among transplant centers. Prophylactic treatment of patients at risk (either donor or recipient positive) with intravenous ganciclovir for 4 to 6 weeks or longer after transplant is one approach [42]. Unfortunately, after prophylactic therapy is discontinued, patients may develop CMV pneumonitis or CMV viremia and require further courses of ganciclovir. The other main approach to CMV involves
the use of rapid immunohistochemical or molecular techniques that identify patients at risk before clinical symptoms develop. Such patients are then given “pre-emptive” therapy [44,45].

**Bacterial lower respiratory tract infection.** Although patients may develop evidence of bacterial lower respiratory tract infection at any point after transplant, they remain at increased risk during this period because of the multiple factors described previously. Acute rejection also remains an important consideration. Although empiric therapy with antibiotics to cover organisms present in sputum culture or prior bronchoalveolar lavage may be successful, lavage and transbronchial biopsy should be performed in patients who have significant illness or failure to respond promptly. A quantitative bronchoalveolar lavage culture that contains more than $10^6$ cfu/mL of an organism (or more than $5 \times 10^5$ cfu/mL with respiratory symptoms) warrants intravenous antibiotic therapy.

**Surgical side effects**

Surgical complications that manifest in the early posttransplant phase include airway complications, gastrointestinal difficulties, and arrhythmias.

**Airway complications.** One of the crucial steps in the success of lung transplantation was the use of an omental wrap to improve the healing of the mainstem bronchial anastomosis [14]. A modification of that technique using a pericardial wrap is currently typically used [12]. Complications at the level of the bronchial anastomosis have diminished significantly with the use of these techniques. A subset of patients continues to suffer morbidity related to the airway anastomoses. The most common scenario involves narrowing at the level of the suture line, usually related to the development of granulation tissue. This process evolves slowly. Patients present in the second or third month after transplant with obstructive spirometry, wheezing, and often a biphasic flow-volume loop. Treatment involves dilation of the involved region using a rigid bronchoscope and balloon catheter. In pediatrics, the placement of silastic or metal airway stents is avoided because of the potential for airway growth and the likelihood of development of granulation tissue at the distal end of the stent.

Partial or complete dehiscence of the anastomosis has been rare in the SLCH experience and most often has been associated with infection.

**Gastrointestinal complications.** Gastrointestinal complications after lung transplant are fairly common. The incidence in one study was 50% [46]. The most common complications in that study were gastrointestinal dysmotility and gastropareis. Dysmotility is hypothesized to be a result of injury to the thoracic vagus nerve during the mediastinal dissection at transplant. Neuropathy, infection (ie, CMV), and effects of underlying disease also have been proposed as potential contributing factors [46]. A significant concern in this group of patients is the possibility that gastrointestinal dysmotility can lead to reflux, microaspiration, lung injury, and ultimately OB [47]. Gastrointestinal dysmotility may be particularly
problematic in infants who are developmentally predisposed to gastroesophageal reflux. In two patients in the SLCH experience, gastrointestinal dysmotility and reflux was believed to be a significant contributor to graft failure [48]. Fundoplication should be considered in any lung transplant recipient with significant reflux.

In recipients with CF, gastrointestinal dysmotility also can predispose to distal intestinal obstruction syndrome. Because narcotics used for pain management may decrease motility further, this complication is more frequent in the early posttransplant period. Distal intestinal obstruction syndrome in the posttransplant patient with CF may be particularly difficult to treat. Several patients with CF in the SLCH experience have undergone exploratory laparotomy in this setting [49]. Lactulose may be used postoperatively as prophylaxis for distal intestinal obstruction syndrome in patients with CF. LDLT recipients (for whom the procedure is generally scheduled in advance) may benefit from more aggressive clearance of the gastrointestinal tract before surgery.

**Arrhythmias.** Arrhythmias after lung transplantation are generally supraventricular, including supraventricular tachycardia atrial flutter, and atrial fibrillation. They are believed to result from alterations in the integrity of the atrial muscle along the suture lines where the donor pulmonary veins are attached to the recipient via a left atrial patch. Although generally well tolerated, the arrhythmias may be associated with hemodynamic compromise. Most arrhythmias respond to conventional therapy and are self-limited [50].

**Medication side effects**

Most pediatric lung transplant centers use a three drug immunosuppression regimen that includes a calcineurin phosphatase inhibitor (CNI), such as cyclosporine or tacrolimus, a purine synthesis inhibitor (azathioprine or mycophenolate mofetil), and a corticosteroid. The common side effects of these medications are well known and are not discussed in depth. However, a few important complications associated with the CNI are discussed.

**Neurologic complications.** Neurologic complications are fairly common in the early phase after lung transplantation. In one series, the incidence was reported to be 47% [51]. Seizures are the most common and concerning complication. Calcineurin phosphatase inhibitors are believed to cause cerebral vasoconstriction, which leads to relative cerebral ischemia and ultimately seizures. This hypothesis is supported by findings on MRI. The predominance of seizures in the early posttransplant period and the poor correlation with calcineurin phosphatase inhibitor levels remain to be explained, however. Most seizures are self-limited and do not require long-term medication. For the small subset of patients with persistent seizures, an anticonvulsant agent should be chosen that does not interact significantly with the metabolism of cyclosporine or tacrolimus.

**Hypertension.** Thirty-six percent of pediatric lung transplant recipients report hypertension at 1 year after transplant, and 71% of patients report hypertension at
5 years after transplant [9]. The cause is likely multifactorial, including the renal vasoconstrictive effects of calcineurin phosphatase inhibitors and the hypertensive effects of systemic steroids. The hypertension is usually amenable to therapy with calcium-channel blockers or angiotensin-converting enzyme inhibitors.

**Diabetes.** Diabetes is reported in approximately 20% of patients at 1 year and 28% of patients at 5 years after lung transplant. Most cases of diabetes occur in patients with CF [9], which is likely related to pre-existing chronic pancreatic islet injury related to their CF. Diabetes may be precipitated by insulin resistance caused by administration of pulse steroids in the context of acute rejection or by institution of tacrolimus therapy (believed to be related to direct pancreatic effects of tacrolimus).

**Renal dysfunction.** Hypomagnesemia and, to a lesser extent, renal tubular acidosis are the most commonly seen renal complications in the early posttransplant period. They are usually amenable to oral supplementation. Significant renal failure early after transplant is usually related to underlying renal disease in the recipient. Chronic renal insufficiency is a late transplant complication, and patients who present for lung retransplantation have a higher incidence of acute renal failure in the early posttransplant period.

**Late phase complications**

The two most important late complications of lung transplantation are bronchiolitis obliterans (OB) and malignancy. These two entities combined account for nearly half of the deaths beyond 1 year after transplant. As the population of pediatric lung transplant recipients ages, chronic renal insufficiency also is becoming more prevalent [9].

**Bronchiolitis obliterans**

Despite nearly 20 years of experience, lung transplantation has not achieved long-term survival rates comparable to other solid organ transplants. The primary reason for this is OB. At 5 years after transplant, approximately half of lung transplant recipients carry the diagnosis of OB. OB accounts for more than 40% of deaths that occur beyond 1 year after transplant [9]. Basic scientific and clinical research is ongoing, yet the etiology of OB remains elusive.

OB is a histologic diagnosis based on the presence of lymphocytic infiltration, fibromyxoid airway deposits, subepithelial fibrosis, and total fibrous obliteration of the bronchioles. Because it is a focal process, transbronchial biopsy is an insensitive diagnostic tool. Even open lung biopsy is not 100% sensitive. For this reason, the term “bronchiolitis obliterans syndrome” was coined as part of a set of clinical criteria based on otherwise unexplained development of obstructive changes in pulmonary function [52]. A bronchiolitis obliterans syndrome grade of 1 or more (which reflects a decline in FEV₁ more than 20% from the posttransplant best) is highly suspicious for OB. The most recent revision of the bronchiolitis
obliterans syndrome clinical criteria recognized that because of growth effects, percent predicted values should be used in calculating the bronchiolitis obliterans syndrome grade for pediatric recipients rather than absolute values [53].

The most comprehensive hypothesis suggests that OB is a process of airway epithelial injury (from ischemic, infectious, immunologic, and perhaps mechanical sources) followed by an aberrant repair response, perhaps driven by alterations in profibrotic cytokines, such as transforming growth factor-β [54] or platelet-derived growth factor [55].

Multiple clinical studies that involved primarily adult populations have described risk factors for OB and are well summarized in a recent comprehensive review [56]. The role of immune-mediated processes is supported by the identification of acute rejection as the most important risk factor. Patients particularly at risk include persons who experience more frequent [57] or more severe [58] rejection episodes. Other immunologic risk factors include lymphocytic bronchitis and bronchiolitis [59] and anti–human leukocyte antigen antibodies [60]. OB was less likely to develop in patients who demonstrated decreased donor alloreactivity, on the basis of peripheral microchimerism and absence of donor antigen reactivity in bronchoalveolar lavage lymphocytes [61,62].

Infection is less clearly defined as an OB risk factor. The most commonly implicated infection is CMV [60,63–66]. In one center, the institution of ganciclovir prophylaxis against CMV infection reduced the incidence of OB in the first year after transplant [67]. Finally, indirect evidence suggests a role for community-acquired viral infections in the development of OB [68,69].

Although bacterial infections are not believed to be a significant risk factor for OB [63], infection clearly becomes a predominant component of the disease. Chronic lower respiratory tract infections may be exacerbated by the augmented immunosuppression used to treat OB and contribute significantly to the cause of death in these patients [70].

Populations with lower risk for the development of OB include young children (Fig. 6) [71] and LDLT recipients at Children’s Hospital of Los Angeles [27] and SLCH (unpublished data). Independent risk factors for OB identified in the SLCH population included acute rejection grade A2 or more and prolonged ischemic time [30]. Based on these data, researchers believe that the lower incidence of OB in infants may be related to a decreased incidence of acute rejection, and in LDLT recipients it may be related to shorter ischemic times.

Attempts to establish an animal model of OB have met with limited success. One widely used approach has been analysis of subcutaneously implanted tracheal or airway segments first described by Hertz et al [72]. A review of this literature is beyond the scope of this article. The data, however, support important roles for immune-mediated injury and profibrotic growth factors [73–75]. The integrity of the airway epithelium seems to play a critical role [76]. Finally, the studies of the effect of immunosuppressive agents using this model support the use of rapamycin and its analogs in the therapy for OB [77,78].

Treatment of OB remains difficult. The cornerstone of therapy remains augmented immunosuppression. There are limited, mostly anecdotal, data to
support such treatments, including antithymocyte preparations [79], cyclophosphamide [80], methotrexate [81], photopheresis [82], and total lymphoid irradiation [83]. Each treatment may be of benefit in selected patients. None is uniformly successful. Altering the baseline immunosuppression from cyclosporine to tacrolimus also may stabilize patients [84,85]. Clearly, the ultimate long-term success of lung transplantation depends on developing more effective therapy for OB.

**Malignancy**

The overall incidence of malignancy in pediatric lung transplant patients is 6.5% at 1 year and 8.2% at 5 years [9]. Most malignancies are posttransplant lymphoproliferative disorder (PTLD), often identified as non-Hodgkin’s lymphoma. In a single center study, the major risk factor for development of PTLD was diagnosis of CF (odds ratio 5.8). With the CF subpopulation, the most significant risk factor was two or more episodes of acute rejection in the first 3 months after transplant (odds ratio 11) [86].

Until recently, initial therapy for PTLD involved empiric reduction in immunosuppression with close follow-up of the tumor. Although many patients with PTLD respond to this approach, in the author’s experience, a significant percentage of patients who do respond develop OB. Patients who fail to respond to reduction in immunosuppression are generally offered chemotherapy. In
contrast to other solid organ recipients [87], standard chemotherapy has had a significant infectious mortality at SLCH.

Therapy for PTLD has been altered significantly in the past few years by the development of monoclonal antibodies that specifically target CD20, a B-cell surface marker [88]. Recent case reports suggest that CD20 antibodies may be used successfully for the initial treatment of PTLD tumors that express the CD20 antigen [89,90]. Patients treated with reduced immunosuppression and CD20 antibodies may achieve rapid remission. This approach has the potential benefits of shortening the period of time that the transplanted lung is at risk for rejection and avoiding the infectious risks associated with chemotherapy.

Renal failure

The chronic renal vascular effects of calcineurin inhibitors and ongoing exposure to nephrotoxic drugs, such as aminoglycosides, may lead to chronic renal insufficiency in lung transplant recipients. Significant renal dysfunction at 1 year after transplant was reported in approximately 7.7% of patients. At 5 years, more than 26% of survivors with complete follow-up had abnormal renal function, including 4.3% who required chronic dialysis and 2.2% who underwent renal transplant [9]. In the SLCH experience, three patients—two adolescents who received transplants because of CF and one patient who received a transplant for OB related to bone marrow transplant who had received long-term tacrolimus—developed severe renal dysfunction and were referred for renal transplantation. Two patients who received living related kidney transplants are doing well. The third patient is awaiting identification of a suitable donor.

Growth

Growth of the patient and the transplanted organ is an ongoing concern in pediatric solid organ recipients [91]. Most centers gradually reduce the dosages of immunosuppressive agents, particularly steroids, in the first year after transplant in an effort to minimize growth impairment. In the SLCH experience, the overall rate of somatic growth was approximately 64% of the predicted values [26].

The assessment of lung growth is more difficult. Routine measurements of pulmonary function primarily assess volumes of gas exchanged. Increases in these values may reflect increase in the average volume of each alveolar unit rather than an increase in the number of alveoli or surface area for gas exchange. Pulmonary function measurements after lung transplant can return to the normal range in infants [92] and older children [26], which suggests that an increase in lung volume and gas exchange proportionate to somatic growth occurs.

General pediatric considerations

After successful lung transplantation, most children return to their home community and receive routine pediatric care there. Although most pediatric lung
transplant centers continue regular follow-up, often the pediatrician or pediatric pulmonologist is the first care provider to assess a lung transplant recipient with an acute illness. Although lung transplant recipients are susceptible to common pediatric illnesses, the presence of their lung graft and their immunosuppressed state require consideration when choosing therapy.

**Acute respiratory illness**

Ideally, the assessment of an acute respiratory illness in a lung transplant recipient should include investigation for common viral illnesses, sputum or deep throat culture, chest radiograph, and measurement of oxygen saturations and spirometry (most centers provide equipment to monitor oximetry and spirometry at home). For patients less than 1 year after transplant, the frequency of acute rejection is high enough that transbronchial biopsy should be considered. New pulmonary infiltrates should be treated aggressively, including diagnostic bronchoscopy, if the respiratory illness is severe or does not respond to empiric therapy. Although it is tempting to treat airflow obstruction or acute wheezing with β-agonists and bursts of oral steroids, these symptoms may indicate the onset of OB. Consultation with the transplant center for management in this context is warranted.

**Assessment of fever**

Fever in a lung transplant recipient should be investigated aggressively. Many patients have permanent central venous catheters that warrant culture. In the absence of an identifiable source, assessment for viral illness with nasopharyngeal swab and viral blood culture is appropriate because CMV is an important treatable disease in this setting. The other potential process that can present with unexplained fever is PTLD. The lung transplant center should be consulted for management of any fever that persists more than 7 days without explanation.

**Medications and immunizations**

It is important to recognize that many medications commonly used in general pediatric practice have the potential to alter the metabolism of the primary immunosuppressive agents (cyclosporine and tacrolimus). Examples of commonly used medications that fall into this category include macrolide antibiotics, antiepileptic medications, and antifungal agents. With appropriate guidance from the transplant center, many of these agents can be used safely with preemptive adjustment of the CNI dosage and more frequent monitoring of drug levels.

Because of the immunosuppressed state of lung transplant recipients, live virus vaccinations are contraindicated. Patients are generally advised to receive live virus vaccines before relocating for transplant. Lung transplant recipients are more susceptible to community-acquired viral infections. A known exposure to a contagious virus warrants immunoprophylaxis (ie, VZIG for varicella exposure).
Future considerations

Well into a second decade of experience, pediatric lung transplantation is firmly established as a viable alternative for pediatric patients with end-stage pulmonary parenchymal and vascular disease. Compared to heart and other solid organ transplants, however, survival rates remain lower. OB accounts for a significant percentage of this difference. The success of adult lung transplant programs also has led to increased competition for organs and significant increases in waiting times. Finally, as survivors accumulate and age, the long-term toxicity of the immunosuppressive protocol is becoming apparent. In particular, the renal toxicity associated with CNI use is beginning to lead to chronic renal failure that requires dialysis and/or kidney transplant.

The challenges that face pediatric lung transplant centers include improving availability of donor organs, minimizing the toxicity associated with the immunosuppressive regimen, and successfully preventing or treating OB.

The availability of donor organs can be improved by focusing public policy initiatives on increased donation, refining donor management strategies to increase the percentage of donors who have lungs suitable for transplantation (including the use of nonbeating heart donors) [93–95], and cautiously increasing the use of living donor lobar transplantation. Although xenotransplantation remains an attractive possibility, significant barriers (including some specific to transplanted lungs) remain [96].

Limiting the toxicities associated with immunosuppressive regimens involves developing more functional methods of assessing the efficacy of immunosuppression (to administer the lowest possible doses), creating a better understanding of the pharmacogenomics of immunosuppressive medications (to better tailor immunosuppression based on a patient’s response to specific medications), and developing new agents and immunosuppressive strategies to limit toxicity (such as a calcineurin inhibitor without significant nephrotoxicity) [97].

Finally, the diagnosis, prevention, and treatment of OB remain the largest obstacles that face the lung transplant community. Despite more than a decade of research, the cause of OB remains obscure. Researchers have learned from the heterotopic tracheal transplant model that there is a complex interaction between the airway epithelium and mesenchymal and inflammatory cells. It is hoped that emerging techniques that allow measurement of gene expression at the level of a single cell will provide the tools to understand the mechanism of injury and dysregulated repair that leads to OB.

Diagnosis of OB remains difficult. Although the “gold standard” is open lung biopsy, many centers avoid this invasive approach and intervene on the basis of the bronchiolitis obliterans syndrome score [53]. Unfortunately, a bronchiolitis obliterans syndrome grading system for infant pulmonary function measurements has not been developed. The use of CT and VQ scans to solidify the diagnosis remains variable. Efforts to identify serum or bronchoalveolar lavage markers of OB are ongoing. Newer pulmonary function techniques, such as impulse oscillometry, may facilitate earlier identification of small airway disease. Treatment regimens
remain empiric and virtually uncontrolled. Standardization of diagnostic approach and multicenter randomized trials of promising therapies is essential to improving the ability to treat OB successfully.

In the past 15 years, pediatric lung and heart-lung transplantation has provided a second chance at life for more than 1200 children and adolescents. Researchers hope that during the next 15 years they will see improved organ availability, advances in diagnosis, and new treatment modalities that will provide hope to even more children.

References


Platt J, DiSesa V, Gail D, Massicot-Fisher J. Recommendations of the national heart, lung, and
