Long-Term Care of the Pediatric Kidney Transplant Recipient

Hilda E. Fernandez1 and Bethany J. Foster2,3,4

Abstract
Pediatric kidney transplant recipients are distinguished from adult recipients by the need for many decades of graft function, the potential effect of CKD on neurodevelopment, and the changing immune environment of a developing human. The entire life of an individual who receives a transplant as a child is colored by their status as a transplant recipient. Not only must these young recipients negotiate all of the usual challenges of emerging adulthood (transition from school to work, romantic relationships, achieving independence from parents), but they must learn to manage a life-threatening medical condition independently. Regardless of the age at transplantation, graft failure rates are higher during adolescence and young adulthood than at any other age. All pediatric transplant recipients must pass through this high-risk period. Factors contributing to the high graft failure rates in this period include poor adherence to treatment, potentially exacerbated by the transfer of care from pediatric- to adult-oriented care providers, and perhaps an increased potency of the immune response. We describe the characteristics of pediatric kidney transplant recipients, particularly those factors that may influence their care throughout their lives. We also discuss the risks associated with the transition from pediatric- to adult-oriented care and provide some suggestions to optimize the transition to adult-oriented transplant care and long-term outcomes.

Introduction
The goal of kidney transplantation in children is to provide a duration and quality of life similar to their healthy peers. The life expectancy benefit of transplantation over dialysis may be as much as 25–30 years (1). Pediatric transplant recipients show superior growth, improved neurocognitive development and academic performance, and better quality of life compared with children treated with dialysis (2). However, many challenges lie ahead when a child receives a transplant. The hope for every pediatric transplant is that it will last for the child’s whole life. But even for an adolescent or young adult, this means ≥50 years of graft function. The vast majority of pediatric patients will require more than one transplant (3). To maintain graft function, pediatric recipients must negotiate numerous challenges. Very small pediatric recipients often must successfully perfuse an adult donor kidney, and the transplanted kidney must accommodate large changes in body size. Viral infections such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and polyoma virus may have more severe consequences in infection-naïve pediatric recipients (4–8). Furthermore, not only must pediatric transplant recipients get through the high-risk interval in the early post-transplant period, but they must also traverse a second high-risk period of adolescence and young adulthood, during which immunologic risk may be heightened and medication adherence may be suboptimal (9–11).

In this review, we describe the characteristics of pediatric kidney transplant recipients, highlight the unique features that distinguish pediatric from adult recipients and may be relevant to their care throughout their lives, and discuss the risks associated with the transition from pediatric- to adult-oriented care. We also provide some suggestions to ensure a smooth transition to adult-oriented transplant care and optimize outcomes after transfer.

Characteristics of Pediatric Kidney Transplant Recipients
Children of all ages receive kidney transplants. Most transplant programs require infants to reach at least 10 kg before considering transplant, but some will transplant babies as small as 6 kg (12,13). The majority of pediatric transplant recipients are adolescents, but a substantial fraction are under 5 years old. Consistent with the male predominance of diseases leading to kidney failure, a greater proportion of pediatric transplant recipients are male than female. The primary kidney diseases leading to kidney failure in children are different from those in adults. In addition, a substantial minority of pediatric transplant recipients have some type of congenital syndrome associated with other conditions, in addition to kidney disease. Depending on the country, between 30% and >50% receive a living donor transplant (14–17).
Currently, almost 30% are transplanted preemptively, having no exposure to dialysis (14–17). Table 1 compares characteristics and outcomes of international cohorts of pediatric kidney transplant recipients (16–21).

### Unique Considerations for Pediatric Transplant Recipients

Many of the issues surrounding post-transplant care are similar regardless of the age of the recipient. Attention to cardiovascular health, bone health, obesity, and anemia are important at all ages, but particularly crucial in developing children (22–25). In addition, there are some issues unique to pediatric recipients that are highlighted below.

### Primary Diseases

The majority of pediatric transplant recipients have congenital anomalies of the kidneys and urinary tract as their underlying disease. A substantial subset of patients with congenital anomalies of the kidneys and urinary tract have developmental bladder abnormalities, resulting in lifelong bladder dysfunction and requiring ongoing urology care. Patients with bladder dysfunction often have poor bladder emptying, putting them at high risk for urinary tract infections and obstructive nephropathy. Many such patients have chronic hydrenephrosis of the graft, leading to interstitial fibrosis and tubular atrophy; a need for intermittent catheterization to maintain continence, ensure complete emptying, and prevent urinary tract infection is also common (26,27). Oxybutynin may be prescribed to improve spontaneous bladder emptying per urethra. Intermittent assessment of bladder function with uroflow or urodynamie testing may be necessary.

A substantial minority of pediatric transplant recipients have inborn errors of metabolism, with important extrarenal manifestations including cystinosis, primary hyperoxaluria, and methylmalonic acidemia. Cystinosis requires lifetime enzyme therapy (28). Both primary hyperoxaluria type 1 and methylmalonic acidemia with kidney failure are preferentially treated with combined liver-kidney transplant (29,30). Isolated kidney transplant is preferred for primary hyperoxaluria type 2 (29).

### Table 1. Comparison of international pediatric kidney transplant recipient characteristics

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient age, yr</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5</td>
<td>510 (23)</td>
<td>983 (26)</td>
<td>177 (24)</td>
<td>640 (20)</td>
</tr>
<tr>
<td>6–10</td>
<td>427 (19)</td>
<td>1540 (41)</td>
<td>157 (21)</td>
<td>918 (28)</td>
</tr>
<tr>
<td>11–17</td>
<td>1298 (58)</td>
<td>1955 (32)</td>
<td>416 (55)</td>
<td>1678 (52)</td>
</tr>
<tr>
<td>Male</td>
<td>1310 (59)</td>
<td>2109 (60)</td>
<td>437 (58)</td>
<td>1935 (60)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1079 (48)</td>
<td>a</td>
<td>597 (80)</td>
<td>2354 (73)</td>
</tr>
<tr>
<td>Black</td>
<td>389 (17)</td>
<td>a</td>
<td>a</td>
<td>86 (3)</td>
</tr>
<tr>
<td>Asian</td>
<td>102 (5)</td>
<td>a</td>
<td>a</td>
<td>447 (14)</td>
</tr>
<tr>
<td>Other</td>
<td>58 (3)</td>
<td>a</td>
<td>153 (20)</td>
<td>349 (11)</td>
</tr>
<tr>
<td><strong>Living donor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preemptive</td>
<td>648 (29)</td>
<td>1098 (30)</td>
<td>497 (66)</td>
<td>1155 (36)</td>
</tr>
<tr>
<td><strong>Kidney diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAKUT</td>
<td>771 (34)</td>
<td>1594 (46)</td>
<td>330 (44)</td>
<td>525 (16)</td>
</tr>
<tr>
<td>GN</td>
<td>192 (9)</td>
<td>463 (13)</td>
<td>231 (31)</td>
<td>315 (10)</td>
</tr>
<tr>
<td>FSGS</td>
<td>271 (12)</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td><strong>Allograft survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased donor</td>
<td>83%</td>
<td>90%</td>
<td>81%</td>
<td>75%</td>
</tr>
<tr>
<td>Living donor</td>
<td>61%</td>
<td>77%</td>
<td>62%</td>
<td>61%</td>
</tr>
<tr>
<td>5-yr</td>
<td>91%</td>
<td>85%</td>
<td>90%</td>
<td>89%</td>
</tr>
<tr>
<td>10-yr</td>
<td>70%</td>
<td>72%</td>
<td>75%</td>
<td>74%</td>
</tr>
<tr>
<td><strong>Patient survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased donor</td>
<td>98%</td>
<td>a</td>
<td>90%</td>
<td>96%</td>
</tr>
<tr>
<td>Living donor</td>
<td>98%</td>
<td>a</td>
<td>75%</td>
<td>92%</td>
</tr>
</tbody>
</table>

Data are shown as n (%). Data obtained from OPTN/SRTR, ESPN/ERA-EDTA, ANZDATA, and NHS/UKTR. OPTN/SRTR, Organ Procurement and Transplant Network/Scientific Registry of Transplant Recipients; ESPN/ERA-EDTA, European Society for Paediatric Nephrology/European Renal Association-European Dialysis and Transplant Association; ANZDATA, Australia and New Zealand Dialysis and Transplant; NHS/UKTR, National Health Service/UK Transplant Registry; CAKUT, congenital anomalies of the kidneys and urinary tract.

aNot reported.
FSGS, the cause of kidney failure in 10%–14% of pediatric recipients (31), has a high risk of recurrence in its idiopathic form; recurrence commonly leads to graft failure, with little hope for successful repeat transplant (32). Atypical hemolytic uremic syndrome also frequently recurs post-transplant, although eculizumab therapy has improved the outlook for these patients (33).

For children with multisystem disease, multidisciplinary care is necessary, and eventual transfer to additional subspecialists for adult-oriented care must be planned.

**Effect of Kidney Failure on Neurodevelopment**

Children who have experienced kidney failure are at high risk for abnormal neurodevelopment (34). The younger the child, the higher the risk of cognitive impairments, with those under 5 years of age at kidney failure onset at highest risk (35). The majority of pediatric kidney transplant recipients show average intelligence. However, compared with healthy children, a greater than expected proportion of pediatric transplant recipients are in the impaired, borderline, or low-average intelligence range, and academic performance is often poorer than in healthy peers (36,37). Memory deficits, disturbances of executive function, and attention problems are common, but may go unrecognized (37–39). Formal assessment of cognitive assessment may reveal deficits in executive functions (e.g., planning, organization, problem solving) that may impair ability to engage in self-care behaviors such as medication adherence, whereas assessment of academic function may guide academic expectations and ensure appropriate provision of academic support (37). Recognition of such deficits will allow appropriate support structures to be put into place before adherence problems result in adverse outcomes.

**Age-Related Differences in Immune Function and Viral Infection Risk**

Immune function is associated with age (40). Both young infants and the elderly have a less robust immune response than other age groups. The age-related trajectory of immune development and senescence mirrors the association between recipient age and graft failure risk (41,42). Kidney and heart transplant recipients aged 17–24 years exhibit the highest risk of graft failure of all age groups (41,42). Although poorer adherence to immunosuppressive medications likely contributes to the peak in graft failure risk seen in adolescence and young adulthood, age-related variation in the immune response may also play a role (43).

The relatively immature immune system of very young infants may permit greater tolerance of transplanted organs; however, it also puts them at higher risk of infection (44). In addition, young pediatric transplant recipients are less likely to have been exposed to important viral illnesses such as BK and JC polyomavirus, CMV, and EBV, and are therefore less likely to have immunity to these viruses. Polyoma virus nephropathy is an important cause of graft dysfunction in children (7). The risks of CMV and EBV viremia are highest in CMV- and EBV-naïve patients who receive transplants from CMV- and EBV-positive donors; about 20% of pediatric recipients fall into this high-risk category for CMV, and 40% for EBV (21). EBV viremia is of particular concern because of the associated risk of post-transplant lymphoproliferative disorder (16). Subclinical CMV and EBV viremia have also been associated with allograft dysfunction and loss in pediatric kidney transplant (45). Routine surveillance for BK polyomavirus and EBV viremia permits early detection and intervention with reduction of immunosuppression to decrease the risk of severe complications (46,47).

**Age-Related Behavioral Issues**

As pediatric recipients transition from childhood to adulthood, the tasks related to transplant care must shift from the parents to the young recipient. This includes scheduling and keeping clinic appointments and routine blood tests, and managing medications. Adolescents and young adults with a broad range of chronic conditions have poorer adherence to both medications and general care than other age groups (48,49). This deterioration in adherence is likely related to the increasing independence combined with incomplete brain maturity. It has been suggested that relatively rapid development of the limbic system (responsible for reward-seeking behavior and emotions), paired with slower maturation of the prefrontal cortex (responsible for planning, impulse control, and organization), may lead adolescents and young adults to choose actions that maximize short-term rewards over those favoring improved long-term outcomes (50). The prefrontal cortex continues to develop well into the mid-20s (51). As parents step back, lapses in adherence may occur.

**Transplant Timing within the Life Course**

The entire life of an individual who receives a transplant as a child is shaped by their status as a transplant recipient. Short stature is common among pediatric transplant recipients and may negatively influence self-esteem (52). Academic and employment prospects may be permanently altered by the illness preceding the transplant and/or complications thereafter. Social development and independence from parents are often delayed. Opportunities to socialize and form romantic relationships may be delayed or impeded by the need for medical care (53). Social isolation owing to illness and frequent medical visits, and uncertainty surrounding future health, may contribute to the high rates of depression and anxiety in this population (54–56). Post-traumatic stress is increasingly recognized (57). The effects of the patient’s illness on siblings and parents must also be considered. Not only must the mental health of family members be addressed, but it should also be recognized that overall family functioning may also affect graft and patient outcomes (58). A multidisciplinary approach, including psychology and social work, is particularly important for young people and their families. Referrals to mental health services are often needed. Adolescents with chronic illnesses require psychosocial support throughout the transition process, with mental health screenings and financial counseling (59). Health disparities in medical care for patients from socially disadvantaged backgrounds also increase a need for psychosocial resources for this at-risk group (60).

Many young transplant recipients have questions about sexual health and fertility. Young women should be counseled...
about the risks of medications such as angiotensin-converting enzyme inhibitors and myophenolate mofetil during pregnancy, and about the importance of contraception and sexually transmitted infection prevention. Women who may wish to become pregnant need information about how to safely plan a pregnancy and the associated risks. Discussions with young men should include information on the risks of medications such as sirolimus.

Transfer from Pediatric- to Adult-Oriented Care

The transfer from pediatric- to adult-oriented care typically takes place at around 18–21 years of age, right in the middle of the period of peak graft failure risk (42,62). It is not completely clear whether the transfer to adult-oriented care contributes to the heightened risk observed during this age period, or rather that other factors associated with adolescence and young adulthood (poorer medication adherence, enhanced immune potency) are responsible for the higher graft failure risk. A study of 413 Canadian kidney transplant recipients found significantly higher graft failure risks in the interval after transfer to adult care compared with before transfer (63). However, there was insufficient overlap of the ages represented in the pre- and post-transfer periods to allow complete adjustment for age. It is possible that the higher risks of graft failure observed after transfer simply reflect age-related risk, rather than any real effect of the care environment.

There is some evidence that the risk of graft failure after transfer depends on age at transfer. A study of 440 American transplant recipients found a 57% higher risk of graft failure among recipients transferred at <21 years of age compared with recipients of the same age transferred at ≥21 years of age (64). There was no significant association between time since transplant and failure risk. These findings were interpreted as reflecting a mismatch between the way care is delivered in adult-oriented settings and the needs of adolescents and young adults. The major concern is that the adult care setting may not adequately support adherence to immunosuppressive medications and health and graft monitoring protocols (65). Substantial differences exist between pediatric and adult-oriented care, which may influence patient behavior. Pediatric care tends to be more nurturing and family focused, whereas adult-oriented care tends to emphasize the autonomy of the patient (66). The pediatric care environment may be better resourced than that of adult care, frequently including a multidisciplinary team of health care professionals who may have more time to spend with each patient; these services are not always available after transfer to adult-oriented care, and adult care providers often have less time available (66–68). These differences between pediatric and adult care may result in young people perceiving their new adult care providers as unavailable and/or disinterested. Other factors unrelated to the care environment, such as loss of medical and prescription drug insurance coverage, may also present barriers to adherence in this age group.

The importance of an engaged and caring parent or other adult caregiver in supporting the young recipient through the transition from pediatric to adult care cannot be overemphasized. Gradual shift of responsibilities for management of medications and transplant care from parent to young person is recommended. But this handover may not be complete when the transfer occurs; continued support after transfer remains important. Many young adults do not master self-management until they are >20 years old (69). Involvement of a supportive parent may be the single most important factor in successful transition (70).

Adherence

A comprehensive discussion of adherence is beyond the scope of this review. The interested reader is referred to other reviews devoted to this topic (71–73). We provide only a brief overview here.

Adherence among children before adolescence depends almost entirely on their parents. Young children are not developmentally capable of maintaining strict adherence. Adolescents and young adults have a reputation for poor adherence. However, although numerous studies showed poorer medication adherence among adolescents than younger children, no well-designed, unbiased studies compared adherence among adolescents and young adults with that in older adults (74–77). Nevertheless, it is likely that adolescents and young adults are at somewhat higher risk for poor adherence than older adults; the magnitude of the difference, however, is unknown. Multiple barriers to adherence have been identified in young people, but the most common are forgetting (29%–56%) and organizational challenges (58%); most nonadherence is unintentional (75,78).

It has been proposed that adherence is influenced not only by patient-level factors unique to the particular patient, but also by the patient’s interactions with those around them, care processes and structures, and health care systems factors, including care and medication cost coverage, and overall care environment (79). Social determinants, including family functioning, social supports, and financial resources, are strongly associated with adherence; health beliefs, self-efficacy, knowledge, symptoms, comorbidities, psychiatric conditions, treatment side effects, and regimen complexity are also associated (80,81). Recognition of the many factors that may influence adherence, including those over which the patient has no direct control, may help clinicians identify ways to support better adherence.

Despite the fact that numerous risk factors for poor adherence have been identified, our ability to predict adherence on an individual level is poor. Therefore, it is important that adherence be assessed regularly in all patients. Options for adherence assessment include using self-report tools (82–84) such as the Basel Assessment of Adherence to Immunosuppressive Medications Scale (85), variability in trough levels of tacrolimus, and electronic monitoring. Each method has advantages and disadvantages. Although self-reporting is believed to overestimate adherence, it is highly feasible; accuracy can be improved by remaining neutral and nonjudgmental when questioning, and by limiting recall to a relatively short time period.

Asking about adherence at every visit may even function as an intervention; by devoting time to this issue, its
importance is emphasized. Questions about adherence also provide a springboard for discussions about reasons for poor adherence and opportunities to help patients find solutions to their adherence challenges. Some relatively simple interventions include reducing the complexity of medication regimens where possible, and using pill organizers and cell phone alarms, although the effectiveness of these interventions has not been well established (73). A randomized controlled trial in kidney transplant demonstrated that once-daily tacrolimus was not inferior in regard to adherence or allograft rejection rate, suggesting a role for simplifying immunosuppression regimen (86). For patients believed to be experiencing difficulty with adherence, more frequent visits and bloodwork may be helpful (87). Only one randomized trial tested an intervention to improve medication adherence in the adolescent and young adult population. The Teen Adherence in Kidney Transplant Effectiveness of Intervention Trial showed significantly better adherence among participants randomized to the multicomponent, adherence-promoting intervention than among those randomized to an attention control (77). The intervention included a combination of electronic monitoring with feedback of adherence data, text message dose reminders, identification of personal barriers to adherence, problem solving, and action planning, in addition to social support. A similar approach was also effective in improving adherence in adult kidney and heart, liver, and lung transplant recipients (88).

Guidelines for Transition from Pediatric- to Adult-Oriented Care

Significant effort has been devoted to identifying approaches to improving the transition from pediatric- to adult-oriented care. A variety of care models exist, including specialized transition clinics, care in a regular adult transplant program, and care by a community nephrologist. Patient satisfaction appears highest with transition clinics (89). However, although it is not clear whether outcomes truly differ by setting, there is some evidence of the success of the transition clinic model. Three small, non-randomized studies compared the outcomes of patients cared for in a specialized transition clinic with outcomes of those who did not attend this clinic. Harden et al. observed no graft failures or late acute rejections after transfer among patients who attended a joint pediatric-adult transition clinic during preparation for transfer, followed by a young adult clinic that included a youth worker after transfer (66). This contrasted starkly with the period before advent of the transition and young adult clinics, during which 67% experienced graft failure and 33% had late acute rejection. Prestidge et al. described similarly superior outcomes after establishment of a transition clinic compared with before (90). Before inception of the transition clinic, 24% experienced graft failure or death within 2 years of transfer, but after inception of the transition clinic, there were no graft failures or deaths within 2 years of transfer. McQuillan et al. (91) showed lower rates of nonadherence among patients attending a transition clinic (12.5%) compared with a group who did not attend this clinic (42.8%), and a smaller change in eGFR during the first year after transfer (−0.9±13.2 versus −12.2±14.9 ml/min per 1.73 m²).

Table 2. Critical milestones for adolescents/young adults before transfer to adult care

| Describe original cause of their organ failure/need for transplant |
| Long- and short-term implications of transplant condition on overall health (infections, cancer surveillance, vocational aspirations) |
| Effect of illness on sexuality and reproductive health |
| Sense of responsibility for their own health care |
| Capacity to provide most self-care independently |
| Expressed readiness to move into adulthood |
| Ownership of medical information in a portable accessible summary |

This list of critical milestones may be used during the preparatory phase of transition to assess readiness for transfer to adult care. Adapted from refs. 98 and 105.

Several professional organizations have provided guidance on best transition practices (92). In 2011, an international consensus statement advocated initiation of transition preparation as early as 12 years of age, with regular assessment of preparedness for adult-oriented care by using age-appropriate assessment tools (93–95). Resources for both pediatric and adult centers are available from Got Transition and the American Society of Transplantation Pediatric Transition Portal (96,97). Use of transition-readiness instruments can assist in identifying specific areas that must be addressed before transfer of care. In 2018, the Organ Procurement and Transplantation Network provided guidance on critical milestones for patients to achieve before transfer to adult care (Table 2) (98). Responsibilities of the transferring pediatric team and the accepting adult team before, at the time of, and after transfer of care are also outlined. Templates for correspondence between pediatric and adult transplant centers are available through several organizations, referenced here (94,96,97,99,100).

A multidisciplinary approach to transition is helpful, with input from social work, adolescent medicine, pharmacy, and financial counselors. Referral for psychologic counseling may be helpful for patients experiencing particular difficulties. For patients with significant cognitive impairments, who may be limited in their capacity to make medical decisions, assessment for guardianship should be addressed before the age of legal adulthood is reached (101). The assistance of a social worker and community legal resources is invaluable in guardianship applications.

Adequate preparation for the transfer to adult care and the transfer of transplant management from parents to the young person is key to long-term graft survival and patient well-being. However, pediatric care providers cannot assume sole responsibility for the transition of young transplant recipients to full independence. Transition to adulthood and independence continues after the transfer to adult care. The most successful transition programs include ongoing support for young people even after transfer, recognizing that this is an interval of high risk. Physicians providing care to transplant recipients are accustomed to providing more intensive follow-up during periods of higher risk. For example, in the early post-transplant period, follow-up visits and blood tests are done more frequently than later post-transplant, when the risk is lower. Figure 1
demonstrates the pediatric to adult transition and transfer of care process. This approach may be applied to young adults, who are also in a period of high risk.

Summary
Pediatric kidney transplant recipients are distinguished from adult recipients by a different distribution of primary kidney diseases, the potential for developmental sequelae of kidney failure, and the need for many decades of graft function. Perhaps most importantly, all pediatric recipients must pass through a period of high risk for graft failure: adolescence and young adulthood. Potential contributors to this high-risk period include enhanced immune activity, age-related reductions in adherence to treatment, and declines in adherence related to transfer from pediatric to adult care. Universal immunosuppressive medication coverage may be helpful in mitigating declines in adherence in young adulthood (102,103). Understanding of the challenges faced by pediatric recipients will aid both pediatric and adult care providers in supporting young recipients across the lifespan. Future research for improving long-term outcomes could focus on effective ways to partner with adult care providers.

Disclosures
B.J. Foster reports being coinvestigator on two grants sponsored by Astellas Canada. The remaining author has nothing to disclose.

Funding
None.

References

Published online ahead of print. Publication date available at www.cjasn.org.