Heart Transplantation in Children

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Orthotopic cardiac transplantation has been performed in 15 consecutive neonates and children since 1987. Diagnoses include hypoplastic left heart syndrome (5 patients), critical aortic stenosis with small left ventricle (1 patient), complex cyanotic heart disease (6 patients), and cardiomyopathy (3 patients). Twelve patients survived operation and have been followed from 1 to 45 months. Patients less than 6 years of age are managed with cyclosporine ± azathioprine; in older patients steroid weaning is attempted. Monitoring for rejection is performed with serial echocardiography in patients under 6 years of age; older patients undergo serial biopsies. Actuarial freedom from rejection was 26% 3 months after operation; 47% were free of infection 6 months after operation. There have been no late deaths. Actuarial survival at 3 years is 79%. Nine patients have undergone postoperative catheterization. Resting hemodynamics were normal in every patient. All long-term survivors are asymptomatic and fully active. It is concluded that cardiac transplantation in neonates and children is an effective treatment option for end-stage cardiomyopathy or otherwise incurable congenital heart disease. Long-term survivors have excellent potential for full rehabilitation.

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CARDIAC TRANSPLANTATION HAS gradually evolved from consideration as an experimental procedure in 1968 to a well-established therapeutic modality in 1990. It has become an accepted form of treatment for adults with end-stage cardiomyopathy with no alternative standard medical or surgical treatment options. In recent years the addition of cyclosporine to the immunosuppressive regimen has lead to a decrease in the number of episodes of rejection and infection, and this drug has improved both the length and quality of life of adult patients after transplantation.[1]

Cardiac transplantation in infants was introduced in December 1967, when Kantrowitz[2] performed a heart transplant in a 3-week-old infant with tricuspid atresia. Very few transplants were performed in children throughout the 1970s. At Stanford University transplantation in children was initiated in December 1980. The use of cyclosporine, as well as improved recipient selection, has improved the survival rate of children undergoing cardiac transplantation such that the long-term results are comparable to those found in adults.[3]

In 1985 neonatal transplantation was introduced by Dr. Leonard Bailey[4] at Loma Linda University Medical Center as a treatment option for infants with the uniformly lethal hypoplastic left heart syndrome.

Cardiac transplantation in neonates and children differs significantly from cardiac transplantation in adults. Unique considerations include the complex congenital anatomic abnormalities of the recipient and the requirement that steroids be minimized to prevent growth arrest. Furthermore monitoring rejection with serial endomyocardial biopsies is more difficult and more dangerous in small children.

This report summarizes our experience with orthotopic cardiac transplantation in 15 consecutive infants and children at Vanderbilt University Medical Center.

Materials and Methods

From February 1987 through October 1990, 15 consecutive infants and children underwent orthotopic cardiac transplantation. All patients except one were 16 years of age or less and had complex congenital heart disease or cardiomyopathy. The diagnoses were hypoplastic left heart syndrome (5 patients), critical aortic stenosis with a small left ventricle (1 patient), complex cyanotic heart

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disease (5 patients), and idiopathic cardiomyopathy (3 patients). One additional patient 20 years of age had congenitally corrected transposition of the great arteries. Each patient with cyanotic heart disease had undergone at least one previous operation (Table 1).

Neonates with hypoplastic left heart syndrome were managed with continuous low-dose prostaglandin E_1 infusion to maintain ductal patency and systemic perfusion. As indicated neonates were also maintained in a low-oxygen environment (fraction of inspired oxygen [FIO_2] < 0.21) to balance the systemic and pulmonary vascular resistances and to prevent florid pulmonary edema from excessive pulmonary blood flow. Other patients were managed with mechanical ventilation and inotropic support before operation as necessary. The mean time on the waiting list before operation was 29 ± 28 days (standard deviation [SD]) (range, 2 to 94 days). At the time of operation, 11 patients were United Network for Organ Sharing (UNOS) status 1 and four were UNOS status 2.

All patients underwent orthotopic cardiac transplantation. In the five patients with hypoplastic left heart syndrome, deep hypothermia and circulatory arrest technique was used. All other patients underwent transplantation using moderate hypothermia and cardiopulmonary bypass. Recipients and donors were matched with respect to body weight and ABO blood group compatibility. Donor cardiac protection was performed with a single dose of crystalloid cardioplegia and immersion of the donor heart in ice-cold Ringer's lactate. Cardiac protection at the time of implantation was aided by both topical and intracavitary cooling during the performance of the various anastomoses. The graft ischemia time was a mean of 203 ± 53 minutes (range, 79 to 263 minutes).

Before operation patients were given cyclosporine (5 to 10 mg/kg), depending on renal and hepatic function. Azathioprine (2 mg/kg) also was administered intravenously. At the time of aortic cross-clamp release, methylprednisolone (7.5 mg/kg) was administered. After operation three doses of methylprednisolone (3.5 mg/kg) were administered every 8 hours. After operation cyclosporine was administered, beginning at approximately 10 mg/kg/day. Whole-blood cyclosporine levels, as determined by high-pressure liquid chromatography, were maintained at approximately 200 ng/mL for the first 6 months. Neonates and children received azathioprine 1 to 2 mg/kg/day to maintain a white blood cell count of approximately 5000/mm^3. No prednisone was administered to the neonates routinely. The older children received prednisone (0.8 mg/kg/day), which was tapered to 0.2 mg/kg/day by 6 weeks after operation and was eventually discontinued in all patients less than 6 years old.

TABLE 1. *Previous Operations in Patients with Cyanotic Conditions*

Diagnosis	Previous Operation
TGA, IVC obstruction	Mustard
TGA, VSD, SVC obstruction	Mustard, VSD
Corrected TGA	VSD
Single ventricle, LSVC	Coarc, Band, B/T, B-Hanlon, A-P Window
Single ventricle, malposed	B/T, Mod B/T, B-Hanlon
Pulm atresia, IVS	B/T, Mod B/T (2), Central, B-Hanlon

TGA, transposition of the great arteries; IVC, inferior vena cava; VSD, ventricular septal defect; SVC, superior vena cava; LSVC, left superior vena cava; IVS, intact ventricular septum; Coarc, coarctation; B/T, Blalock-Taussig shunt; B-Hanlon, Blalock-Hanlon; A-P, aortopulmonary; Mod, modified.

In children older than 6 years of age, the diagnosis of allograft rejection was made by serial cardiac biopsy. The hallmark of rejection requiring treatment was myocyte necrosis. Neonates and children younger than 6 years were followed for rejection by clinical criteria and serial echocardiography only, a system developed jointly with Loma Linda University Medical Center. The echo indices indicative of rejection in neonates included detailed analysis of left ventricular wall mass and volume.

Hospitalized patients with allograft rejection were treated with intravenous methylprednisolone (250 mg twice a day or 15 mg/kg/day) for 3 days. Repeat biopsies or echocardiograms were performed 48 to 72 hours after completion of therapy to determine response to treatment. A second course of methylprednisolone was given if rejection was ongoing or if an independent second episode of rejection occurred. If a third episode of rejection occurred, rabbit antithymocyte serum was administered intravenously for 7 days at a dose of 0.2 mL/kg/day, and circulating T cells were monitored with the dosage adjusted to keep the total T cells less than 10%.[5] Two teenagers had persistent or recurrent rejection episodes and received a course of methotrexate, and one received a course of vincristine.

Outpatients who had documented rejection episodes were treated with an increase in the oral prednisone dose, which was then tapered over approximately 1 week. Follow-up evaluation with repeat biopsy or echocardiography was obtained to determine the response to treatment.

Actuarial curves were computed by the method of Kaplan-Meier and compared by the method of Gehan.[6,7] Linearized rates, expressed as events/100 patient-days, and calculated on a cumulative basis, were compared using the maximum-likelihood test ratio.[8]

Results

Fifteen consecutive patients have undergone orthotopic cardiac transplantation. Two of the five patients with hypoplastic left heart syndrome died in the operating room. One child had a severely hypoplastic right pulmonary artery and minuscule anomalous pulmonary veins detected

only at the time of cardiectomy. This patient died of donor right ventricular failure. Another patient died of left ventricular failure caused by technical problems with the aortic anastomosis that resulted in residual aortic narrowing. One of the six patients with complex cyanotic heart disease died 1 week after operation of right ventricular failure thought to be due to persistently elevated pulmonary vascular resistance. The hospital stay after operation was 29 ± 22 days (range, 13 to 89 days).

There have been no late deaths. Actuarial survival at 36 months is 79 ± 11% standard error of the mean and is the same as in our adult heart transplant recipients (Fig. 1). Follow-up ranges from 1 to 45 months and is complete and timely in all patients.

The linearized rejection rate (events per 100 patient-days) was 1.4 and 0.67 at 1 and 3 months after operation, respectively. When compared with the adult patients, the linearized rejection rates were similar (Fig. 2). Actuarially at 1 month after operation, 62% of children were free from rejection, and only 26% were free from rejection 3 months after operation. A similar trend was noted in the adult patients (Fig. 3).

Infectious complications were due to bacterial, viral, and protozoan causes. There were no instances of fungal infection noted. A total of 20 episodes of infection occurred. These included four pulmonary infections, four urinary tract infections, three blood-borne infections, one episode of central line infection, one episode of mediastinitis, and seven other episodes. All patients recovered from their infections without significant residual problems.

An actuarial analysis of the percentage free from infection indicates that 85% of children were free of infection at 1 month after operation, and 47% were free of infection 6 months after operation. The actuarial curves for freedom from infection are similar for children and adults (Fig. 4).

Serum creatinine, blood urea nitrogen (BUN), and creatinine clearances were determined serially. In most neonates and children, these values were stable during the course of follow-up with minimal evidence of declining renal function. At the most recent follow-up, the mean BUN was 19.8 ± 6.7 mg/dL, the mean creatinine was 1.0 ± 0.38 mg/dL, and the mean creatinine clearance was 81 ± 48 mL/min/m^2.

Hypertension significant enough to warrant treatment was noted at most recent follow-up in 6 of the 12 long-term survivors. All of the children with hypertension are greater than 6 years of age and are still receiving corticosteroids as part of their immunosuppressive regimen. These patients were treated with either calcium channel-blockers or acetylcholinesterase inhibitors or both. In all instances excellent blood pressure control was obtained.

Three patients have each undergone three yearly follow-up cardiac catheterizations, one patient has undergone restudy at both 1 and 2 years after operation, and five additional patients have undergone follow-up study 1 year after operation. In all patients graft function is normal at rest. Only minor gradients have been detected across ar-

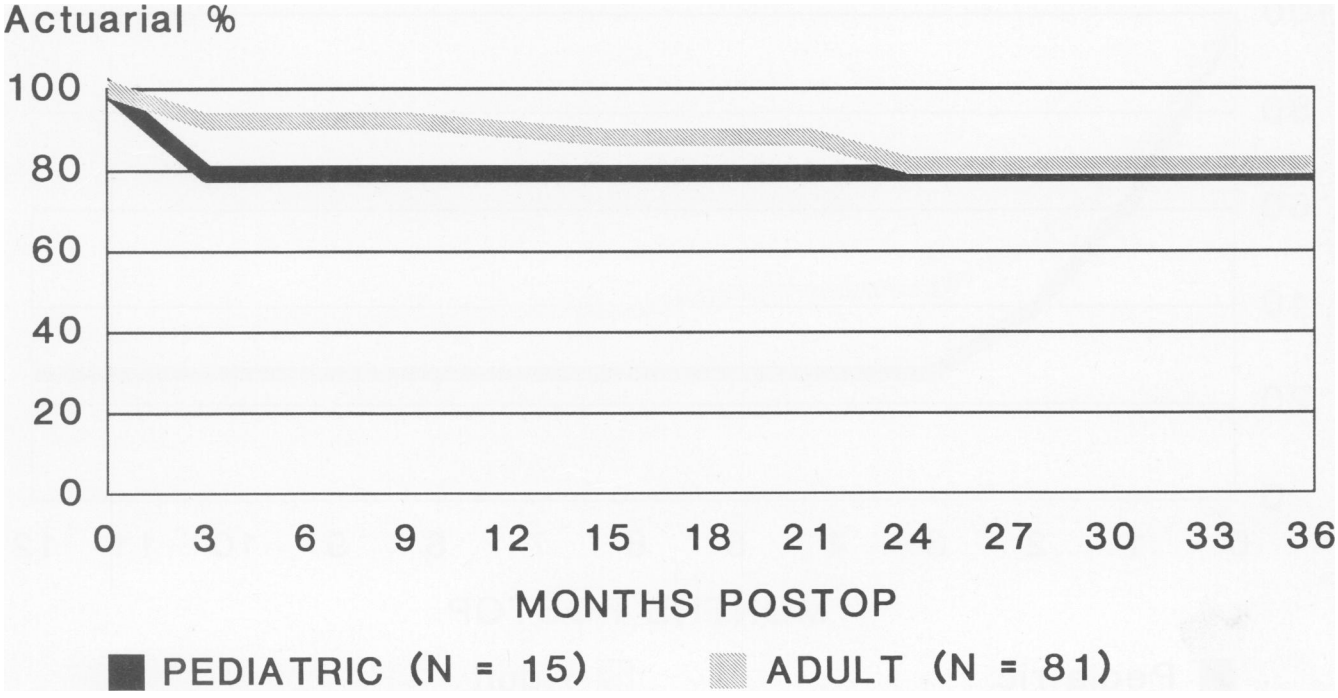

FIG. 1. Actuarial survival for pediatric and adult heart transplant recipients.

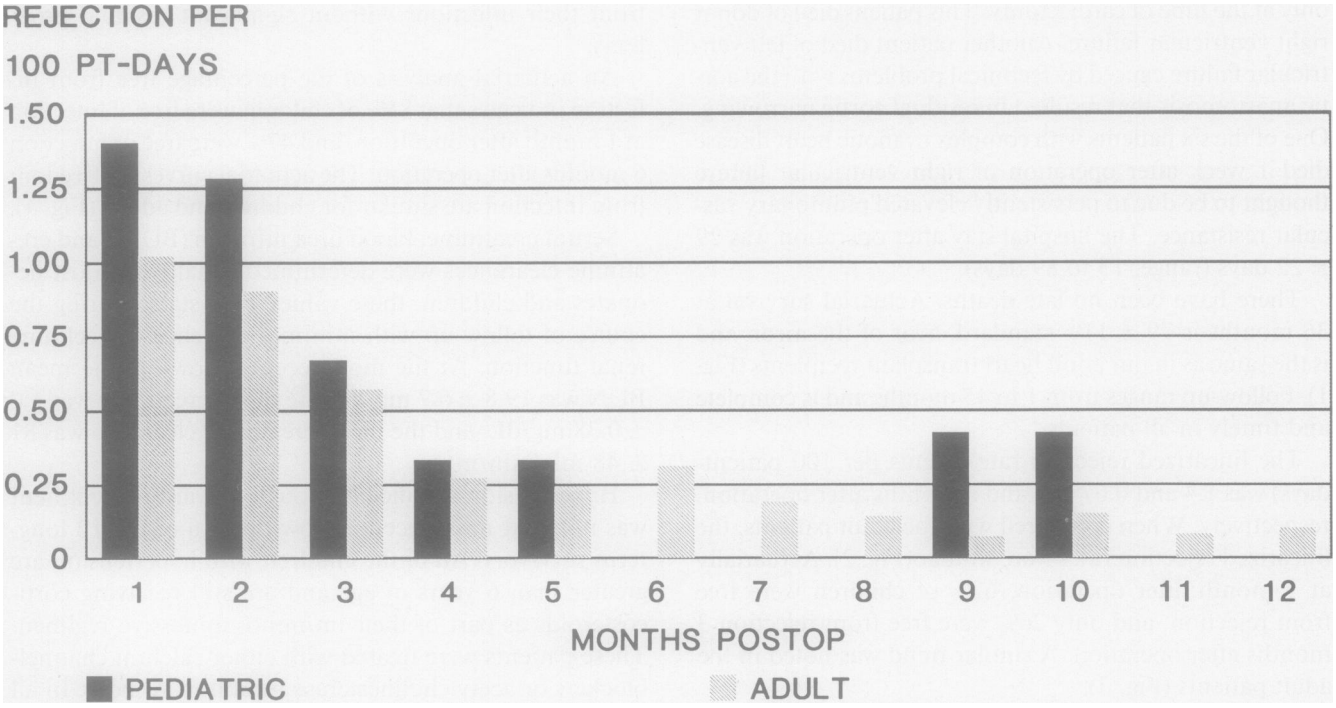

FIG. 2. Cumulative linearized rejection rate.

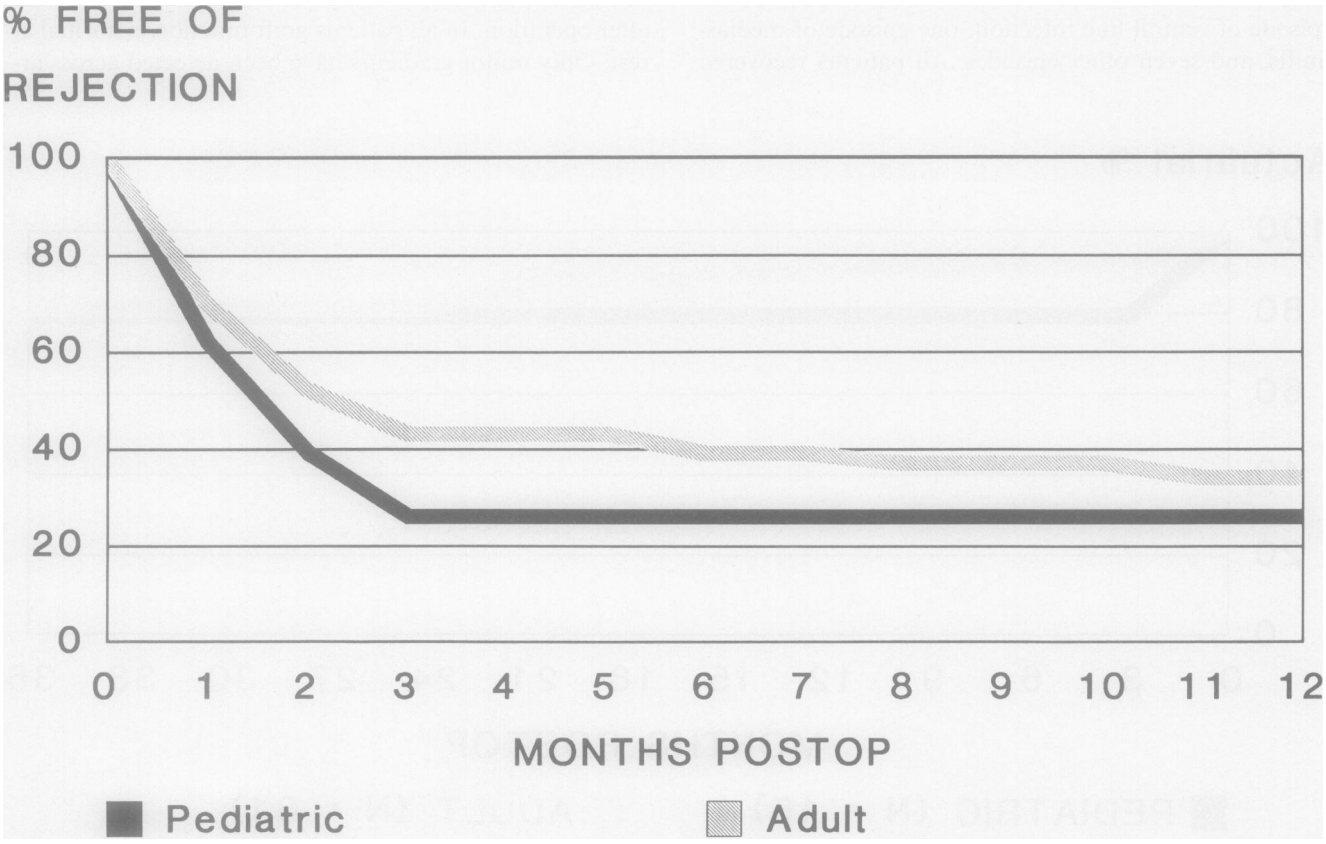

FIG. 3. Actuarial freedom from rejection.

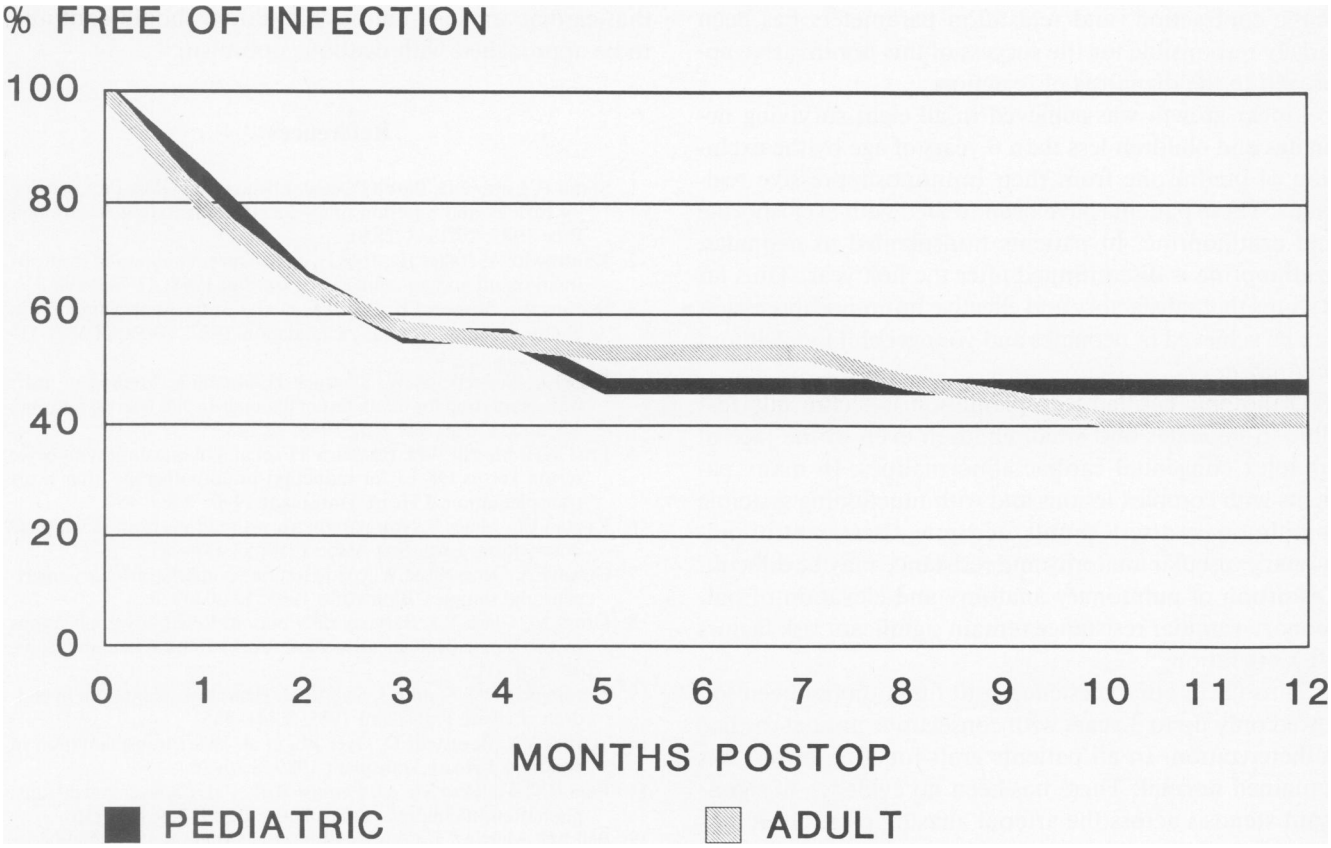

FIG. 4. Actuarial freedom from infection.

terial anastomoses, and no coronary artery disease has been noted.

All of the 12 long-term survivors are doing well and have no significant residual problems. No patient has symptoms related to cardiac transplantation. All are fully active and carrying out normal activities for their age.

Discussion

Heart transplantation in neonates and children has evolved into an accepted therapeutic modality for complex congenital heart disease and for end-stage cardiomyopathy when there are no medical or surgical treatment alternatives. Transplantation in young patients has gained acceptance due to improved immunosuppression and due to results that are comparable to those found in the adult experience. Pennington et al. have noted the rapid rise in the number of children undergoing heart transplantation.[9]

One of the major concerns in young children with heart transplants is the possibility of growth retardation.[10] Steroids have been implicated in retardation of skeletal growth.[11] Because of this potential problem, efforts have been extended to wean patients off steroids or to switch to an alternate-day steroid regimen in an attempt to minimize growth retardation.[12] It has been postulated that the newborn child may be the best possible recipient of organ transplantation because host immune responses are less aggressive and more easily controlled when transplantation is accomplished shortly after birth. It may be possible to sustain children who underwent heart transplantation as neonates with minimal immunosuppression, including the absence of steroids.[13]

Special problems are posed by the small size of neonates and young children with regard to the diagnosis of cardiac rejection. It is not feasible to perform frequent biopsies in infants and small children because of their small size and the need for anesthesia.[14] Nonetheless these young patients require frequent monitoring of rejection. In our experience the rate of rejection in children is similar to that in adults. Rejection is most frequent in the first several months after transplantation, but the need for monitoring rejection remains constant.

None of the neonates who have been followed for rejection by noninvasive echocardiographic criteria have died from untreated rejection. In this experience there has not been a higher frequency of treatment for rejection than in other series of children and adults followed by serial endomyocardial biopsy. The use of a multifactorial computer-assisted analysis of left ventricular volume,

mass, contraction, and relaxation parameters has been largely responsible for the success of this noninvasive approach to the diagnosis of rejection.

Linear growth was achieved in all eight surviving neonates and children less than 6 years of age by the exclusion of prednisone from their immunosuppressive regimens. These patients have been treated with cyclosporine and azathioprine. In patients transplanted as neonates, azathioprine is discontinued after the first year. Thus far it seems that satisfactory and effective immunosuppression can be achieved in neonates and younger children without prednisone.

Orthotopic cardiac transplantation is technically feasible in neonates and small children even in the face of complex congenital cardiac abnormalities. In many patients with complex lesions and with functioning systemic to pulmonary artery shunts, accurate assessment of pulmonary vascular anatomy and resistance may be difficult. Distortion of pulmonary anatomy and elevation of pulmonary vascular resistance remain significant risk factors after operation.[15]

Thus far in our experience graft function has been followed only up to 3 years with consecutive annual cardiac catheterization. In all patients graft function at rest has remained normal. There has been no evidence of significant stenosis across the arterial anastomoses. Graft atherosclerosis has not been encountered.

In conclusion orthotopic cardiac transplantation in neonates and children is an effective treatment option for end-stage heart disease or otherwise incurable congenital heart disease. In properly selected patients, the perioperative mortality is low. There is excellent potential for full rehabilitation in the long-term survivors. Thus far these data, plus those presented by others, seem to indicate that cardiac transplantation in children should continue to be approached with cautious optimism.

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Discussions

Dr. Timothy Gardner (Glyndon, Maryland): One of the most exciting developments in the field of heart transplantation has been the realization that this therapy can be applied to children. These excellent data from Vanderbilt and clinical results from other transplant centers are making this point clear. It's also very gratifying to realize that patients with the otherwise untreatable or poorly treated entity of hypoplastic left heart syndrome may also be a target group for this therapy.

The experience at Johns Hopkins in the last several years parallels the results just presented by Dr. Merrill, with a couple of minor exceptions. Of our 14 patients who have had heart transplants—and there were several others that had heart–lung transplantation—nine of the patients had cardiomyopathies. The favorable experience in these patients who tend to be a bit older is not very surprising. There were many teenagers early on with cardiomyopathies, in the Stanford series and although they do present somewhat different considerations in the long term, this isn't the subgroup of young patients that creates the excitement.

It is the younger children, the infants, especially those who have hypoplastic left heart syndrome as well as those who have otherwise uncorrectable congenital defects for whom heart transplantation is so unique. Our experience at JHH has been exclusively with children having hypoplastic left heart syndrome.

We have not yet undertaken transplantation, at least heart transplantation, to treat children with complex and otherwise incurable congenital heart defects. Our survival data is very similar to that presented by Dr. Merrill. We have a 79% late survival rate, with two deaths in the cardiomyopathy group, while one of the five patients with the hypoplastic left heart syndrome have died.

Three of our five hypoplastic left heart syndrome patients had undergone stage 1 Norwood repair, had developed ventricular failure and were accepted for transplantation at that point.

We had two early deaths. Both of these two patients were moribund at the time of surgery. One late death occurred in an older child with cardiomyopathy who had persistent severe rejection, and had early changes of coronary artery disease in the grafted heart.

Our long-term management also includes cyclosporine and imuran. We attempt to taper or wean steroids, decreasing the dose during the first year. We have attempted frequent follow-up surveillance, but of these patients are not from our immediate geographic area and require follow-up by their pediatricians, which has generally been successful. As