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INVITED COMMENTARY

# Retransplantation after nonadherence-related kidney allograft failure – forgive or forget?

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Despite advances in kidney transplant medicine and surgery, long-term transplant outcomes continue to languish, in part because of the problems with nonadherence (NA) to immunosuppressive drug therapy [1]. It has been reported that NA is very common after solid organ transplantation especially after kidney transplantation – up to 36%, which also contributes to increased medical morbidity and costs [2,3].

There has been a long-standing interest in evaluating the impact of NA after kidney transplantation since it is considered a leading avoidable cause of graft failure with odds of failure sevenfold greater for nonadherent vs. adherent renal transplant recipients [4]. Allograft rejections associated with NA are particularly troubling because they are often antibody-mediated, occur late after transplant, and are frequently refractory to treatment [1]. Therefore, evidence for NA routinely raises concerns regarding re-listing patients for another kidney transplant given the possibility of repeating the same behavior with the second allograft. Since much of the transplant community and regulators have focused on 1-year graft outcomes [5], there is a strong need to better understand the role of prior NA on subsequent kidney retransplantation.

Although NA has in general been associated with diminished graft survival and an increased risk for graft rejection, a direct association of NA with worse outcomes after retransplantation is inconsistent. This association is particularly challenging to study, as the definition of NA is not universal. It includes both intentional and unintentional behaviors, and voluntary and involuntary observations or measurements (drugs levels, refills, and clinic visits). Most transplant recipients are not forthcoming about NA with the medical staff for fear of the stigma that such behavior engenders, namely poor communication and the erosion of trust with the transplant team. Likewise, some centers are reluctant to document NA because of fostering poor future


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interactions with undesirable medical consequences, including the potential to preclude a subsequent kidney transplant. In addition, NA after a living donor kidney transplant can be exceptionally stressful and can generate widespread antipathy among families and friends.

In the current issue of Transplant International, Manickavasagar *et al.* reported on a longitudinal cohort of kidney transplant recipients using the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) who had graft failure and received a second kidney transplant [6]. This well-designed study allowed the authors to evaluate the risk of NA-related second allograft failure in patients with prior graft loss because of documented nonadherence. The total cohort included 2450 kidney recipients, of those 2.4% ($n = 59$) lost their first graft because of NA-related causes. According to the authors, these 59 regrafted patients represented only about 1/3 of their NA first graft losses. In agreement with prior reports, patients who lost their first graft because of NA were significantly younger at the time of the first allograft (median age 19) [7]. This observation highlights the vulnerability of the adolescent age group when considered for transplant listing.

Interestingly, the authors reported that patients who lost their first graft to NA had a longer wait time until they received a second graft in spite of similar peak panel-reactive antibodies when compared to patients who lost their first graft because of other causes (>5 years: 54% vs. 20%, $P < 0.001$). This observation possibly reflects transplant center reluctance to consider such patients or an enforced period of observed compliance before another transplant. The authors reported no significant risk of second allograft failure or acute rejection following retransplantation in the NA group. However, patients who lost their first graft because of NA were more likely to lose their second graft because of NA-related causes if they experienced second kidney graft loss. A prior similar study by Dunn *et al.* included 119 patients who lost their first graft secondary to NA as defined by discontinuation of immunosuppression medication for prolonged duration and/or lost to follow-up with the transplant team. Of these, 32% underwent a retransplant after careful evaluation. Over 8 years of follow-up, there was no significant difference in graft or patient survival between retransplanted patients who lost their first graft to NA vs. other causes [8]. Not surprisingly, both studies detected a higher risk of recurrent NA behavior after a second transplant, although excess second graft loss was not confirmed. Thus, choosing those patients who exhibited first graft NA for a subsequent kidney transplant remains somewhat arbitrary and problematic. Unfortunately, registry analysis does not permit a detailed description of how those offered retransplant were actually assessed.

In the report by Manickavasagar *et al.*, the authors concluded that allograft outcome after repeat transplantation in recipients who lost a first kidney because of NA was similar to other patients. Given the fact that graft loss because of NA mostly occurs in the younger age group, it comes as no surprise that these patients will potentially need a second and perhaps a third transplant in the future. The authors do not suggest that prior NA should be a hard barrier for repeat transplantation but advised careful patient selection and aggressive monitoring for adherence to the medical regimen should be embraced. From the transplant center perspective, such candidates need to demonstrate growth and responsibility, family support, reliable living conditions, financial stability, absence of substance abuse, and psychosocial health. These measures all require direct professional assessment and careful deliberation into the final decision to retransplant.

As a prelude to retransplantation, focused education is essential. Prior reports have demonstrated that patients were better able to adhere to immunosuppression medication when they received adequate information regarding mechanism of action, expected side effects, and adverse effects resulting from discontinuation of their medication [9]. Additionally, healthcare professionals need to tailor the method of delivery of information to patients based on their learning and cognitive abilities [1,8,10].

In conclusion, the study by Manickavasagar *et al.* in the current issue of Transplant International supports continued access to retransplantation for selected patients who lost a first kidney because of NA, noting that a marginally increased risk for recurrent NA existed. Clearly, intensified long-term support and heightened vigilance are required. Selecting these candidates remains more art than science, and new approaches should be shared among transplant centers worldwide.

## Disclosure

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