# Early primary graft failure after a pediatric heart transplant and successful rescue with plasmapheresis, immunoglobulins, and alemtuzumab

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## ABSTRACT

**Early primary graft failure after pediatric orthotopic heart transplantation (OHT) has a high mortality rate and can occur due to several causes including but not limited to prolonged graft ischemia time, suboptimal preimplant myocardial preservation, hyperacute rejection, and maladaptation of the graft to the host's hemodynamic status. Mechanical circulatory support with either extracorporeal membrane oxygenation (ECMO) or ventricular assist device has been used for the rescue of primary graft failure in pediatric patients after heart transplant. Cardiac arrest before ECMO initiation in these patients is associated with adverse neurologic outcome although those surviving to hospital discharge generally have excellent long-term outcome. We report a case of early primary graft failure after OHT who required ECMO support and successful rescue with plasmapheresis, immunoglobulins, and alemtuzumab.**

**Keywords:** Alemtuzumab, extracorporeal membrane oxygenation, graft rejection, heart transplantation, plasmapheresis, ventricular assist device

## INTRODUCTION

Early primary graft failure after pediatric orthotopic heart transplantation (OHT) has a high mortality rate and can occur due to several causes including but not limited to prolonged graft ischemia time, suboptimal preimplant myocardial preservation, hyperacute rejection, and maladaptation of the graft to the host's hemodynamic status.[1,2] Mechanical circulatory support with either extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD) has been used for the rescue of primary graft failure in pediatric patients after heart transplant.[1,2] Cardiac arrest before ECMO initiation in these patients is associated with adverse neurologic outcome although those surviving to hospital discharge generally have excellent long-term outcome.[3]

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## CASE REPORT

A 15-year-old boy with idiopathic dilated cardiomyopathy was bridged to a left VAD (HeartWare LVAD®) after he presented with severe congestive heart failure and was listed for OHT. Two months after HeartWare LVAD placement, he developed left hemiparesis secondary to right middle cerebral artery thromboembolic stroke despite therapeutic anticoagulation with warfarin. He subsequently had significant clinical improvement with normal gait and full recovery of speech on follow-up. Six months after LVAD placement, he underwent a well cross-matched bicaval OHT. The transplant operative course included cardiopulmonary bypass (CPB) time of 4 h and 45 min and donor cold ischemia time of 166 min.



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He was successfully weaned off the CPB and demonstrated sinus rhythm with good biventricular function on transesophageal echocardiography. However, by 10 h posttransplant, he developed signs of poor cardiac output and worsening lactic acidosis requiring escalating doses of vasoactive medications culminating in cardiac arrest and required brief period of cardiopulmonary resuscitation. He was subsequently placed on venoarterial ECMO due to depressed biventricular function. Although the pretransplant crossmatch for donor-specific antibodies (DSAs) against Class I and Class II human leukocyte antigens (HLAs) was negative, we suspected acute graft failure associated with humoral rejection given the timeline after the implantation. An emergent myocardial biopsy revealed mild to moderate acute cellular rejection (International Society for Heart and Lung Transplantation [ISHLT] Grade 1R) with an antibody-mediated rejection component (ISHLT Grade pAMR1) with microvascular inflammation (capillaritis) composed of macrophages and occasional T-cells (as seen by immunohistochemistry) along with focal staining of perimyocytic capillaries with complement fragments C4d and C3d. He was treated with plasmapheresis, intravenous immunoglobulin, methylprednisolone, and alemtuzumab (Campath). After 72 h, cardiac function improved and he was weaned off ECMO. The follow-up endomyocardial biopsies performed on day 7 and day 14 posttransplant demonstrated ISHLT Grade 0R. Viral and bacterial studies both pre- and post-transplant were negative. A review of DSA since transplant listing showed negligible levels of HLA-A24 and moderate levels of HLA-A1 [Figure 1]. However, only HLA-A24 was present in the donor. Interestingly, there was drop in alloantibody levels immediately following OHT, suggesting that the immunoglobulins were binding to the graft; thereafter, levels again began to rise. He was discharged home after a hospital course of 17 days. He continues to do well on follow-up at 3 years with minimal levels of anti-HLA-24 antibodies (1235 mean fluorescence intensity) and no evidence of antibody-mediated rejection.

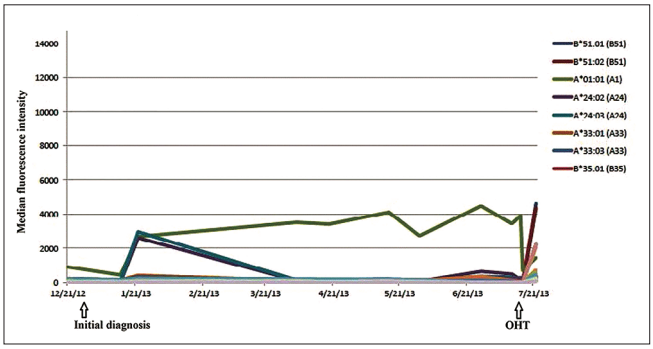


**Figure 1: Panel reactive antibodies in the pediatric patient with dilated cardiomyopathy and left ventricular assist device since the time of diagnosis until after orthotopic heart transplantation**

## DISCUSSION

Children with heart failure bridged to mechanical circulatory support are at high risk for early graft rejection after OHT.[3] Panel reactive antibody (PRA) testing to screen humoral sensitization due to HLA and nonHLA antigens and aggressive immunosuppressive therapy are utilized in sensitized patients before OHT. Low levels of DSA before OHT may not trigger a positive crossmatch, but *in vivo* exposure to graft alloantigen after OHT may lead to a rapid rise in DSA causing acute rejection. Plasmapheresis, high dose corticosteroids, intravenous immunoglobulins, and immunotherapy are the mainstay of treatment of symptomatic hyperacute rejection after OHT that may help in the rescue of graft function.[4] Alemtuzumab is a humanized anti-CD52 monoclonal antibody that binds to CD52 expressed on the surface of several cells including B- and T-lymphocytes causing profound, rapid, and sustained lymphopenia. It is a commonly used agent for induction after solid organ transplantation although there is only very scant experience with its use in pediatric OHT patients, with no published trial data. We report the first successful use of alemtuzumab as treatment for hyperacute rejection in pediatric OHT.[5] There is some evidence that infants and younger children supported on ECMO during the pre-OHT period are at increased risk for HLA sensitization when compared with similar children of older age on VAD support.[6] This could presumably be due to more intact immune responses coupled with a longer blood exposure to a nonbiologic surface leading to a more robust anti-HLA antibody response. Luminex assays have shown to be complementary to more conventional PRA methods by quantitatively identifying potential donor-specific antibodies that could facilitate the virtual crossmatch process, and help minimize the humoral-mediated rejection in the posttransplant period. In a large retrospective single-center study, pretransplant allosensitization was associated with decreased freedom from graft vasculopathy (coronary artery disease [CAD]) and history of VAD was a univariate predictor of shorter CAD-free survival and an independent predictor of earlier onset of CAD after transplantation.[7] There is recent evidence of induction therapy being associated with improved survival in pediatric OHT patients who have PRA >50% and those with prior congenital heart disease although its role in those supported on VAD before OHT is not known.[8]

In conclusion, we report the first successful use of alemtuzumab as rescue for hyperacute rejection in pediatric OHT and our case to highlight the fact that multiple variables including age, type of pre-OHT mechanical circulatory support, and methods of

evaluating PRA should be assessed in determining the risk of post-OHT humoral-mediated rejection.

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**Conflicts of interest**

There are no conflicts of interest.

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