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Transitional care in solid organ transplantation

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ABSTRACT

Pediatric solid organ transplantation has become an accepted modality of treatment in the last few decades. The number of childhood recipients of solid organ transplantation surviving to adulthood is correspondingly rising. This review examines the epidemiology of pediatric solid organ transplant recipients, and the challenges faced during transition to adult services, with suggestions for improvement in collaborative and coordinated care. Transition to adulthood has been established as a vulnerable period for recipients of a solid organ transplant. Assessment of readiness for transfer, allowing sufficient time for preparation before the actual transfer, involvement of all stakeholders, and inclusion of a transition coordinator are some of the components that can facilitate successful transition to the adult transplant program. This programmatic approach improves both quality of life and long-term graft and patient survival. Moreover, the economic benefits associated with avoiding frequent hospitalizations for graft dysfunction and preventing re-transplantation more than compensate for the costs related to establishing and maintaining a robust transition program.

Solid organ transplantation has become the standard of care in a majority of patients with end-stage solid organ failure and disease states refractory to medical therapies. Donation after cardiac death and hepatocyte transplantation are some of the other avenues being explored both here in the United States and worldwide. Increasing success over the decades in pediatric solid organ transplantation has led to increased patient and graft survival, with greater than 80% of patients surviving into adolescence and young adulthood. Successfully transitioning care from the pediatric service to the adult transplant services is essential in achieving excellent long-term outcomes. Transition to adulthood has been established as a vulnerable period for recipients of a solid organ transplant. This period includes a "transition" process whereby adolescents/young adults become responsible for managing their post-transplant course as well as a static event, a shift in service location, or the actual "transfer." This review examines the epidemiology of pediatric patients with transplanted solid organs and the challenges faced in transitioning those patients to adult care providers and offers recommendations for improvement in collaborative and coordinated care.

Epidemiology

Based on Organ Procurement and Transplantation Network data, more than 40,000 pediatric solid organ transplants have been performed in the United States in children aged 1–17 years.[1]

Childhood recipients of solid organ transplantation surviving to adulthood manage new clinical and psychosocial consequences of transplantation, although they no longer have the original problems that required them to undergo transplantation. The fewer the complications related to their procedure and the smaller the adverse event profile of immunosuppression, the better their quality of life (QOL) is likely to be. There is no doubt that social factors may impair QOL and impact adherence to medical recommendations regardless of graft function.

Growth failure in transplant recipients with long-standing end-organ disease is well known. Up to 50% of individuals who have received their liver transplant in childhood have been reported to have a final adult height 1.3 standard deviations lower than their genetic potential.[2] Short children have been found to have difficulties with behavior and cognition, and have higher frequency of anxiety, attention-seeking behavior, and underachievement.[3] In addition, short stature has been associated with low likelihood of marriage, less education, and poorer vocational opportunities.[4] Minimizing the duration of corticosteroids, facilitating nutritional rehabilitation with vitamin supplementation, and using

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recombinant growth hormone in selected patients are strategies that can help transplant recipients achieve their projected height. The obesity epidemic has not spared solid organ transplant recipients. In adult liver transplant recipients, one-third are obese and have diabetes, while almost two-thirds have hyperlipidemia and hypertension. This illustrates the importance of monitoring the body mass index of pediatric transplant recipients on a regular basis and reinforcing healthy diet and life style recommendations, particularly during transition to adulthood when weight gain is more likely. Cardiovascular disease risk factors are also significantly increased in solid organ transplant recipients. This has been attributed to several factors, including use of immunosuppression, hypertension, hyperlipidemia, renal dysfunction, and diabetes.

Good graft function is related to integrity of the hepatic vasculature as well as biliary drainage and the absence of rejection or recurrence of disease. The majority of vascular problems, including hepatic artery thrombosis, hepatic artery stenosis, and portal vein thrombosis, occur in the first three months after the transplant, although they may occur at any time in the life of the graft. On the other hand, hepatic outflow tract obstruction and biliary complications are seen more commonly later in the post-transplant period. Immunological problems like acute rejection, late acute rejection (occurring at least three months post-transplant), and chronic rejection, are usually related to non-adherence or medical need to reduce immunosuppression secondary to infections, most commonly viremia related to Epstein–Barr virus (EBV) and post-transplant lymphoproliferative disease (PTLD).

Symptomatic EBV infections and EBV-related PTLD are more common in the pediatric population as children are often seronegative pre-transplant and seroconvert after receiving a seropositive organ whilst being immunosuppressed to prevent rejection. However, the practice of regular surveillance for EBV and cytomegalovirus (CMV), as well as using antiviral prophylaxis preemptively, and reducing immunosuppression once seroconversion occurs, has reduced the incidence of severe morbidity and mortality secondary to EBV-related PTLD in children. De novo malignancies like skin cancer are rare in the first 10–15 years after liver transplantation. Transplant recipients are encouraged to wear protective clothing, use sunscreen, and have regular screening for skin lesions. There is a higher incidence of malignancy after intestine, heart, and lung transplantation versus liver and kidney transplantation.[5]

Success of transplantation requires prevention of infectious complications. Hospitalization after infectious complications exceeds that for rejection across solid organ transplantation. In the first month after transplant, bacterial and nosocomial viral infections are common. Thereafter, primary EBV or CMV infection or reactivation of latent virus or persistence/recurrence of chronic viral infections like hepatitis B or C. Chronic kidney disease after non-renal solid organ transplantation is an important cause of morbidity and includes electrolyte disturbances, acute tubular necrosis, chronic nephritis, and chronic kidney disease.[6]

Given the adverse event profile of immunosuppression, the goal in transplantation is to achieve operational tolerance, i.e., normal or near-normal graft histology after complete withdrawal of immunosuppression. In a multicenter pilot trial in the US designed to assess the feasibility of immunosuppression withdrawal for pediatric recipients of parental living donor liver transplants with stable liver tests, 12 of 20 (60%) were operationally tolerant, maintaining normal allograft function for more than one year after immunosuppression cessation.[7] A Japanese study, on the other hand, reported that 88 of 581 (15%) pediatric living donor liver recipients were operationally tolerant.[8] Of the 88, 54 were pediatric recipients with normal liver function who had survived for more than two years with no episode of rejection during the preceding year and with parental permission, who had scheduled discontinuation of their immunosuppression. In 33 others, immunosuppression was discontinued secondary to EBV infection or other complications.[8] Despite differences in how immunosuppression was withdrawn, it has been suggested that operational tolerance occurs more frequently in children than in adults. Methods used to define a multiparameter "finger-print" of tolerance have included peripheral blood gene expression profiling, blood cell immunophenotyping, and microarray profiling in order to reliably discriminate tolerant recipients from immunosuppression-dependent patients.[9] Major efforts continue in delineating the mechanisms of tolerance as well as validating newly discovered biomarkers of operational tolerance.

Non-adherence to medical regimens is common in organ transplantation and is associated with significant morbidity and mortality. Evaluation of adherence is particularly important during adolescence. Using objective measures such as degree of fluctuation of medication blood levels rather than relying on subjective measures like direct questioning or questionnaires.[10] Adherence may be improved by increasing the frequency of clinic visits, using reminders like text messaging, and by facilitating outpatient peer mentoring.[11,12]

A multicenter cross-sectional analysis of health-related quality of life as assessed by the PedsQL 4.0 in 167 patients who were 10-year survivors enrolled in the Studies of Pediatric Liver Transplantation (SPLIT) database registry, revealed lower patient self-reported total scores compared with matched healthy children.[13] At 10 years after pediatric liver transplant, only one-third of recipients had achieved an ideal profile for a first allograft (stable on immunosuppression monotherapy, normal growth, and absence of adverse events secondary to immunosuppression). Another longitudinal study from SPLIT has recently reported that more young liver transplant recipients than expected were at risk for lasting cognitive and academic defects.[14]

In contrast, a prospective study looking at QOL in adults surviving >10 years after pediatric heart transplantation showed patient perception of physical and mental health to be similar to the general population despite serious late complications.[15] The young adults were engaging in social relationships and leading full lives, with most working or attending school. Therefore, for some pediatric transplant recipients, transitioning to young adulthood is a relatively seamless process but for others it may be a difficult, dangerous time.

Challenges faced in transitioning patients to adult care providers

Changes in outcomes during transfer

While there has been little empirical study of the overall transition process, more is known about how transplant recipients respond to transfer. Across organ types, studies have illustrated the greater risk for poor outcomes like graft loss and death conferred after transferring out of pediatrics. In a seminal study, it has been reported that graft loss was unexpectedly common among recently transferred renal transplant recipients.[16] More recently, data derived from the Scientific Registry of Transplant Recipients, acquired between 1987 and 2010, showed that renal transplant recipients between the ages of 17 and 24 years were at higher risk for poor outcomes than both younger and older cohorts, regardless of characteristics such as age at transplant, sex, socioeconomic status, type of renal disease, and donor type.[17] Among liver transplant recipients, the mortality rate was significantly greater for a small sample of transferring patients than older adolescents receiving care in pediatrics or young adults already established in the same adult program.[18] Additionally, high rates of rejection