

Cardiothoracic Transplantation

Bronchial airway anastomotic complications after pediatric lung transplantation: Incidence, cause, management, and outcome

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Objective: Airway complications are a recognized surgical complication and an important source of morbidity after adult lung transplantation. Little is known about these complications after pediatric lung transplantation.

Methods: Data of pediatric lung transplants performed between January 1990 and December 2002 in a single pediatric institution were reviewed retrospectively.

Results: A total of 214 patients, with a mean age of 9.8 ± 6.1 years (range 0.01-19.7 years), underwent 239 lung transplants: 231 bilateral and 8 single. Mean follow-up was 3.4 years. Forty-two airway complications requiring interventions (stenosis = 36; dehiscence = 4; malacia = 2) developed in 30 recipients (complication rate: 9% of 470 bronchial anastomoses at risk). There were airway complications in 29 bilateral lung transplants (13%) and 1 single lung transplant (13%). Mean time to diagnosis was 51 ± 27 days (median: 53, range 1-96 days), and diagnoses were made in 90% of patients within the first 3 months after transplantation. Preoperative *Pseudomonas cepacia*, postoperative fungal lung infection, and days on mechanical ventilator were found to be significant risk factors on multivariate analysis ($P = .002$, $P = .013$ and $P = .003$, respectively). Treatment included rigid bronchoscopic dilatation in 17 patients, balloon dilatation in 13 patients, and stent placement in 12 patients. Other treatments consisted of debridement, fibrin glue application, chest tube placement, and pneumonectomy followed by retransplantation. No patients died as a direct result of airway complications. There was no significant difference in the incidence of bronchiolitis obliterans or overall survival in comparison with patients who did not have airway complications.

Conclusions: Airway complications are a significant cause of morbidity after pediatric lung transplantation. The majority are successfully treated, and patient outcomes are not adversely affected.

The first human lung transplantation was reported by Hardy and colleagues¹ in 1963. For 2 decades after that, airway complications, mainly dehiscence, were the most frequent cause of early mortality and a major reason for the failure of clinical lung transplantation.² The development of improved anastomotic techniques resulted in the first clinically successful lung transplantation in 1983 and a subsequent decline in the frequency of airway complications.³⁻⁵

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Abbreviations and Acronyms

BLT = bilateral lung transplant
SLT = single lung transplant

Reports of adult lung transplantations show the rates of airway complications to be between 9% and 15% of the anastomoses at risk, with a related mortality of 2% to 3%.^{5,6} Pediatric lung recipients are unique in several ways in comparison with their adult counterparts in that they are younger, smaller, and with bronchial cartilage that has a higher compliance. In recognition of the scarce data in the literature regarding airway complications after pediatric lung transplantation, we reviewed our experience in this area in a single pediatric center.

Patients and Methods

Patients

Between January 1990 and December 2002, a total of 214 patients underwent 239 isolated lung transplants at the St Louis Children's Hospital; 231 were bilateral sequential lung transplants (BLTs) and 8 were single lung transplants (SLTs). Twenty-five of the BLTs were retransplantations. Because the study was to evaluate only bronchial anastomotic complications, this series excluded the 10 heart-lung transplants performed in this hospital in which none of the patients had any airway complications. The mean follow-up was 3.4 years. The median age at the time of transplantation in the study population was 11.2 years (range 0.1-19.7 years), with a mean age of 9.8 ± 6.1 years. Analysis was performed by a retrospective review of prospectively collected pediatric data and medical records.

Operative Technique

The methods for standard donor lung harvest and implantation have been described.⁷ The donor lungs are perfused with alprostadil (prostaglandin E₁), flushed with modified Euro-Collins solution, excised, and transported on ice to the recipient's surgical suite. BLT was performed through a bilateral anterolateral trans-sternal (clamshell) thoracotomy incision through the fourth intercostal space. SLT was performed through an anterolateral thoracotomy extended across the sternum into the contralateral chest. Cardiopulmonary bypass was used in all patients because the airways in children are too small to safely accommodate the double-lumen endotracheal tubes that are necessary for single-lung ventilation. The donor bronchus was trimmed to within 2 cartilaginous rings of the take-off of the upper lobe bronchus on each side. Early in our experience, 7 bronchial anastomoses in 5 patients (3 SLTs and 2 BLTs) were performed using a telescoping technique with continuous absorbable running suture to the membranous portion and interrupted mattress sutures to the cartilaginous portion. All other subsequent bronchial anastomoses were performed as an end-to-end anastomosis with continuous absorbable monofilament suture to the membranous portion and simple interrupted absorbable sutures to the cartilaginous portion. Omentum was initially used in the beginning of our transplantation program to

wrap around 4 bronchial anastomoses in 2 patients who underwent BLT. Omentum was substituted by pericardium and used to wrap 45 bronchial anastomoses in the subsequent 24 patients (3 SLTs and 21 BLTs). Since 1993, peribronchial tissues have been used to wrap around all the bronchial anastomoses; 5-0 monofilament absorbable suture was used in children up to the age of 10 years, and 4-0 suture was used in the older children. The arterial and venous anastomoses were performed in an end-to-end fashion using continuous suture of the same material. A Broviac catheter (C. R. Bard, Inc, Murray Hill, NJ) was placed in all patients for long-term vascular access.

Immunosuppression

"Triple drug" (cyclosporine [INN: ciclosporin], azathioprine, steroids) immunosuppression is used. For the first year after transplantation, the target trough cyclosporine blood level is 300 to 400 ng/mL, and for subsequent years it is 200 to 300 ng/mL. The initial steroid dose is 0.5 mg/kg daily for prednisone. The steroid dose is progressively tapered over time, but we do not believe it is appropriate to stop this drug entirely. An azathioprine dose of 1.5 mg/kg daily is administered as long as the patient's white blood cell count exceeds 4000 cells/mm³.

Posttransplant Surveillance

An examination with a flexible fiberoptic bronchoscope was performed within 24 hours of transplantation to assess airway anastomosis. Thereafter, surveillance was performed by periodic spirometry and flexible bronchoscopy with biopsies and bronchoalveolar lavage. These were performed at 2 weeks, 1 month, 2 months, 3 months, and every 3 months thereafter, as well as at any time that a change in clinical status occurred in which rejection was a plausible explanation. A 3.3-mm flexible pediatric bronchoscope was used in children younger than 1 year of age. A 4.5- or 5-mm flexible bronchoscope was used for the older children. Bronchoscopy was performed in the operating room under laryngeal mask anesthesia for children aged less than 2 years and as an outpatient procedure for children aged 2 years or older. The technique of transbronchial biopsy performed in infants has been described.⁸ When tissue sampling was inadequate, and a change in clinical status persisted, open lung biopsy was performed. Formal pulmonary function measurements were performed at the same intervals as for bronchoscopy. Children aged less than 5 years are generally not able to fully cooperate for standard pulmonary function tests. They are therefore evaluated with infant pulmonary function tests using standard techniques.^{9,10}

Statistics

Descriptive statistics were used to describe the patients' characteristics and outcomes. Normally distributed continuous data are expressed as means \pm SD throughout. Medians with ranges are used when continuous data are not normally distributed. Categorical data are expressed as counts and proportions. The chi-square or Fisher exact test was used to analyze the categorical data. Kaplan-Meier (product-limit) graphs were used to demonstrate survival over time and freedom from bronchiolitis obliterans. Survival and event-free survival comparisons between groups of patients were completed using the Mantel-Haenszel log-rank test. Logistic regression analysis was used to discriminate independent

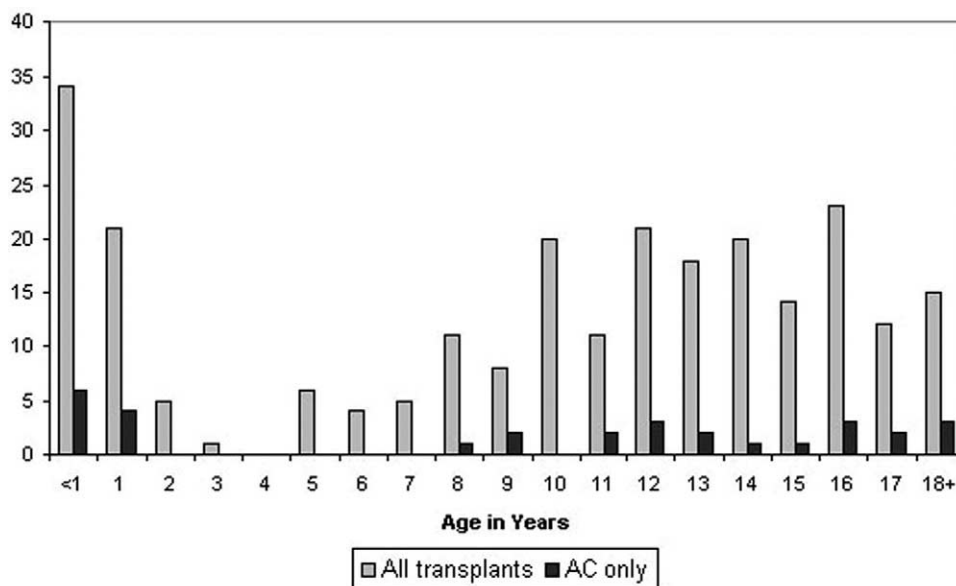


Figure 1. Age distribution of patients. AC, Airway complication.

risk factors for development of an airway complication after pediatric lung transplantation. The development of airway complication was selected as the primary outcome. The likelihood ratio method was used to determine hazard ratios, and the hazard ratio was used to approximate the relative risk. All data analysis was performed using SPSS (SPSS 11.0 for Windows; SPSS Inc, Chicago, Ill).

Results

For the purpose of this review, an airway complication was defined as a finding of stenosis, malacia, or dehiscence that necessitated intervention such as dilatation, debridement, or stent placement. Mucosal necrosis or slough detected by bronchoscopy was not considered an airway complication when satisfactory healing occurred without intervention. Of 470 bronchial anastomoses, 42 airway complications requiring intervention developed in 30 recipients with an incidence of 9% of the 470 anastomoses at risk. Thirty-six of these complications were bronchial stenosis, 3 were partial dehiscence, 1 was a complete dehiscence, and 2 were bronchomalacia. The age distributions of patients with and without airway complications are shown in Figure 1. The incidence of airway complications was 19% (10/53) in patients aged less than 2 years and 14% (16/117) in older children aged 11 to 18 years. There was no significant difference when these groups were compared ($P = .39$). The incidence of airway complications was 17.6% (18/102) for transplants performed between 1990 and 1996, and 10.7% (12/112) ($P = .145$) for transplants performed between 1997 and 2002. The median time to diagnosis was 53 (1-96) days with a mean of 51 ± 27 days. Ninety percent of these airway

complications were diagnosed within the first 3 months after transplantation. Airway complications were detected incidentally in 11 patients during surveillance bronchoscopy. These patients were asymptomatic. Clinical presentations that led to the diagnosis of airway complications in the other patients were failure to wean from mechanical ventilation in 6 patients, worsening of pulmonary function tests in 6 patients, unexplained respiratory failure in 2 patients, wheezing in 2 patients, stridor in 1 patient, retained secretions in 1 patient, and fever in 1 patient.

Risk Factors

Independent predictors for airway complications when accounting for the other covariates are shown in Table 1. Preoperative *Pseudomonas cepacia*, postoperative fungal lung infection, and days on mechanical ventilator were found to be significant factors on multivariate analysis ($P = .002$, $P = .013$ and $P = .003$, respectively). Pretransplant diagnosis, age 2 years or less, preoperative steroid usage, cytomegalovirus infection, ischemic time, and re-transplantations were not significant risk factors. Early in our lung transplant program, 7 bronchial anastomoses were performed using a telescoped technique. Two bronchial stenoses and 1 partial dehiscence occurred in 3 of these patients with an incidence of 43%; the technique was abandoned after that.

Treatment

All bronchial stenoses were initially treated by dilatation. Up to 1995, the technique was to place a grasping forceps through

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TABLE 1. Pretransplant diagnosis and risk factors for airway complications

Variable	AC (n = 30)	Non-AC (n = 184)	P value	Relative risk (CI)
Pretransplant diagnosis			.68	NA
Cystic fibrosis (n = 106)	11 (37%)	95 (52%)		NA
Pulmonary vascular disease (n = 39)	5 (17%)	34 (18%)		NA
Pulmonary fibrosis (n = 5)	1 (3%)	4 (2%)		NA
Bronchiolitis obliterans (n = 9)	2 (7%)	7 (4%)		NA
Statistical analysis				
Age (y)	9.6 ± 6.9	9.9 ± 6.1	.961	NA
Ischemic time (min)	249 ± 68	247 ± 93	.908	NA
<i>Pseudomonas cepacia</i> infection	3 (10%)	1 (0.5%)	.002	29.36 (2.84-303.26)
Postoperative fungal infection	8 (27%)	23 (13%)	.01	3.81 (1.39-10.49)
Days on ventilator	12 (1-254)	4 (1-128)	.003	1.02 (1.01-1.04)

AC, Airway complication; CI, confidence interval; NA, not available.

the stenotic orifice and enlarge the stenosis by opening the forceps within it. After that, the stenosis was gradually dilated using a rigid bronchoscope. The sizes of rigid bronchoscopes used were dependent on the age and size of the child. Since 1995, balloon dilatations performed through the rigid bronchoscope were used instead of using the rigid bronchoscopy itself to dilate. The balloon technique was thought to be a simpler, safer, and less traumatic approach while at the same time achieving similar dilatation results as that of rigid bronchoscopy. The balloon diameter sizes were 8 mm for children aged less than 1 year, 10 mm for children aged between 1 and 8 years, 12 mm for children aged between 8 and 12 years, and 14 mm for children aged 12 years or older. After the initial dilatation, bronchoscopy was performed 3 weeks later. Dilatation was repeated if the stenosis recurred. Up to 1995, a silicone rubber stent (Silastic; Dow Corning Corp, Midland, Mich) was inserted if the stenosis was severe and had narrowed the orifice down to 50% or more of the baseline. The baseline used for comparison was normal looking, healthy bronchus proximal or distal to the anastomosis or the contralateral bronchial anastomosis. The technique has been described.¹¹ Care is taken to place these stents such that the upper lobe bronchi remain patent and unobstructed by the stent. Since 1995, we have used dilatation alone for the treatment of stenosis to avoid the complications associated with stents such as mucus impaction, granulation tissue formation, dislodgment, and migration. Subsequent bronchoscopy was then arranged at various time points ranging from 3 weeks to 3 months dependent on the degree of residual stenosis and response to treatment.

Between 1990 and 1995, there were 12 bronchial stenoses that were treated by rigid bronchoscopic dilatation. The median number of interventions was 2 (range 1-22), and the mean was 4.2 ± 6.2. Between 1995 and 2002, there were 9 bronchial stenoses that were treated with balloon dilatation. The median number of balloon interventions was 5 (range 1-7), and the mean was 4.1 ± 2.2. Silicone rubber stents were placed in 12 bronchial anastomoses. These stents were left in place for a minimum of 6 months. Four of the 12

stents placed caused complications that required interventions. These complications included dislodgment, obstruction by mucus impaction, and granulation tissue formation. All silicone rubber stents were ultimately removed with resolution of the stenosis. One patient with *Aspergillus* infection of the airway had a complete dehiscence of the right bronchial anastomosis 1 day after surgery and underwent reoperative repair. The repaired anastomosis completely dehisced again, and a pneumonectomy was performed 8 days after the repair. Retransplantation was performed 25 days after the pneumonectomy. Partial dehiscence of the anastomoses developed in 3 other patients, 1 of whom had a bronchopleural fistula and pneumothorax requiring chest tube insertion and drainage of the pneumothorax. One patient with partial dehiscence had bronchial stenosis that necessitated dilatation, and another patient had formation of granulation tissue that necessitated debridement. The remaining patient with partial dehiscence was successfully treated with topical fibrin glue sealant. Two patients had bronchomalacia and were treated with wire mesh metal expandable stents. Metal stents were used for these patients because they had bronchiolitis obliterans and had a limited long-term survival; thus it was reasonable to use the metallic stents despite the disadvantages of restricting the growth of the bronchus and not being able to remove it.

Late Complications

Fifteen of the 30 patients who had an airway complication had bronchiolitis obliterans (50%). This finding was not significantly different in comparison with patients who did not have airway complications (Figure 2). The 1-, 3-, and 5-year Kaplan-Meier freedom from bronchiolitis obliterans for patients with and without airway complications are 73.2%, 49.6%, 36.2%, and 81.1%, 57.2%, and 47.6%, respectively (log rank 1.88, P = .17).

No patients died as a direct result of airway complications. There was no significant difference in the overall

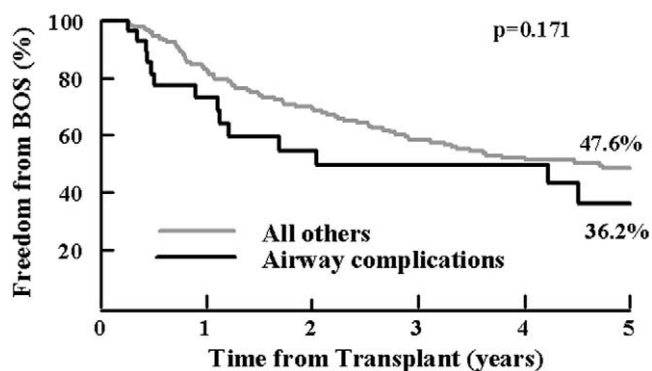


Figure 2. Kaplan-Meier freedom from bronchiolitis obliterans. BOS, Bronchiolitis obliterans.

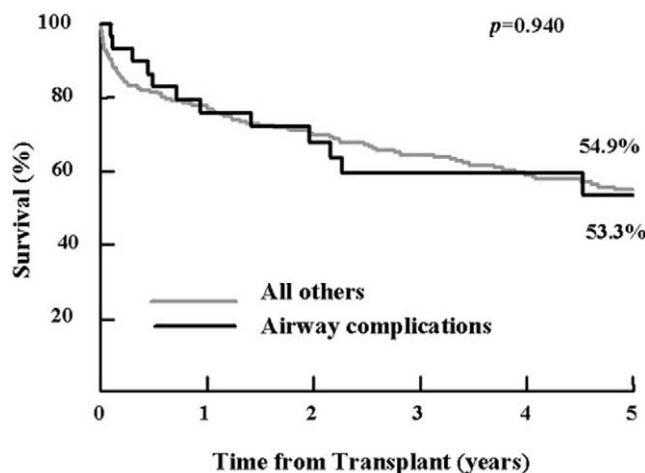


Figure 3. Kaplan-Meier overall survival.

survival in comparison with patients in whom airway complications did not develop (Figure 3).

Discussion

The bronchial anastomosis in lung transplantation is unique in that there is no direct blood supply to the bronchus to promote healing. Circulation to this area depends on retrograde filling of the bronchial vessels from the pulmonary arterial circulation through the communications with pulmonary capillaries and other precapillary anastomoses. Maintenance of blood flow through these tenuous channels is critical for the healing of the airway anastomosis until systemic neovascularization of the bronchial circulation through collaterals occurs, which may take 3 to 4 weeks.¹² Direct bronchial revascularization has been proposed by some centers in an effort to lower the incidence of airway complications.¹³ The disadvantages are that it prolongs the operation, increases the risk of bleeding, is technically difficult, and may be more so in the pediatric population with their smaller arterial sizes. For these reasons, we have not adopted the technique of direct revascularization. Indirect revascularization using omentopexy was at one time standard practice.¹⁴ There is experimental evidence of new vessel ingrowth to the area of bronchial anastomosis with omentopexy as early as 4 days after transplant.¹⁵ The use of viable peribronchial tissue to wrap around the bronchial anastomosis is now the standard practice and has provided results similar to omentopexy and is less complicated.⁵

Technical factors such as the shortening of the donor bronchus to within 1 to 2 cartilaginous rings of the take-off of the upper lobe bronchus have also been implicated as important factors that impact the healing of bronchial anastomosis.¹⁶ These factors have been shown to minimize the degree of ischemia at the level of the anastomosis. Telescoping the anastomosis by intussuscepting the donor bronchus into the recipient has been adopted by some centers

with good results.¹⁷ It is usual to have some telescoping because the donor bronchus is frequently smaller than the recipient. In our series, telescoping using mattress sutures was performed during the initial phase of the program and was associated with a high incidence of complications in which 3 of 7 of the anastomoses became stenotic. Others have had a similar experience.¹⁸ The telescoped technique was used during the early part of our pediatric lung transplantation program, and it may be that the difference in results simply represents the effect of the learning curve. It may also be possible that the smaller airway diameter of pediatric patients may be more prone to stenosis with the telescoped technique. Because the technique was abandoned early, it is unknown whether the prevalence of anastomotic narrowing would decrease if we had continued to use this technique. The small number of telescoped anastomoses in comparison with the end-to-end technique is also a limitation in comparing the difference in the prevalence of anastomotic narrowing between the 2 techniques.

As our transplant program took on smaller children, we were concerned about potential airway complications in infants. We were concerned that any narrowing induced by swelling or inflammation would be detrimental to the small infantile airways and that the small diameter of the airway may be a risk factor for the development of stenosis. In our experience, the incidence of airway complication was not significantly different between the children aged less than 2 and older children aged between 11 and 18 years. Eleven of the 30 recipients (37%) who had airway complications were asymptomatic, and the airway complications were detected incidentally on surveillance bronchoscopy. These findings emphasize the importance of performing routine surveillance bronchoscopy in this population.

Various treatment modalities have been reported for the management of airway complications after lung transplan-

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tation. These include dilatation, wire mesh expandable stents, laser therapy, and resection of stenotic bronchus with reanastomosis.^{11,19,23} Our preferred choice in the treatment of bronchial stenosis is balloon dilatation, which has the advantages of being less traumatic, easier to apply, and more accurate dilatation of the stenotic segment in comparison with rigid bronchoscopic dilatation. This has been successful in our experience as well as that of others.^{5,24} As opposed to vascular structures, there is no intraluminal pressure to help maintain airway patency during healing. During inspiration, the intraluminal pressure of airway anastomosis is generally higher than the extraluminal intrathoracic pleural pressure, and this may contribute to the maintenance of airway patency when a stricture is not particularly severe. Intraluminal silicone rubber stents were believed to be useful when the stenosis was severe. We have previously placed silicone rubber stents in severe strictures; however, mucus plugging, dislodgement of the stent, and incitement of granulation tissue growth complicate their use. We now perform periodic balloon dilatation instead of stenting and have found that this effectively remodels the airway stenosis to a satisfactory diameter without the stents. Expandable metal stents have been reported to be a useful treatment modality for airway complications.^{25,26} These stents, however, cannot be used unless the airway is completely epithelized and in general cannot be removed. They can also incite granulation tissue that may grow through the wire mesh producing obstruction. The removal of the stenotic segment either as a sleeve resection of the airway or lobectomy has been performed with excellent results.²² However, the reported series included all adult patients and was a treatment option reserved for patients in whom conventional treatment failed or in whom the stenosis extended down into the more distal airway. Retransplantation is a final option but carries with it the unpredictable waiting time. Retransplantation is associated with higher morbidities and mortalities.^{27,28} When the stenosis extends down into the lobar orifices, there may not be a plausible alternative treatment.

In conclusion, the incidence of airway complications in our pediatric series was similar to that reported in the adult lung transplant population. Airway complications were a significant cause of morbidity after pediatric lung transplantation. The majority was however successfully treated, and patient outcomes were not adversely affected.

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