Young adult and adolescent kidney transplant recipients have shorter graft survival than older and younger recipients. Although multifactorial, the tendency toward premature graft loss in young kidney transplant recipients has often been attributed to medication nonadherence and the transition from pediatric to adult care. Multiple interventions for medication nonadherence in kidney transplant recipients have been studied. Potential preventative interventions include pre-transplant screening, transition and young adult clinics, technologies such as reminders or mobile applications, and simplification of the post-transplant medication regimen. There are also recent advances in monitoring interventions for nonadherence in transplant recipients, including electronic monitoring devices such as wireless pill bottles and the Ingestible Sensor System, which incorporates ingestible microsensors into medications. Treatment interventions for medication nonadherence include cognitive behavioral programs, behavioral contracts, and screening and treatment for depression. Several of the interventions reviewed are currently available to providers caring for young kidney transplant recipients, without any complex programmatic changes. Further research in all of these areas would be of great value.
Background

According to data collected in the United States by the United Network for Organ Sharing, graft survival of young adult and adolescent kidney transplant recipients (KTRs) is the shortest of any cohort aside from 50-plus-year-olds [1] (Figure 1). As of 2016, the 5-year graft failure rate for patients age 11 to 17 years is 22%, a marked increase from 12% for patients age 6 to 10 years [1]. While older recipients in the United States experience decreased patient survival [2], young adult KTRs are living longer after transplant, but with early graft failures that are often due to acute and chronic rejection. These rejection episodes are commonly attributed to medication nonadherence (MNA) [3–7].

It is important to note that a causative relationship of MNA and early graft loss has been suggested but not proven in young KTRs. There are other potential causes for premature graft loss in this age group, including acute rejection in the setting of more robust immune response [3], recurrent kidney disease, and complicated urologic conditions. Yet, early post-transplant MNA has clearly been shown to predict late acute rejections and increased serum creatinine in the general kidney transplant population [8]. MNA, which may be active or passive, is a complex issue with many contributing factors that may be inside or outside of the patient’s control [5,9]. These include psychiatric disorders, cognitive impairment, asymptomatic disease, inadequate follow-up, medication side effects, patient lack of trust in the treatment, and treatment cost [9]. An open-ended survey of 80 adolescent KTRs and their families in 2009 revealed that the primary barriers to adherence in this patient population include simply forgetting, poor planning, medication issues, and attempts to be normal among peers [10].

In young KTRs, the peak age of vulnerability for graft loss occurs during the developmental stage of “emerging adulthood” between the ages of 18 and 25 years [1,11,12]. One hypothesis is that the transition from pediatric to adult care, which occurs during this time frame, may fracture healthcare delivery and predispose patients to MNA. Foster et al. in 2011 found that graft failure rates in the United States begin to increase after age 11 years and peak at age 19 years no matter what age the transplant takes place [1]. This “High-Risk Age Window” is present regardless of sex, race, cause of kidney disease, or type of induction [12]. Patients who receive their first kidney transplant between the ages of 14 and 16 years are at a particularly increased risk for graft loss, and this association is compounded further in patients at risk for systemic health disparities including minorities, patients with poor social support, and patients on public health insurance [4,5].

Early graft loss increases morbidity and mortality in kidney disease and shortens overall life expectancy in young KTRs [13], so we must work to prevent this outcome. However, there is limited evidence on consistent and effective therapeutic targets for improving patient engagement in young adult and adolescent KTRs. A recent study by Massey et al. provides a clue to the difficulty in reaching this patient population: although two-thirds of the young adults in this Netherlands-based study were classified as nonadherent, the patients’ overall self-rating of their own medical adherence was high [6]. The patient sits at the center of any intervention, and it is possible that young KTRs may not engage in creating personal strategies to change behavior if they do not feel that there is any problem to resolve. Therefore, a tailored approach is needed, taking into account the unique barriers to adherence in each specific case.

While there are many MNA interventions available to transplant providers caring for young KTRs, these have not recently been collected in one place. Thus, we provide here a review of potential MNA interventions. This begins with preventative interventions including psychosocial evaluation in the pre-transplant setting, support during the transition from pediatric to adult care, informatics technology, and possible alterations to the medication regimen. Next, monitoring interventions are reviewed, including behavioral monitoring as well as serological monitoring. Finally, we discuss potential treatment interventions that are available after MNA has been detected. Whenever possible, studies done in adolescent and young adult KTRs are explored. At other times, we have extrapolated from findings in adult KTRs in areas where further research is needed in young KTRs.

Preventative Interventions

Pre-transplant evaluation

The first step in preventing MNA would be to accurately screen for patients likely to become nonadherent while they are still in...
the pre-transplant setting and address modifiable factors prior to surgery where possible. In practice, this is an extremely difficult task to accomplish. One of the most commonly used tools for pre-transplant psychosocial evaluation, the Stanford Integrated Psychosocial Assessment for Transplantation, is able to predict higher rates of post-transplant rejection episodes in adults, but not graft failure, mortality, or MNA [14].

Similarly, in a recent study of the Transplant Evaluation Rating Scale in adult living donor KTRs in Germany, differing scores did not correlate with eGFR decline, rejection episodes, or development of donor specific antibodies within the first year post-transplant [15]. In an absence of well-validated predictive tools, many transplant centers focus on proxies for post-transplant MNA including dialysis attendance, markers of renal diet and volume adherence, and diabetes management as selection criteria for transplant candidacy. However, this strategy is inadequate to maintain consistency across, or even within, transplant centers, and so it is imperative that the transplant community continues to refine the tools that are available in the pre-transplant setting.

**Support during transition of care**

In response to the risk to allograft survival observed during transition from pediatric to adult care, several sites have developed transition clinics for young adult KTRs. Our adult kidney transplant program at University of Washington Medical Center has partnered with Seattle Children’s Hospital to create a developmentally appropriate transition program leading to a mutually agreed-upon transfer of care. There is growing evidence that this approach can reduce episodes of graft failure in Canada, the United Kingdom, and elsewhere during the high-risk age window from age 18 years to 25 years [16–18]. The American Society of Transplantation has created a “Pediatric Transition Portal”, available at www.myast.org, which provides an age-specific toolkit for patients heading into this transition [19]. Yet another idea is to create specific “young adult transplant clinics” for transplant patients in their teens and twenties, which incorporate peer support and one-on-one counseling [20].

**Informatics technology**

Although this is a relatively new area of research, studies regarding the role of informatics technology in MNA interventions for KTRs hold promise. A small randomized trial using the mobile application Transplant Hero, a reward-based medication adherence app created specifically for transplant patients, showed an improvement in tacrolimus level variability compared with nonusers after 1 month of use, but this difference had disappeared at 3 months [21]. In another study, 120 adult KTRs at a single center were randomly assigned to 1 of 3 arms: wireless pill bottles to monitor adherence alone, customized reminders (alarms, texts, telephone calls, and/or emails) and wireless pill bottles, or customized reminders plus provider notification of decreased adherence according to the wireless pill bottles. Both intervention arms had significantly improved adherence over the control arm [22]. The TAKE-IT trial followed 169 KTRs age 11 years to 24 years at 8 transplant programs in Canada and the United States over 4 years. In this randomized controlled trial, patients were assigned a “coach” who was otherwise unrelated to the transplant team and who met with patients every 3 months to provide either non-specific support (control) or action-focused problem solving which addressed barriers to adherence along with electronic reminders (intervention). Patients in the intervention arm had significantly better timing and taking adherence than controls [23].

In one survey, 78% of adult KTRs indicated that they had a positive attitude toward mobile health for medication management, and this was especially true for patients under age 55 years [24]. While the evidence for any one form of mobile health in improving post-transplant adherence remains lacking, there is certainly room to grow the role of mobile health technology and patient generated health data in self-directed healthcare.

**Medication regimen**

Medication adherence correlates inversely with dosage frequency [9]. Therefore, once-daily dosed calcineurin inhibitors present one possibility for simplifying the post-transplant medication regimen. Once-daily tacrolimus is bioequivalent to twice-daily tacrolimus, and has similar incidences of acute rejection, graft survival and patient survival [25]. A study of 219 adult KTRs showed that significantly more patients on once-daily tacrolimus took the prescribed number of daily doses compared with those on twice-daily tacrolimus [26].

Research is underway for the role of intravenous maintenance immunosuppression, such as belatacept, in order to minimize calcineurin inhibitors and steroids in the post-transplant regimen [27]. A single-center retrospective study concluded that belatacept is a good primary immunosuppressive option for nonadherent adolescent KTRs [28]. With medication side effects being a driver of MNA [9], providers should explore alternative treatments for patients with persistent side effects to the current immunosuppressive regimen.

**Monitoring Interventions**

**Behavioral monitoring**

To complement the prevention techniques discussed, we should also monitor for early signs of MNA and then initiate treatment as needed. Electronic monitoring devices, such as the
wireless pill bottles discussed, are quickly becoming the gold standard in monitoring patients’ medication adherence, particularly in a research setting [29].

A new method of medication adherence monitoring is the Ingestible Sensor System, a microsensor that is ingested along with a prescribed medication and becomes activated after ingestion. It is used in conjunction with a wireless monitor affixed to the skin, which in turn transmits data to the patient’s smartphone. The benefit of this technology over electronic monitoring devices, particularly in rigidly timed medication regimens such as the post-transplant course, is that both pill quantity and timing are documented. However, a study of 20 adult KTRs who ingested microsensors incorporated in mycophenolate pills showed that only 60% were able to complete the 12-week study due to skin reactions, gastrointestinal issues, or inadequate mobile service. The positive detection accuracy was 100% in 34 directly-observed ingestions during the study [30]. Although these monitoring interventions are very promising, they may be poorly utilized due to concerns over cost and privacy.

Serological monitoring

Although typically followed as an adherence marker post-transplant, variations in trough tacrolimus levels cannot necessarily signal deviations from the prescribed medical regimen. A recent study in Germany found that immunosuppressant trough level variability, percentage of sub-therapeutic trough levels, and patient-reported MNA were all significantly associated with rejection, but not with each other [31]. Protocol kidney biopsies have a low yield for discovering subclinical acute rejection [32], and for-cause kidney biopsies often come too late, after irreversible damage has been done to the kidney. Perhaps there is a role for early biomarkers such as donor specific antibodies in the blood [33,34] or cell-free DNA [35], among others, although much research is needed in this area.

Treatment Interventions

Research on cognitive behavioral interventions targeting young adult KTRs has been limited. A 2009 systematic review of medication adherence interventions in solid organ transplant recipients found poor overall evidence for any of the interventions reviewed; most included a combination of patient-focused cognitive/education, counseling/behavioral, and psychologic/affective dimensions [36]. Unfortunately, the strength of studies in this area has not improved markedly since that time. An updated review of MNA interventions in KTRs by Nevins et al. in 2017 discussed 13 studies from the United States, United Kingdom, Switzerland, Belgium, Germany, Brazil, and Sweden since 2000; although the included studies were typically small, several of these suggested improvement in short-term adherence after behavioral and educational interventions [5]. The largest of the behavioral intervention trials reviewed followed 150 post-transplant patients in the United States who either created a behavioral contract with a clinical pharmacist or received standard pharmacy care. The contracts included goal setting, motivation, social support, memory techniques, and problem solving; and were reviewed and updated with the study pharmacist at 3, 6, and 9 months post-enrollment. The intervention group showed significantly improved adherence at each time point in the study compared with the control group, up to 12 months post-enrollment, as well as decreased re-hospitalizations and costs [37]. This patient-centered problem-solving approach is similar to the use of adherence “coaches” in the TAKE-IT trial discussed, and has a place in the continuum of care for young KTRs, from prevention to treatment of MNA.

Depression, which is associated with poor motivation, has been shown to increase post-transplant morbidity and mortality in KTRs and may also be a contributing factor in MNA that is potentially treatable [38,39]. Therefore, routine screening and treatment for depression are encouraged.

Conclusions and Perspectives

Adolescent and young adult kidney transplant recipients have shorter graft survival than patients of older and younger age groups. Medication nonadherence and the transition from pediatric to adult care are both hypothesized to play a role in premature graft failure for young KTRs. Although conclusive evidence is lacking for the preventative, monitoring, and treatment strategies reviewed, multiple studies reflect incremental benefit.

Several adherence interventions are immediately available to transplant patients and providers without complex programmatic changes. These include use of the Stanford Integrated Psychosocial Assessment for Transplantation, simplified medication regimens such as once-daily tacrolimus or infusion-based therapy, digital resources such as mobile applications and the American Society of Transplantation Pediatric Transition Portal, collaborative creation of behavioral contracts, and routine screening and treatment of depression.

While these patient-level interventions are underway, we must simultaneously engage in system-wide approaches to improve patient-provider relationships and remove barriers to healthcare access. Further research is needed to improve graft survival and longevity among adolescent and young adult KTRs in the future.

Conflicts of interest

None.
References:

1. Organ Procurement and Transplantation Network. Kidney Kaplan-Meier Graft Survival Rates For Transplants Performed: 2008–2015. Retrieved from https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/ on December 13, 2017

2. Organ Procurement and Transplantation Network. Kidney Kaplan-Meier Patient Survival Rates For Transplants Performed: 2008–2015. Retrieved from https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/ on December 13, 2017

3. Foster BI, Dahnou M, Zhang X et al: Association between age and graft failure rates in young kidney transplant recipients. Transplantation, 2011; 92(11): 1237–43

4. Andreoni KA, Forbes R, Andreoni RM et al: Age-related kidney transplant outcomes: Health disparities amplified in adolescence. JAMA Intern Med, 2013; 173(16): 1524–12

5. Nevis TE, Nickerson PW, Dew MA: Understanding medication nonadherence after kidney transplant. J Am Soc Nephrol, 2017; 28(8): 2290–301

6. Massey EK, Meys K, Kerner R et al: Young adult kidney transplant recipients: Nonadherent and happy. Transplantation, 2015; 99(8): e89–96

7. Feinstein S, Keich R, Becker-Cohen R et al: Is noncompliance among adolescent renal transplant recipients inevitable? Pediatrics, 2005; 115(4): 969–73

8. Vlaminck H, Maes B, Evers G et al: Prospective study on late consequences of subclinical non-compliance with immunosuppressive therapy in renal transplant patients. Am J Transplant, 2004; 4(9): 1509–13

9. Osterberg L, Blaschke T: Adherence to medication. N Engl J Med, 2005; 353(5): 487–97

10. Watson AR: Non-compliance and transfer from paediatric to adult transplant unit. Pediatr Nephrol, 2000; 14(6): 469–72

11. Van Arendonk KJ, James NT, Boyarsky BJ et al: Age at graft loss after pediatric kidney transplantation: A prospective study of medical and psychosocial outcomes. Psychosom Med, 2015; 77(9): 1018–30

12. Prestidge C, Romann A, Djurdjev O, Matsuda-Abedini M: Utility and cost of the Stanford Integrated Psychosocial Assessment Rating Scale (TERS) and Medical Outcomes in Living-Donor Kidney Transplant Recipients – a retrospective analysis. Transplant Proc, 2018, 50(5): 1276–80

13. Bertram JF, Goldstein SL, Pape L et al: Kidney disease in children: Latest advances and remaining challenges. Nat Rev Nephrol, 2016; 12(3): 182–91

14. Maldonado JR, Sher Y, Lolak S et al: The Stanford Integrated Psychosocial Assessment for transplantation: A prospective study of medical and psychosocial outcomes. Psychosom Med, 2015; 77(9): 1018–30

15. Diepinger G, Mokhabee N, Wahba R et al: Correlation between the Transplant Evaluation Rating Scale (TERS) and Medical Outcomes in Living-Donor Kidney Transplant Recipients – a retrospective analysis. Transplant Proc, 2018, 50(5): 1276–80

16. Prestidge C, Romann A, Djurdjev O, Matsuda-Abedini M: Utility and cost of a renal transplant transition clinic. Pediatr Nephrol, 2012; 27(2): 295–302

17. Kuchenbauer K, Mansfield C, Amidon L et al: The impact of professional care on the success of kidney transplantation. Nephrol Dial Transplant, 2009; 22(8): 780–97

18. Kidd EA, Campbell MJ, Nicholls SJ et al: Using mobile health technology to promote immunosuppressant adherence. J Am Soc Nephrol, 2017; 28(7): 2221–32

19. Browning RB, McGillicuddy JW, Treiber FA, Taber DI: Kidney transplant recipients’ attitudes about using mobile health technology for managing and monitoring medication therapy. J Am Pharm Assoc (2003), 2016; 56(4): 450–54

20. Posadas Salas MA, Srinivas TR: Update on the clinical utility of once-daily tacrolimus in the management of transplantation. Drug Des Devel Ther, 2014; 8: 1183–94

21. Kuypers DR, Peeters PC, Sennesael JJ et al., ADMIRAD Study Team: Improved adherence to tacrolimus once-daily formulation in renal recipients: A randomised controlled trial using electronic monitoring. Transplantation, 2013; 95(2): 333–40

22. Talamila N, Pengel LH: Does belatacept improve outcomes for kidney transplant recipients? A systematic review. Transpl Int, 2015; 28(13): 1251–64

23. Lerch C, Kanzelmeyer NK, Ahlenstiel-Grunow T et al: Belatacept after kidney transplantation in adolescents: a retrospective study. Transpl Int, 2017; 30(5): 494–501

24. Robiner WN, Flaherty N, Fossum TA, Nevis TE: Desirability and feasibility of mobile health technology for managing and monitoring medication therapy. J Am Soc Nephrol, 2017; 8: 1183–94

25. De Bleser L, Matteson M, Dobbels F et al: Interventions to improve medication adherence in kidney transplant recipients: A systematic review and meta-analysis. Transplantation, 2015; 100(5): 988–1003

26. Kuypers DR, Peeters PC, Sennesael JJ et al., ADMIRAD Study Team: Improved adherence to tacrolimus once-daily formulation in renal recipients: A randomised controlled trial using electronic monitoring. Transplantation, 2013; 95(2): 333–40

27. Talawila N, Pengel LH: Does belatacept improve outcomes for kidney transplant recipients? A systematic review. Transpl Int, 2015; 28(13): 1251–64

28. Lerch C, Kanzelmeyer NK, Ahlenstiel-Grunow T et al: Belatacept after kidney transplantation in adolescents: a retrospective study. Transpl Int, 2017; 30(5): 494–501

29. Robiner WN, Flaherty N, Fossum TA, Nevis TE: Desirability and feasibility of mobile health technology for managing and monitoring medication therapy. J Am Soc Nephrol, 2017; 8: 1183–94

30. De Bleser L, Matteson M, Dobbels F et al: Interventions to improve medication adherence in kidney transplant recipients: A systematic review and meta-analysis. Transplantation, 2015; 100(5): 988–1003

31. Eisenberger U, Wüthrich RP, Bock A et al: Medication adherence assessment: high accuracy of the non-invasive Sensor System in kidney transplants. Transplantation, 2013; 96(3): 245–50

32. Scheel J, Reber S, Stoessel L et al: Patient-reported non-adherence and immunosuppressant trough levels are associated with rejection after renal transplantation. BMC Nephrol, 2017; 18(1): 107

33. Cruzado JM, Melliñi E: Looking for the needle in the kidney transplantation haystack. Clin Kidney J, 2017; 10(1): 95–96

34. Wiebe C, Gibson IW, Blydt-Hansen TD et al: Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. Am J Transplant, 2012; 12(5): 1157–67

35. Bloom RD, Bromberg JS, Poggio ED et al., Circulating Donor-Derived Cell-Free DNA in Blood for Diagnosing Active Rejection in Kidney Transplant Recipients (DART) Study Investigators. Cell-free DNA and active rejection in kidney allografts. J Am Soc Nephrol, 2017; 28(7): 2221–32

36. De Bleser L, Matteson M, Dobbels F et al: Interventions to improve medication adherence after transplantation: A systematic review. Transplant Int, 2009; 22(8): 780–97

37. Christholm-Burns MA, Spivey CA, Griff Zivin J et al: Improving outcomes of renal transplant recipients with behavioral adherence contracts: A randomized controlled trial. Am J Transplant, 2013; 13(9): 2364–73

38. Cukor D, Ver Halen N, Pencille M et al: A pilot randomized controlled trial of mobile health technology to promote immunosuppressive adherence in adult kidney transplant recipients. Nephron, 2017; 135(1): 658–65

39. Dew MA, Rosenberger EM, Myaskovsky L et al: Depression and anxiety as risk factors for morbidity and mortality after organ transplantation: A systematic review and meta-analysis. Transplantation, 2015; 100(5): 988–1003