

Occurrence, Implications, and Risks of Late Sensitization after Kidney Transplant Failure

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Abstract

A previously failed kidney transplant represents one of the major factors leading to the generation of antibodies against human leukocyte antigens. The ensuing sensitization results in prolonged waiting times for non-primary kidney transplants and also has a negative impact on graft survival following retransplantation. Weaning of immunosuppression and transplant nephrectomy have both been incriminated in increasing the risk of sensitization after a failed transplant. Removal of immunosuppression may directly result in the increased generation of donor-specific and non-donor-specific antibodies, while removal of the failed allograft may remove a “sink” for absorption of such antibodies. However, continued immunosuppression is associated with a risk of infection, while retention of the failed allograft may result in inflammation, anemia, and an enhanced risk of cardiovascular disease. Data from our center suggest that weaning of immunosuppression may be a more potent stimulus to human leukocyte antigen sensitization than removal of the allograft. However, further research is needed to determine the optimal strategies for managing the patient with a failed allograft. Such strategies should be designed to minimize the risk of sensitization and to increase the chances of expeditious and successful retransplantation. (Trends in Transplant. 2014;8:10-6)

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Key words

Transplant failure. Sensitization. Repeat transplantation. Nephrectomy. Immunosuppression.

Background

The number of patients returning to dialysis following kidney transplant failure

increased twofold from 1996 to 2006 in the USA and continues to climb¹. Sixteen percent of the patients on the current kidney transplant waiting list are patients relisted after failure of a previous transplant^{2,3}. Compared to dialysis, repeat transplantation renders improved survival after primary kidney transplant loss. However, only 12% of kidney transplants performed annually are repeat transplants^{3,4}. One reason for the low number of repeat transplants after kidney transplant failure may be late alloantibody sensitization.

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Definition and etiology of sensitization

Preformed antibodies to human leukocyte antigens (HLA) or ABO blood group antigens occur in the setting of blood transfusions, pregnancy, prior transplantation, or chance environmental exposures⁵. Several reports indicate that sensitization increases after weaning immunosuppression or after the removal of the allograft in patients with kidney transplant failure⁶. These preformed antibodies may be donor-specific or non-donor-specific. The level of these antibodies, or degree of sensitization, for any single potential transplant recipient or repeat transplant recipient is conventionally measured by a panel of reactive antibodies (PRA)⁷. The techniques for measuring PRA have gradually evolved to the flow cytometry methodology now used at most transplant centers.

Implications of sensitization

Failure of primary transplantation

Pretransplant sensitization, *de novo* antibody formation following transplantation, and late sensitization after transplant failure all have been shown to be detrimental to transplant outcomes⁸. Several studies demonstrate that sensitization is directly associated with an increased risk of graft failure^{8,9}. Pre-sensitization against HLA class I and II antigens confers an especially high risk of graft failure in primary kidney transplants that are mismatched¹⁰. Single-center studies show that the development of *de novo* donor-specific antibodies (DSA) in patients without pretransplant DSA occurs in 15-27% of patients with functioning allografts over a range of three months to 12 years. *De novo* DSA are strongly associated with transplant failure within years of detection^{11,12}.

The incidence of sensitization in one single-center study was reported as 70% after transplant failure. Eighty-one percent of these

patients were not sensitized prior to transplant failure, and a majority of the antibodies detected after failure were against donor antigens. Sensitization occurred in the majority within 12 months of transplant failure¹³. In another single-center cohort, 85% of patients with transplant failure who were not sensitized with DSA at the time of transplantation were free of DSA at the time of failure. However, emergence of both DSA (up to 81%) and non-DSA (up to 85%) occurred in a majority of these previously non-sensitized patients after transplant failure¹⁴.

We recently analyzed a cohort of 119 patients with a failed kidney transplant to determine the rate of alloantibody sensitization after returning to dialysis therapy¹⁵. In this cohort, 57% of patients were highly sensitized with either a class I or II PRA $\geq 80\%$ by flow cytometry at 6-24 months after failure. Over a quarter (27%) had both class I and II PRA $\geq 80\%$. A subgroup of 28 patients in this cohort had PRA levels available at the time of allograft failure while on immunosuppression, and antibody levels were compared to late levels after weaning immunosuppression. Median PRA at the time of failure in these 28 patients was 7 and 0% for HLA class I and II, respectively, but increased to 52 and 82% for HLA class I and II by 6-24 months ($p < 0.001$ for both comparisons). Six of 28 patients (21%) were highly sensitized at the time of allograft failure, while an additional 13 patients (68% overall) became highly sensitized by late PRA ($p < 0.001$ vs. the time of transplantation).

Repeat transplantation

Repeat transplantation is associated with a 23 and 45% reduction in mortality for non-diabetic and type I diabetic patients with a failed transplant, respectively². Although some patients with failed kidney transplants are not relisted due to personal preference, comorbidity, or death, one limitation for those who are relisted is the high rate of sensitization.

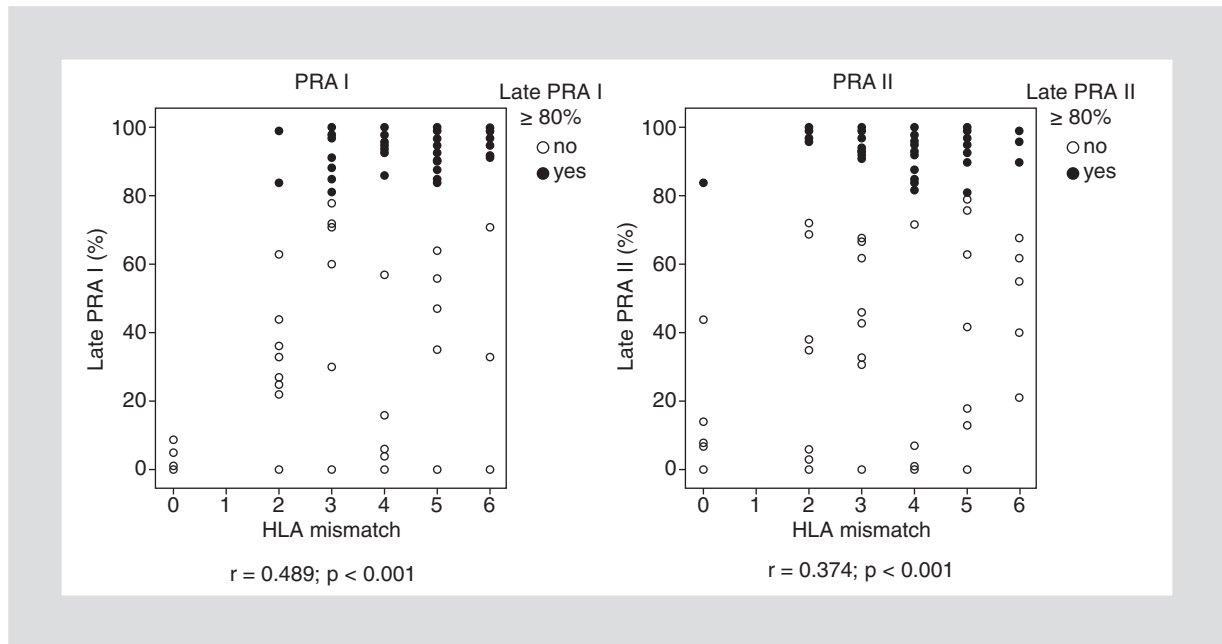


Figure 1. Correlation between panel reactive antibody (PRA) values after transplant failure and human leukocyte antigen (HLA) matching from the original failed transplant. Class I (left) and II (right) PRA values are shown in 95 patients at 6-24 months after failure, stratified by HLA mismatch. Correlation coefficients are shown. The shaded circles denote a PRA value $\geq 80\%$.

The rate of transplantation for all registrants on the deceased donor kidney transplant waiting list decreases dramatically as PRA increases and a majority, 65%, of all actual recipients have a PRA $< 20\%$ ³. For patients seeking repeat transplantation, nearly one-third have PRA $> 20\%$ and a majority of repeat transplants occur more than 10 years after the initial transplant⁴.

Importance of human leukocyte antigen matching

Considering that increased sensitization leads to increased risk of primary graft failure, that graft failure further exacerbates sensitization, and that repeat transplant candidates with high PRA levels will wait longer for a second transplant, the importance of HLA matching of the first kidney transplant should not be underestimated. The likelihood of new sensitization in a non-sensitized patient after primary kidney transplantation increases as the total number of HLA mismatches increases.

Moreover, the overall change in PRA for any patient (initially sensitized or not) after primary kidney transplantation increases with the increase in HLA mismatches between donor and recipient¹⁶. In our recently described cohort, the number of HLA mismatches from the original transplant correlated with the PRA level at 6-24 months after failure in 95 patients who were weaned off of immunosuppressive therapy ($r = 0.352; p < 0.001$) (Fig. 1)¹⁵. One analysis suggests that HLA A and B mismatches confer a greater independent effect on PRA than HLA donor/recipient mismatches¹⁶. Although it may not affect relisting, the negative impact of poor HLA matching translates to inferior rates of repeat transplantation compared to well-matched HLA donor and recipients¹⁷.

Outcomes of non-primary transplantation

Sensitization after primary graft failure has an important influence on graft survival,

delayed graft function, and mortality in patients who undergo repeat transplantation. In an early study of repeat transplantation, data collected in the UCLA International Transplant Registry over a 10-year period compared patients in three categories of sensitization defined as low (PRA 0-10%), moderate (PRA 11-50%), and broad (PRA > 50%) sensitization. A total of 25-32% of repeat transplant recipients were moderately sensitized, while 38-46% of repeat transplant recipients were broadly sensitized. One-year graft survival in these moderately-to-broadly sensitized patients was up to 14% lower than in those with low sensitization⁵. However, as crossmatch techniques have improved to include prospective flow cytometry techniques, so have outcomes in highly sensitized patients.¹⁸ At the same time, more sensitive crossmatch techniques will mean more patients may be excluded from transplantation due to a positive crossmatch.

In a dataset reported to the United Network for Organ Sharing (UNOS), the incidence of delayed graft function was up to 50% in patients who were broadly sensitized⁵. Furthermore, the incidence of primary non-function for repeat transplantation increases directly as sensitization increases¹⁹.

Overall graft survival at one, three, and five years for repeat kidney transplantation, irrespective of sensitization level, is inferior in repeat living-donor transplants as well as deceased-donor transplants when compared to primary transplants²⁰. Furthermore, repeat transplantation with an expanded-criteria donor does not confer a mortality advantage as compared to remaining on the waiting list or receiving a non-expanded-criteria donor at a later time. However, repeat transplantation with a non-expanded-criteria donor renders a survival advantage as compared to patients with failed kidney transplants who remain on the waiting list²¹.

Risks for sensitization: weaning immunosuppression and nephrectomy

There are competing schools of thought regarding the importance of transplant nephrectomy versus weaning of immunosuppression in promoting sensitization after allograft failure. As shown in figure 2, each of these management strategies is associated with advantages and disadvantages above and beyond their putative effects on sensitization.

What is the role of nephrectomy in contributing to alloantibody sensitization after transplant failure? Multiple studies have demonstrated an association with allograft nephrectomy and antibody sensitization after transplant failure²²⁻²⁴. We similarly found a high correlation in our patient population. Seventy-nine percent of patients were noted to be highly sensitized following nephrectomy for cause, compared to 38% of patients with no history of nephrectomy ($p < 0.001$)¹⁵.

However, there appears to be a complex interaction between weaning of immunosuppression, rejection, and nephrectomy in the development of sensitization after allograft failure. In our cohort, patients maintained on immunosuppression after failure did not require nephrectomy and were much less likely to become sensitized¹⁵. Alternatively, after weaning immunosuppression, 39/95 (41%) patients required nephrectomy early after failure because of symptomatic rejection. Many of these patients required admission to the hospital for fever, allograft pain, or hematuria. Given the known risk of antibody formation after acute rejection in a functioning transplant, it stands to reason that such symptomatic rejection after weaning immunosuppression may frequently lead to HLA formation independent of allograft nephrectomy²⁵.

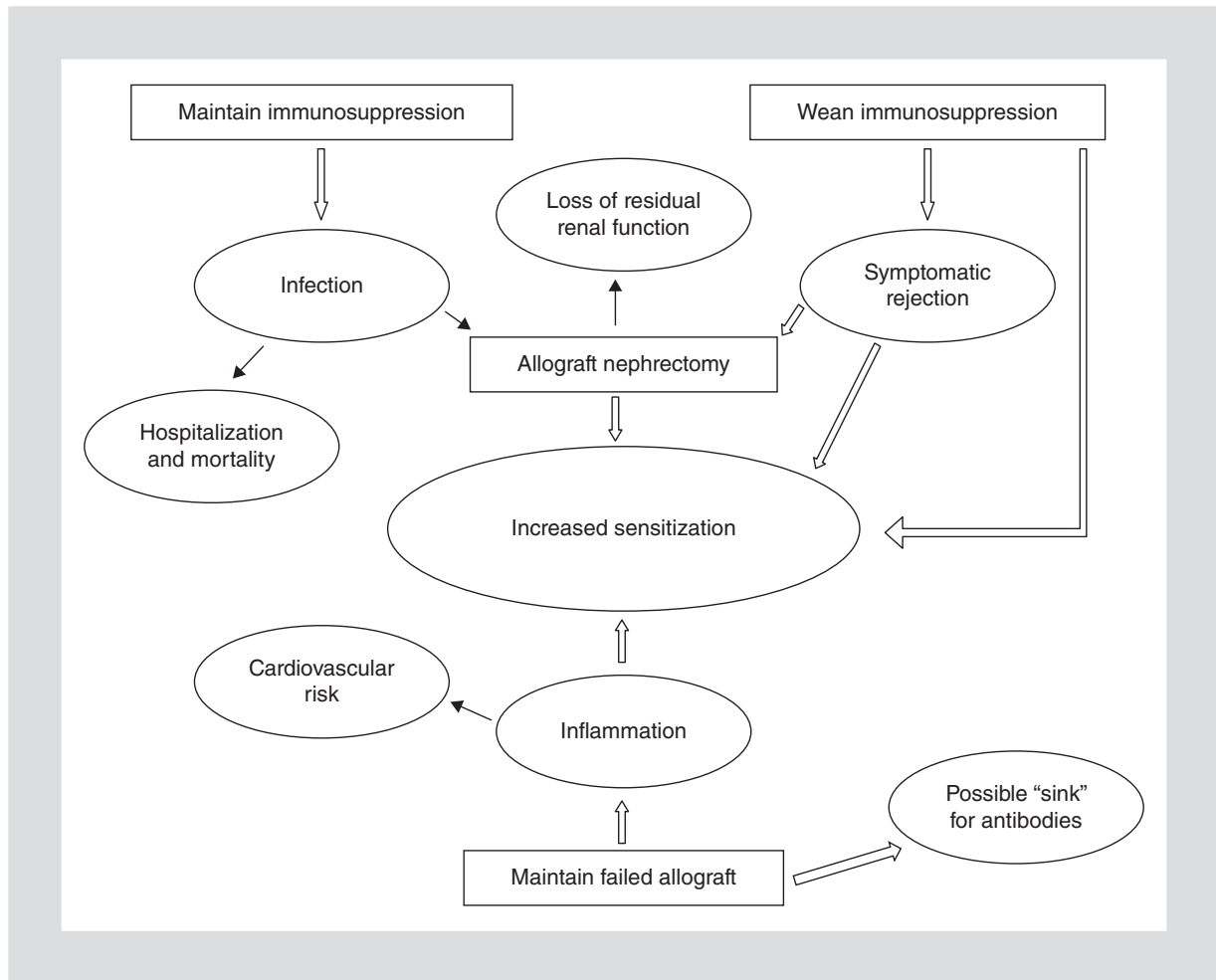


Figure 2. Risks for sensitization, management strategies (boxes), and their effects (ovals) that impact risk for sensitization. Open arrows represent direct relationships while solid arrows represent secondary consequences.

Indeed, we observed a high rate of antibody sensitization in patients who were weaned from immunosuppression even in the absence of nephrectomy (62% with a late class I or II PRA $\geq 80\%$). Patients who underwent nephrectomy did have a higher class I PRA in our cohort, but after controlling for immunosuppressive status and other factors, only HLA matching, African American race, and weaning of immunosuppression remained significant predictors of sensitization after failure¹⁵.

Data supporting a causal relationship between nephrectomy and sensitization come from the recent report of Del Bello, et al.¹⁴. They reported on 69 patients with failed allografts and compared rates of DSA formation between

those who underwent nephrectomy ($n = 48$) vs. those who did not ($n = 21$). All patients underwent withdrawal of immunosuppression at the time of failure, and some nephrectomies were undertaken for symptomatic rejection. However, 17 nephrectomies were undertaken electively as a new standard-of-care. In these 17 patients there was a rise in DSA within months of nephrectomy similar to the other nephrectomy group and to a greater extent than patients without nephrectomy. It should be noted that 14/48 (29%) patients undergoing nephrectomy required perioperative blood transfusion, although DSA was said to increase similarly in patients not transfused. The data suggested that nephrectomy itself, performed after weaning immunosuppression,

may stimulate antibody formation via antigenic exposure or may reveal antibodies previously absorbed by the allograft²⁶. Analogous to our PRA data described above, Del Bello, et al. found a low rate of DSA present at the time of failure (13%)¹⁴. The rate of DSA rose to approximately 50% in all patients independent of nephrectomy, again suggesting that the elimination of immunosuppression is the paramount factor leading to sensitization after transplant failure.

Do we dare keep patients on immunosuppressive therapy after kidney allograft failure? A single patient admission with dialysis catheter-related sepsis can be enough to discourage such a practice. In our experience, patients kept on immunosuppression after allograft failure were more likely to be admitted early after transplant failure with documented infection. Moreover, hospitalization with infection was associated with a 25% one-year mortality rate in 40 patients (unpublished data). A significant percentage of these patients were type I diabetics with functioning pancreas transplants who may have been particularly susceptible to infection. Regardless, catheter-related sepsis was the most common source of infection for all patients after allograft failure, reflecting the need for vigilant access planning for return to dialysis therapy by the transplant nephrologist. In contrast to patients with infection, patients admitted with symptomatic rejection had a low one-year mortality rate. Such patients improved after undergoing transplant nephrectomy, which tended to lead to a dramatic resolution of symptoms. Thus the risk of infection on immunosuppression must be balanced with the high risk of antibody sensitization after withdrawal.

Patients likely to be retransplanted quickly may be reasonable candidates for continued immunosuppression after transplant failure, and early relisting with preemptive retransplantation may avert the risk of sensitization altogether. An alternative approach may

be to perform an early allograft nephrectomy while still on immunosuppression. This strategy has been advocated in cases where kidney allograft survival is less than one year²⁷. It remains to be shown whether elective nephrectomy in patients on immunosuppression may prevent sensitization by removing the stimulus for late rejection after weaning. While this procedure could paradoxically increase DSA, it may be prudent to remove a retained allograft prior to immunosuppression withdrawal in any case. The retained kidney transplant has been identified as a source of inflammation, and markers of inflammation and anemia were shown to improve after allograft nephrectomy^{28,29}. In theory, elimination of inflammation and correction of anemia could be beneficial from a cardiovascular point of view. Indeed, one retrospective analysis suggested that transplant nephrectomy was associated with improved patient survival, possibly related to elimination of inflammation³⁰. However, that study may have been flawed by patient selection bias as patients undergoing transplant nephrectomy tended to be younger and to have fewer preexisting comorbidities compared to the group that did not undergo nephrectomy. One disadvantage of elective nephrectomy is loss of residual urine output with the subsequent need for tighter fluid restriction on dialysis (Fig. 2)

Treatment strategies in highly sensitized patients

Strategies such as desensitization protocols and paired kidney exchange programs have been utilized to expedite transplantation for highly sensitized patients.

It is intriguing to consider immunotherapy as a means to reduce preexisting antibody levels in sensitized patients. Agents such as intravenous immunoglobulin and plasmapheresis have shown modest benefit, albeit with significant expense^{31,32}. A recent report utilized mycophenolate sodium therapy and found

some reduction in PRA over time, although there was no control group for comparison³³. There was also some reduction in mean channel shifting on crossmatch, allowing a few patients to undergo live donor transplantation. Perhaps with more targeted B-cell therapies on the horizon, we may gain valuable agents in the armamentarium against sensitization. However, unless novel agents are developed to specifically reduce HLA antibodies, we may see a greater risk of infection associated with widespread antibody reduction.

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