

Kidney Transplant Recipient Emerging Adulthood and Transition to Adult Care

**Maryam Shafiei Sabet
Adult Nephrologist**

Transition of kidney transplant recipient

- The burden of chronic illness in adolescence has increased in the past few decades.
- One result of this changing pattern is that larger numbers of adolescents with chronic illness will need to make the transition from specialist pediatric to equivalent care in an adult health-environment at some time.
- Making a successful transition to adult health care is increasingly recognized as an important health outcome for young people with chronic disease.

Emerging Adulthood

- The transition from childhood to adulthood. This period has been conceptualized as a socially-defined developmental stage termed 'emerging adulthood'
- Emerging adulthood is defined as the interval between 18 and 25 years of age during which young people become independent and is characterized by instability

Emerging adulthood

- Although people in this age group appear physically mature, brain maturation is not complete until the end of this period.
- Immaturity and a resulting inferior ability to manage chronic illness emerging adults with a variety of chronic health conditions are at a high risk for adverse outcomes.
- Any healthcare transition involving a change in care providers may result in an interval of increased risk

Emerging Adulthood

- Emerging adulthood constitutes a period during which the risk for graft failure is particularly high, and possible reasons for this spike in risk—including:
 - Age-related adherence behavior
 - Changes in care organization, processes and structures associated with transfer from pediatric to adult-oriented care

Graft survival during emerging adulthood

- It has been known for over a decade that individuals receiving a transplant during adolescence have poorer graft survival than those in other age groups.
- 13–17 year-old living donor transplant recipients the 5-year graft survival rate was 77 % compared with 83 % for 6–12 year-olds.
- recipients of deceased donor grafts the 5-year graft survival rate was only 63 % for 13–17 year-old recipients compared with 70 % for 6–12 year-old recipients

Graft survival during emerging adulthood

- A study of 1,252 pediatric deceased donor recipients from the United Kingdom showed a hazard ratio for graft failure of 1.25 for those transplanted at 15–17 years of age compared with those transplanted at 10–14 years of age.
(*Pediatr Transplant* 2002 6:367–377)
- We subsequently demonstrated that graft failure rates peak between 17 and 24 years of age regardless of age at transplant (*transplantation* 2011, 92: 1237-43)
- Multivariable analysis showed that failure risk was highest in 17–24 year-olds and next highest in 25–29 year-olds.
- Interestingly, this corresponds almost exactly to the period of emerging adulthood that has been suggested to have two phases: early (18–25 years) and late (19–29 years) (*Am Psychol* 2000, 55:469–480)

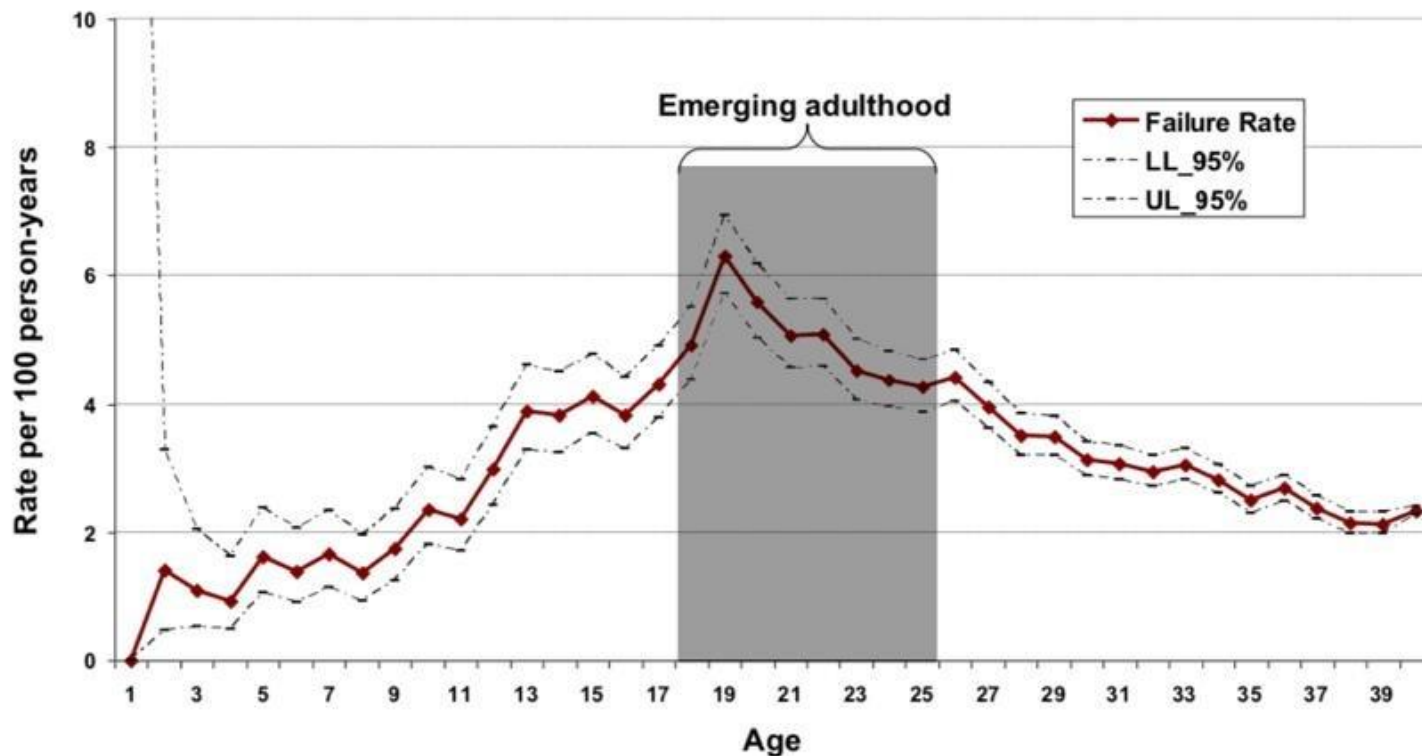


Fig. 1 Crude age-specific death-censored graft failure rates (failures per 100 person-years) in each one-year age interval are shown with 95 % confidence intervals for recipients under 40 years of age at first transplant with at least one year of graft function recorded in the Organ Procurement

and Transplantation Network registry (1988–2009). These rates are not adjusted for time since transplant. The grey box represents the interval of ‘emerging adulthood’. (Adapted with permission from [15])

Graft survival during emerging adulthood

- United States Government Accountability Office report that showed a greater proportion of patients who were <18 years at transplant and ≥ 18 years at follow-up had experienced graft failure at 3, 5, and 7 years post-transplant than those who were younger than 18 years at follow-up or older than 18 years at transplant.
- Poor treatment adherence is believed to be the main cause of increased graft failure risk in emerging adulthood.
 - Medication adherence
 - Adherence to general care (e.g., clinic appointments, routine blood monitoring)

Definition of adherence

- Adherence is defined as the extent to which a person's behavior (e.g., taking medication, following a diet or fluid targets, catheterizing on a timed schedule, and/or executing lifestyle changes), corresponds with agreed recommendations from a health care provider.
- There are various components of adherence:
 - dosing adherence
 - timing adherence
 - taking adherence
 - Persistence
- Adherence also refers to additional important healthcare tasks, including scheduling and attending clinic appointments, getting the necessary blood work, returning provider phone calls, maintaining proper diet and exercise, avoiding alcohol and drug use, or globally following the treatment regimen

Adherence in pediatric kidney transplant

- Among pediatric kidney transplant recipients 43 % of adolescents were poorly adherent compared with 22 % of younger children. (Pediatr Transplant 2010, 14:603–613)
- A meta-analysis of pediatric solid organ transplant recipients showed a rate of poor adherence that was three times higher among adolescents than younger children. (Transplantation 2009, 88:736–746)
- Compared with adults between 24 and 44 years old rates of poor adherence were almost 60 % higher in adolescents. (Am J Transplant 2009, 9:2597–2606)
- Although some have suggested that changes in immune function may contribute to higher graft failure risk in emerging adulthood.

Adherence in pediatric kidney transplant

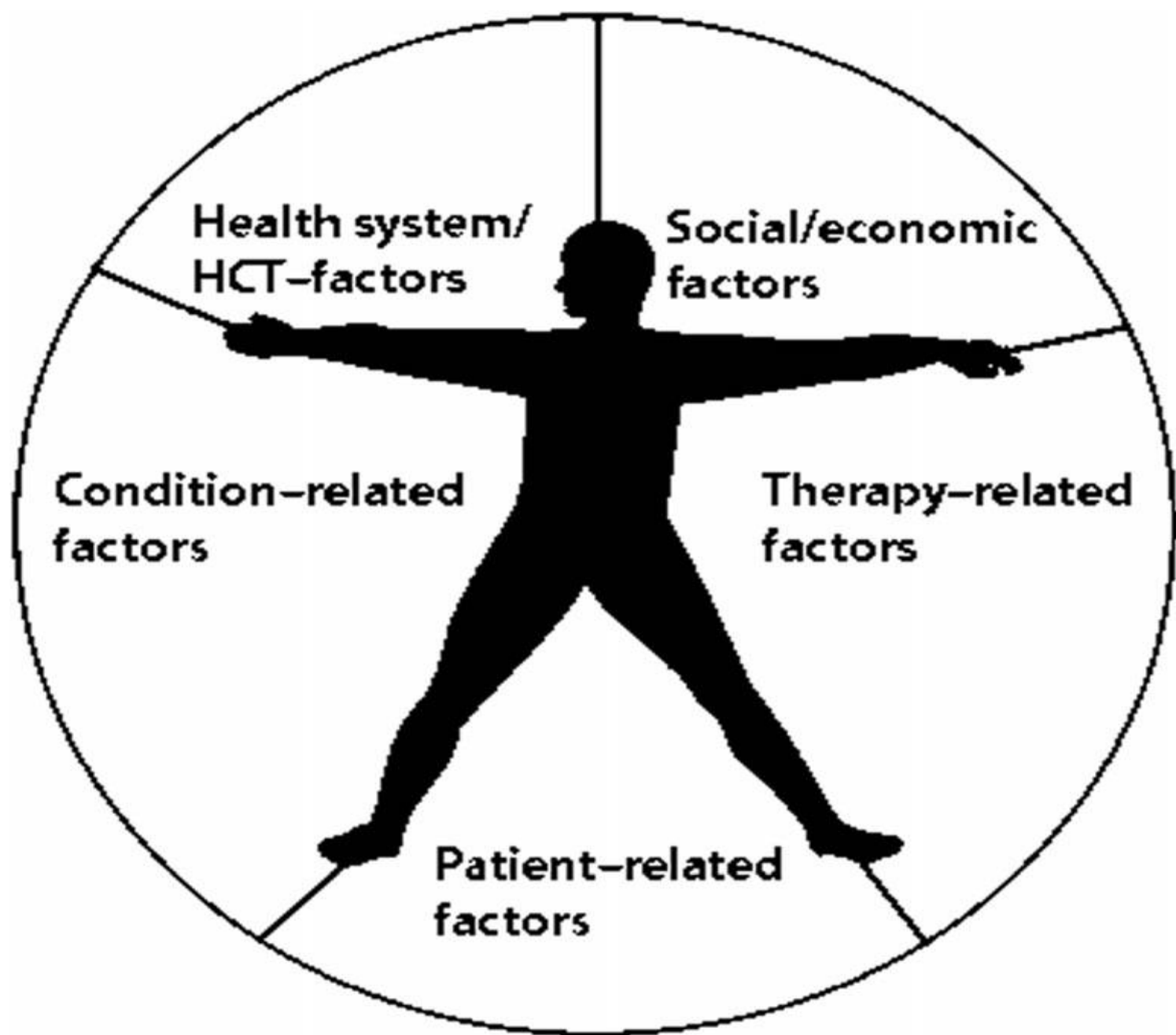
- Non-adherence has significant implications for kidney transplant patients including
 - Increased healthcare utilization
 - Medical complications
 - Allograft rejection and loss
 - Patient death
 - Non-adherence is the leading cause of antibody-mediated rejection [
- Non adherence remains a significant problem among pediatric and adult renal transplant recipient
- Estimates of non adherence range from 30 to 70 percent between pediatric recipients.
- Every 10 percent decrement in adherence is associated with 8% higher hazard of graft failure and mortality

Adherence in pediatric kidney transplant

- Research in adolescent and young adult transplant recipients has demonstrated that death censored graft failure rates are highest in 17- to 24-year-olds
- Non-adherence preventing retransplantation.
- Non-adherence has significant economic consequences.
- Estimates of annual healthcare systems costs for adherent kidney transplant recipients are \$16,844 (USD) versus \$82,765 for a patient in graft failure versus \$70,581 for a dialysis patient

Determinants of Adherence

- The World Health Organization has identified five interrelated risk and protective categories that impact adherence
 - **Patient-related factors** (knowledge and understanding of disease and medications, mental health concerns, cognitive functioning, coping mechanisms, and social support)
 - **Socio-economic factors** (socioeconomic status, family support and functioning, and race/cultural background)
 - **Condition-related factors** (duration of illness, health beliefs, time since transplant, and living donor renal transplantation)
 - **Therapy-related factors** (side effects, number of medications and doses per day, complexity of medication regimen, and cost of medication)
 - **Healthcare factors** (insurance and overall organization of healthcare and culture of care)



Non-adherence Post transition

- Difficulties with communication and coordination among pediatric and adult teams
- Lack of planning
- Resistance of patients and families to transition
- Insufficient skills and knowledge of health management tasks
- Unclear transition timelines

Adherence in pediatric kidney transplant

- In Dobbels et al.'s meta-analysis, rates of immunosuppressive medication non-adherence were estimated at 43.2% among adolescent kidney transplant recipients (compared to a rate of 22.4% non-adherence in kidney transplant recipients younger than 10 years of age)
- A >5 years post-transplant follow-up study deemed outcomes significantly worse in adolescent age groups than in younger transplant recipients.

Meta-analysis of medical regimen adherence outcomes in pediatric solid organ transplantation

- A meta-analysis investigating non-adherence in pediatric kidney transplant recipients found that missing clinic appointments and tests is the most prevalent form of non-adherence (rate = 12.7, standard error = 4.4, N = 4 studies)
- This meta-analysis also found that non-adherence to substance use restrictions, exercise, diet, and additional healthcare tasks ranged from 0.6 to eight cases per 100 patients per year

Determinants of Adherence

- Berben et al. proposed a framework to conceptualize the determinants of adherence at different “levels” :
 - patient-level (WHO patient-, condition-, and therapy-related factors)
 - “micro”-level (social factors and interactions with the care team)
 - “meso”-level (organization and expertise of the healthcare team and care processes)
 - “macro”-level (high-level healthcare systems factors, including care and medication cost coverage and overall care environment)

Why does adherence decline in emerging adulthood-1

- Although emerging adults are fully physically mature, neuroanatomical and cognitive function studies indicate that brain maturation is not complete until the end of this period
- This neurocognitive immaturity may impair the ability to manage chronic illness
- Neuroscientists hypothesize that relatively rapid development of the limbic system (associated with reward-seeking and emotion) paired with slow maturation of the prefrontal cortex (associated with impulse control, planning, and organization) may bias emerging adults toward preferring choices that maximize immediate rewards over those optimizing long term outcomes
- The prefrontal cortex continues to develop well into the mid-twenties

Why does adherence decline in emerging adulthood-2

- The possibility that longstanding chronic disease may interfere with normal development, resulting in delayed maturity, must also be considered.
- Children and adolescents with chronic kidney disease showed significantly poorer short term memory than healthy children and poorer performance on executive function tasks.
- ESRD at ≤ 16 months had significantly lower intelligence and metacognitive function.
- About 20 % of very young children with ESRD show generalized developmental delays; more severe renal failure is associated with more severe delays.
- Among 368 children with mild to moderate chronic kidney disease (CKD) a greater than expected proportion had performance ≥ 1 SD below average for intelligence, achievement, attention and executive function.
- Adult survivors of childhood CKD also demonstrate lower than average IQ

Why does adherence decline in emerging adulthood-3

- There was a significant correlation between poorer everyday problem solving and poorer adherence.
- An important event occurring during emerging adulthood is the transfer from pediatric to adult-oriented care. Transfer may exacerbate poor treatment adherence leading to adverse outcomes.
- There may be important differences in factors such as:
 - Time spent with the nurse and/or physician
 - Availability of a multidisciplinary team
 - Frequency of clinic visits
 - Frequency of routine blood monitoring.
- A strong relationship with care providers was also associated with better adherence.

Transfer from pediatric to adult care and graft failure risk

- In a case series of 20 kidney transplant recipients transferred to adult care at a median age of 18 years he reported unexpected graft failures within 3 years of transfer in 35 %. These compelling findings prompted several additional studies. (Pediatr Nephrol 2000 14:469–472)
- A Dutch study of 162 kidney transplant recipients 14 to 22 years old is the only study to date to find a significantly higher risk of graft failure before transfer than after. (Nephrol Dial Transplant 2010 25:1662–1667)

Graft failure and adaptation period to adult healthcare

- 149 Canadian patients who experienced transfer to adult-oriented care at a median of 18 years old to examine the graft failure risks during an 'adaptation' period compared with the risks prior to adaptation.
- Adaptation intervals of three different lengths, beginning 6 months prior to the first adult care visit, were considered: a 3-year interval, a 2-year interval, and a 1-year interval.
- Compared with the period before adaptation the adjusted hazard ratios were 2.24 [1.19, 4.20] for the 3-year interval, 3.14 [1.67, 5.90] for the 2-year interval, and 5.43 [2.83, 10.39] for the 1-year interval.
- There was insufficient overlap of the ages represented in the pre-adaptation and adaptation periods to allow complete control for age.

Risk of Hospitalization

- Among the 92 patients who had been transferred the risk of avoidable hospitalizations was highest in the period 3–4 years after transfer (RR 3.19 [1.42, 7.18] compared with the year before transfer). Avoidable hospitalization rates increased age among the 257 who had received all of their care in an adult-oriented center.

The impact of age at transfer from pediatric to adult-oriented care

- The study included individuals who had received a transplant at <21 years of age, had maintained graft function for at least 1 year, and who had been transferred to adult-oriented care.
- Age at transfer was classified as early (<21 years) or late (≥ 21 years).
- The crude failure rate among those transferred early was 12.9 per 100 person years of observation compared with 8.7 per 100 person-years in those transferred late.
- The adjusted hazard ratio for graft failure for early compared with late transfer was 1.57 (1.07, 2.34). *Pediatr Transplant* 15:750–759

Transition Clinic

- Harden et al. compared the outcomes of 9 patients observed between 2000 and 2005 with those of 12 patients observed from 2006 to 2011 [49].
- In the early period patients were transferred at a median of 18 years; a referral letter was sent to the receiving nephrologist to facilitate the transfer. During this period six patients (67 %) experienced graft failure at a median of 40 months (range: 1–62) after transfer and 33 % had late acute rejection.

Transition Clinic

- In the later period patients were seen in a joint transition clinic where they received care from a single pediatric nephrologist and pediatric nurse specialist and a single adult nephrologist and adult nurse specialist until ready for transfer (a youth worker was included on the team from 2009); the goal was transfer by 18 years of age.
- Once transferred they received care in a young adult clinic staffed by a youth worker in addition to medical staff. At a median of 26 months (range: 18–60) of follow-up there were no graft failures and no late acute rejections.

Role of Transition Clinics

- Prestidge et al. examined the outcomes of 33 patients transferred to adult care between 2000 and 2006 during which period the timing of transfer was decided by the treating nephrologist; there was no transition clinic [53].
- The outcomes of these patients were compared with those of 12 patients cared for from 2007 to 2009; in this period patients were cared for in a transition clinic staffed by a single pediatric nephrologist, nurse specialist, youth health specialist, social worker, renal pharmacist, and dietician.
- The timing of transfer to the regular adult clinic was flexible depending on medical and psychological readiness.
- In the 2000 to 2006 period there were 8 graft failures or deaths (24 %) within 2 years of transfer.
- In contrast, after inception of the transition clinic there were no graft failures or deaths within 2 years of transfer.

Table 1 Association between transfer and graft failure risk

Reference & Data source	Age at transfer (y)	Study design	Main findings	Limitations
Watson, 2000 [42]: Single pediatric centre and 3 adult centres in England (medical records)	Mean: 17.9 (Range 15–20)	Case series (<i>n</i> =20)	7/20 (35 %) patients experienced an unexpected graft failure within 3 years of transfer	<ul style="list-style-type: none"> • Single centre • Uncontrolled; findings may reflect effect of age rather than transfer • Small sample
Van den Heuvel, 2010 [47]: Two Dutch pediatric kidney transplant units (medical records)	Median: 18 (Range 14–22)	Retrospective cohort (<i>n</i> =162)	Hazard ratio for acute rejection after transfer compared with before transfer of 0.1 (95 % CI 0.04, 0.28) in native Dutch patients and 0.69 (0.33, 1.40) in immigrant patients	<ul style="list-style-type: none"> • Did not control for time post-transplant; the immediate post-transplant period was represented almost exclusively in the pre-transfer experience • Surveillance for acute rejection may have differed pre- and post-transfer
Samuel 2011 [41]: Canadian Pediatric End Stage Renal Disease Database	Median: 18.1 (IQR: 18.0–19.4)	Retrospective cohort (<i>n</i> =149)	Compared with the period before ‘adaptation’ to adult care the adaptation interval was associated with a 2.5× higher risk of graft failure. Risks were highest in the period immediately following transfer.	<ul style="list-style-type: none"> • Unable to adjust completely for the association between age and graft failure risk
Foster, 2011 [5]: United Network for Organ Sharing Scientific Registry of Transplant Recipients (SRTR) database	Median: 20.7 (IQR: 19.5–21.7)	Retrospective cohort (<i>n</i> =440)	Compared with patients transferred to adult care at ≥21 years old the HR for graft failure was 1.58 [95 % CI 1.07, 2.34] for those transferred at <21 years old	<ul style="list-style-type: none"> • Unable to capture all transfers; sample may be biased • If patients were transferred early due to poor adherence this would bias to higher risks in those transferred early
Prestidge, 2012 [44]: Single centre	Mean in pre-intervention period: 18.9 (range 17.3, 20.0) for those who failed Mean: 19.9 (range 17.8, 23.2) for those who didn’t fail	Pre- vs. post-intervention (<i>n</i> =45)	Compared with graft failure or death in 24 % within 2 years of transfer before inception of the transition clinic there were no failures or deaths after	<ul style="list-style-type: none"> • Secular trends may favour better outcomes in more recent periods • Small sample • Single centre
Harden, 2012 [40]: Two pediatric centers and 1 adult centre in England	Mean in pre-intervention period: 18 (range 16, 18)	Pre- vs. post-intervention (<i>cpax</i> =21)	Compared with graft failure in 67 % before inception of the young adult clinic there were no failures or deaths after	<ul style="list-style-type: none"> • Observation time at risk not equal in the pre-intervention and post-intervention periods • Small sample • Small sample

Guidance on transition practice

- The question of who should provide care to this high risk population remains unanswered.
- Some argue that pediatricians trained to care for developing adolescents are best positioned.
- Others suggest that these young adults need care and services that are best provided by professionals accustomed to ‘adult’ problems.
- There is merit to both positions—which may be why transition clinics and young adult clinics jointly staffed by pediatric and adult care providers have shown such promise

Guidance on transition practice

- The best available evidence suggests that those transferred at an older age to adult care have outcomes superior to those transferred at a younger age.
- Adult clinics are overwhelmed with the high volume of patients needing care. make it difficult to provide optimal care for these high risk patients in the traditional adult care setting.
- When an interested and dedicated adult care provider is available to act as a 'champion' for young people it may be possible to tailor care to the needs of this high risk group.
- Pediatric care is already commonly structured in away that may better support the needs of these young patients.

Guidance on transition practice

- The first stage: in this process aims to encourage greater responsibility and independence with health care in adolescents.
- The second step: the adolescent meets a specific transition adult nephrologist (RW) over several clinic visits at a transition clinic.
- The third stage, commonly after two to four appointments within the Transition Clinic, involves the formal transfer of care to an adult nephrology service.
- The timing of the second and third stages is decided by the medical and nursing teams in consultation with the adolescent and their family and depends largely on the young person's physical and psychological maturity together with his/her self-management skills and social situation

The transition of kidney transplant recipients: a work in progress

- Eleven patients (six male) were transferred from the RCH pediatric renal unit to adult providers during the identified study period.
- The mean age of transfer to adult services was 19.5 years (range 18–23 years).
- Following transfer to adult services, nine patients remained clinically stable while two patients experienced a worsening of clinical status.
- One patient already had advanced chronic kidney disease at the time of transfer and, as anticipated, eventually required dialysis (12 months later). Another patient unexpectedly experienced antibody-mediated rejection soon after transfer and required treatment with intravenous immunoglobulin and plasma-exchange.
- It seems provide a more consistent, informed and coordinated approach to the transfer of patients to adult services is helpful.

summary

- The collected evidence supports the contention that transfer from pediatric to adult-oriented care is a high-risk event associated with a heightened risk for graft failure.
- Poor treatment adherence is the most important factor mediating the associations between higher graft Pediatric failure risk and both the emerging adult period and transfer of care. (Nephrol (2015) 30:567–576 573)
- Transition clinics and young adult clinics may be a solution.
- Further research is needed to identify care delivery models and characteristics that promote the best outcomes for the high-risk emerging adult population and to estimate the costs and benefits of these new models.
- Ultimately, young people themselves may be the best judges of the most suitable care models.