EDITORIAL

Can we push the boundaries of ABO-incompatible pediatric heart transplantation?

Kathleen E. Simpson, MD, and Charles Canter, MD

From the Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri, USA.

Since the first successful reports in children,1 ABO-incompatible (ABOi) heart transplantation has become the standard option for infant heart transplant recipients with acceptable isohemagglutinin titer levels. Despite early concerns, infant ABOi recipients can expect outcomes and graft survival rates comparable to those seen in other similarly aged heart transplant patients.2–4 Transplant success in very young children is attributable to the relative immature immune system in the first 1 to 2 years of life, contributing to tolerance to donor A/B antigens.5 Current practice includes intra-operative plasma exchange transfusion (PET) to remove circulating isohemagglutinins, generally to a titer of at least 1:2. However, the need for at least 2-fold patient volume during PET has typically limited ABOi candidates to smaller children for practical reasons. PET also includes exposure to relatively large amounts of blood products and risk of potential transfusion-related morbidity.

To address the limitations of PET related to ABOi heart transplantation, Robertson et al describe a technique of using anti-A/B immunoabsorption columns intra-operatively to remove anti-A/B isohemagglutinin in children.6 Immunoabsorption columns have been used previously for antibody removal, including isohemagglutinins, pre- and post-transplant in children and adults, but not routinely in place of PET intra-operatively. The authors report ex-vivo data showing essentially linear and reliable removal of isohemagglutinins, effectively allowing them to calculate the number of passes needed through the immunoabsorption column to achieve the desired titer level. Subsequent in-vivo experience was described in a 43-month-old, 15-kg child with anti-A immunoglobulin M isohemagglutinin. Titers became undetectable intra-operatively, with a mild, brief rebound at 2 weeks post-transplant, but remained low at nearly 2 months, with no reported complications.

Robertson and colleagues conclude that the use of intra-operative immunoabsorption columns for isohemagglutinin removal has several potential positive implications for heart transplantation. The apparent predictability and efficiency of the technique allows for planning of time needed for isohemagglutinin removal before graft reperfusion without increasing intra-operative time when compared with standard PET. Patients would also be expected to have less blood product exposure and hemodynamic instability from fluid shifts associated with PET. Perhaps, most significantly, the authors note how the technique has the potential to expand the application of ABOi heart transplantation to larger children and recipients with higher anti-A/B isohemagglutinin titers. Given the increasing demand within a relatively constant level of donor availability, this may assist in increasing the donor pool for some recipients and improving overall organ utilization.

Despite the potential of using immunoabsorption columns in ABOi heart transplantation in place of PET, challenges remain with regard to practical clinical application among the wider heart transplant population. The immunoabsorption columns used by Robertson et al are not universally available to all institutions across all continents, including the United States. In addition, although Robertson et al report low levels of detectable isohemagglutinin titers during short-term follow-up post-transplant, it is unclear how much rebound in titer levels would occur long term even if satisfactorily decreased intra-operatively. Development of donor-specific isohemagglutinins after PET at time of heart transplant has been noted in ABOi infant recipients and is associated with older age, higher titers and HLA sensitization at transplant, but not necessarily outcomes, such as survival or antibody-mediated rejection (AMR) episodes.7 Similar studies in pediatric and adult ABOi kidney transplants showed no difference in rejection rate despite donor-specific isohemagglutinin rebound in some patients post-transplant.8–10

The authors’ assertion that use of immunoabsorption columns intra-operatively would greatly expand candidacy for ABOi heart transplantation may be limited despite the
noted efficiency and effectiveness of the technique described. The greatest barrier may not be so much patient size as development of immune maturity with age, as evidenced by the high isohemagglutinin titers. United Network for Organ Sharing (UNOS) policy has changed over time in response to acceptable reported outcomes with higher titer levels and currently allows for children between 1 and 2 years of age to be listed for ABOi heart transplantation if titers are \( \leq 1:16 \). ABOi transplantation in children with higher isohemagglutinin titers remains controversial, mainly due to concern for poorer survival and increased AMR post-transplant. Although some centers have reported no additional rejection with titers >1:16 pre-transplant, \(^{11}\) others identified a higher incidence of early AMR but similar survival. \(^{12}\) Urschel et al reported on ABOi heart transplantation in children up to 90 months of age with titers up to 1:32, with 2 of 8 patients with titers >1:8 having AMR and overall survival comparable to that expected. \(^{13}\) One of the larger center long-term cohorts in Toronto reported 7 of 35 ABOi heart transplant patients up to 14 months old had titers of >1:8, 2 of whom developed early AMR related to high donor-specific titers. \(^{3}\) Adult ABOi heart transplant was associated with increased 30-day and 1-year death or re-transplant in the Registry of the International Society for Heart and Lung Transplantation (ISHLT), although survival improved in the later era. \(^{14}\) Adult ABOi patients had more hyperacute rejection and acute rejection, leading to death compared with other patients.

Overall, Robertson and colleagues describe a technique and speculate on how its routine use will allow for ABOi transplantation in patients with higher titers and body size. Nevertheless, further investigation and clinical experience will be needed.

**Disclosure statement**

The authors have no conflicts of interest to disclose.

**References**