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# Single-center experience with extracorporeal photopheresis in pediatric heart transplantation

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**BACKGROUND:** The pediatric heart transplant literature contains little information regarding extracorporeal photopheresis (ECP), despite International Society for Heart and Lung Transplantation guidelines recommending it for recurrent/recalcitrant rejection. We report our experience with ECP in pediatric heart transplantation.

**METHODS:** Data were obtained on heart transplant patients who were aged $\leq$ 18 years at the time of transplantation and received ECP between 1990 and 2012 at our institution.

**RESULTS:** Twenty heart transplant patients underwent 22 courses of ECP. Median ages were 12.7 years (range, 0.3–18.5 years) at transplant and 15.3 years (range, 7.3–31 years) at initial ECP. Median time from transplant to ECP was 1.4 years (range, 0.1–12.6 years). The median ECP duration was 5.8 months (range, 1.9–16.1 months). Indications for ECP included rejection with hemodynamic compromise (HC) in 4 patients, rejection without HC in 12, and prophylaxis in 2. Eleven patients died at a median time of 3.1 years after the start of ECP. Survival after ECP was 84% at 1 year and 53% at 3 years. Eleven patients were considered non-compliant and had a trend toward lower survival of 75% at 1 year and 18% at 3 years ($p = 0.06$ compared with compliant patients). One patient developed *Pneumocystis carinii* pneumonia during ECP and post-transplant lymphoproliferative disease 21 months after finishing ECP. No other adverse effects or infectious complications associated with ECP were noted.

**CONCLUSIONS:** This case series represents the largest reported experience with ECP in pediatric heart transplantation. ECP can be safely applied in this patient group. Despite EPC, non-compliant patients showed a trend toward lower survival than compliant patients.

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Allograft rejection remains an important cause of morbidity and the leading cause of death in the first 5 years after heart transplant in children.[1] Medical immunosuppression represents the primary means of rejection prophylaxis and treatment. Extracorporeal photopheresis (ECP) is an immunomodulatory therapy that has documented effectiveness in transplantation and other pediatric disorders such as graft versus host disease and cutaneous T-cell lymphoma.

The most recent American Society for Apheresis (ASFA) guidelines for the clinical applications of apheresis considers ECP for rejection prophylaxis or treatment of cellular or

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recurrent rejection as category II indications: "second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment." ECP for treatment of rejection received a grade of 1B ("strong recommendation, moderate quality evidence"), and rejection prophylaxis, grade 2A ("weak recommendation, high quality evidence").[2] The 2010 International Society of Heart Lung Transplantation (ISHLT) Guidelines for the Care of Heart Transplant Recipients suggest ECP as a class IIb therapy for recurrent or recalcitrant rejection.[3]

Despite these recommendations, the pediatric heart transplant literature contains very little information related to ECP, which may be a reflection of the technical difficulties of performing ECP in small patients, its unfamiliarity, and/or its unavailability, particularly in free-standing children's hospitals. Furthermore, query of the Pediatric Heart Transplant Study database reveals that most instances of ECP use occurred at our institution (personal communication). Our objective is to report our unique experience with ECP in pediatric heart transplant patients.

## Methods

After obtaining approval from the Institutional Review Board, data were obtained from medical records of heart transplant patients aged 18 years or younger at the time of transplant who received ECP between 1990 and 2012. Heart–lung transplant recipients were excluded. Basic demographic and peri-transplant variables were collected. The transplant team defined medical non-compliance at the time clinical care was administered based partly on evidence of non-compliance with immunosuppression medication that compromised the patient's clinical course. The primary outcome of interest was death. Secondary outcomes studied were ECP complications, infections, rejection episodes, and coronary artery vasculopathy (CAV).

Immunosuppression protocols evolved during the study interval and have been summarized previously.[4] Rejection episodes were routinely treated with intravenous pulse methylprednisolone or oral prednisone for 3 days. Patients with persistent or recurrent rejection additionally received lytic therapy (OKT3 or anti-thymocyte globulin) and conversion to tacrolimus and mycophenolate mofetil if not already receiving them. Patients with rejection with hemodynamic compromise (HC) additionally received 3 or more therapeutic plasma exchanges (TPE).

ECP was generally used after these therapies at the discretion of the clinical care team. The presence of non-compliance was considered in the ECP decision making with the assumption that ECP would provide additional background immunosuppression that might reduce the likelihood of rejection if further non-compliance occurred. Occasionally, ECP was used prophylactically, and indications evolved during the study period.

The standard adult ECP protocol, as previously published, was used.[5] Most commonly, ECP was performed through a subcutaneous port accessing a subclavian vein. With this protocol, the total extracorporeal volume should be limited to 15% of the patient's blood volume. The standard adult protocol was typically used for most patients in this series, including a 36-kg 17-year-old and a 38-kg 10-year-old. The modified pediatric protocol was used for Patient 3, a 24-kg 8-year-ol. The modification included priming the ECP circuit with crossmatched leukocyte-reduced packed red blood cells and giving an albumin bolus to the patient at the beginning of ECP. The apheresis team individualized the exact volumes of red blood cells and albumin according to the patient's total blood volume and hematocrit. To prevent fluid overload, the same volume given during ECP was removed from the patient at the end of the procedure. Other ECP pediatric modifications have been further described previously.[6]

In addition, the duration of the protocol changed during the study period. One course of ECP originally consisted of 15 series of 2 treatments on consecutive days, separated by 3 to 6 weeks, over 18 months. After 2000, the protocol was modified, such that 1 course of ECP now consists of 10 series of 2 treatments on consecutive days initially weekly but spacing out to monthly and finishing approximately within 6 total months. For purposes of this analysis, patients who received more than 1 ECP course separated by less than 6 months were not considered to have received distinct courses.

Basic statistical analysis included a chi-square analysis using a Pearson test for significance. Kaplan-Meier curves were generated for the entire cohort and were also stratified by medical compliance vs non-compliance. Log-rank analysis was used to analyze survival differences.

## Results

Twenty heart transplant patients underwent 22 courses of ECP. Table 1 summarizes the characteristics of our ECP cohort. These patients received transplants at a mean age of 12.9 years (range, 0.3–18.5 years). Indications for transplantation included dilated cardiomyopathy in 14 patients, congenital heart disease in 4, restrictive cardiomyopathy in 1, and myocarditis in 1.

ECP use has been relatively stable since 2001, averaging approximately 1.5 patients per year in the pediatric/young adult cohort (Figure 1). Median age at the time of the initial ECP was 15.7 years (range, 7.3–31 years). Only 1 patient was older than 19 years at the initial ECP. Median time from transplant to ECP was 1.4 years (range, 0.1–12.6 years). Nine patients underwent ECP within the first year after transplant. Indications for ECP varied and are listed in Table 1. The indication could not be ascertained in 2 patients. There were no important procedural complications related to ECP.

Typically, immunosuppression was augmented before ECP (Table 1). Data were unavailable for 3 patients. All patients received steroid pulses after rejection. The following were also used depending on the rejection characteristics and era of transplantation: TPE in 6 patients, intravenous immunoglobulin in 2, rituximab in 2, Thymoglobulin (Genzyme Corp, Cambridge, MA) in 5, OKT3 in 2, and the addition of sirolimus in 2. Seven patients received more than 1 of these therapies.

Two patients underwent a second course of ECP. Patient 17 had rejection with HC (felt to be mixed cellular and antibody-mediated) 7 years after her initial ECP and underwent a second course of ECP but died 1 month after completing the ECP course of terminal rejection with HC. Non-compliance was not a concern. Patient 7 had recurrent rejection episodes beginning 2 years after the initial ECP; he received nearly 1.5 years of monthly ECP before dying of rejection. Non-compliance was a chronic concern in this patient.

Thirteen patients died at a median of 3.1 years (range, 0.3 -13.8 years) from the start of ECP. Cause of death was