Special Considerations in Pediatric Transplant Patients

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Introduction

Pediatrics is defined by the American Academy of Pediatrics as the "specialty of medical science concerned with the physical, mental, and social health of children from birth to young adulthood…that deals with biological, social, and environmental influences on the developing child and with the impact of disease and dysfunction on development. Children differ from adults anatomically, physiologically, immunologically, psychologically, developmentally, and metabolically [1]." It is for these reasons and then some that children are more than simply little adults. By encompassing a broad range of developmental stages, pediatric transplant presents unique complexities and specific considerations that warrant attention when caring for these patients.

Pediatric solid organ transplant (SOT) began in the early 1950s with the first pediatric kidney transplant. Heart and liver transplants quickly followed in the 1960s [2]. The implementation of immunosuppressant medication in the 1980s to delay organ rejection guaranteed SOT as the gold standard treatment for pediatric patients in organ failure. In 1984, the United Network for Organ Sharing (UNOS) was created to oversee organ donation, procurement, and transplantation across transplant centers and to collect data on patients and outcomes [3]. Based on Organ Procurement Transplant Network (OPTN) data as of December 2017, there have been a total of 51,078 pediatric SOTs since 1988. In 2016, 1878 of the transplants were in youths ranging from less than 1 year old to 17 years old. The largest group of pediatric recipients fell between the ages of 11 and 17. With advances in medical care, pediatric SOT patients today benefit from better medical outcomes, but they also face distinct challenges as they navigate development with a transplant. Attention and support can be helpful both during the pre-transplant period and following transplant.

Evaluation

Medical Aspects

The OPTN calls for pediatric and adult transplant teams to be good stewards of a valuable, limited resource. This obligation is balanced with the need to best serve one's patient. "Because donated organs are a severely limited resource the best potential recipients should be identified. The probability of a good outcome must be highly emphasized to achieve the maximum benefit for all transplants [4]." Therefore, a thorough medical evaluation is necessary to determine the need for transplant as well as listing status, with each organ type weighing specific considerations.

For example, the timing of lung transplantation is influenced most by the underlying allocation system. In 2005, the allocation of lungs in the United States was modified to apply to candidates over 12 years of age based on a combination of transplant benefit and medical urgency by means of a calculated score. All lung transplant candidates aged 12 years or older are listed on the Adult Lung Transplant Allocation List by means of a calculation, resulting in the lung allocation score (LAS) [5]. Each year, there are approximately 100 times more adults than children undergoing lung transplantation. Thus, older children and adolescents "compete" with adults for organs. Once evaluated, perhaps the most difficult decision for pediatric lung transplant physicians is determining the appropriate time to accept organs that will best secure

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a survival benefit. Donor availability is of issue, given size matching, as well as cultural issues, but the most difficult issue is predicting survival without transplant. Even in the case of cystic fibrosis (CF), for which the natural history of the disease process in children has been modeled [6, 7], many factors, including the improvement in care in recent years, have led to better quality of life (QOL) and survival to adulthood. Thus, the limited predictive data, variable course, and unique diagnoses lead most pediatric centers to carefully consider multiple factors, including waiting list survival estimates, growth and nutrition status, frequency of hospitalizations, and potential for improvement in overall QOL before committing a child to lung transplant.

With regard to heart transplant, the United Network for Organ Sharing (UNOS) developed a recipient priority system for candidates awaiting a heart transplant. Similar to the listing practices for adult candidates, Status 1A individuals have top priority and will be offered the heart first. They are severely ill, not expected to survive more than a month, and in intensive care or on advanced life support. Status 1B individuals are the next priority and are receiving intravenous medication and/or mechanical assistance to make their hearts work, either in the hospital or in their home. They are expected to survive longer than a month. Status 2 individuals are usually not hospitalized and not receiving intravenous medication or mechanical assistance.

The criteria for pediatric kidney transplant candidates involve determining the estimated post-transplant survival (EPTS) score. This score reflects several factors including age, time on dialysis, diabetes status, previous organ transplants, and sensitization status. It is a percentage score indicating length of time one candidate will need a donated kidney as compared to other candidates. In the kidney allocation system (KAS), the EPTS is considered against the kidney donor profile index (KDPI), a score describing the potential longevity of the donated kidney, in order to determine matches. Notably, pediatric patients are given priority in the KAS [8].

Alternatively, pediatric liver transplant candidates aged 12 to 17 years are assigned a PELD (pediatric end-stage liver disease) or MELD (model for end-stage liver disease) score. Children younger than 12 years of age are assigned a PELD score. The PELD is a disease severity scoring system for children, designed to improve the organ allocation in transplantation based on the severity of liver disease rather than time on the waiting list. The MELD/PELD ranges from 6 (less ill) to 40 (gravely ill). The urgency of liver transplantation for pediatric acute liver failure (ALF) is typically not reflected by their PELD/MELD score. Patients with ALF and in need of liver transplantation are given priority over those listed with a PELD/MELD score and are listed as Status 1A or 1B. Transplant rates were highest in 2014–2015 for candidates with MELD/PELD 35 or higher, compared to those with MELD/PELD less than 15 [9].

Psychosocial Aspects

The OPTN bylaws mention that a psychosocial evaluation for transplant candidacy should occur to identify good candidates. Just as is true for adult transplant, however, no specific requirements are provided with regard to what is to be included in the psychosocial evaluation, and OPTN encourages transplant centers to develop their own guidelines, examining each candidate individually [4]. The works of Annuziato and Lefkowitz have provided general guidelines that allow teams to utilize the psychosocial evaluation to identify both risk and protective factors present for the family. These works also advocate for the evaluation to include recommendations for mental health interventions that would address and hopefully mitigate the identified risk factors, which may result in medical morbidity or in some cases mortality [10, 11]. Specific risk or protective factors that are to be assessed often vary between transplant centers, as only suggestions or guidelines exist. Annuziato and colleagues reviewed the adult transplant literature and proposed that psychosocial evaluations should include the following content areas for children and adolescents: comprehension, expectations and outlook, mental health screening, cognitive assessment, family functioning, social support, and behavioral health. Similarly, recommended domains of assessment in Lefkowitz and colleagues' review include adherence, patient psychological and cognitive functioning, and family functioning.

Given that family issues are often out of the pediatric patient's control, children's behavior can be more dynamic, and that future behavior may be more challenging to predict, psychosocial factors as exclusions for transplant listing are less common than what one might see with adult programs [10, 11]. However, given the limited resources, teams are forced to consider the likelihood of success for a pediatric patient and their family. This need is counterbalanced with the difficulty that arises when considering declining a pediatric patient, given the unique and often emotionally charged factors that can be at play [11]. During the psychosocial evaluation, it is recommended that the patient and family's expectations for transplant be explored, so that true informed consent and assent can be obtained. Considerations for whether one believes transplant to be a cure; anticipation of expected treatment demands, including a lifetime of immunosuppressant medications; and understanding of the potential side effects of the treatments or medications should be assessed.

Furthermore, best practices for pediatric psychosocial evaluations encourage clinicians to specify at the outset what information will be collected and how it will be utilized; implement a standardized assessment process, while also varying assessment procedures based on age, developmental level, illness factors, and other pediatrics specific factors; and attend to and acknowledge the influence cultural factors have on health beliefs or health behavior [11]. Moreover, assessing all domains for all patients and families will improve standardization across centers [11].

Killian examined the relationship between physician reports of adherence with a number of familial risk factors in a pediatric transplant population. Association was established with the age of the child at the time of transplant, parental education levels, having a two-parent family, significant psychosocial problems, and the pre-transplant life support status of the patient. However, this was a retrospective study; unfortunately, as Lefkowitz et al. noted, there is scant prospective research examining the role of pre-transplant psychosocial risk and protective factors on post-transplant outcomes. Therefore, the effectiveness of interventions to mitigate pre-transplant risk factors also remains unknown. Taken together, these works conclude with the need to develop standardized and evidence-based pediatric pre-transplant psychosocial assessments, which include a focus on familial risk factors [12].

Due to the significant role that caregivers play in the pediatric transplant patient's overall life and specifically with the management of their medical care, pediatric clinicians need to ensure that they have assessed the functioning and readiness of the caregivers in addition to the patient. Taken one step further, one should evaluate the functioning of the family unit as a whole. Family functioning has been shown to impact behavioral symptoms, adjustment to the illness, and adherence to a medical regimen; strong family cohesion and support have been linked to better adherence, less behavioral symptoms, and better adjustment to the illness [13–15].

Moreover, pediatric practices cover a range of developmental categories, ranging from infancy to young adulthood, with each stage having its own unique set of exclusions or exceptions, further complicating evaluations. For instance, caregiver involvement should adapt to the patient's changing developmental needs, necessitating that one's evaluation or assessment can account for these nuances involving degree of caregiver participation. It is for these reasons that pediatric teams can't simply administer adult measures to a pediatric population. A pediatric-specific tool is needed, and attempts to create a standardized psychosocial evaluation tool have been made.

Fung and Shaw created the Pediatric Transplant Rating Instrument (P-TRI) [16]. They modeled the instrument on existing adult measures but adapted it for the pediatric population by incorporating a developmental perspective and evaluation of family factors. Following a literature review of the relevant pediatric risk factors, they designed a 17-item rating scale to identify and describe risk factors that may affect post-transplant outcomes. The P-TRI presented a standardized and systematic approach to pediatric transplantation, which was groundbreaking [16]. Unfortunately, the P-TRI had psychometric issues with interrater reliability, which prevented clinicians from implementing it in such a way that a meaningful cutoff score is obtained representing a level of risk [17]. Given that it is the only pediatric measure to date, a number of centers incorporate the questions from the P-TRI into a psychosocial evaluation, but don't present a cutoff score.

Continued interest remains within the pediatric transplant community to clarify the role that psychosocial factors play in medical outcomes as well as to develop a well-validated psychosocial screening tool that is valid, reliable, and easy to use. Schneider, Almond, and Shaw, investigators at Stanford University, have leveraged lessons learned from the P-TRI and in 2016 developed the Stanford Pediatric Psychosocial Optimization Tool (SPPOT) [18]. SPPOT is a self-report questionnaire that has two self-report versions for children and adolescents/young adults and four versions for parents of patients ranging in age from 0 to 30, corresponding with different developmental modules. The parent versions include an infant, toddler, school age, and adolescent/young adult versions. Domains include adherence, caregiver supervision, medical coping, psychiatric history (both patient and parent), cognitive, developmental and behavioral issues, family issues, social support, and relationship with the medical team [18]. Lastly, the SPPOT incorporates a screen of current psychiatric problems utilizing the Patient Health Questionnaires [19]. Efforts are underway to study its predictive validity vis-a-vis the relationship between baseline SPPOT scores and medical outcomes, including patterns of nonadherence and episodes of graft rejection and graft loss. The authors' goal is to develop a tool that can identify risks and then provide recommendations to minimize the risks, in a systematic way that can be applied to all participants and hopefully eventually allow for a fair and equitable evaluation process in child and adolescent transplant candidates (Table 46.1).

One area that deserves attention is the recognition of neurocognitive impairments in this patient population and ways to appropriately and ethically address this in the pre-transplant evaluation. Building from earlier findings [20–24], Reed Knight and colleagues found that pediatric kidney, liver, and heart patients' intellectual functioning at the time of the pre-transplant evaluation was within the average range overall; however, scores were significantly lower than the normal population across organs. Academic achievement scores were also significantly lower than the normal population, with means in the low average to average ranges [25].

Antonini and colleagues also found preschool-aged heart and liver transplant patients to have cognitive delays at the time of transplant evaluations, though, as is often the case, limitations due to a small sample size and variable scores are to be noted [26]. Given the rapid maturation that occurs during childhood with regard to neurological development, as discussed by Mohammed, identification of and early interventions targeting deficits are particularly important [26, 27]. It is, therefore, recommended that intellectual and academic functioning be evaluated at the time of the pre-transplant evaluation, so that appropriate accommodations or supports can be implemented. This will also help medical teams to set

Table 46.1 Components of a pediatric psychosocial evaluation from the Stanford Pediatric Psychosocial Optimization Tool [18]

	Self-report: school age	Self-report: adolescent/young adult	Parent report: infant	Parent report: young child	Parent report: school age	Parent report: adolescent/young adult
Demographic information	X	X	X	X	X	X
Concerns about transplant	X	X	X	X	X	X
Motivation for transplant	X	X	X	X	X	X
Adherence	X	X	X	X	X	X
Parental supervision			X	X	X	X
Medical coping	X	X		X	X	X
Relationship with the medical team	X	X	X	X	X	X
Patient social support	X	X				
Family support	X	X	X	X	X	X
Logistical issues			X	X	X	X
Parental social and logistical support			X	X	X	X
Externalizing problems	X	X		X	X	X
Cognitive/developmental issues			X	X	X	X
Trauma history	X	X				
Parent psychiatric history – Self-report			X	X	X	X
Patient psychiatric history – Parent report				X	X	X
Patient psychiatric history – Self-report (18yo+)		X				
Self-report rating of current psychiatric concerns		X	X	X	X	X

appropriate expectations for the role that patients or caregivers will have in the patient's disease management. For example, it may be helpful to increase adult supervision during medication administration times if a patient is unlikely to be able to manage the regimen independently or customize transplant education accordingly [11]. If over time the patient is able to increase their role in their self-care, expectations are to then be adjusted [11]. It is worth noting that identification of intellectual impairments or more specifically intellectual disability at the time of transplant is not to be done so as to in any way allow for discrimination of this patient group; rather, as mentioned in Dobbels' editorial, pre-transplant screening on a case-by-case basis, irrespective of intellectual disability, should occur [28].

While attention has been on the initial pre-transplant evaluation, it is considered best practice to reevaluate patients and families. Dew et al. demonstrate the need for ongoing evaluation, as fluctuations in caregiver and patient presentations occur with adult patients [29]. Perhaps ongoing reevaluations are of even greater importance in a pediatric population, with the ever-evolving and constant development of children and adolescents. Furthermore, Annunziato et al. discussed how reevaluation is of importance, given that new findings may be uncovered once a more trusting relationship is established and also after one has had the opportunity to receive mental health interventions that were recommended at the initial pre-transplant evaluation to address identified risk factors [10].

Selection/Listing Process

Solid organ transplant first begins with consent. The consent process requires members of the medical team to ensure that both patients and parents/caregivers understand the risks and benefits of SOT in order to give informed consent, which is obtained for pediatric patients over the age of 18 and from parents or caregivers of patients under 18 [30]. In addition to gaining consent from parents, it is ethically responsible to also gain assent or agreement from the minor patient [31]. As with all types of candidates, assurance that the patient and support system can and will adhere to the rigorous therapeutic plan before and after the transplant must be obtained. Should the patient decline transplant, the medical team and caretakers must then weigh the benefits of respecting the patient's wishes while also balancing the need for an indicated and life-saving treatment [31].

Similar to adult transplant, following informed consent and a comprehensive pre-transplant evaluation, the medical team will present the patient and discuss the varied risks and benefits of transplant. Ethical issues regarding the scare medical resource are considered, including psychosocial concerns [30]. At the conclusion of the multidisciplinary team meeting a decision is provided regarding treatment planning, and if approved the patient is placed on the transplant wait list.

Wait List

Based on OPTN data as of December 2017, there were 1995 patients under the age of 18 waiting for an organ transplant. Wait times for organs can vary widely based on the organ type. The 2012 UNOS annual data report shared that 40% of pediatric renal transplant patients waited less than a year, and the remainder of patients waited between 1 and 4 years for a transplant [32]. Conversely, the majority of pediatric heart transplant patients are transplanted within a year of being listed active on the transplant list [32].

The demand for heart transplants continues to grow steadily, as heart transplant continues to afford advanced heart failure patients the best option for long-term survival. The number of heart transplant candidates who are listed and the number of heart transplants performed continue to increase. As found at the end of 2015, the number of active candidates on the heart transplant waiting list increased by 130% over the last decade. The number of heart transplants increased by 26.8% in the past decade and only by 5.2% between 2014 and 2015. It is apparent that the growth in the waiting list has exceeded the growth in the number of transplants. This may reflect the increase of effective employment of cardiac assist devices that allow patients to survive longer on the waiting list. At the end of 2015, 230 pediatric candidates remained actively listed, 34% of whom were 11–17 years of age, followed by ages younger than 1 year (25.8%), 1 to 5 years (24.2%), and 6 to 10 years (16.0%). Fifteen percent died on the wait list or were too sick to undergo transplant. However, 48 (7.6%) children were removed due to improved condition.

Similar to heart transplant, the ratio of wait list deaths to transplants in pediatric lung candidates is higher than that in adults. Despite the highest lung transplant rates in 2015 for both populations combined, the 2014–2015 overall mortality rate was 16.5 deaths per 100 wait list years compared with 8.6 in 2004–2005, and was highest for candidates aged 12 to 17 years, at 40.0 deaths per 100 wait list years likely due to the increasingly sick candidate pool [33]. The number of active candidates on the lung transplant waiting list at year-end has grown by 14.7% over the past decade, while the number of active and inactive new additions to the waiting list has increased by 42.4% over the same time period [33]. Data from the Scientific Registry of Transplant Recipients (SRTR) report in 2016 measured a range of wait times for as brief as 30 days, to between 2 and 3 years.

According to OPTN data as of December 2017, there were 1051 pediatric patients awaiting kidney transplant with 566 of those patients being adolescent patients, aged 11 to 17 years old. The majority of pediatric kidney patients wait between 6 months and 2 years for transplant. In 2015, ten patients aged 1–17 died while waiting for transplant. Unique to kidney transplant is that patients can incorporate their time on dialysis prior to being listed as part of the overall wait time for transplant. With regard to liver transplant, in 2015, the number of new active candidates added to the pediatric liver transplant waiting list was 689, down from a peak of 826 in 2005. Waiting time has decreased slightly over time such that 52.7% of candidates waited for less than 1 year in 2015, compared with 36.4% in 2005.

Recipient characteristics, wait list mortality, and patient and transplant outcomes differ for intestine transplant and intestine-liver transplant. Over the past decade, the age distribution of candidates wait listed for intestine and intestine-liver transplant shifted from primarily pediatric to increasing proportions of adults. In 2015, a total of 141 intestine transplants were performed in both adults and children. Between 2006 and 2015, the number of intestine transplants declined by 19.4%, from 175 to 141. Numbers of intestine transplants without a liver increased from a low of 51 in 2013 to 70 in 2015. Intestine-liver transplants increased from a low of 44 in 2012 to 71 in 2015. Most of the listed candidates receive a graft within 1 year of listing. In 2015, transplant rates were highest for adult intestine-liver transplants, at 151.5 per 100 wait list years, and lowest for pediatric intestine transplant, at 18.8 per 100 wait list years.

The time waiting for transplant can be emotionally taxing for patients and their families as patients face the threat of dying before receiving an organ [34, 35]. This time is understandably marked by anxiety and uncertainty. Often patients and families are adjusting their lives to prepare for transplant. For example, families may be asked to temporarily relocate to be closer to their transplant center in case an organ becomes available. If the entire family moves or if only the patient and one parent move, disruptions to the family's life are guaranteed, with potential impacts on the schooling of the children, employment of the parents, and overall support of the community or extended family.

Concerns regarding the potential donor may also arise as the patient and family learn about the deceased donor process. Children and adolescents may have questions or worries both before and after transplant about their donor, their donor's family, and the circumstances around the donor's death. Alternatively, patients pursuing living donation must also process their own unique considerations, such as who

will donate the organ and whether the patient is comfortable with a living donor donation. A major benefit to living donation is that it can be scheduled, which can alleviate the uncertainty of waiting. However, with living donation you must identify caregivers for both the pediatric patient and the donor. Oftentimes one parent would like to donate, which in turn strains the entire family system when two members are recovering from an invasive surgery. Similarly, siblings are sometimes asked to donate. Special attention should be given to ensure that the sibling does not feel coerced or pressured. Lastly, the patient will also require individual attention to assess for and discuss potential guilt or disinterest in living donation, which may be particularly relevant for older children, adolescents, and young adults, who are aware of and sensitive to these potential issues.

Transplant Outcomes

Medical Outcomes

Medical outcomes have generally improved over time and vary per organ group. Although survival after pediatric lung transplantation has improved over the past decade, long-term survival rates remain well below heart and other solid organ transplants. Lung transplantation is considered in children with end-stage or progressive lung disease or life-threatening pulmonary vascular disease, for which there is no other medical therapy. Regardless of the underlying diagnosis, all candidates have a clear diagnosis and trajectory of illness such that the child is at high risk of death, despite optimal medical therapy. Mortality after lung transplant is greatest in the first year, with approximately 15% of all recipients dying because of infection and graft failure [34]. Nonetheless, the overall survival rate has improved over the last 30 years. Survival is similar among pediatric recipients under the age of 12, including infants, but worst among adolescents, when conditional survival to 1 year is considered. Before 2000, median survival was 3.3 years among all children, but median survival improved substantially to 5.8 years after 2000, and, upon conditional analysis limited to survival to 1 year, pediatric median survival has increased to 8.7 years compared with 9.6 years in adults [36]. The ongoing challenges to better outcomes include optimization of patient selection and altering allocation policies to ensure that pediatric lung transplantation confers survival and/or QOL benefit.

Patient mortality following heart transplant has declined. Among pediatric patients who underwent heart transplant in 2014, the 1-year survival rate was greater than 90%. Overall, in 2015, 1-year and 5-year patient survival rates were 88.7% and 77.2%, respectively, among recipients who underwent transplant in 2003–2010. Five-year patient survival was 71.2% for recipients aged younger than 1 year, 78.4% for ages 1 to 5 years, 87.5% for ages 6 to 10 years, and 77.4% for ages 11 to 17 years.

Outcomes for pediatric renal transplant recipients are generally very good. Data from 2008–2015 showed that 1-year graft survival rates for renal patients were 95.2% for ages 1–5, 96.4% for ages 6–10, and 97.0% for ages 11–17. Survival rates decreased at the year 5 point, with ages 1–5 and ages 6–7 demonstrating 87.6% and 87.9% graft survival, respectively, and ages 11–17 showing 78.1% graft survival rate [35]. Notably, adolescent renal patients are considered to have the worst long-term outcomes compared to all other age groups, with the only exception being adults over the age of 65 [37]. Nonadherence to medications has been identified as a principle explanation for this pattern [38].

The 5-year graft survival within the adolescent-age group after liver transplant is slightly lower than for the 6–10-year-old age group (79% vs. 87%, respectively) but was 75.0% for recipients aged younger than 1 year and 78.2% for ages 1 to 5 years. For all ages combined, the 5-year survival averages 85% [9].

Demand for pancreas transplants overall has declined dramatically in the past decade, likely due to a combination of factors including improvements in noninvasive therapies for diabetes weighed against the difficulty and potential complications of the transplant surgery. Annually, the number of pediatric pancreas transplants appears to be stable at about 30–50 per year since 2008. The overall survival rate for recipients of a pancreas is high, at approximately greater than 97% at 5 years, but the survival of functioning grafts are reported in the range of 55–65% at 5 years after transplant [39].

The number of intestine transplants has remained low over the decades. Intestine and intestine-liver transplant remains important in the treatment of intestinal failure, despite decreased morbidity associated with parenteral nutrition. Intestine transplants may be performed in isolation, with a liver transplant, or as part of a multi-visceral transplant. Short gut syndrome (congenital and non-congenital) is the main cause of disease leading to intestine and to intestine-liver transplant. Intestine graft survival has improved since the early 1990s but has plateaued over the past decade. Patient survival was lowest for adult intestine-liver recipients (1- and 5-year survival 68.6% and 35.7%, respectively) and highest for pediatric intestine recipients (1- and 5-year survival 88.1% and 74.6%, respectively), though rates differ among age groups, with longest survival of both patient and graft occurring in the 6–10-year-old recipients and lower in the children aged either <1 year of age or adolescent age range [40].

Psychosocial Outcomes

Solid organ transplant is associated with complex treatment regimens, frequent doctors' appointments, and lifestyle restrictions [41, 42]. The majority of patients adaptively cope with the changes that come with transplant, but a significant subpopulation experiences difficulties with the transition to post-transplant care [43].

Health-related quality of life captures the domains of physical functioning, mental health, and general health perceptions [44]. QOL for the first 1 to 2 years following transplant is rated lower than expected and lower than patients with other chronic conditions; however, it has been found to increase over time [45]. Other studies have found that transplant patients generally report lower QOL compared to healthy peers but similar to other chronic illness groups [46, 47]. Parents of pediatric transplant patients tend to rate QOL as worse than the patients themselves [48]. Additionally, this pattern of lower-rated QOL has been found in both children and adolescents [37, 45, 49, 50]. Care needed post-transplant may disrupt social development such as playing sports and staying out late with friends and in turn impacts QOL [50]. Times of particular vulnerability may include transitioning home from the hospital; returning to previous routines, such as reintegration into school or readopting an exercise regimen; and reestablishing family functioning [45, 51].

Research has shown individual characteristics related to adherence (i.e., rescheduled clinic appointments or medication adherence) predicted lower QOL in adolescent transplant patients [44]. Similarly, the perception of adverse side effects from medications was significantly related to both physical and psychological well-being of the patient. Side effects from medications can include a decrease in energy, weight gain, and changes in facial appearance, all of which can impact an adolescent's sense of self [42]. Adolescents who perceived these side effects as worse reported a lower QOL [42]. Adolescents may then stop taking medications to avoid side effects, leading to issues with nonadherence. Similarly, transplant has been associated with a negative impact on biological aspects of development, which may contribute to lower perceived QOL [37, 52].

Family functioning following transplant is vulnerable to the impact of stress and burden that is associated with SOT [53]. Research has shown that factors such as parental income and family conflict can negatively impact QOL [44]. Taken in combination with the new medical requirements, financial obligations, increased monitoring of the patient, and lifestyle changes, families may experience more conflict and decreased functioning [53]. Furthermore, families with high levels of parental stress, worse child behavior, and more dysfunctional child-parent interactions were found to have worse medication adherence [54].

Based on the abovementioned research, it is not surprising that the development of distress and, in some cases, psychiatric disorders occurs after SOT [55–57]. Depression and anxiety related to illness uncertainty, organ rejection, medical procedures, and body image distortions commonly develop following transplant [58]. Furthermore, patients with a history of psychiatric illness prior to transplant are at increased risk of experiencing emotional difficulties [43, 56]. Adolescent renal transplant patients had a significantly higher incidence of depression in addition to anxiety and phobias compared to healthy peers [59]. Shaw et al. found that almost a third of their renal transplant sample carried a psychiatric diagnosis, with a statistically higher occurrence in adolescents compared to children [60]. Psychiatric diagnoses for the entire sample included major depression (50%), adjustment disorder (50%), psychological factors affecting other medical condition (20%), oppositional defiance disorder (10%), and substance use disorder (10%) [60]. DeMaso et al. found that approximately one fourth of their pediatric heart transplant sample exhibited emotional difficulties at some point in the first 5 years following transplant.

Posttraumatic stress symptoms may develop in both pediatric SOT patients and their parents or caregivers following transplant, as the process may qualify as medical trauma [61]. Understanding the development of posttraumatic stress in patients and families dealing with chronic illness is of particular importance as it relates to nonadherence [61]. Difficulties taking medication or attending required medical appointments may be a manifestation of avoidance symptoms [62]. Mintzer and colleagues found that approximately 16% of their sample of pediatric solid organ transplant patients met full criteria for posttraumatic stress disorder (PTSD) following transplant [63]. An additional 14% endorsed significant subthreshold symptoms and met criteria for two out of the three clusters of symptoms [63]. Furthermore, Young and colleagues have documented 50% of parents of transplant patients reported at least moderately severe PTSD symptoms, and 44.6% reported that the symptoms resulted in moderate to severe impairment in their functioning. Further, 27.1% of parents reported symptoms that met diagnostic criteria for PTSD [64]. Therefore, models such as those proposed by Kazak and colleagues that explain the development of posttraumatic stress symptoms in patients and families dealing with pediatric chronic illness deserve attention and possible modification to the transplant population [65, 66].

Quality of life and psychological problems are areas that warrant assessment post-transplant, given documented deficits. Similarly, assessment of neurocognitive functioning is

equally important. In 2009, Alonso reviewed the available literature on neurodevelopmental outcomes in pediatric solid organ transplant recipients and found that in all cases neurologic comorbidities increased the risk of delay [67]. Given urges to assess this functioning at the time of the evaluation and then after transplant, it is hoped that more longitudinal data can be gathered to better understand these processes and the impact of transplant on pediatric patients.

Adherence

Treatment adherence has emerged as a critical issue for pediatric patients following SOT [38, 68, 69]. Adherence is a term used to describe a patient's ability to comply with a medical treatment plan [68, 70]. It is often defined behaviorally by how consistently a patient takes prescribed medication, attends regularly scheduled clinic appointments, and adapts to recommended lifestyle changes [68, 71]. Adherence to medications is heavily emphasized in SOT because of the large role it plays in graft survival [68, 70]. Failure to properly take immunosuppressant medications can lead to increased hospitalizations, organ rejection, organ failure, and in some cases death [46, 68–70, 72]. The complexity of the immunosuppressant medication regiment (e.g., doses per day, number of medications needed, and timed schedule) directly affects adherence rates [69]. For example, in pediatric kidney transplant patients, adherence decreased as number of medications increased [69].

Adolescent SOT patients have the highest occurrence of nonadherence compared to other age groups [60, 70, 72–77]. Approximately 30% of SOT patients are nonadherent, with adolescents demonstrating higher rates of nonadherence compared to children; approximately 42%–45% of adolescents have been documented as nonadherent compared to approximately 20% of younger children [60, 78]. Dew et al. (2009) conducted a meta-analysis to determine a prevalence rate of nonadherence in pediatric transplant patients and found that 12.9 cases per 100 patients per year were nonadherent to appointments and lab tests and that accounted for the largest occurrence of nonadherence in the pediatric sample. Additionally, 6 cases out of 100 patients were nonadherent to their immunosuppressant medications [38].

Several risk factors have been linked to nonadherence, including age, socioeconomic status, race, family functioning, and psychological status [38, 72, 76, 79–81]. Adolescence serves as a significant risk factor, as this stage of development is marked by impulsivity, increased risky behaviors, increased attention to body image, and increased emotionality [79, 80]. Psychiatric diagnoses have also been found to be related to nonadherence after transplant [55, 56, 60, 75, 82]. Patients experiencing higher levels of anxiety, depression, and posttraumatic stress endorsed more barriers to medication adherence and demonstrated poorer medication adherence overall [83]. Notably, barriers to medication adherence remain stable over time [84].

Given that difficulties with adherence and psychosocial concerns have been well documented in the adolescent population, recent research has focused on identifying evidence-based treatments [74, 85]. However, small sample sizes, inconsistent and nonstandardized means of measuring adherence, and a lack of randomized clinical trials have made it difficult to identify best practices and determine appropriate interventions [86]. Tailoring interventions to the specific needs of particular populations may have the best chance to demonstrate efficacy [87, 88].

Multicomponent treatments employing a variety of interventions, such as psychoeducation, behavioral strategies, and cognitive tools, have proven effective with other groups and may benefit pediatric transplant patients [74]. Educational and instructional interventions on their own have been shown to have only a small effect on adherence in adolescent transplant patients [89, 90]. Interventions should incorporate the patient, the family, and the medical team [91]. Further, they should be skills-based and cover several domains, including education, emotional response, and social supports [91].

Research has shown promising results with regard to multicomponent interventions for pediatric SOT patients. Fennel et al. showed improvements in adherence to prednisone for renal transplant patients following a brief intervention that combined education and behavioral strategies [92]. Shemesh et al. found improvements in graft functioning after participation in an intervention that combined increased medical visits with behavior strategies to improve adherence [93]. Hashim, Vadnais, and Miller adapted dialectal behavioral therapy to address nonadherent adolescent renal transplant patients and found that the combination of multiple behavioral interventions improved adherence [94]. Lastly, Naclerio found that renal transplant patients were six times less likely to lose their graft after participation in a multicomponent therapy that addressed adherence and adjustment to transplant through behavioral strategies, problem solving, and cognitive processing [95]. Larger studies are needed to better understand mechanisms of change.

With society seeing rapid advancements in technology, the electronic delivery of psychosocial interventions has the potential to be a powerful tool. While some research has reported that the effect of technology on adherence has not yet been shown to be efficacious [90], others recognize the utility and developmental appropriateness of the technology when working with adolescents. Text messages have been used as behavioral interventions to improve adherence, such as reminders to take medications or attend laboratory appointments [52, 96]. Online portals have been used to deliver education, such as information on medications and adherence, as well as foster communities of peers to provide support, discuss common fears and worries, and process the transplant experience [97–99].

Transitioning

Transitioning refers to the process of graduating a patient from pediatric to adult medical teams [100, 101]. For some patients, this can be a vulnerable time period as they are expected to take on more responsibility in their medical care. Negative outcomes, such as nonadherence, rejection, and graft loss, are possible during this period [100]. Therefore, pediatric medical teams have begun to focus on readiness to transition by administering questionnaires that assess key components of self-management [100].

Mixed evidence has been found regarding the impact of transitioning to adult care on medication adherence [73, 102]. One study found that adherence was not significantly worsened when kidney transplant patients were transitioned to an adult care setting within the same institution [102]. Other researchers have argued that young adults, ages 18–24, experience similar difficulties as adolescents with regard to adherence and suffer from similar poor outcomes as they begin to transition from pediatric to adult medical care [73].

Transitioning to adult care impacts many levels of a system, including the patient, the family, the pediatric medical team, and the adult medical team. Barriers to a successful transition can include patient's developmental stage, family's ability to support increasing patient responsibility, pediatric team's bond with patient, and adult team's uncertainty of treating issues specific to adolescence/young adulthood [101]. Providing education on diagnoses, medications, and how to navigate the health-care system is recommended. It is also important to address concerns from the family and encourage that they support the adolescent or young adult to take on more responsibility in care. Medical teams can benefit from having team members specifically assigned to aiding in transition-related issues [103]. Evidence-based practice guidelines as well integrated psychosocial programs are now a focus of research in order to better address potential barriers to transitioning [101, 104].

Conclusions

With medical outcomes improving significantly in recent years, pediatric SOT patients are living longer than ever before and, in turn, are faced with unique challenges requiring further attention and research. QOL following transplant can be negatively impacted by increased medical appointments, hospitalizations, medication side effects, and changes in typical routines. Nonadherence to a new medical regimen is also not uncommon and is associated with a host of medical and psychological consequences. Taken in combination, pediatric SOT patients and their families juggle multiple demands leaving the entire family system taxed. Standardized, multidisciplinary evaluations aimed at identifying and addressing both medical and psychosocial factors that pose risk to successful transplantation are recommended for comprehensive, patient-centered support. Moreover, understanding how to minimize the effects of transplantation and immunosuppression on these critical processes in children is paramount. Lastly, identifying the etiologies responsible for and addressing the poor outcomes in the adolescent population remain an important area for study.

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