



# Transition of young adult kidney transplant recipients

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## Abstract

Survival of pediatric kidney transplant recipients has improved over the past six decades. However, adolescents and young adults still have the highest graft failure rates of any age group. There is a growing need for well-designed transition programs to ensure the successful integration of young adults into adult society with eventual transfer of care and management in adult transplant centers. In this review, we discuss the risk factors contributing to the high risk of kidney graft failure observed between 17 and 24 years of age, including the role of transfer from pediatric to adult care. We also address the unique challenges of adolescents with kidney transplant: the impact of chronic kidney disease on neurocognition, age-related changes in immune activity, and suboptimal adherence during the transition process. We then describe strategies to mitigate these risks by designing developmentally appropriate transition programs, and review the evidence supporting the benefits of well-designed multidisciplinary transition programs.

**Keywords** Adolescent, Young adult, Kidney transplantation, Transfer, Transition to adult care

## Introduction

There have been tremendous advances in the care of children and adolescents with kidney failure over the past six decades [1]. Kidney transplantation is the treatment of choice for children and adolescents with kidney failure, and the low graft failure rates among children and very low mortality rates among young people with kidney failure mean that most children and young people survive into adulthood. The prevalence of pediatric kidney transplantation has increased over the past decade in Europe and in Australia, while the prevalence has remained stable in the USA

and New Zealand [2–4]. The vast majority of pediatric kidney transplant recipients worldwide will eventually require transfer to adult care. Maintaining graft function is the most important factor predicting patient survival [5] and is also critical to quality of life. Despite the fact that pediatric and young adult patients typically receive the highest quality donor kidneys [6], adolescents and young adults have the highest rates of graft failure of any age group [7–13]. In this review, we will examine the factors contributing to the “high-risk window” observed between 17 and 24 years of age, including the role of transfer from pediatric to adult care, discuss strategies to mitigate these risks by designing developmentally appropriate transition programs, and review the evidence supporting the benefits of transition programs.

Throughout this review, we will discuss both “transition” and “transfer.” Transition is the anticipated, coordinated process of movement from child-centered to adult-oriented health care, whereas transfer (only one component of transition) is the discrete event marking the movement to a new healthcare setting, new provider, or both.

## Concurrence of the high-risk age window and transfer to adult care

Regardless of age at transplant, graft failure rates begin to increase around 12 years of age, peak at 17–24 years (the “high-risk window” [7, 8]), and decline thereafter [7]. This

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relationship between age and graft failure risk is remarkably constant, showing the same pattern across races, sexes, primary kidney diseases, insurance types, pre-transplant dialysis histories [8], living and deceased donor recipients, peak panel reactive antibody (PRA) levels, HLA mismatch levels, and centers' transplant volumes [8]. No recipient subgroups are exempt from the increase in graft loss during late adolescence and early young adulthood [8].

The transfer from pediatric to adult-oriented care most commonly occurs during the “high-risk window,” when patients are approximately 16 to 21 years of age [7, 14]. This concurrence of the high-risk age window with transfer of care may not be simply coincidental. Transfer of care involves changing providers and healthcare settings, which can contribute to poor outcomes, as shown in other patient populations [15, 16]. Furthermore, the adult model of care may not be structured to meet the needs of young people, augmenting the risk of adverse health outcomes. In a study of 440 American transplant recipients, those transferred before the age of 21 years had a 57% higher risk of graft failure compared with those of the same age who were transferred at 21 years of age or older [12]. Practices such as monthly blood investigations and generous nursing support [17], common in pediatric programs but less available in adult programs, may promote better medication adherence contributing to the superior outcomes observed in those transferred at older ages [18].

The fact that transfer to adult care almost always occurs during a high-risk period is a key consideration when planning a transition program, which should involve a preparatory phase prior to the transfer event itself and post-transfer phase.

## Unique challenges of adolescent and young adult kidney transplant recipients

### Developing brain and impact of childhood-onset chronic kidney disease

Brain structural and functional imaging studies show different rates of maturation in different brain regions, with the prefrontal cortex continuing to mature into the mid-twenties [19]. The prefrontal cortex is responsible for impulse control, regulation of emotion, and decision-making in which risks are appropriately balanced against rewards [20]. In contrast, the limbic system, responsible for emotion and reward-seeking, develops earlier. It has been suggested that this lag in the development of executive function may bias young people towards decisions that maximize immediate rewards rather than optimizing

long-term outcomes [21], which makes chronic illness difficult to manage.

In addition to the challenges related to normal brain maturation processes, children and young people with kidney transplants are also vulnerable to impairments in executive function and memory due to their exposure to chronic kidney disease during childhood [22]. These neurocognitive deficits may be under-recognized without a standardized assessment completed by a psychologist, but may further contribute to difficulties throughout adult life with self-management, including non-adherence to medications.

As young people become increasingly independent from their parents, parental supervision of self-management activities, including medication ordering and administration, as well as fluid management, catheterization, attendance at monitoring blood investigation appointments and clinic visits, diminishes. In addition, adolescents and young adults (AYA) are expected (and legally permitted) to make decisions independently; any deficits in judgment, risk perception, or reasoning may compromise outcomes. These unique neurodevelopmental challenges of young kidney transplant recipients must be acknowledged in the design of transition programs and highlight the importance of continued parental support for some young adults who may need more time to reach full independence in self-management. Management of AYA who have intellectual disabilities and may never reach independence requires additional attention and planning during the transition process.

It is also common for adolescents and young adults to have concerns about their body image related to scars from previous surgeries and presence of tubes or catheterizable channels. Concerns about body image may influence decisions among young people in different ways than in more mature adults.

### Social factors during adolescence and young adulthood

Adolescence and young adulthood is a time of major life changes: graduation from secondary school, entering the work force or starting post-secondary education, living independently for the first time, and achieving legal autonomy all usually occur in this time period. Managing all of these major milestones can be challenging even without the addition of a complex chronic health condition.

### Biologic risk factors during adolescence and young adulthood

Biological factors may also contribute to poorer graft outcomes in AYA [23]. An association between age and

immune function has been shown in numerous studies. Both infants and the elderly have a less robust immune response than other age groups [24, 25]. Age-related changes in many immune cell types have been demonstrated across a wide age range [25–27]. After young adulthood, absolute numbers of total T-cells (CD3 +), CD4 +, CD8 +, and naïve T-cells decrease with increasing age [27]. In contrast, several other T-cell subsets (such as memory cells) increase with age across the entire lifespan [28]. This results in an accumulation of antigen-experienced T-cells relative to naïve T-cells and therefore a dramatic reduction in diversity of the antigen recognition repertoire with age beyond young adulthood [26]. A recent study also demonstrated a role for estradiol in immune activation in females: young oophorectomized mice showed patterns of reduced T-cell proliferation, reduced interferon-gamma and interleukin-17 production, and increased regulatory T-cells, similar to what has been observed in males and older female mice [29]. These animal data suggest that high estradiol levels among women of peak reproductive age and low levels after menopause may at least partly explain the fact that graft failure rates are highest in young women and lowest in older women (compared with women/girls of other ages and men of the same age) [30]. Together, these observations suggest that immune potency may be highest in late adolescence and early young adulthood, contributing to the higher graft failure risks in this interval.

### **Non-adherence: the major risk associated with transition**

Kidney transplant recipients who have the cognitive ability to be independent must be experts in self-management. Perhaps most importantly, they must develop strategies to remember to take their immunosuppressive (and other) medications on time every day. They must also attend regular appointments for blood tests and clinic visits. Some may need to perform intermittent bladder catheterizations several times per day, or blood pressure monitoring at home. Poor adherence to medications, appointments, or other self-care activities is likely to compromise both patient and graft survival. Adherence is a skill that must be learned and practiced. Complete independence in transplant-related self-care will normally take years to achieve. Learning transplant self-management is analogous to learning to drive a car. New drivers are not given the keys to the car the day they turn 16 or 17 years of age, but rather learn theory, then practice under supervision. Similarly, young transplant recipients must understand their own chronic condition as well as reasons for adherence to treatment, and then be trained, with supervision, in all of the necessary self-care activities. The best approach is to give graded responsibility over time [31].

### **Preparation for independent decision-making**

Adult-oriented transplant healthcare professionals will generally expect patients to be able to engage in discussions about their own care and make decisions about various treatment options. While this may be unrealistic for some patients and difficult for some parents, most young transplant recipients will eventually be able to make informed health decisions independently. A basic understanding of their underlying kidney disease, and some knowledge about the medications they take, what they do and possible side effects are generally expected. An ability to advocate for oneself is also an asset.

### **Designing a transition program**

The goal of a transplant transition program is to gradually prepare adolescents and their families for successful integration into the adult healthcare system in an uninterrupted manner. A successful transition requires an integrated effort from both the pediatric and the adult transplant programs [32]. There are different models of transition from pediatric to adult services, but many now incorporate a transition clinic or an adolescent service and young adult service as bridge from pediatric to adult care.

The American Institute for Health Care Improvement developed a framework, the “triple aim” [33] (health, care, cost) as an approach to optimize health system performance. The objectives of the “triple aim” are improving the health of populations, improving patient experience of care, and reducing healthcare costs. This framework can be adapted to the transition of care for young transplant recipients. An effective transplant transition program will optimize the care experience, improve the health of young people with kidney transplant, and reduce costs associated with transfer [33]. There are three key features of an effective transplant transition care program:

- 1) Early start to graded transfer of responsibility from parent(s) to adolescent

In order to successfully establish self-management skills and habits by the time the young person reaches adulthood, the transplant team needs to support parents in gradually shifting the responsibility for transplant self-management tasks to the young person [31]. It is suggested that one task be transferred to the young person at a time, and only once this task is mastered should another task be added. Initially, the young person may need prompting from a parent with parental supervision. Once the young person shows consistency in carrying

out the task, parents may only need to check to ensure the task was performed. For example, a parent may give their child the responsibility to remember to take their medications. In this case, the parent and child may agree on a time period during which it is acceptable that the medications be taken. Only if the medications are not taken within the agreed timeframe will the parent intervene. As there are numerous tasks related to transplant self-care, this graded transfer of responsibility from parent to child will take time and will progress at different rates for different people. Therefore, the transition process needs to start as early as possible. Many suggest that 11 to 13 years of age is a reasonable age to start [34, 35]. Patients who develop kidney failure and receive a transplant later in adolescence will need a more rapid schedule for transfer of responsibility.

It is important to note that some flexibility is needed during this graded transfer of responsibility. Both patients and parents must understand that mistakes are normal and expected; nobody is perfect. Transition is a period where young people are provided the appropriate support to develop the confidence and skills necessary to manage their kidney transplant. It is equally important that all parties (patients, parents, and care providers) understand that it is normal that young people will continue to develop their self-management skills after transfer to adult-oriented care.

The overarching goal of the graded transition of responsibilities is that the young person becomes the main actor in their own care, responsible for adherence to treatment. Because adherence is central, adherence should be assessed at every clinical encounter, and adherence-promoting strategies emphasized. The Teen Adherence in Kidney Transplant Effectiveness of Intervention Trial (TAKE-IT) showed significant improvement in adherence among AYA transplant recipients randomized to a multi-component adherence-promoting intervention compared to the control group [36]. The intervention included a combination of electronic monitoring of medication-taking 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 [37].

During the transition process, young people also need to learn how to communicate with their healthcare team, self-advocate, and manage the stress and anxiety that can be associated with all the increased responsibility of self-management. Adolescents should be seen initially without a parent at clinic visits to teach them to communicate with their care providers on their own. Parents should be invited to the second part of the visit to support their child and maintain engagement. Parents are key facilitators of adolescents' development of

self-management skills for successful transfer to adult services [38].

The anticipated impact of successful transition of self-management tasks to young people is better adherence, fewer visits to the emergency department, fewer hospitalizations [39], and therefore lower healthcare costs [31].

## 2) Engagement of the adult transplant team

Given that the high-risk age period extends from 17 to 24 years, and that most transfers occur from 16 to 21 years of age [13, 32, 40, 41], it is important that adult-oriented care providers understand that the patients they receive in transfer are high-risk patients, with special requirements. It is equally important that adult-oriented care providers recognize that the transition process does not end with transfer of care. Neurodevelopment is still ongoing when most patients are transferred, and many have not yet mastered all of the tasks related to self-management. Therefore, it is important for adult transplant programs to encourage continued parental support and involvement whenever needed.

It is essential to engage key healthcare providers from the adult kidney transplant team early in the development of a transition program [32]. When feasible, establishing a dedicated young adult kidney transplant clinic is ideal; this focused strategy may be helpful in ensuring that evidence-based care protocols and approaches relevant to high-risk young adult patients are applied consistently. In a Canadian study, transplant recipients cared for in a young adult clinic after transitioning from a pediatric program showed significantly lower non-adherent behavior in the year post-transfer compared to the cohort prior to the establishment of a transition program [42]. In this study, non-adherent behavior included missing clinic visits, missing regular blood tests, and undetectable calcineurin inhibitor levels (18.8% versus 62.5%,  $p=0.03$ ) [42]. Furthermore, the median change in estimated glomerular filtration rate (eGFR) in the year following transfer was smaller in the group that attended the transition clinic ( $-0.9 \pm 13.2$  ml/min/1.73 m<sup>2</sup>) compared to those who did not ( $-12.29 \pm 14.9$  ml/min/1.73 m<sup>2</sup>),  $p=0.045$  [42]. A prospective, observational cohort study of 270 prevalent kidney, liver, and heart transplant recipients aged from 14 to 25 years identified two program-level factors associated with better medication adherence. The odds of adherence were 12% higher for each additional routine blood test prescribed per year and 15% higher for each 5-min increment in average amount of time the transplant nurse spent with a patient at clinic visits [17]. These findings suggest that appropriate staffing, allowing more nurse time per patient, and maintaining more frequent routine blood monitoring (i.e., monthly) for all high-risk young adult

transplant patients may have a meaningful impact on adherence and therefore on outcomes. A dedicated young adult transplant clinic will also allow the adult team to become familiar with rare pediatric diseases that require specialized care, such as cystinosis [43].

### 3) Use of checklists to guide the transition

Young people should reach a series of milestones as the responsibility of care is gradually shifted from the parent to the young person [44]. A number of tools have been developed to track progress during transition, assess individual readiness, and facilitate communication of medical information (e.g., <https://www.myast.org/education/specialty-resources/peds-transition>). These tools can help providers identify key areas in which the patient may require additional education and support and make an action plan.

## Transition and transfer

The International Society of Nephrology and the International Pediatric Nephrology Association jointly published a consensus statement in 2011 [45], emphasizing the requirement for an individualized transition plan. They also stated that transfer from pediatric to adult care should take place during a period without crises [45]. Ideally, there should be some flexibility in exact timing of transfer from the pediatric program, so that in times of crises such as transplant rejection, an unprecedented pandemic, or family or societal instability, the transfer of care can be postponed [46]. Similarly, it would be reasonable for the adult program to have some flexibility in accepting the care of a young person who may need to be transferred slightly sooner than anticipated, for example, for the management of a pregnancy in an adolescent with a kidney transplant.

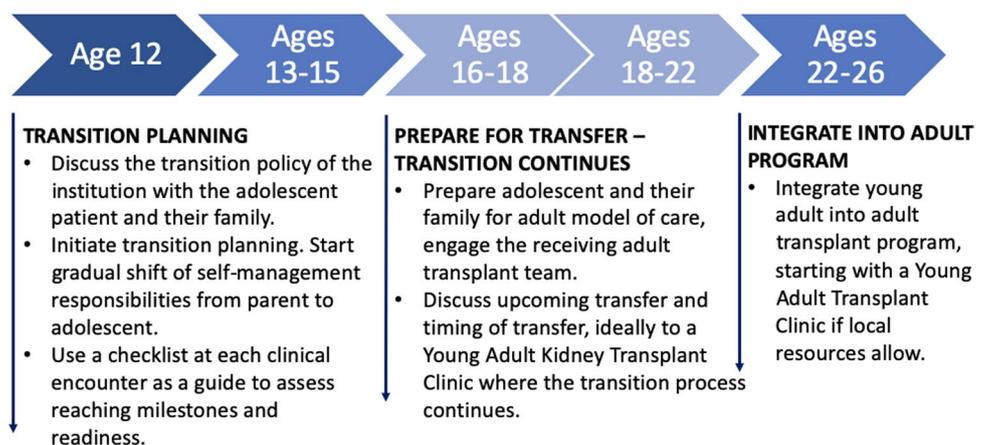
An extended transition period, beginning as early as 12 years of age and continuing after the transfer to adult-oriented care, allowing graded transfer of responsibility is recommended. However, some patients may present at

an older age, in which case the timeline of transition may need to be modified. The “Six Core Elements of Health Care Transition (2.0)” [<http://www.gottransition.org>] [47] include establishing a policy, tracking progress, administering transition readiness assessments, planning for adult care, transferring, and integrating into an adult practice (Fig. 1).

There are a number of transplant transition programs that have been implemented at different institutions worldwide [13, 32]. Most programs involve joint efforts of transition champions from the pediatric as well the adult transplant teams. The actual integrated clinic structure differs depending on the local geography and available resources, but regardless of the clinic model, the goal is an integrated transition pathway that allows the young transplant recipient and their family to progressively gain trust in the adult healthcare program [13, 32].

A well-designed transplant transition clinic can improve both patient and graft outcomes [13, 32, 42]. A multidisciplinary approach to transition is important, where the team includes transplant physician(s), nurse(s), adolescent medicine specialist, social worker, pharmacist, dietitian, and psychologist as required. The team members of each multidisciplinary transition team will of course depend on the resources available at a particular transplant center. In a Canadian study, a comparison of patient and kidney graft survival among adolescents transferred to adult care after receiving care in a multidisciplinary transition clinic with a cohort of patients transferred prior to the establishment of the transition clinic showed dramatically better outcomes in those exposed to the transition clinic: over a minimum 2 years of follow-up, there were no deaths or graft losses in the transition clinic cohort whereas 24% of the cohort who did not receive care in the transition clinic experienced death or allograft loss [13]. The cost estimate analysis showed that the operating cost of this transition clinic was much less than the cost associated with graft loss and return to dialysis, even without considering the costs related to loss of work for patients and family members or the cost

**Fig. 1** A proposed timeline for transition of care



of untimely death of a young person [13]. A similar study in Switzerland showed that a structured transition program significantly reduced episodes of acute rejection and slowed the decline of eGFR, compared to the transplant patients prior to the introduction of the multidisciplinary transition program [40]. Another study in the UK also showed that an integrated pediatric–young adult joint transition clinic and care pathway significantly reduced kidney transplant failure rates [32].

## Conclusion

With improved long-term survival of pediatric kidney transplant recipients, there is a growing need for comprehensive planned transition programs to ensure that emerging adults are optimally supported at the time of transfer of care. Transition programs provide the young kidney transplant recipient with the necessary skills for self-management and prepare them for successful integration into an adult transplant program, while supporting the parent(s) in their gradual “letting go” process. A well-designed transition program is anticipated to improve the health outcome of young adults with kidney transplant, positively influence their experience of care, and reduce or control healthcare costs.

## Key summary points

- Adolescent and young adult kidney transplant recipients are at an increased risk of graft failure, with a peak at age 17 to 24 years referred to as a “high-risk window.”
- A comprehensive planned multidisciplinary transition of care program with involvement of both pediatric and adult care providers is critical in improving transplant outcomes of young adults.
- A multi-component adherence-promoting strategy is a key element of a successful transition.

## Multiple choice questions (answers can be found after the reference list)

1. Which of the following statements is true?
  - a) Poor adherence is the only risk factor for poor graft outcomes in adolescents.
  - b) Kidney transplant recipients age 17 to 24 years have the worst graft outcomes compared to other age groups.
  - c) Transition of care interventions occur at pediatric centers in preparation for transfer to adult-oriented care.
  - d) Age 17 is the best time to start the transition process.
2. Which of the following contribute to the high-risk age window?
  - a) Age-related changes in immune potency
  - b) Mismatch between needs of young people and care practices in adult-oriented care
  - c) Age-related deterioration in treatment adherence
  - d) All of the above
3. Which of the following statements regarding brain development is false?
  - a) The prefrontal cortex (responsible for executive function) develops more slowly than the limbic system (responsible for emotion and reward).
  - b) Young people who receive kidney transplants as children may have neurological sequelae from exposure to chronic kidney disease during development.
  - c) The vast majority of young kidney transplant recipients have completed neurological development by the age of 19 years.
  - d) The rate of neurological maturation is highly variable.
4. Adult-oriented transplant care providers should expect?
  - a) Young people to be transferred only after they have become fully autonomous in all aspects of self-care
  - b) To continue the gradual transfer of self-care responsibilities to young people after the transfer
  - c) Minimal involvement from the parents of young transplant recipients
  - d) That graft loss shortly after the transfer of care is inevitable for young people
5. Which of the following statements is true?
  - a) Transfer of care in and of itself can be a risk factor for poor health outcomes.
  - b) Parents should discontinue involvement in their adolescent’s care at age 18, so that the adolescent can take over the sole responsibility of self-management.
  - c) There is no evidence that care protocols and practices have any impact on adherence.
  - d) There is evidence to show that a young adult transplant clinic is the best model of successful transition of care.

## Declarations

**Conflict of interest** The authors declare no competing interests.

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**Answers** 1. b 2. d 3. c 4. b 5. a.