

Review Article

Post-transplant adjustment – The later years

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Abstract: As survival rates for pediatric solid organ transplantation have continued to improve, researchers and healthcare providers have increasingly focused on understanding and enhancing the HRQOL and psychosocial functioning of their patients. This manuscript reviews the psychosocial functioning of pediatric transplant recipients during the “later years,” defined as more than three yr post-transplant, and focuses on the day-to-day impact of living with a transplant after the immediate period of adjustment and early years after surgery. Key topics reviewed include HRQOL, cognitive functioning, impact on the family, regimen adherence, and transition of responsibility for self-management tasks. Overall, pediatric transplant recipients evidence impairment in HRQOL, neuropsychological outcomes, and family functioning as compared to non-transplant recipients. However, the degree of impairment is influenced by a variety of factors including, disease severity, age, solid organ type, and study methodologies. Studies are limited by small samples, cross-sectional design, and the lack of universal assessment battery to allow for comparisons across solid organ populations. Areas for future research are discussed.

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As survival rates for pediatric solid organ transplantation have continued to improve, researchers and healthcare providers have increasingly focused on understanding and enhancing the HRQOL and psychosocial functioning of their patients. Furthermore, as five-yr graft survival rates for liver, kidney, and heart transplant are nearing 80% (1–3), researchers and clinicians have been able to start addressing HRQOL in the later years after transplant, which, depending on the age of the child at transplant, can encom-

pass early childhood through to adolescence. The five-yr graft survival rates for pediatric lung (4) and intestine transplant recipients (5) are generally lower, yet long-term outcomes in these groups are also improving. This manuscript will review the psychosocial functioning of pediatric transplant recipients during the “later years,” defined as more than three yr post-transplant, and will focus on the day-to-day impact and reality of living with a transplant after the immediate period of adjustment and early years after surgery.

An initial literature search was conducted to identify key topics related to the later years post-transplant, using keywords such as “pediatric transplant by each the content domains including: QoL, HRQOL, adjustment, psychological adjustment/functioning, family functioning, parent adjustment, as well as more specific search terms related to mood (depression, anxiety),

Abbreviations: ALL, acute lymphoblastic leukemia; BASC-2, behavior assessment system for children; CHQ, child health questionnaire; HRQOL, health-related quality of life; PedsQL, pediatric quality of life inventory™; PTSD, post-traumatic stress disorder; QoL, quality of life; s.d., standard deviations; STEM, sociocultural transplant experience model; VAD, ventricular assist device; WISC-IV, Wechsler intelligence scales for children.

behavior, social functioning, neuropsychological/cognitive/academic achievement functioning, adherence, and transition. Searches were also conducted by organ groups separately (i.e., kidney/renal, heart/cardiac, lung, liver, pancreas, small bowel). Articles were eliminated if they were (i) studies that were only focused on physical functioning rather than psychological (medical comorbidities/infections or medical indicators like GFR, BP, BMI), (ii) adjustment of organ donors rather than organ recipients, (iii) studies that were performed with adult organ recipients, (iv) studies of transplant recipients within the pretransplant period or the first three yr post-transplant, (v) abstracts without full published articles.

There is some limited work on long-term transplant survivors who reach adolescence and this is reviewed within the context of more general adolescent issues. Transition to adult services was also identified but as this is the focus of a later manuscript in this series of articles it will not be addressed in detail in the current article. In many articles considered during this review, authors did not specify particular periods of follow-up but reported cross-sectional evaluation of patient groups with variable follow-up, often ranging from a few months to several years. Where possible, findings referring to the later years after transplant have been teased out, but in some instances, this was not possible. Areas for future research are suggested.

HRQOL

The majority of research in recent years has been in discerning the degree of HRQOL relative to healthy controls, with a few studies documenting HRQOL compared to functioning prior to the transplant and relative to other chronic illness groups. Most often, studies of HRQOL in pediatric solid organ transplant recipients are based on parent reports, which may differ from child self-report with regard to degree of perceived functioning as well as specific domains that are impacted. Furthermore, majority of the studies published examined HRQOL in liver transplant patients and to a lesser degree in heart and kidney patients; similar research is almost non-existent with other organ groups. It is possible that there are important differences in HRQOL across organ types (6), underscoring the importance of continued work in this area.

Although there is documented improvement in QoL after children receive an organ transplant, about a third of the recipients remain at risk for experiencing adjustment difficulties over the

years (7, 8). For instance, heart transplant recipients (mean age = 10.6 ± 4.7 yr; time interval since transplant 6.0 ± 4.1 yr), liver transplant recipients (mean age = 8.17 ± 4.43 yr; 1 to 13 yr post-transplant with median time 3.10 yr), and kidney transplant recipients (median time since transplant 3.2 yr) reported poorer HRQOL than did healthy controls (9–11). These studies consistently point to lower QoL as perceived by transplant recipients across the solid organ groups. Prevalence rates of significantly impaired HRQOL (defined as scores of more than one standard deviation below the population mean for healthy norms) range from approximately 31% (9, 10) to 44% (12). Although to varying degrees, parents of solid organ transplant recipients similarly perceive their children to experience challenges over time (13). For example, in a recent study of 47 liver transplant recipients at a mean time of 6.2 yr (± 3.9 yr) post-transplant approximately 40% of parents surveyed indicated that their children had lower HRQOL scores on the PedsQL (a generic HRQOL measure) in addition to sleep-disordered breathing, excessive daytime sleepiness, and sleep-related syndromes (12).

Research has attempted to identify the areas of functioning that seem to be most challenging for transplant patients. Fredericks and colleagues noted lower HRQOL in the domains of overall functioning, physical and psychosocial health, as well as social and school functioning, with fairly consistent findings on the PedsQL and CHQ measures (14). Focusing specifically on the adolescent liver transplant patients (mean age = 15 ± 1.9 yr; average time interval since transplant 7.5 ± 5.7 yr) revealed similarly impaired HRQOL relative to published norms, particularly in overall functioning as well as problems on the psychosocial health and school domains (15). Parent reports of adolescent functioning were also lower across domains on the CHQ-PF50 measuring self-esteem, general health perceptions, parental impact and family activity scales, as well as across emotional, social, and physical domains of the PedsQL (15). Other researchers found that the primary impact on HRQOL as reported by parents was within the physical domain, with the total psychosocial scores comparable to the norms (13). Overall, concerns with physical appearance, the experience of symptoms, difficulty with peer and family interactions, and school disruption seem to affect pediatric recipients for years following transplantation (11).

Several studies compared pediatric organ transplant recipients to individuals with other

chronic health conditions, rather than to healthy controls. Liver transplant patients who were up to five yr from transplant endorsed a level of HRQOL that was comparable to renal transplant recipients, but better than children with rheumatologic disease (16), and lower than children with diagnoses of cancer (14) and diabetes (14, 16). Another study conducted in Norway compared pediatric renal transplant recipients (2–16 yr post-transplant; median interval since transplant 4.9 yr) to patients diagnosed with ALL and found that transplant patients were at risk for more mental health problems and lower HRQOL (17). Others, however, did not find significant differences between transplant recipients and children with other chronic illnesses. In a study of 77 liver transplant patients evaluated with the PedsQL and CHQ-PF50 at a mean of 5.8 ± 3.8 yr after transplant, liver recipients had comparable scores to that of other pediatric chronic illness groups on most domains of HRQOL and health status, with the exception of social and school areas in which liver transplant patients had lower functioning (18). In another study, liver transplant survivors fared similarly to patients with cancer with regard to social and school functioning and even better on domains of physical functioning (10).

Correlates of HRQOL

Studies have documented demographic and medical variables that may impact HRQOL among transplant recipients. Specifically, HRQOL has been positively correlated with older age, longer time since transplant, and fewer comorbid medical conditions (18–20). A recent study conducted in Finland examined the long-term HRQOL and psychosocial adjustment in organ transplant patients up to 15 yr post-transplant (mean age 11.5 yr; mean time since transplant 7 yr) and found that pre-adolescent patients endorsed worse HRQOL than adolescent patients, as did those who were fewer years since transplant (20). Similarly, younger age at transplant has been associated with lower scores in intestinal transplant patients (21). In contrast, others reported that younger age at the time of the transplant was associated with better coping and adjustment than in those transplanted later (22, 23), suggesting that they were more likely to view the condition as part of their normal development. Additionally, family related variables (parental QoL, whether patient lived with both parents or in a single parent home, maternal education) were associated with HRQOL outcomes (18–20). Existence of comorbid diagnoses (psychiatric,

neurological comorbidities, acquired disease) and specific medical variables (being on antiseizure medications, longer hospital days, frequency of medical appointments, rejection episodes) were predictive of poorer psychosocial adjustment such as increased prevalence of somatic complaints and internalizing problems (19, 20, 24). These demographic and medical variables appear to be consistently salient in their association with HRQOL, perhaps above and beyond the contribution of baseline levels of HRQOL (24).

Few studies have investigated behavioral and psychological factors that may be related to post-transplant QoL. In a study of 66 adolescent and young adult heart, kidney, liver, and double-lung recipients seen on two occasions after transplant, 18 months apart, the best predictor of HRQOL in the domains of physical QoL, mental health and general health perceptions was the baseline functioning in those same domains (median age at baseline = 15.8 ± 2.4 yr; median interval since transplant 3.79 yr) (24). Adherence to the prescribed regimen has also been linked to HRQOL (15) and emotional adjustment (anxiety, hope, illness, uncertainty) among adolescent transplant patients (25, 26). Adolescents who were determined to be non-adherent reported lower HRQOL, particularly in health perceptions, self-esteem, mental health, and family cohesion, as well as limitations in social and school activities related to physical, emotional, and behavioral problems (15). The only study to examine sleep issues in the transplant population found that sleep-related problems accounted for a significant portion of variance in the psychosocial, physical, and total domains of the PedsQL as perceived by parents, as well as school functioning as reported by the children (12). Sleep issues are not commonly reported in the literature, but seem to influence overall adjustment and QoL. Although few in number, these studies provide potential areas for further exploration.

Long-term HRQOL: 10–20 yr post-transplant

Several studies have recently examined adjustment and functioning of pediatric patients up to 10–20 yr after the transplant surgery. Most of the long-term follow-up has been conducted with liver transplant recipients, who have been found to have significantly lower scores on HRQOL measures, particularly on physical domains, even when mental health domains were comparable to the general population (18, 23, 27, 28). A large Canadian sample (27) of 167 patients surviving liver transplant by 10 yr (median time interval

8.97 yr) reported significantly lower HRQOL scores on the PedsQL, with 14% of the patients endorsing functioning that was 2 s.d. below the healthy population norm. There are some mixed findings, however, with possible differences in long-term outcomes across organ groups. For example, in contrast to findings above regarding liver transplant participants, young adults aged 18–34 yr who had a heart transplant (mean time 16.2 ± 3.0 yr post-transplant) (29) or a kidney transplant (median time interval since transplant 7.4 yr; range 1.7–16.9 yr) (30) in childhood were reported to have fairly good QoL. They endorsed levels of functioning comparable to healthy norms across physical and mental health domains and perceived social support, despite experiencing some medical complications, re-transplantation, and acute rejections, suggesting resilience over a long period of time.

It is also noteworthy that survivors up to 20 yr post-organ transplant maintained active productive lives as young adults. Functioning at this age may be gauged by indices such as the level of schooling achieved and ability to maintain a job. Specifically, studies indicated that most have completed high school (74%) (23) and attended college (63%) (28) or were employed (20–50%) (28, 30); 35.4% were engaging in regular physical activity (30), and about a third of the young adults got married (23). Despite reporting significant side effects and lower HRQOL (particularly in physical domains) relative to the norms, young adults who were transplanted as children were accomplishing age-appropriate academic, personal, and professional milestones. However, it should be noted that the number of studies reporting long-term outcome data for survivors of pediatric organ transplantation are few in number and have largely been conducted in North America.

Qualitative studies of long-term adjustment

Several qualitative studies also shed some light on the experiences of organ transplant recipients that may not easily emerge from quantifiable data. Interviews with transplant patients revealed that the most salient theme was a desire to achieve a sense of normalcy (31, 32), emphasizing development of their own identity, peer acceptance, wanting to feel free and energetic, and ensuring strong support as the facilitating factors of better QoL. On the opposing side, identity crisis, peer rejection (being teased for their appearance due to side effects), aversion to medications, lifestyle limitations, and feelings of fear and uncertainty about graft survival were identified

as potential barriers. In a group of children who had undergone an organ transplant in Canada and their parents, semi-structured interviews were conducted and subjected to qualitative content analysis (i.e., code identification, category saturation, theme generation). The children expressed difficulties with adherence, fear of needles, restriction on activities, and medication side effects, while their parents were concerned with post-transplant complications and self-management as the children got older (33). A qualitative study, using semi-structured interviews and adopting a grounded theory approach (i.e., a methodology that develops theory from an analysis of patterns and common themes identified in observational research), was undertaken with 27 adolescents who had undergone heart transplantation (median age at interview: 15.5 yr; median time since transplant: 3.2 yr) (34). The results revealed a diversity of psychological, physical, and social well-being factors which are important determinants of QoL. Patients described the experience of a “transplant journey” with stages, each with unique challenges such as “the struggle to survive” pretransplant (e.g., diminished ability to participate in activities, pain), “difficult transitions” when managing the transplant surgery (e.g., accepting someone else’s heart, hospitalization, school reintegration) and finally “an awakening and transformation” post-transplant (e.g., feeling that life is more vibrant, return to normalcy, improved self-perception, enhanced interpersonal relationships and altered life philosophy). The study described how young people are not only able to adapt to transplantation, but may also experience enhanced psychological and emotional growth and life satisfaction.

Psychological adjustment of pediatric transplant recipients

Findings on emotional and behavioral functioning among solid organ transplant recipients have been mixed, with some studies showing adjustment comparable to that of healthy samples, while other studies suggest impaired functioning. Some early work (35, 36) documented generally good-to-excellent adjustment in physical, psychological, and family domains several years after children received a liver transplant. Relationships with peers, feeling lonely, and socialization skills were rated as more problematic, however. In a larger study of 146 patients aged between four and 25 yr (mean 10.32 ± 4.31 yr) who had undergone liver transplantation between 24–150 months previously (median: 74 months, with all but three patients transplanted for more than

three yr) older, but not younger, recipients perceived themselves as less competent than their healthy peers (37). This study also reported gender differences, with adolescent boys and young adult males obtaining significantly higher internalizing and total behavior problem scores than healthy norms, whereas the scores for females aged between 12 and 25 yr did not differ from those of their healthy counterparts. More recently, a Finnish sample of 32 school-aged renal transplant recipients (mean age: 9.6 ± 1.6 yr) who had been transplanted before the age of five yr (38) had total scores on the Child Behavior Checklist in the normal range. However, somatic complaints, social problems, and attention difficulties were reported more frequently in the transplant population compared with healthy norms. A study investigating internalizing problems among pediatric renal and liver transplant patients (mean time since transplant $5.97 + 4.13$ yr) found that hope and uncertainty predicted levels of depression and anxiety over a three-month period, with depression mediating the relationship between hope and adherence (25). In a further study, parents of pediatric kidney and liver transplant patients (time since transplant 6.2 ± 4.1 yr) reported them to have internalizing problems on the BASC-2 but children themselves did not endorse psychosocial issues outside of the normal range (26).

Fewer studies have examined long-term adjustment after pediatric heart transplantation. A sample of adolescents who received a heart transplant in infancy overall scored within normal limits on measures of psychosocial functioning, self-concept, and QoL, with worse outcomes for general health perception and bodily pain and discomfort, with about a quarter of the sample at risk for long-term adjustment difficulties (39). Specifically, deficits were noted in the areas of social skills and isolation from peers by 20–24% of the parents and 15–23% of the patients, as well as low self-esteem and self-concept by about 30% of the parents and adolescents. Additionally, 40% of parents and 25% of patients reported behavior problems, attention difficulties, depression and anxiety. These findings are similar to studies by DeMaso and colleagues (40), who reported that the majority of the heart patients had good psychological functioning that was within the normal range on standardized measures about six to 12 yr after transplantation (median time since transplant 9.6 yr) but 27% endorsed emotional difficulties. They point out, however, that approximately one-fifth of the U.S. population has symptoms of mental health disorders; thus these results are

comparable. Lastly, transplant recipients may endure difficult or distressing hospital experiences in which they may have believed their life was at risk. As such, researchers have examined the prevalence of PTSD in pediatric transplant patients and found rates to be elevated as compared with the general population (41, 42). For example, in a sample of 104 adolescents post-solid organ transplant, 16% were found to meet the threshold for PTSD, with an additional 14% reporting symptom clusters of PTSD at a level causing distress. These rates are higher than the prevalence of PTSD among adolescents based on data from the National Survey of Adolescents using DSM-IV criteria, which reported a six-month prevalence of 3.7% for boys and 6.3% for girls (43). Furthermore, a small study of 19 adolescent liver transplant patients found a positive association between PTSD symptoms and non-adherence with medication (42), further highlighting the importance of considering the impact of traumatic experiences frequently associated with transplant.

Summary

Children who have undergone transplantation are at increased risk for poor HRQOL, impaired psychosocial adjustment, and family distress. Despite these risks, studies have demonstrated that pediatric transplant recipients transition into young adulthood and achieve age-appropriate developmental milestones. Future studies are needed to further examine the long-term psychosocial outcomes for pediatric transplant recipients.

Neuropsychological effects

Cognitive functioning

Cognitive ability in childhood is a predictor of educational achievement, later occupational outcomes and health behaviors (44, 45) and thus is an important consideration for the transplant recipient. It is recognized that children who have undergone solid organ transplantation are at increased risk of cognitive impairment (46) and a number of factors related to the underlying disease, transplant surgery and post-operative course may be implicated in deficits in cognitive functioning. However, much of the existing literature reports either cross-sectional or longitudinal post-transplant data only, thus limiting determination of cause of impairments in functioning. Furthermore, many of the studies are single center and comprise small sample sizes with a variable period of follow-up.

Despite the limitations mentioned above, there are some patterns emerging in terms of cognitive ability in the longer-term after transplant. A common finding is that transplant recipients have overall levels of cognitive ability which are in the normal to low normal range but that a greater proportion score in the below average range than is seen in the healthy population (47–55). For example, in a study of 64 liver transplant recipients at an average of nine yr after liver transplantation, mean IQ scores on the WISC-IV were in the lower normal range and scores on verbal comprehension, perceptual reasoning and processing speed were significantly below those of a group of age- and gender-matched healthy children. Compared to the children in the reference group, twice as many children in the transplant group obtained total IQ scores of <70 (9.4% vs. 4.7%). Lower height percentile at transplant and a diagnosis of a genetic-metabolic disease were associated with poorer cognitive functioning (47). Similarly, a study of 12 children diagnosed in infancy with end-stage renal failure who had undergone transplantation at an average of 31 months found mean scores on the WISC-IV at a minimum of three yr after transplant to be at least one standard deviation below the mean, with full-scale IQ scores significantly lower than those of sibling controls (56). Younger age at transplant was associated with higher scores on measures of processing speed, and full-scale IQ and processing speed were negatively correlated with total months on dialysis prior to transplant. Results for heart transplant recipients follow a similar pattern, with low-average mean full-scale IQ scores and a higher proportion of children obtaining scores in the below average range compared with healthy norms (39, 57, 58). In one study of 55 primary school children who had undergone heart transplantation in infancy, mean IQ scores were in the low-average range (59). A number of operative (e.g., bypass time), longer-term medical (e.g., number of serious infections), and socioeconomic factors were associated with performance on cognitive and academic tests. More recently, children bridged to transplant with a VAD have been compared with those not requiring bridging and while the number of VAD patients was very small ($n = 6$) the findings indicated that at a median of 54 months after transplant those who had been treated with a VAD did not differ on measures of cognitive function from those not requiring bridging to transplant (60).

Academic achievement

Assessment of academic achievement indicates that solid organ recipients perform less well than do their healthy peers in the later years after transplant. Interpretation of results is again limited by small sample sizes and cross-sectional studies, together with a lack of standardization in the measures used to assess academic performance. In one of the few longer-term follow-up studies, scores on measures of academic achievement were in the low-average to average range for a group of 21 adolescents (aged 12–17 yr) who underwent heart transplantation in infancy (39), with 30–45% performing in the borderline to impaired range on the arithmetic, reading, and/or spelling scales. However, academic scores were higher than expected based on overall cognitive scores, which the authors suggest indicates that their ability to learn is “intact.” Below/low average academic abilities have been documented for other groups of heart, heart–lung, liver, and kidney recipients with mathematical and spelling abilities seemingly more impaired than are reading skills (53, 58, 61). There is no clear reason why reading skills seem to be less impaired than arithmetic, but transplant recipients do appear to be at an increased risk for non-verbal learning difficulties (59). A further issue may be related to the tests used to assess academic abilities, with those used to assess reading being less sensitive and therefore less able to identify difficulties, particularly in older children.

Other areas of functioning

Children and adolescents late after transplant are also at risk for impairments in a number of other domains, including visuospatial functioning, memory, expressive and receptive language, executive function and attention (39, 52, 57, 62–64), although these domains have been less well studied than cognitive or academic functioning and there are limited data on long-term neuropsychological outcomes. Studies typically have small sample sizes and are cross-sectional in nature. Comparison of study results reveals few consistent patterns but impaired visual-motor integration has been identified in several groups of patients (39, 57, 59, 62, 63). In a number of studies, working memory was found to be impaired, which it has been suggested was due to the toxicity of corticosteroids to the hippocampus, a structure important for learning and memory (39, 47, 50, 52). However, this is not a consistent finding—for example, in a small ($n = 18$) study of liver recipients children obtained lower visual-motor integration scores but performance on

tasks assessing attention, learning and memory was in the normal range (57). There have been some attempts to look at correlates of poorer function—for example, in a study of 50 renal patients, verbal working memory and complex (but not simple) auditory attention were associated with poorer renal function (52). However, it is clear that further longitudinal evaluation of larger patient groups is necessary before any conclusions can be drawn about risk factors for specific neuropsychological outcomes. Although the evidence base to inform the choice of domains to assess is somewhat limited, the findings suggest that visual-motor integration and memory in particular should be assessed. The neurocognitive vulnerability of children and adolescents after transplantation is clearly an important consideration, particularly when planning educational services and assessing academic and social performance in the school environment (65).

Learning support

More than a third of children and adolescents who have undergone solid organ transplantation have learning disabilities (39, 65, 66). In some cases, this will have been present prior to transplant but in other situations it may be at least in part attributable to the surgery, subsequent treatment, and missed schooling. For example, in one study of renal transplant recipients, two of 26 children attended a special school purely due to hearing problems which developed after the transplant (48), supporting findings that high levels of tacrolimus can result in sudden hearing loss after transplant, with significant psychosocial and educational consequences (67). While a proportion of transplant recipients attend schools for children with learning disability or receive additional learning support, within mainstream schooling there is little in the literature describing the school experience for children and adolescents who have undergone transplantation (65). Furthermore, where research has been conducted, the focus has been on school re-entry and the early years after transplant, with very little mention of the later years. School performance is an important functional outcome for school-aged children (68), but cognitive and academic delays in transplant recipients appear to be frequently under-recognized in the school environment, thus precluding early intervention and targeted learning support (53).

Summary

Children who have undergone transplantation are at increased risk for cognitive, neuropsycho-

logical and academic impairment, particularly those who have been transplanted for congenital disorders or who had prolonged periods of critical illness after transplant. Small sample sizes and cross-sectional study design limit our ability to identify specific risk factors but more recent registry studies are now beginning to address that. Professionals working in health and education need to be better informed about the risks of cognitive and academic impairment following solid organ transplantation so that problems can be identified early and appropriate support put in place.

Adolescent issues post-transplantation

As survival rates continue to improve, an increasing proportion of long-term survivors will have to negotiate the additional challenges of adolescence, although the focus of research in this area has been on the young person transplanted in adolescence, rather than on the issues for those who become an adolescent in the later years after their transplant. However, there are a few studies which have specifically investigated variables unique to adolescence. Puberty may be delayed in young people post-transplant (69, 70) and there may therefore be periods when adolescent transplant recipients are smaller and less developed than their peers, which can impact on their developing self-identity and adjustment. Nedilskyj and colleagues examined body image satisfaction and explored its relationship with self-concept, depression, and social stress among 31 adolescents who received a heart transplant in infancy or childhood (mean age at transplant 2.4 ± 5.4 yr; time since transplant 13.6 ± 5.4 yr) (22). When comparing the transplant participants to non-clinical controls no differences were found in body image satisfaction, but the relationship between these variables was more salient for the healthy sample.

The need to establish a sense of self is probably the most important developmental challenge met by adolescents (71). Adolescents with a chronic condition such as those who have undergone transplantation have to cope with an extra challenge: that of integrating one's identity as a person with a chronic health condition with other dimensions of one's identity, to experience one's life and illness as challenges worth living. Risks may arise and translate into self-management difficulties when an adolescent's identity as a person with a chronic illness overshadows other identities (72). *Illness centrality* refers to the extent to which the illness experience plays a central role versus a role that is more peripheral to

the individual's self-definition, and there is some evidence that illness centrality is detrimental to the development of self-care abilities (72–74). Only one study was found which specifically examined the concept of identity formation in transplanted adolescents (75). Eighty-five adolescents with a renal transplant or diabetes were found to have more difficulty gaining independence and establishing peer relationships in school, leading to delayed identity development (“diffusion”) relative to healthy controls, who achieved “foreclosure” of identity. These findings highlight challenges that are unique to adolescents due to their desire for autonomy, which is difficult to achieve when grappling with a chronic illness, and their concerns about body image due to their heightened self-consciousness about physical appearance. Collectively, findings indicate that even when pediatric transplant recipients achieve medical stability and perhaps improved QoL, challenges remain in specific areas of psychosocial adjustment, namely social interactions and concerns about physical appearance.

Regimen adherence and self-management

Non-adherence to the post-transplant care plan is associated with significant consequences for all patients including graft rejection, overall post-transplant mortality, other increased medical complications, psychological distress, family dysfunction, and poor HRQOL (14, 15, 76, 77). Dimensions of non-adherence include medication non-adherence, failure to attend clinic appointments and tests, and non-adherence with lifestyle recommendations, such as diet, exercise, tobacco, and substance use. Among all pediatric transplant recipients, non-adherence with immunosuppressive medications is estimated to be as high as 50–65% (78–83). Adolescent transplant recipients are at an increased risk for medication non-adherence. Indeed, the prevalence of medication non-adherence has been documented to be higher in adolescents (30–53%) than among adults (15–25%) (84) and younger children (3–19%) (81). Conversely, meta-analysis that included 61 articles by Dew et al. in 2009 (85) showed relatively modest non-adherence rates in pediatric patients on all these aspects as compared to adult patients in another meta-analysis by the same authors (86). Indeed, whereas the expected non-adherence rate in adult patients would be 23% per year, it is only 6% per year in adolescent patients (85). Unsurprisingly, the age of the recipient was found to be significantly associated with non-adherence. These data

support adolescence as a risk factor for regimen non-adherence (81, 84, 87–89). Moreover, non-adherence also correlated with greater distress and poorer psychosocial functioning in both the recipient and the family (85). Non-adherence in pediatric transplant recipients has the potential to negatively impact long-term health outcomes and QoL, particularly in those instances when it persists during the transition from pediatric to adult-centered health care (90, 91).

Unfortunately, there is a lack of randomized controlled trials investigating the effectiveness of adherence-promoting interventions among pediatric transplant recipients. Self-management has been effective in improving medication adherence in children with other chronic health conditions (92, 93). Key elements of self-management include the promotion of health education, communication skills, decision-making and problem-solving skills, and self-care (94). A meta-analysis by Kahana et al. (95) that included 32 studies on psychological interventions to promote treatment adherence in pediatric patients with chronic health conditions, showed that behavioral or multicomponent interventions (as opposed to educational interventions) are the most effective to enhance adherence in pediatric patients. In general, adherence is likely to be improved when the burden of transplant and treatment are reduced; for example, by simplifying medication regimens, ensuring that young people have a good understanding of the rationale for treatment, opportunities to ask questions, realistic goals, and appropriate behavioral strategies to minimize forgetting or organizational difficulties (96).

In order to successfully promote improved self-management in adolescents healthcare providers need to be familiar with their developmental needs and adapt health services accordingly. In the field of pediatric transplantation, preliminary studies have demonstrated the utility of peer networks in the promotion of self-management skills among adolescent transplant recipients. Encouraging findings have been reported from Harden and colleagues' integrated transition pathway for young people post kidney transplant (97). This utilizes community-based clinics and integrated peer support, facilitated by a youth worker. Over a four-yr period, none of the 12 young people had lost their grafts, as compared with 67% of the nine young people in the previous six-yr period under a simple adult transfer model.

In addition to developing relationships among adolescents of a similar age, a recent study demonstrated other potential benefits of a peer mentor program (98). Nine young people (aged

16–30 yr) were trained to take a leadership role in supporting younger post-transplant patients. As compared with a waiting list control group, the peer mentors evidenced clinically significant decreases in the variability of their mean trough tacrolimus blood levels ([s.d.]; indicating an improvement in adherence to medication), but no significant changes in their self-rated self-management skills or HRQOL. The program was shown to be feasible, and mentors described it as highly acceptable. These studies highlight the potential benefits of peer support in improving self-management in young people post-transplant throughout their adolescence and as they transition into adult services. Further research with larger sample sizes is needed to evaluate the best means of facilitating peer support networks and the range of benefits this might bring.

The use of emerging technology to deliver adherence-promoting interventions is also increasing. For example, Miloh et al. (99) found that a text message reminder intervention significantly increased medication adherence rates, as measured by reduction in the mean tacrolimus level SD and reductions in the number of episodes of rejection. As part of improving accessibility and approachability of services, transplant services for young people benefit from using developmentally appropriate communication, including text and email.

Transition of self-managed care within the family

Self-management skills are integral to both optimal medication adherence and the achievement of independence necessary for successful health-care transitions (100, 101). To enable adolescents to develop into successful young adults, their families also need to adjust their roles to allow for their increased independence and responsibility (102). This process can be complex in young people who have had transplants, particularly those who are many years out from their initial surgery, as their families often have long-standing relationships with the transplant team and have taken responsibility for their child's care.

Age has been shown to be associated with increased patient responsibility for health management in a pediatric transplant population (103–105). However, older adolescents/young adults are also known to be at higher risk for non-adherence to their recommended treatment regimen; thus this transition to independence can be challenging (90, 106). There is evidence from qualitative work with adolescent liver transplant recipients that managing the transition of responsibility for key tasks, such as managing

medication and attending appointments alone, is a process which can present challenges (107, 108). In a mixed methods study of adolescents who had undergone renal transplantation, 70% of participants had their parents taking primary responsibility for medication management (109). Navigating the transition of responsibility from parent to adolescent can have an influence on medication adherence. For example, among pediatric kidney transplant recipients, increased patient–parent disagreement regarding AoR was significantly associated with medication non-adherence as measured by electronic medication monitoring devices (MEMS[®] TrackCaps) (103). The Allocation of Treatment Responsibility Scale (103), which has demonstrated acceptable psychometric properties in families of children with a kidney transplant, could be useful for assessing how medical regimen tasks are divided between patients and their caregivers, with potential benefits for monitoring adherence and transition readiness, particularly for those adolescents transplanted as young children.

Adjustment of parents and families

The role of parents and family in child health has been long recognized. Among pediatric transplant recipients, low QoL has been linked with family conflict, disruption of family activities, and lack of family cohesion (14, 110–112). In addition, increased stress related to parenting a child with a chronic health condition has been shown to be associated with lower child QoL (14, 112). Therefore, it is important to consider the psychological functioning of parents when addressing psychological and QoL parameters of children and adolescents. Research on caretakers of children following an organ transplant has mostly focused on adjustment during the pre-transplant period and the early years after the surgery. The long-term psychosocial outcomes of parents caring for a child years after a transplant are sparse. What is known is that about a quarter of parents report a burden on their time, an impact on their emotional functioning and disruption in family activities (11, 13, 21, 39). An investigation of the long-term psychological functioning among parents of pediatric heart transplant recipients reported that 40% of the parents (mostly mothers) endorsed moderate to severe post-traumatic stress symptoms, and 19% met criteria for PTSD (113). These rates are much higher than the prevalence of PTSD among adults in the U.S., estimated to be 6.8% by the National Comorbidity Survey Replication study completed in 2003 (114).

Parents in this sample also had significantly higher rates of general psychological distress relative to normative adult samples. In addition, parents of transplant patients report more difficulties in managing the child's illness on the Pediatric Inventory for Parents relative to parents of diabetes patients, but comparable to parents of patients with cancer (15). Another study relayed that parents experienced stress related to their child's illness more frequently than did parents of patients with cancer, but endorsed less difficulty in managing the stress. Greater disease severity of their child's condition impacted the parents' psychological outcomes, more so than did demographic variables or time since transplant. Interestingly, despite the diminished QoL, the emotional toll on parents, and the disruption to the family routine, studies report stable family functioning and family cohesion (13, 15).

Limitations and future directions

Current studies are limited by methodological differences making it difficult to draw conclusions across studies, and across organ transplant populations. The majority of research studies compared QoL and psychological functioning of transplant recipients to healthy controls; a few studies made comparisons to functioning prior to transplant or in relation to other chronic illness groups. One consideration is whether it is fair to compare functioning to that of healthy controls, as children and adolescents continue to manage a demanding life-long regimen with potential for medical complications. Perhaps improved QoL after the transplant and a consistent stable or upward trend over the long haul should be the goal.

There were slight differences in the documented outcomes which may be attributed to varying measurements utilized (e.g., PedsQL, CHQ, SF-36) and whether the authors chose to report overall scores vs. functioning in specific domains. As most of these studies have been conducted, the Transplant Module has been developed for the PedsQL with good validity and reliability to the Generic Core Module (6). Thus, researchers may elect to include this measure to ensure that they are assessing QoL domains that are focused on the transplant process and that would ensure more consistency across studies. It is also recommended that future studies include parent-proxy and patient self-report, as important differences in the perception of HRQOL are likely to arise.

Evaluating long-term outcomes in pediatric solid organ transplant recipients is also

influenced by the variable definition of "the later years." Many studies investigating psychosocial outcomes in post-transplant recipients include patients spanning wide age ranges, and broad time post-transplant (e.g., 12 months-20 yr). This makes conclusions about how psychosocial functioning relates to physical milestones at intervals comparable to the published UNOS data on patient or graft survival data (e.g., three, five, 10 yr) difficult. Further, when the time since transplant is reported there is variability in the type of statistics that are provided (average time vs. median number of years) making valid comparison of the findings across studies challenging.

Most of the studies have utilized cross-sectional research design, documenting outcomes at a given point in time. How HRQOL and adjustment changes over time after a transplant, particularly at critical developmental milestones, is not clear from this body of the literature. In addition, not knowing the baseline level of functioning prior to or even immediately after the transplant surgery makes the interpretation of long-term outcomes difficult. That is, even when QoL scores are lower relative to healthy patients that may still mean that functioning has improved dramatically since their end-stage disease state. Without prospective longitudinal research, it is unclear yet whether these difficulties had previously existed prior to transplant but were not as salient relative to other areas of functioning or whether as the patients get older the gap in socialization is widened, becoming more pronounced.

Finally, it is clear from the literature that kidney and liver transplant recipients, and to a lesser extent heart recipients, have been the focus of most of the research addressing functioning in the longer term, with very little attention being given to recipients of lung or small bowel transplants. While this may be a reflection of the smaller numbers of patients and their poorer outcomes, these groups are now increasing in both numbers of transplants performed and duration of survival, making longer-term evaluation a possibility.

Recommendations for future research

The importance of regular testing and screening, including later after transplantation, is now being recognized (68, 115), together with the need to identify brief, reliable and valid assessment measures (116), and clinical and treatment-related correlates and predictors of post-transplant outcome are also being

identified. Research to date is limited by small, largely cross-sectional studies, using different assessment tools and involving varying follow-up periods, and it is often difficult to tease out early and later follow-up data. However, involvement of multiple centers, increasing use of databases and transplant registries and a more rigorous approach to psychological follow-up with larger cohorts of patients, such as that adopted by the Functional Outcomes Group of the SPLIT consortium (117), will help to address some of these limitations and provide the evidence to inform interventions and optimize outcomes for pediatric transplant recipients.

A further topic which has been poorly addressed later after transplant is the role of sociocultural factors. Maloney, Clay, and Robinson propose a STEM to enable practitioners to explore the interaction of sociocultural factors with each stage of transplant, including families' health beliefs and adherence. As the number of transplants being undertaken in culturally and ethnically diverse populations continues to increase it will be important to address these factors from both a clinical and research perspective (118).

Finally, adherence and adolescent management of treatment regimens are key areas where evidence-based interventions need to be implemented. Randomized controlled trials of non-clinical interventions are few and far between in pediatric transplantation but adherence is one area where a trial with well-defined and measurable outcomes would be very valuable.

Conclusions

The survival rates for pediatric solid organ transplant recipients have increased dramatically, and attention has shifted to focus on determining optimal long-term outcomes, which include optimizing graft function as well as enhancing HRQOL and psychosocial functioning. Future studies should continue to focus on the assessment of psychosocial functioning in the years post-transplant, but should also begin to test interventions to promote HRQOL, adherence, and the transition to adulthood.

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