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Expansion of the Pediatric Donor Pool for Liver Transplantation in the United States

Matthew B. Goss, Michael L. Kueht, Nhu Thao Nguyen Galvan, Christine Ann O'Mahony, Ronald Timothy Cotton, Abbas Rana*

Department of Surgery, Division of Abdominal Transplantation, Michael E. DeBakey, Baylor College of Medicine, Houston, TX, USA

***Corresponding author:** Abbas Rana, Department of Surgery, Division of Abdominal Transplantation, Michael E. DeBakey, Baylor College of Medicine, One Baylor Plaza, MS: BCM390, Houston, Texas 77030, USA. Tel: +17133218423; Fax: +17136102479; Email: abbas.rana@bcm.edu

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Abstract

As the greatest survival benefit owing to Orthotopic Liver Transplantation (OLT) is achieved in the pediatric population (< 18 years of age), the United States (US) annual unmet need of more than 100 pediatric liver allografts warrants an innovative approach to reduce this organ deficiency. We present a three-pronged strategy with the potential to eliminate the disparity between supply and demand of pediatric liver allografts: (1) optimize the current supply of donor livers, (2) further capitalize on technical variant allografts from cadaveric and living donation, and (3) implement a novel donation approach, termed 'Imminent Death Donation' (IDD), allowing for donation of the left lateral segment prior to life support withdrawal in patients not meeting brain death criterion.

Abbreviations

ABOi	:	ABO-Incompatible
BA	:	Biliary Atresia
BCAA	:	Branched-Chain Amino Acid
CNS	:	Central Nervous System
DBD	:	Donation After Brain Death
DCDD	:	Donation After Circulatory Determination of Death
DDR	:	Dead Donor Rule
IDD	:	Imminent Death Donation
MSUD	:	Maple Syrup Urine Disease
OLT	:	Orthotopic Liver Transplantation
UNOS	:	United Network for Organ Sharing
US	:	United States

Introduction

Only 50 years after the transformative work of transplant pioneer Dr. Thomas Starzl, pediatric OLT has become a standard of care with 1-year survival outcomes achieving a previously inconceivable 95%. Moreover, transplanted liver allografts have demonstrated exceptional durability [1], providing otherwise terminally-ill patients with the opportunity for long, healthy lives. However, the full potential of OLT, particularly in pediatric patients, remains to be realized due to organ scarcity. The pediatric population is notoriously disadvantaged considering size discrepancy with available allografts, which is exacerbated by the significant increase in the proportion of children < 1 year of age listed for OLT. An analysis of the topical United Network for Organ Sharing (UNOS) deidentified patient-level data between January 1, 2017 and November 30, 2017 reaffirms the long-standing imbalance between donor liver allograft supply and OLT demand in the US pediatric populace. During this time frame, 692 pediatric patients were added to the OLT waiting list while only 552 pediatric OLTs were performed. As the US annual unmet need of over 100 pediatric liver allografts persists alongside the

recalcitrant pediatric OLT waitlist mortality, surging beyond the 10% mark in recent years [2], expansion of the pediatric donor pool for OLT demands immediate examination. Our aim is to present a strategy designed to eliminate the disparity between supply and demand of pediatric liver allografts.

Proposed Methods for Pediatric Donor Pool Expansion

Optimization of Donor Liver Supply

To reduce the liver allograft shortage and waitlist mortality in pediatric OLT, we first propose optimization of the current donor liver supply. We suggest a five-fold approach: (1) increase the use of Donation after Circulatory Determination of Death (DCDD), (2) overcome the erroneous stigma associated with donation after drowning, (3) expand OLT access for acutely-ill patients via utilization of ABO-incompatible (ABOi) allografts, (4) accept the viability of OLT from deceased donors with a central nervous system (CNS) malignancy, and (5) capitalize on domino OLT in patients presenting with Maple Syrup Urine Disease (MSUD).

While only 59 pediatric patients have been transplanted with DCDD livers in the US since 1987, the data suggests that patient survival is comparable to OLT with Donation after Brain Death (DBD) liver allografts [3] (Figure 1).

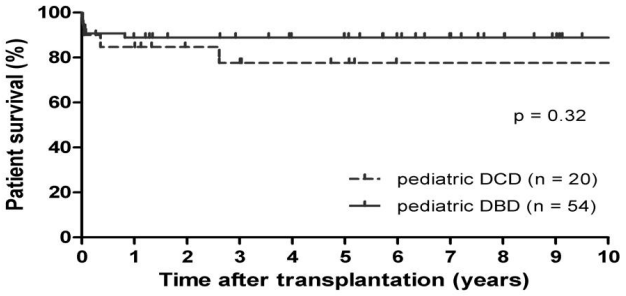

Figure 1: Kaplan-Meier patient survival curves after pediatric DCDD and DBD OLT. Patient survival rates are equivalent for pediatric DCDD and DBD OLT. Abbreviations: DCDD, donation after circulatory determination of death; DBD, donation after brain death; OLT, orthotopic liver transplantation. Abscissa: years post-OLT. Ordinate: percentage of patient survival. Adapted with permission from Harring, et al. (2012) [3].

illustrates these commensurate outcomes following 20 pediatric DCDD liver allograft recipients and 54 pediatric DBD liver allograft recipients 10 years post-OLT [3]. Despite the increase in ischemic cholangiopathy using DCDD organs, pediatric DCDD OLT's acceptable outcomes warrant its expanded implementation given insufficient DBD organ availability. Providing further justification for the increased use of pediatric DCDD allografts, van Rijn, et al. [4] reports equivalent patient and allograft survival rates between recipients of pediatric DCDD (warm ischemia time < 30 minutes) and DBD livers, with comparable incidence of biliary or non-biliary complications.

Anecdotally, organ allografts from drown donors have been deemed high risk over concerns for infection and allograft dysfunction. As drowning may represent a large donor pool for pediatric OLT, reexamination of this potentially misplaced stigma is essential. Contrary to the prevailing opinion, studies demonstrate drown donor allografts do not portend comparably worse outcomes in lung transplantation [5,6] or pediatric OLT [7], revealing a donor source yet to be appropriately exploited (Figure 2), demonstrates a single pediatric center's OLT experience with 33 drown donor recipients relative to head trauma donor OLTs [7].

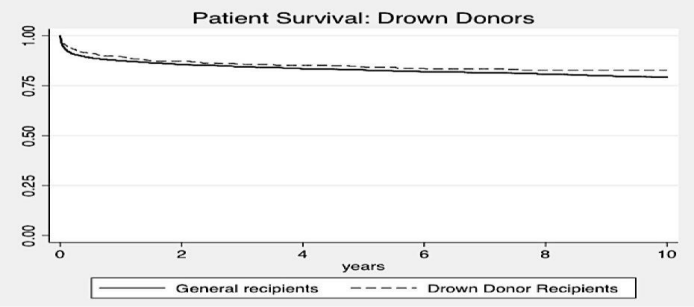

Figure 2: Kaplan-Meier patient survival curves after pediatric OLT stratified by recipients receiving liver allografts from general DBD or drown donors. Patient survival rates are comparable for both donation sources. Abbreviations: OLT, orthotopic liver transplantation; DBD, donation after brain death. Abscissa: years post-OLT. Ordinate: fraction of patient survival. Adapted with permission from Kumm, et al. (2017) [7].

Pediatric OLT with ABOi allografts has been suggested to provide acutely-ill patients with greater access to transplantation in a critical time. While initial clinical experience revealed higher incidence of hepatic artery and biliary complications and decreased allograft survival [8,9], modern technological advancements and therapeutic approaches have qualified the use of ABOi allografts for pediatric OLT as an acceptable option [10]. Most published data are limited to small case series from select US centers. However, as demonstrated in (Figure 3) when the UNOS database is queried, irrespective of post-transplant immunosuppression protocols, postoperative outcomes of ABOi pediatric OLT are comparable to those of blood type-matched pediatric OLT [10] As ABOi OLT's best outcomes are reported in children younger than 2 years of age [11], potentially attributable to their immature immune systems [12], and the number of children < 1 year of age listed for OLT has recently increased, ABOi OLT represents a promising opportunity to reduce waitlist mortality [13].

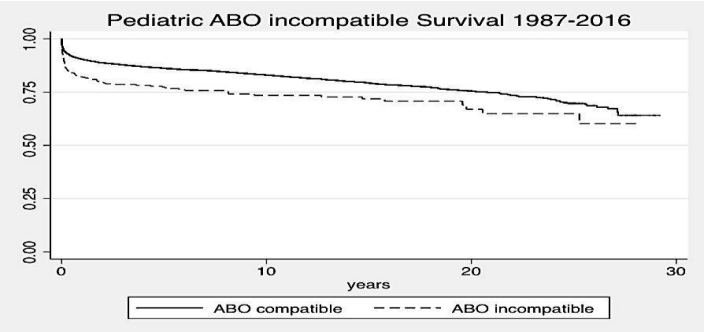

Figure 3: Kaplan-Meier patient survival curves after pediatric OLT stratified by donor/recipient blood type relationship. Patient survival rates are comparable for ABO-incompatible and ABO-compatible pediatric OLT. Abbreviation: OLT, orthotopic liver transplantation. Abscissa: years post-OLT. Ordinate: fraction of patient survival. Adapted with permission from Goss, et al. (2017) [10].

There is controversy in the transplant literature regarding the use of organs from donors with primary brain tumors for OLT. This reluctance stems from the small risk of donor tumor cell migration and donor-derived tumor development in the recipient, as such donor-transmitted malignancies have been reported in the literature numbering over 20 cases [14,15]. However, recent studies demonstrate the feasibility of OLT with CNS tumor donors [16,17] and call for this donor source's expansion from its 1.7% contribution to deceased donor organ transplants [18]. Given the 0.05% risk of donor-donor derived cancer development [17], this nominal transmission likelihood must be evaluated against the perspective of OLT's lifesaving benefits. In view of the persistent liver allograft shortage, these minimal risk, extended criteria donors should be considered for pediatric OLT. Domino OLT enables young individuals suffering from the rare genetic disorder MSUD to be both liver donors and recipients. The enzymatic defect in MSUD results in the accumulation of neurotoxic metabolites of Branched-Chain Amino Acids (BCAAs) [19] OLT has demonstrated success in these patients, allowing for the restoration of a normal diet and avoidance of further neurological damage [20,21] As others on the OLT waiting list, not affected by MSUD, possess sufficient enzyme activity in extrahepatic tissues and MSUD livers are structurally normal, MSUD livers may be used as donor allografts with demonstrated success [22,23] Therefore, domino OLT represents a safe therapeutic option to expand the US pediatric donor pool for OLT by approximately 10 liver allografts annually (10% of the allograft deficiency for pediatric OLT).

Technical Variant OLT

Progress towards overcoming the pediatric liver allograft shortage has been realized in part by innovative surgical techniques. When Dr. Starzl performed the first pediatric OLT in 1963, on a 2-year-old child afflicted with Biliary Atresia (BA), the sole technical option for pediatric liver replacement was full-size ABO-compatible OLT, which held true into the mid-1980s [24]. Given the need for stringent donor-recipient size and weight homogeneity compounded with the low number of pediatric donors, pediatric OLT waitlist mortality approached 50% during this interval [25]. The advent of techniques enabling surgeons to transplant portions of livers from adult donors in pediatric recipients, e.g. reduced-size, split-liver, and living donor OLT, revolutionized the field of pediatric OLT. First described by Bismuth, et al [25]. in 1984, reduced-size OLT is most often performed in pediatric patients presenting deteriorating clinical condition for whom no full-size allografts may be located. This procedure consists of size reduction of the whole liver from an adult cadaveric donor, accomplished in the present-day via anatomic right or extended right hepatectomy. The resulting left lobe (segments II, III, and IV) or left lateral segment (segments II and III), lacking the donor's vena cava, is then transplanted anastomosing the allograft left hepatic vein to the recipient's vena cava, allowing OLT from donors with body weights up to 12 times the recipient's [26]. Despite the greater complexity of reduced-size OLT, in conjunction with the higher frequency of critically ill recipients selected for the procedure, outcomes between reduced-size and full-size OLT are comparable [27-29] Nonetheless, considering its interference with the likewise limited adult donor pool and the development of split-liver and living donor OLT, reduced-size OLT is not the primary option for pediatric OLT.

Split-liver transplantation, initially reported by Pichlmayr, et al. [30]. In 1988, demonstrated the possibility of using one donor liver for two recipients. The most common approach of the split-liver procedure involves liver division into a left lateral segment for a pediatric recipient and a right extended lobe to be transplanted into a larger pediatric or adult patient. A technically more challenging variant of this procedure also exists in which the liver is split into 2 hemigrafts with the left side used for a smaller adult or teenage recipient and the right side for a medium-sized adult [31] Two splitting techniques have been employed, either on the back table (*ex situ*) or during the procurement procedure prior to donor cross clamp (*in situ*). Derived from living donor transplant experience and first described by Rogiers, et al. [32] in 1996, the *in situ* splitting technique confers numerous advantages: minimization of total ischemia time, shortened pre-transplant waiting times, decreased waitlist morbidity, increased potential for inter-center sharing, better control of bleeding from the cut surface upon recipient reperfusion, and enhanced evaluative ability concerning the viability of segment IV [31]. While the *ex situ* splitting procedure results in patient and allograft survival rates comparable to full-size OLT in elective adult patients [33], its longer ischemia time has led to higher incidence of postoperative complications [34-36], hence its delegation to elective recipients. In current split-liver transplantation, *in situ* splitting is the method

of choice resulting in two allografts of optimal quality capable of application to the entire spectrum of transplant recipients and long-term outcomes comparable to those of full-size OLT [33,37,38].

Dating back to 1988 [39,40], pediatric living donor OLT involves the procurement of liver segments from an adult living donor, with segment selection contingent on the size of the recipient's abdominal cavity and metabolic needs (left lobe vs left lateral segment). Living donation of the left lobe and the more common left lateral segment impart comparably minimal complication risks to donors and recipients [41]. Aside from combating the relative paucity of infant and child donors, this technique provides the only source of organ procurement in countries prohibiting cadaveric donation [42] Furthermore, pediatric living donor OLT provides the following benefits: the possibility to perform OLT prior to the waning of recipient clinical condition, timing convenience for both the transplant center and recipient, and psychosocial value for the donating party. The psychological burden of living donation mandates consideration, in addition to the procedure's physical demand, to ensure that no long-term harm is caused. Living donation's longitudinal, psychological effects have been well-characterized through single-center studies, reporting living donors' psychological well-being as equivalent to or better than a normative general population's six to twelve months following donation [43,44]. Despite the overall stability in living donors' mental health, it is not the case that all donors fare equally well, and there is a need for close psychosocial monitoring of donors whose recipients died [45]. While disadvantages to this procedure exist, e.g. an increased need for resources, as living donor OLT is not covered by Medicaid in certain states, and the potential violation of unique ethical considerations [46], experienced centers report encouraging survival rates exceeding 90% after 1 year [47-50]. In fact, living donor OLT has been found to afford survival benefits compared to both staying on the waiting list without OLT and receiving a DBD liver [51], prompting the narrative that pediatric living donor OLT should be expanded given the deficit of DBD allografts.

While each method of technical variance demonstrates comparable outcomes with full-size OLT [27,33,43], given sufficient transplant center volume, their respective implementations should vary. As reduced-size livers for pediatric recipients remove a potential allograft for larger recipients on the waiting list, who are also plagued by organ deficiency, this procedure's employment in pediatric OLT should be limited to emergent situations unassailable with a size-matched allograft, split-liver grafting, and/or living donation. Contrastingly, split-liver transplantation enables a single liver allograft to be used in both a pediatric and adult recipient expanding the donor pool for both age cohorts. This method typifies the significance of modern medical innovation and its tangible, life-saving corollaries. Living donor OLT, despite its encouraging survival rates, only constitutes 10.7% (1,751 OLTs) of the 16,399 pediatric OLTs performed since 1988. Whenever possible, living donor OLT must garner consideration allowing cadaveric donor allografts for pediatric patients lacking the option of living donation.

Imminent Death Donation (IDD)

The final facet of our pediatric donor pool expansion proposal suggests the implementation of the novel donation approach IDD. IDD would only be considered in patients having previously consented to DCDD. Currently, in cases where patients have serious illness without hope of recovery yet do not meet brain death criterion, donation may only occur via DCDD. As a majority of DCDD candidates do not proceed to organ donation, with extreme rarity for a resulting pediatric OLT, we propose IDD as a method to increase organ yield in these cases. IDD would allow left lateral segment donation prior to withdrawal of life support. This segment's procurement would mirror living donor surgical techniques to avoid violation of the Dead Donor Rule (DDR). While IDD critics allege the procedure hastens death, no greater risk is posed than routinely undertaken in living donor donation. Moreover, IDD proponents highlight living left lateral liver donation's minimal complication risk [52], insubstantial enough to bring about sudden death, and our current system's separation of clinicians responsible for the medical care of the donor and recipient, thus preventing substandard care for prospective donors. While this novel donation approach mandates the rectification of an ethical dilemma, its potential to expand the donor pool is apparent. To spotlight the pediatric donor pool expansion capacity of IDD, based on the selection criteria outlined in Ackah, et al. [53]. 102 of the 1,482 potential DCDD donors in 2015 would have been ideal candidates for IDD. These 102 additional liver allografts could have effectively eliminated the disparity between supply and demand of liver allografts (109) in pediatric OLT that year.

Conclusion

Pediatric OLT is one of the great feats of modern medicine as demonstrated by 1-year survival outcomes of 95% and transplanted allografts' exceptional durability. These successes are marred by the persistent donor allograft shortage that manifests an unacceptable waitlist mortality. As a means to expand the pediatric donor pool, we first propose optimization of the current supply of donor livers. By increasing the use of DCDD and ABOi liver allografts, recognizing the limited additive risk in drown and CNS tumor donors, and capitalizing on domino OLT, donor liver supply may be optimized to expand the pediatric donor pool while reducing waitlist mortality. Additionally, we hope to further advance the promising trajectory of technical variant allografts. Whether from cadaveric donation, through reduced-size and split-livers, or living donation, the ability to transplant portions

of livers from adult donors has changed the fate of pediatric liver transplantation. Lastly, we present IDD, a novel donation methodology with the exclusive potential to virtually eliminate the current liver allograft deficit for pediatric OLT. We hope to galvanize the medical community to both recognize the feasibility of and furthermore act on pediatric donor pool expansion for OLT as we work together to eradicate waitlist mortality.

Disclosure Information

The authors of this manuscript have no conflicts of interest to disclose.

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