Medication non-adherence is a leading modifiable cause for renal graft loss in childhood

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Introduction

- Advances in Immunosuppression and surgical technique have greatly improved paediatric renal transplant outcomes.
- However adolescents and young adults still have the highest rates of renal graft loss[1,2].
- This study examines the causes and characteristics of graft failure in childhood before transition to adult services.
- We further investigated the role of medication non-adherence as a risk factor for graft loss in childhood.

Methods

- Analysis of all children under 18 years of age who underwent kidney transplantation at the Evelina London Children's Hospital between January 2003 and September 2015.
- Graft lifespan was compared between adherent and non-adherent patient groups using an unpaired T-test for equal variance (F-test confirmed equal variance).
- Non-adherence with immunosuppressive medication was classified after meeting 3 international key criteria[3]:
  1. Persistent non-adherence recorded in clinical notes by the transplant team and psychological assessment confirming non-adherence AND
  2. Persistently low calcineurin-inhibitor (CNI) levels AND
  3. Repeated acute rejection episodes confirmed on biopsy.

Results

- 171 paediatric kidney transplants were performed with a median follow up of 8 years (IQR 10 years).
- 15 grafts failed before adulthood (9%).
- Average age at transplant – 4.8 years (range 1.7-15.4).
- Average age at graft loss – 14.3 years (range 2-17.9).
- LRD and DD transplants were evenly distributed and well matched.

Figure 1: Causes of Graft Failure

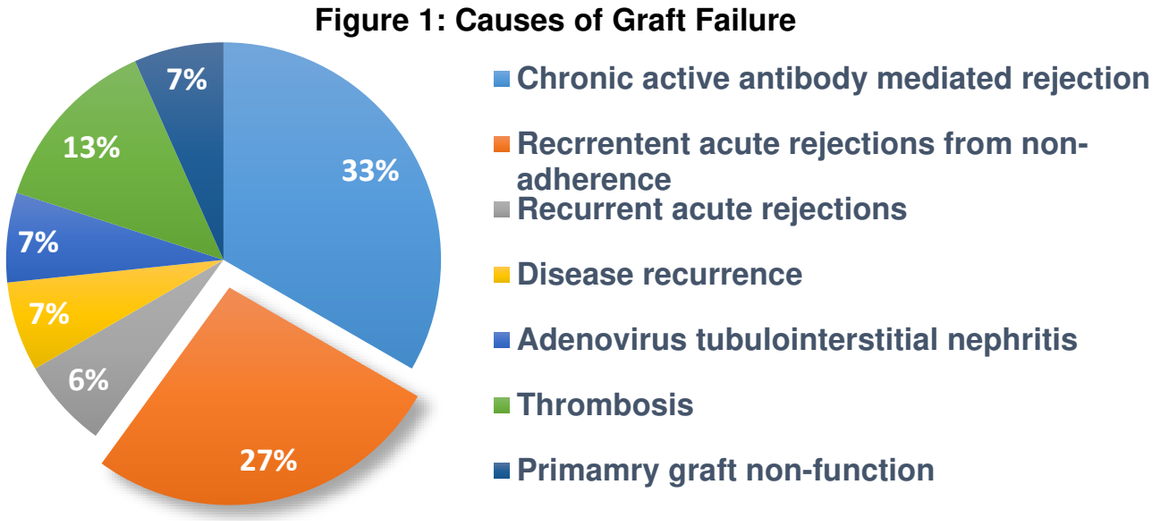
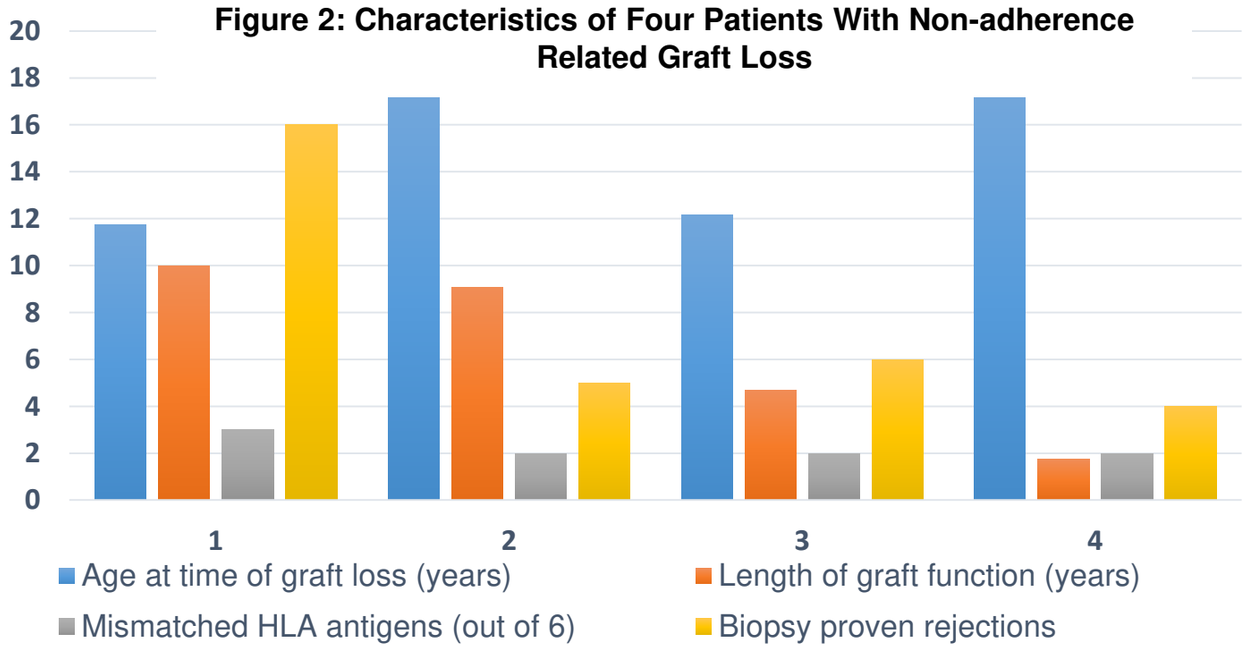


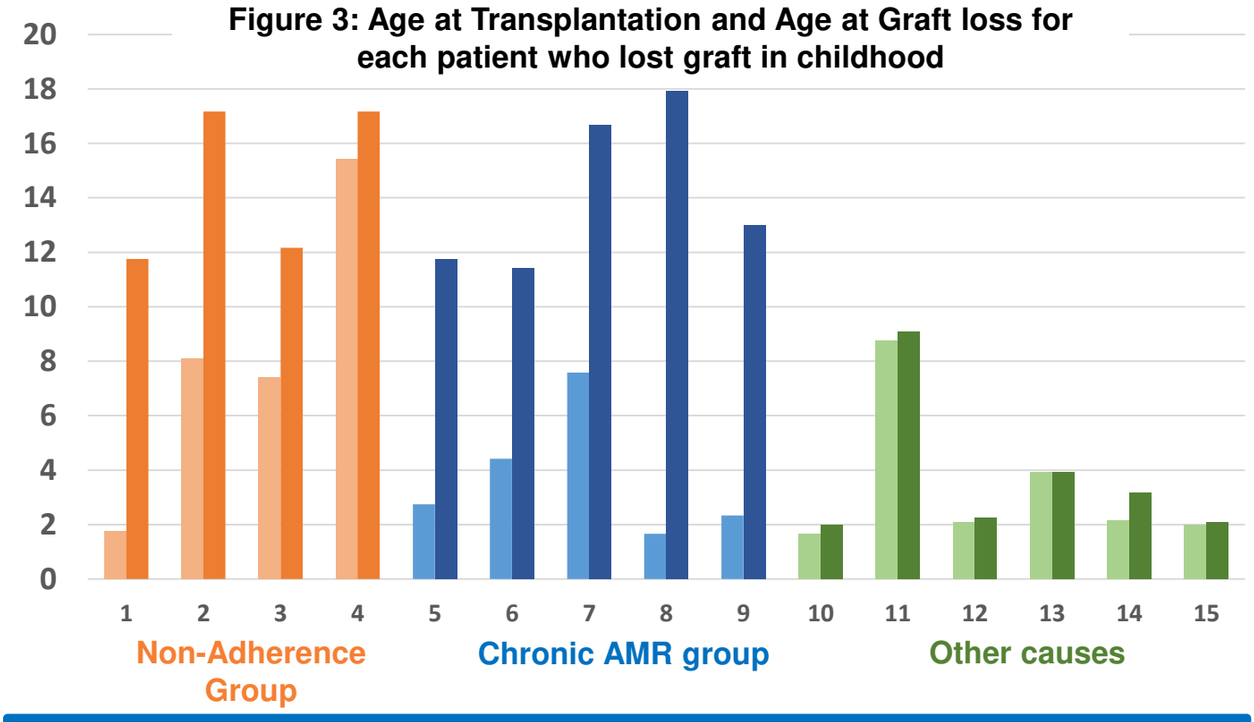
Figure 2: Characteristics of Four Patients With Non-adherence Related Graft Loss



Persistent medication non-adherence caused graft failure in 27%.

- All were 12-17 years old at the time of graft loss.
- All well matched (MM 110/111) with negative or low EBV/CMV.
- Multiple episodes of rejection (Banff 2013 2b and 4a) with an average of 7.8 biopsy proven episodes each.
- Each had persistent low/undetectable CNI levels.
- Donor specific antibodies positive in all (cRF 42-100%).
- 75% required haemodialysis prior to transplantation.
- In comparison, 17% of chronic AMR group (good adherence) required haemodialysis prior to transplant.

Figure 3: Age at Transplantation and Age at Graft loss for each patient who lost graft in childhood



- Average graft lifespan in medication non-adherence – 6.4 years.
- Average graft lifespan in chronic AMR – 10.4 years.
- ***No significant difference in graft longevity (P=0.07).***

Discussion

The leading modifiable cause of graft loss was medication non-adherence. Evidence suggests that up to 12% of graft loss in adolescence is due to medication non-adherence[3]. We have shown a higher incidence (27%), suggesting that this an important contributor to poorer transplant outcomes in this population.

Graft survival is shorter in non-adherent patients compared to those with chronic AMR. However, these findings were not statistically significant (p=0.07) which may be due to small sample size.

Haemodialysis patients are more vulnerable. Graft failure from non-adherence correlated with pre-transplant dialysis whereas graft failure from chronic AMR correlated with pre-emptive transplantation. This identifies dialysis patients as particularly vulnerable and early psychosocial interventions should be targeted here.

Non adherent patients represent a particularly vulnerable group. Two patients endured complete family breakdown, one had bipolar disorder and one required child protection intervention to support the family in administering medications correctly. This highlights the high level of vulnerability to psychosocial challenges amongst this young age group.

Conclusion: It is important to recognise that adolescence is an indiscriminately challenging time which can lead to medication non-adherence and graft loss. Identifying vulnerable young patients and intervening earlier may prolong overall graft survival.

Limitations of this study: There are no standardized methods of recording non-adherence with a level of subjectivity[3]. This makes comparisons difficult.

We propose an "Adherence Pathway"

Pathway is divided into preventative and management phases in a stepwise approach. It encompasses early identification of vulnerable patients, enrolment into a hospital passport program overseen by play specialists, MDT meetings, preventative parent workshops, adherence workshops, early clinical psychology referral pathways at the time of pre transplant work up and CAMHS referral pathways.

1) Van Arendonk, K *et al.,* Age at Graft Loss after Pediatric Kidney Transplantation: Exploring the High-Risk Age Window. *Clin J Am Soc Nephrol.* 2013. 8(6): 1019–1026.
2) Kaboré, R *et al.,* Age dependent risk of graft failure in young kidney transplant recipients. *Transplantation.* 2016. [Epub ahead of print]
3) Rianthavorn P and Ettenger RB, Medication non-adherence in the adolescent renal transplant recipient: A clinician's viewpoint. *Paediatric Transplantation.* 2005. 9: 398–407.