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REVIEW

Improving Patient Outcomes Following Pediatric Liver Transplant: Current Perspectives

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Abstract: Over the last 50 years, considerable advances have been made in pediatric liver transplantation. The long-term 10-year patient and graft survival following pediatric liver transplant have improved considerably to greater than 90% and 75%, respectively. With longer living grafts, patients are now struggling with different issues, such as the consequences and morbidity of immunosuppression and/or chronic hospitalization. This review will discuss some of the current outcomes and obstacles in pediatric liver transplantation, such as sequelae of long-term maintenance immunosuppression, worsened neurocognitive development, and shortages in allografts that lead to waitlist mortality. Though the future is bright and certainly better than it once was, there are clearly areas of in the long-term clinical care of these patients that deserve focus and attention. This review will highlight some of these concepts, as well as novel strategies to treat and address some of these issues in this complex and fragile patient population.

Keywords: liver transplant, outcomes, immunosuppression, neurodevelopmental, socioeconomic, pediatric

Introduction

As of the most recent analysis of the Scientific Registry of Transplant Recipients (SRTR), a total of 599 pediatric liver transplants were performed in 2017.[1] This number has remained fairly static over the last decade, as have the excellent mortality and graft-related outcomes in pediatric liver transplantation.[1] Since the first pediatric liver transplant by Starzl in 1963, outcomes in liver transplantation and specifically pediatric liver transplantation have improved dramatically from a 5-year survival of approximately 20% in the 1960–70s to 60–70% in the 1980s.[2,3] Current outcomes are better still, and according to the most recent SRTR report, 1-, 5-, and 10-year pediatric patient survival are 90%, 80%, and 70%, respectively, following deceased donor liver transplant.[1] The reasons for these improvements in patient outcomes have been attributed to advances in critical care, immunosuppression, and surgical technique. However, the average life of a liver allograft in the pediatric age group is only approximately 13 years, with primary graft 5-year survival is approximately 86% and retransplanted graft survival is less than 70% at 5 years.[1,4] As greater than one-third of pediatric liver transplant recipients are <5 years old, longer allograft survivals are clearly desired to limit the need for additional transplants.[5]

With the significant increase in both allograft and patient survival, attention has turned to the complications and morbidity associated with liver transplantation in the pediatric population. For example, longer years lived means increased exposure

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of high levels of immunosuppressive medications, predisposing transplant recipients to chronic kidney injury, diabetes, decreased immune surveillance and increased cancer risk, as well as infection. In addition, the effect of long-standing toxic, although necessary, medication regimens and hospitalizations may lead to deficits or delays in childhood development and the achievement of milestones. Also, once the child has reached adolescence, significant issues have been reported with medication noncompliance and allograft rejection, which suggest that more efforts are needed to maintain close relationships with adult transplant programs for appropriate transition of care.

The focus of this review will be centered on current obstacles and progress in pediatric liver transplantation. First and foremost, the most current immunosuppressive medication regimens, their side effects, and clinical strategies/trials to reduce or withdraw immunosuppression will be discussed. Second, an overview of whether or not technical complications associated with the age of recipient is still an issue will be described. Next, the manuscript will discuss our current management principles and progress with preventing developmental delays in pediatric transplant recipients. In addition, other potential obstacles to care of the pediatric recipient such as differences in outcomes based on socioeconomic status will be examined. Finally, this review will also highlight areas for future directions for study and research and what steps we can take to improve care in this particularly vulnerable population.

The Burden Of Immunosuppression

Arguably, the most important challenge to the pediatric transplant patient is the titration of long-standing immunosuppression. At younger ages, pediatric patients have to be put on higher doses secondary to increased hepatic metabolism, poorer enteric absorption secondary to shorter gut length and changes in body surface area, all of which make titration and level adjustments difficult.[6,7] All these factors complicate the balance between avoiding rejection and unnecessary exposure to the side effects of immunosuppression. A comprehensive list is included in Table 1.

The standard induction agents used in pediatric transplant are anti-thymocyte globulin, basiliximab, and high dose corticosteroids.[8] While basiliximab is generally well tolerated, anti-thymocyte globulin is a polyclonal antibody cocktail that is associated with side effects in patients that include serum sickness, cytokine storm reactions, and post-transplant lymphoproliferative disorder (PTLD).[8] High doses of corticosteroids are also used in the induction period and subsequently weaned but have been associated with gastric ulcers, glucose intolerance/diabetes, hypertension, impaired wound healing, and pancreatitis.[8] While a significant amount of effort has been devoted to developing, corticosteroid minimization or early withdrawal, most of these strategies are focused on the maintenance period. However, the use of ATG and other T cell depleting agents during the induction phase has somewhat allowed for a decrease in the amount of steroids given during induction and the addition of anti-metabolites, such as mycophenolate mofetil, has allowed for a similar reduction or withdrawal during the maintenance phase. While these agents are efficacious, patients do require some amount of corticosteroids not only for host immunosuppression but to help prophylax against anti-antibody responses. Works with either novel antibody or immunosuppressive compounds, as well as cellular therapies are ongoing.

In the maintenance phase following transplant, corticosteroids continue to be associated with the above-listed side effects but are also deleterious to growth and bone mineralization[9] (Table 1). In the longitudinal studies for pediatric liver transplantation (SPLIT), Ng et al demonstrated a strong association with steroid use and lower z scores for height 10 years following liver transplant.[9] In addition, chronic steroids are also associated with higher risk of diabetes and hypertension. Also, older children and adolescents are affected by the cosmetic effects of cushingoid features which can lead to multiple effects such as social/emotional withdrawal and poor confidence.[8] Fortunately, many centers are moving towards steroid-free maintenance regimens. While this ostensibly decreases some of the side effects associated with corticosteroids, patients may be at more risk for acute rejection and glucocorticoid-resistant rejection. Based on a recent study by Fairfield and colleagues, patients that were being managed with steroid withdrawal or avoidance protocols had increased risk of acute rejection (RR 1.33) and steroid resistant rejection (RR 2.14).[10] This Cochrane meta-analysis also looked at mortality and graft loss but found no statistically significant differences between steroid avoidance/withdrawal vs steroid containing regimens.[10]

Transplant recipients are also maintained with calcineurin inhibitors (CNIs) that prevent downstream IL-2 signaling and T cell proliferation and responses. With the introduction of calcineurin inhibitors, first cyclosporine and then tacrolimus, graft survival dramatically increased. Unfortunately, so did the deleterious effects of these

Table 1 Immunosuppressive Regimens

Induction Agents	Reported Side Effects
Steroids	Gastric ulcers Glucose intolerance/Diabetes Hypertension Impaired wound healing Pancreatitis Adrenal insufficiency Depression/Mood changes Posterior reversible encephalopathy syndrome
Antithymocyte globulin (ATG)	Serum sickness/Cytokine storm Pancytopenia PTLD Hyperkalemia Peripheral edema Electrolyte disturbance
Campath	Cytokine storm (less so than ATG) PTLD Peripheral edema Rash Abdominal pain
Basiliximab	Mild SIRS response Peripheral edema Abdominal pain/GI distress Insomnia
Maintenance agents Steroids	 Gastric ulcers Glucose intolerance/Diabetes Hypertension Impaired wound healing Pancreatitis Cushingoid facies Delay in growth/bone mineralization
Tacrolimus	Chronic kidney injury Diabetes Neurotoxicity/Paresthesia/Seizure Hypertension Hyperlipidemia Infection Alopecia PTLD
Cyclosporine	Gingival hyperplasia Hirsutism Nephrotoxocity Electrolyte disturbance Arrythmia Multi focal leukoencephalopathy Infection
mTOR inhibitors (Sirolimus etc)	Hyperlipidemia Myelosuppression Impaired wound healing/oral ulcers Interstitial pneumonitis Hepatic artery thrombosis Acne
Azathioprine	GI distress/Diarrhea (less than MMF) Associated with carcinogenesis Alopecia Rash Pancreatitis
Mycophenolate mofetil (MMF)	GI distress (diarrhea) Teratogenic Pancytopenia Electrolyte disturbance Multi focal leukoencephalopathy Hypertension Infection

(*Continued*)

Table 1 (Continued).

medications that have been demonstrated to cause renal vasoconstriction, chronic kidney injury, and diabetes.[6,8] In the above-mentioned SPLIT study, despite excellent 10-year liver allograft survival of 88%, calcineurin use was associated with chronic renal insufficiency and was noted in 9% of the patients with one undergoing a renal transplant.[9] In addition, use of cyclosporine has been associated with gingival hyperplasia and hirsutism, which can be socially stigmatizing in adolescent patients.[8]

In addition to steroids and CNIs, many patients are maintained on antimetabolites or antiproliferative agents such as mycophenolate mofetil (MMF), Azathioprine (Imuran), or mTOR inhibitors (sirolimus or everolimus). The most common side effects of MMF are gastrointestinal symptoms such as nausea and diarrhea which are improved in the enteric-coated form, Myfortic. In addition, MMF has been associated with teratogenic effects which should be included in the education of older sexually active female pediatric population. Azathioprine also causes diarrhea and other GI symptomology but is thought to be less than MMF. The side effects associated with the mTOR inhibitors have been described to be mainly hyperlipidemia and bone marrow suppression.

The risk of cancer has also been demonstrated to be significantly higher in pediatric transplant patients, presumably

as a result of reduced immunosurveillance. In a large retrospective review of the scientific registry of transplant recipients between 1987 and 2011, the rates of lymphoma/leukemia such as NHL, myeloma, PTLD (>50% of all reported cancers) and cancers of the skin/soft tissue, liver, genitourinary system, and thyroid were all found to be increased in pediatric recipients of solid organ transplants compared to the general population.[11] Other studies have demonstrated similar findings, with PTLD and skin cancers being the most commonly reported malignancies in pediatric transplant recipients.[12–14] Strategies to prevent these malignancies such as minimization of immunosuppression through steroid withdrawal and constant vigilance in reducing either CNI levels and/or antimetabolite dosages are actively employed.

Children are known to be more susceptible to EBV infection and subsequent PTLD than adults, possibly as a result of more frequent transplant of an EBV positive donor organ to an EBV naïve recipient. The risk is moderate compared to intestine (high) vs kidney (low) recipients. The risk appears to be higher in the first year and the severity and prognosis of the PTLD may be different depending on the onset of the PTLD. In addition, agents such as the T cell depleting OKT3 and anti-thymocyte globulin have been associated with the development of PTLD and other lymphomas.[15] With respect to common maintenance medications, the calcineurin inhibitors tacrolimus and cyclosporine have also been associated with the development of PTLD though controversial, whereas in case of the antimetabolite, azathioprine or mycophenolate mofetil, the data are even less clear.[14] More rigorous study is needed to further define if there is any role or association with these medications and the development of PTLD.

Due to the complications associated with current immunosuppression regimens, many transplant centers have worked toward the utilization of less potent T cell depleting induction regimens (used in only 17% of the patients in 2017) and by reducing or eliminating chronic immunosuppression. Clearly, the overall goal would be to identify the minimum immunosuppression required to prevent graft rejection, while maintaining immune surveillance and anti-pathogen responses. Though no one strategy has been established or widely adopted, centers have examined the role of protocol biopsy or immune function testing to determine whether patients would be candidates for immunosuppression withdrawal. Fortunately, this is a very active area of study.

Another emerging issue with changes in immunosuppression over the life of a pediatric transplant recipient is the development of donor-specific antibodies or DSAs. While the role of de novo DSAs in liver transplantation is unclear, several studies have suggested a potential association between the development of DSAs with rejection and allograft loss. DSAs are also thought to develop more frequently with time post-transplant, retransplantation, chronic rejection, as well as inflammatory or infectious insults that may occur over the life of the graft.[16–18] While the liver is typically thought to more resistant to antibody-mediated rejection and create a more tolerogenic environment post-transplant, these antibodies have been shown to bind complement and therefore could potentially be deleterious.[19–22] In one meta-analysis, high levels of DSA were associated with increased risk of both allograft loss (HR 3.09) and allograft rejection (HR 3.75).[20]

A recent study from Dr. Feng's group in UCSF highlights another finding of particular concern which is the association of DSAs and a specific genomic signature with fibrosis and inflammation in biopsies from liver transplant patients without clinical evidence of rejection.[22] This is somewhat alarming because these histological changes are subclinical and so no changes to immunosuppression would typically be made. This study does bring to light a potential diagnostic tool to identify those patients that would be at higher risk of developing rejection and would allow the clinician to perhaps increase immunomodulatory regimens in this particularly vulnerable population.

In another 2012 multicenter landmark paper, Dr. Feng's group identified a subset of pediatric liver transplant patient's that would be the best candidates to wean immunosuppression.[23] Twenty pediatric liver recipients of parental living donor transplants were identified with stable allograft function and no evidence of acute or chronic rejection or significant fibrosis on liver biopsy.[23] Patient's selected had to be 4 or more years from their transplant. Sixty percent of the patients remained off of immunosuppression at 1 year. A 5-year follow-up study was also published in 2017 which demonstrated that 12 of 12 patients were able to be maintained off of immunosuppression and were defined as operationally tolerant.[24] In addition, the investigators also examined allograft biopsies and demonstrated no progressive increase in either inflammation or fibrosis.

Although these data are encouraging, the transplant cohort in this study are highly selected. While a full discussion of these and other trials is beyond the scope of this review, larger trials investigating the withdrawal of immunosuppression are ongoing and with hopefully will have similar findings. This is certainly an area that will continue

to evolve and have a dramatic impact on the pediatric solid organ population as they will bear the brunt of the consequences of long-term immunosuppression.

Several groups have suggested several novel biomarkers of tolerance as a method to monitor a given patient's risk for rejection and to potentially guide immunosuppression withdrawal. For example, transcriptomic or genetic signatures or either whole PBMCs or isolated cell types could yield a relatively simple diagnostic tool and give a window into the relative alloreactivity of a patient.[25] In addition, flow cytometry tracking relative percentages of immunosuppressive cell populations such as T regs and B regs may be a useful tool that would allow the clinician the ability to potentially personalize and modify a patient's immunosuppression regimen.[25] DSAs have also been suggested as possible biomarkers of tolerance and could be used diagnostically to guide care.[25] While the data from these studies have to be tempered by considering the effect of the current immunosuppression on the results, a reliable biomarker to assess for tolerance would be invaluable in the pediatric solid organ transplant population.

High-Risk Pediatric Transplant Subgroups

Two early studies from prominent transplant centers suggested that outcomes in infants less than 1 year are worse than in older children and adults. The UCLA group examined their 13-year 569 patient experience with pediatric liver transplant and found that in a subset of 111 patients that were aged 1 year or less, outcomes were significantly worse prior to 1993.[26] In particular, hepatic artery thrombosis rates and 3-year patient survival rates were found to be 19% and 64% compared to 4% and 84%, respectively, in their contemporary group (post-1993).[26] In another study smaller but earlier study, Colombani and colleagues found that complications were higher in their 13-patient experience with infant (<1 yo) pediatric transplant compared to the older children and adult liver recipients.[27] Their data demonstrated primary nonfunction rates of 15%, vascular/biliary complications of 46%, and infectious complications were quite high at 75%[27]

Though the reasons for increased complications in those patients less than 1-year-old are likely multifactorial, both biliary/vascular complications were thought to be at least partially attributable to technical learning curves with performing a transplant in a child of this age, which included both donor and recipient factors. However, with the introduction of split liver techniques from either living donor transplants or deceased donor in situ split liver procurements, as well improvements in operative technique on the recipient end, patient survival has increased dramatically from 50–60% in the pre-1990s to approximately 90% in the most recent SRTR report.[5]

Of course, the introduction and subsequent increased usage of tacrolimus in the 1990s have also improved patient and graft survival outcomes as well. Therefore, while initially a concern, liver transplant in the less than one-year-old population is less of an issue which is encouraging since they comprise the majority of patients on the waitlist and have the highest pretransplant mortality.[1]

Another potential concern in the pediatric liver transplant population is the graft type and patient survival in those patients that receive split vs whole liver grafts. For example, outcomes from the pediatric liver transplantation or SPLIT study from patients enrolled between 1995 and 2006 demonstrated that those patients that received a split or reduced liver transplant had significantly higher rates of complications across the board and 4-year patient and graft survival of 80% and 75% in the split liver group vs 90% and 85% in the whole liver graft group.[28] The interpretation of this data should be guarded as recipients of split or reduced liver grafts were also significantly younger than those patients that received whole liver grafts thus potentially increasing both the technical learning curve and difficulty of the operation in the recipient.[28]

In a more contemporary study, the Segev group used the SRTR to retrospectively examine pediatric patients that received liver transplants from 2002 to 2015 and subsequently split them into 2 cohorts: those that received transplants between 2002 and 2009 vs those that received transplants between 2010 and 2015[29] Interestingly, though there were significant differences in patient survival at one year in the early 2002 to 2009 cohort when comparing those patients that received split vs whole grafts, 90% vs 94%, respectively, there was no difference in 1-year survival noted between these groups in the more recent 2010 to 2015 cohort which was 95%.[29] Similar differences were noted in graft survival in the early cohort but subsequently disappeared in the more recent group.[29] While admittedly the differences were small in the early group and the data represent early follow-up, the data suggest current equivalence between the usage of split vs whole liver grafts in the pediatric population.

Therefore, the question is do we now consider all donors of good quality for potential split grafts to increase the pool of organs for both adult and pediatric patient populations as currently less than 5% and approximately

30% of all adult and pediatric transplants, respectively, are split or partial grafts. A recent study from Italy examined the effect of a mandatory split liver policy in which all standard risk donors that were anatomically able to be split between the ages of 18 and 50 were offered to a suitable non-Status 1 pediatric recipient.[30] Once a suitable pediatric recipient is found, a suitable adult liver transplant recipient is then matched to the extended right graft. Both patients and graft survival outcomes for adults and pediatric liver transplant recipients of split grafts were not statistically different at 18 months of follow-up between those patients transplanted before and after the policy was instituted. In addition, waitlist times for pediatric patients decreased from approximately 7 months to 3 months and mortality decreased by approximately 40%.[30] This suggests that despite a more aggressive approach to split liver usage and allocation, the policy was safe and had a positive effect on important metrics in pediatric transplant. The study also investigated adult liver transplant waiting list times and mortality. While no difference was found with respect to median waitlist times 282 vs 299 days, waitlist mortality dropped by 50% from 9.7% to 5.2%. This dramatic decrease in waitlist mortality is surprising since fewer transplants were actually performed (1503 vs 2069 liver transplants) and a only modest increase in percent of split livers were used during the new split study versus the control study (2.8 vs 4%). No such policy exists in any other country and certainly raises interesting questions as to whether or not such a policy would be accepted in the US.

In addition to high-risk recipients, very young donors have implicated as high risk as well. Desai et al performed a retrospective review of UNOS STAR data examining those recipients of donors less than 20 kg.[31] The authors divided the cohort into increments of 5 kg and found that recipients of those donors that were less than 5 kg had significantly lower 1-year graft survival and significantly higher incidence of hepatic artery thrombosis compared to those recipients of donors 15–20 kg.[31] No difference was seen in overall patient survival between these two groups. Another single-center review of 91 patients demonstrated similar findings, with elevated rates of hepatic artery thromboses in those recipients of donors 5 kg or less compared to 5–20 kg (32.1% vs 12.7%) and no difference in patient survival.[32] While the mechanisms for this increased risk are still poorly understood, large portal vein diameter which may result in portal hyperperfusion, low donor to recipient weight ratio, and technical consideration have been implicated.[33]

Neurocognitive Delay And Milestone Development

As patient and graft survival outcomes continue to improve, so does the long-term morbidity associated with chronic illness in the pediatric liver transplant population. For example, the development of liver failure in infancy is thought to predispose or increase the risk of long-lasting neurocognitive delay.[34] In a study by Wayman et al, 40 pediatric liver recipients with a history of biliary atresia less than 2 years of age were evaluated for their mental and psychomotor scores by the Bayes Scale of Infant development, an accepted standardized assessment.[35] Patients in the study were found to be low average to one standard deviation (SD) below the mean pretransplant which then decreased significantly to 1 to 2 SD below the mean at 3 months post-transplant, to a pre-transplant baseline at 12 months.[35] Age less than 6 months, low albumin, and weight below the 5th percentile were all found to be associated with delayed neurodevelopmental outcome.[35] Long-term studies of pediatric liver recipients with a history of biliary atresia have demonstrated that IQ scores of these patients are lower overall and in a small but significant percentage of patients less than 70[36] More contemporary studies have supported these earlier findings and have added single-parent households and lower parental education as possible risk factors for the development of neurocognitive delays.[37,38]

While the reasons for these neurodevelopmental outcomes are multifactorial, it highlights an opportunity for improvement and intervention. Certainly, non-organic risk factors such as single-parent households and lower parental education, while difficult to completely remedy, could be targeted for social and financial support.[39] In addition, early intervention with special education could also improve both mind and psychomotor outcomes to give these children the best chance for success. Other strategies include modifications to immunosuppressive regimens which can have detrimental effects on neurodevelopmental outcomes.[40] For example, glucocorticoids have long been implicated in growth failure and poor musculoskeletal development.[41] This is another reason why there is fairly wide acceptance of steroid-free or minimization protocols post liver transplant in children. Again, these data highlight the need for more

research and a multidisciplinary approach to solve these complex problems.

Changing Landscape And The Role Of Transplant In BA

Biliary atresia remains the most common reason for pediatric transplantation, comprising approximately 34% of the liver transplant candidates based on the most recent SRTR report.[1] The majority of these patients undergo a Kasai portoenterostomy drainage procedure; however, only approximately 30% of the native livers survive after 15 years.[42] Despite these outcomes, every effort is made to wait as long as possible to perform or list a patient for a liver transplant, as liver transplants in the very young are more technically challenging and increases the exposure time to risks of immunosuppression.

Though this has been the standard of care, a recent study in JAMA surgery has challenged this paradigm to suggest that all biliary atresia patients should undergo a primary liver transplant.[43] The authors performed a retrospective administrative database review of 626 patients that either underwent a primary liver transplant (n=351) or a Kasai procedure (n=351).[43] They found that patients that underwent primary liver transplantation had significantly lower long-term mortality risk than those that underwent Kasai procedure followed by a salvage liver transplant (HR 0.19 vs 0.43).[43] Unfortunately, the study suffers from a number of limitations the most important of which is selection bias as it is unknown why the patients that underwent a primary liver transplant were not treated first with a Kasai portoenterostomy. Though the median age at which salvage and primary liver transplant performed was approximately equal (315 vs 313 days of age), performing a primary liver transplant in all patients with biliary atresia without primary biliary drainage would have an unknown effect on the age at which these patients would require liver transplantation and condemn approximately 30% of this patient population to lifelong immunosuppression not to mention a significantly more dangerous and technically challenging procedure. Despite this, the study does raise an important point about the safe nature of liver transplant in the pediatric population which approaches a 90% 10-year survival.

Differences In Outcome Based On Socioeconomic Status And Race

While the surgical and acute complications associated with pediatric liver transplantation are in the forefront of most clinician's minds, the financial and time burden required for care of these patients cannot be overstated. In addition, several investigators have examined what the role of socioeconomic status plays in pediatric transplant outcomes and have found significant differences in pre and post-transplant outcomes. For example, a retrospective cohort study of the UNOS database by Hsu et al suggested that white children with private insurance were more likely to have an exception score request.[44] This would ostensibly increase their MELD/PELD score as well as their chances of being transplanted in a timely fashion. In another study, though no differences were noted in pre-transplant mortality, non-white minorities had an HR of 3.59 for mortality and an HR of 2.77 for allograft failure, even after socioeconomic status was controlled.[45]

An important unknown in all of this is potential racial or socioeconomic bias in referral for transplantation and wait listing, which may be even more pronounced that any post-wait list disparities.

Studies designed to further define these gaps in care associated with socioeconomic, cultural, or racial differences will allow us to target and examine what we can do as clinicians to improve transplant outcomes. They reveal potential and real bias between how we interact with different communities and encourage better interaction to facilitate the teaching and education that are so integral to transplant medicine.

Adolescence And Transition Of Care

Another significant barrier in pediatric liver transplant is in maintaining medication adherence through the adolescent period. Currently, adult medication non-compliance is documented to be in the 15–25% range, while adolescent non-adherence has been reported to be as high as 50%.[46] Medical non-adherence leads to graft rejection, graft loss, and in severe refractory cases, death.[46,47] Some of the risk factors for medical non-adherence have been reported to be related to lower socioeconomic status, single-parent status, medication side-effect profiles, and older age at transplant.[46]

As these risk factors encompass a number of clinical arenas, the approach should be multidisciplinary and should encompass three main facets: 1) educational/cognitive, 2) counseling/behavioral, and 3) affective/psychologic.[47] No one approach has been demonstrated to be completely effective which is understandable considering multiple risk factors likely co-exist with each patient.[47] In addition to this, more

rigorous study is needed to implement and test these interventions to ascertain which combination will yield the greatest impact on non-adherence.

Another area that deserves attention is in the transition of care of these patients to adult centers. A recent study from our group has suggested that patients transplanted at centers with close affiliation to adult centers had better follow-up than those transplanted at non-adult affiliated centers.[48] As the pediatric transplant surgical team also participate in the adult program, this allows for seamless transition of care and perhaps early identification of patients with risk factors for either medication non-adherence or loss to follow up.[48] However, this can also be facilitated with better communication between geographically close centers and should be an area for active collaboration as all the clinicians involved in the patient's care are invested in their long-term success.

Therefore, health care transition represents a significant problem in our patient population with regards to medication non-adherence and follow-up once these patients reach the age for transition. The American Association of Pediatrics recognizes this as well and have articulated a set of guidelines for this transition that are based on:[49]

1. The creation of an infrastructure to facilitate preventative maintenance, identify patients at risk, and to expand and provide better access to clinicians who perhaps specialize in health care transition.
2. The development of educational programs and training opportunities for individuals interested in health care transition.
3. To incorporate health care transition delivery systems with payment incentives from public and private payors such that the planning, transfer, and integration of an adolescent into an adult are seamlessly integrated into the insured patient's care plan.

Again, with more attention and multidisciplinary focus on this at-risk population, graft survival and by corollary, patient quality of life and survival should improve.

Future Directions And Conclusions

In sum, current outcomes in pediatric liver transplant are excellent, especially considering historic mortality and graft survival figures during the development of these techniques and immunosuppressive regimens. With the introduction of tacrolimus and development of steroid-free regimens and complete immunosuppressive medication withdrawal, a select group of patients is able to enjoy stable allograft function without rejection or the morbidity associated with these medications. With better imaging to allow for preoperative planning and the development of split liver techniques, we are able to offer 2 grafts to transplant more adult and pediatric recipients than ever before. Now the focus of research and investigation has shifted to the increase in the number and quality of organs for transplant, as well as strategies to improve the quality of life and decrease the long-term morbidity associated with liver failure and transplant.

Would a mandatory split policy or some variation of this work here in the US? Certainly, differences in mortality and graft survival have narrowed between those patients receiving whole vs partial/split grafts. In addition, priority is already given to pediatric recipients in every setting when compared to adults in our current allocation scheme. One study by Braun et al examined the percent of waitlisted children with non-standard exception points and found that 44% of the waitlist had placed non-standard exception requests of which 93% were approved.[50] It is conceivable that with more aggressive diligence that a mandatory split policy would not really be needed. Even when instituted in Italy, the overall number of split liver transplants only increased from 2.8% to 4% suggesting that in most cases when a liver could be split, it was being split even before the policy change. Despite this, however, it stands to reason that with more education about equivalent outcomes between split and whole grafts and encouragement on the part of the adult centers during the transplant evaluation, more adults would be willing to accept partial grafts and more livers that are deemed "split-able" would be split. The goal should be that no child should die on the liver transplant waiting list, while maintaining adult outcomes, and a mandatory split policy could theoretically get us closer to the outcomes to the UK center.

More subtle areas of multidisciplinary focus should be in improving and relieving some of the barriers to education, physical and occupational therapy, and methods to create a supportive home environment. It should be obvious that our patients require extra assistance to achieve their developmental milestones and that the process of their disease and the treatment come with an inexorable cost and toll. In addition, cultural barriers and differences in how medical professionals are perceived need to be understood and integrated into how we educate and interact with our patients and their families. The seamless integration of multiple fields of specialty in clinical transplant care, such as social work, pharmacy,

transplant hepatology, transplant surgery, and psychology/psychiatry, makes it the ideal setting in which to develop individualized care plans to improve outcomes in these often overlooked but critically important areas.

What else can be done? Ideally, to further understand and improve outcomes in pediatric liver transplant, we should combine our efforts and develop national registries and programs to facilitate multicenter collaboration. The rarity of these pediatric conditions and the number of transplants each center does, even at relatively high-volume centers, make interpretation of clinical data difficult. With advances in understanding allograft tolerance and the mechanisms that control it, perhaps we can better generalize these tolerance protocols to everyone as opposed to just a select few. With the development of novel therapeutics to treat hepatitis C and methods to potentially rehabilitate fatty or livers that we once considered unusable, we can further decrease the organ shortage.[51] Though short- and long-term outcomes in transplant-related metrics are excellent, they are stagnant and have not really improved in the last several years. It is important to consider this and to continue to make efforts to address the concerns raised above to provide the most optimal care for our patients.

Disclosure

The authors report no conflicts of interest in this work.

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