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COMPREHENSIVE REVIEW

The failing kidney allograft: A review and recommendations for the care and management of a complex group of patients

Michelle Lubetzky[1] | Ekamol Tantisattamo[2] | Miklos Z. Molnar[3] | Krista L. Lentine[4] | Arpita Basu[5] | Ronald F. Parsons[5] | Kenneth J. Woodside[6] | Martha Pavlakis[7] | Christopher D. Blosser[8] | Neeraj Singh[9] | Beatrice P. Concepcion[10] | Deborah Adey[11] | Gaurav Gupta[12] | Arman Faravardeh[13] | Edward Kraus[14] | Song Ong[15] | Leonardo V. Riella[16] | John Friedewald[17] | Alex Wiseman[18] | Amtul Aala[7] | Darshana M. Dadhania[1] | Tarek Alhamad[19]

[1]Weill Cornell Medicine, New York Presbyterian Hospital, New York, New York

[2]Division of Nephrology, University of California Irvine, Orange, California

[3]Division of Nephrology and Hypertension, University of Utah, Salt Lake City, Utah

[4]Internal Medicine-Nephrology, Saint Louis University, St. Louis, Missouri

[5]Division of Transplantation, Emory University, Atlanta, Georgia

[6]Department of Surgery, Section of Transplantation, University of Michigan, Ann Arbor, Michigan

[7]Division of Nephrology, Beth Israel Deaconess Medical Center, Boston, Massachusetts

[8]Division of Nephrology, University of Washington and Seattle Children's Hospital, Seattle, Washington

[9]Division of Nephrology, Willis Knighton Health System, Shreveport, Louisiana

[10]Division of Nephrology and Hypertension, Vanderbilt University, Nashville, TN

[11]Division of Nephrology, University of California San Francisco, San Francisco, California

[12]Department of Internal Medicine, Virginia Commonwealth University, Richmond, Virginia

[13]SHARP Kidney and Pancreas Transplant Center, San Diego, California

[14]Department of Medicine, Johns Hopkins, Baltimore, Maryland

[15]Division of Nephrology, University of Alabama at Birmingham, Birmingham, Alabama

[16]Division of Nephrology, Massachusetts General Hospital, Boston, Massachusetts

[17]Division of Medicine and Surgery, Northwestern University, Chicago, Illinois

[18]Division of Nephrology, University of Colorado, Denver, Colorado

[19]Division of Nephrology, Washington University in St. Louis, St. Louis, Michigan

Correspondence
Michelle Lubetzky, Cornell Hospital, New York, NY.
Email: Mil9044@med.cornell.edu

The return to dialysis after allograft failure is associated with increased morbidity and mortality. This transition is made more complex by the rising numbers of patients who seek repeat transplantation and therefore may have indications for remaining on low levels of immunosuppression, despite the potential increased morbidity. Management strategies vary across providers, driven by limited data on how to transition off

Abbreviations: AZA, azathioprine; BTS, British Transplantation Society; CKD, chronic kidney disease; CNI, calcineurin inhibitor; cPRA, calculated panel reactive antibody; cRF, calculated reaction frequency; CRP, c-reactive protein; CTOT, Clinical Trials in Organ Transplantation; DAGL, dialysis after graft loss; DOPPS, dialysis outcomes and practice patterns study; DSA, donor specific antibody; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; FK, tacrolimus; GIS, graft intolerance syndrome; HD, hemodialysis; IS, immunosuppressive medications; KDIGO, Kidney Disease: Improving Global Outcomes; MMF, mycophenolate mofetil; NSAID, non-steroidal anti-inflammatory drugs; PD, peritoneal dialysis; PRA, panel reactive antibody; PRLT, preemptive relisting or transplantation; SF-36, Short Form 36; SRTR, Scientific Registry of Transplant Recipients.

Darshana M. Dadhania and Tarek Alhamad are co-senior authors for this manuscript.

immunosuppression as the allograft fails and a paucity of randomized controlled trials to support one approach over another. In this review, we summarize the current data available for management and care of the failing allograft. Additionally, we discuss a suggested plan for immunosuppression weaning based upon the availability of re-transplantation and residual allograft function. We propose a shared-care model in which there is improved coordination between transplant providers and general nephrologists so that immunosuppression management and preparation for renal replacement therapy and/or repeat transplantation can be conducted with the goal of improved outcomes and decreased morbidity in this vulnerable patient group.

KEYWORDS
clinical research/practice, immunosuppression/immune modulation, immunosuppressive regimens, kidney transplantation/nephrology, retransplantation

1 | INTRODUCTION

Returning to dialysis after transplantation is a complex transition. Currently, the number of patients returning to dialysis after a failed kidney transplant is steadily rising.[1] Furthermore, dialysis after graft loss (DAGL) is associated with increased mortality.[2] Patients with failed allografts may encounter difficulties in the transition of care back to referring nephrologists, who may not be familiar with the management and goals of immunosuppression after allograft loss. Unfamiliarity with immunosuppression management and communication barriers between transplant centers and general nephrologists resuming care may lead to unfavorable outcomes. Continuation of immunosuppressive therapies may be associated with increased infections and mortality.[3] Despite those risks, remaining on low dose immunosuppression may be associated with some benefits such as preventing sensitization, decreasing the risk of graft intolerance syndrome (GIS), and maintaining residual kidney function.

In this review, we will discuss the current challenges in the management of a patient with a failing allograft, including the risks and benefits of maintaining immunosuppression, management of rejection and graft intolerance syndrome, and propose a shared care model between transplant nephrologists and general nephrologists during this multi-faceted transition period. This manuscript is a work product of the American Society of Transplantation (AST) Kidney and Pancreas Community of Practice (KPCOP) "Kidney Recipients with Allograft Failure–Transition of Care" (KRAFT) work group.

2 | MATERIALS AND METHODS

The review paper was divided into six main topics. Each subtopic was approached and reviewed by three to four authors. The whole group met monthly, in addition to the subgroup meetings. A literature review was then performed, and references were saved in DropBox. Each subgroup performed a further literature review based on their specific topic. All members participated in monthly teleconferences to share the findings and discuss the key points. Three authors were responsible to merge the work of the six groups into one file. As transplant centers may have different protocols, a general consensus was taken during the monthly meetings in terms of management guidelines for the manuscript. All meetings were performed virtually. First and senior authors did a thorough review and outline of the topics covered, edited the manuscript, and created the final document.

3 | WHAT IS A FAILING ALLOGRAFT?

There is no consensus on the definition of a failing kidney allograft. Allografts with different degrees of dysfunction including chronic kidney disease (CKD) stage 4 and CKD stage 5 may be perceived as failing. However, many kidney allografts with stable but low baseline estimated glomerular filtration rate (eGFR), even below 20 ml/min per 1.73 m^2, might continue to function for years. Given the heterogeneity in this group of patients, there are many ways to define a failing allograft, and there may be some debate as to when the transition to a shared care model should optimally occur. We propose that the failing allograft should be broadly defined to include all of the following: stable but low allograft function, declining function (when there is irreversible and progressive decline in kidney function with anticipated allograft survival of less than 1 year), and return to renal replacement therapy. This characterization supplements the accepted definition of kidney allograft failure based on resumption of maintenance dialysis, new wait-listing, or repeat transplantation.[4]

4 | CURRENT PHYSICIAN PERSPECTIVES ON IMMUNOSUPPRESSION WITHDRAWAL

Management of immunosuppression in a patient with a failing allograft may vary based on a variety of factors including (1) physician training and experience (transplant versus general nephrology), (2) candidacy

for repeat transplant, (3) expected waiting time, and (4) availability of a kidney donor for re-transplantation. Prior assessments of the best approach to withdrawal of immunosuppression have been reported and, as expected, suggest a wide range of approaches but also signal that there needs to be improved management and care of this group of patients.[5,6] A survey of 93 kidney transplant centers in the United States was conducted in 2012 to examine differences in immunosuppression management in patients with failing allografts. The survey showed that 57.6% of respondents first stop antimetabolites (mycophenolate mofetil [MMF] or azathioprine [AZA]), 38% taper the calcineurin inhibitor (CNI) first, and 21.5% continue prednisone indefinitely. Forty percent responded that being listed for a re-transplantation was the single most important factor for continuing immunosuppression.[7] A more recent survey that was performed by the KRAFT workgroup in 2019 that included 101 respondents and found that the most common approach was withdrawal of the antimetabolite first (64.2%), whereas 9.4% would stop the CNI first, and 24% reported no unified protocol.[8] Overall, 57.4% providers felt that there was a need for a standardized approach to taper immunosuppression in the failing allograft.[8] Comparing the 2012 and 2019 surveys, the percentage of providers that would stop the CNI first decreased from 38% to 9.4%.[7] Several studies may have led to this change in practice. A retrospective single center study examined the impact of weaning of immunosuppression and reported that 0 out of 24 patients who were maintained on CNIs required transplant nephrectomy, compared with 41% of patients who were weaned off of immunosuppression.[9] The Clinical Trials in Organ Transplantation (CTOT)-09 study of patients with functioning transplants also reported data on immunosuppression withdrawal from very low risk patients that were weaned from CNIs at 6 months post-transplantation. In this study, MMF was maintained in all patients along with steroids. If the trough mycophenolic acid level was <1.9 ng/ml, the MMF dose was titrated upward as clinically tolerated in an effort to achieve a dose of at least 750 mg twice daily. The study was terminated early due to the high rates of donor specific antibody (DSA) development and acute rejections, lending further support that CNI is a vital medication to prevent DSA formation and acute rejection even after allograft failure.[10]

5 | FACTORS TO CONSIDER FOR THE MANAGEMENT OF IMMUNOSUPPRESSIVE MEDICATIONS

There are several factors that should be taken into consideration for adjusting immunosuppressive medications in the setting of a failing allograft (Figure 1). The benefits of continuing immunosuppression after allograft loss must be weighed against the risks. Below, we discuss three factors that can guide practitioners in balancing the

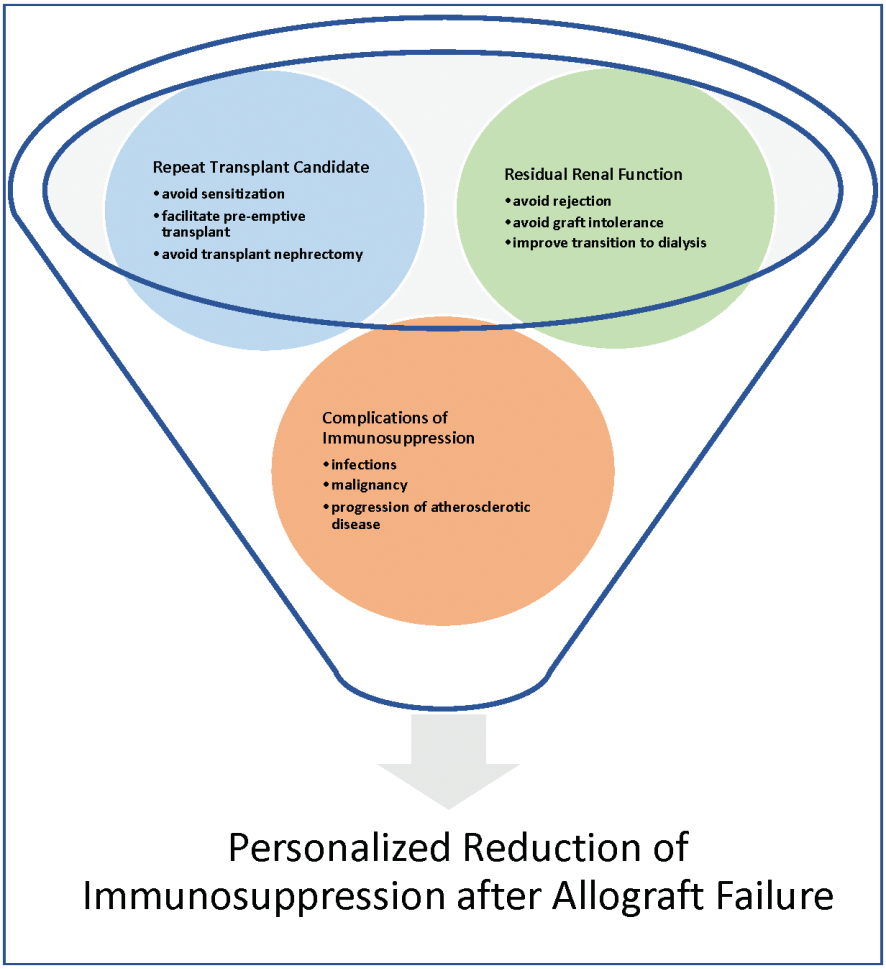

FIGURE 1 Juggling the complexities of a failing allograft. This figure highlights factors for clinicians to consider in immunosuppression management of the failing allograft

benefits and risks of maintaining immunosuppressive medications after allograft loss. These include (1) candidacy for subsequent kidney transplantation, (2) residual renal allograft function, and (3) potential unacceptable complications from an overimmunosuppressed state.[11]

5.1 | Candidacy for subsequent kidney transplantation

Although tapering or discontinuing immunosuppressive medications decreases risks from complications of an overimmunosuppressed state, these changes can potentially lead to the unintended consequence of becoming sensitized, which in turn decreases the opportunity to find acceptable donors for subsequent kidney transplantation. Therefore, there are some caveats that need to be considered for immunosuppressive medication management in patients with a failing allograft. Complete withdrawal of immunosuppression medications within a short period carries a notable risk of increased sensitization, which is important for patients who are listing for repeat kidney transplantation. A recent single center study that examined 41 patients with failing allografts between 2005 and 2015 showed that patients with immunosuppression cessation had a significant stepwise increase of the calculated reaction frequency (cRF)/calculated panel reactive antibody (cPRA) from 13% pre-weaning to 40% post-weaning and 62% post-cessation of immunosuppression medications with reduced chance of transplant.[12] A study by Augustine and colleagues demonstrated that in 119 patients with failing allografts, 56% of patients developed a high level of panel reactive antibodies (PRA) of ≥80%.[9] Multivariate analysis associated weaning of immunosuppression with a 14-times higher risk of sensitization.[9] Another retrospective study demonstrated that patients who remained on immunosuppression for more than 3 months after allograft failure had significantly less sensitization than those whose immunosuppression was withdrawn within 3 months, without any adverse safety signals.[13] It should be noted, however, that there is a small subset of patients with a very high PRA who may benefit from an even further increase in PRA given the new kidney allocation system. Such patients should be evaluated on a case-by-case basis. All of these factors need to be taken into consideration, especially if the patient is a candidate for re-transplantation and if remaining on immunosuppression does not pose significant risk of morbidity. Particularly, this approach is important for patients who are anticipated to receive a subsequent kidney transplantation in a short period of time, such as those with potential living donors or those who reside in locations with relatively short waiting times for deceased donor transplantation (although there is no strict time point, a relatively short wait time is one that is anticipated to be less than 1 year). Additionally, patients with a history of graft loss due to polyomavirus BK who plan to receive a repeat transplant need to be closely monitored for clearance of BK viremia in anticipation of repeat transplant and may require more aggressive decrease in immunosuppression medications.[14]

5.2 | Residual allograft function

Maintaining residual renal function by continuing maintenance immunosuppression may have theoretical benefits, although it has not been shown that continuing immunosuppression leads to preservation of residual renal function. However, in a study by Jassal et al., a Markov model suggested an associated small survival benefit with continuing immunosuppression when compared with withdrawal in all patients with allograft loss who returned to peritoneal dialysis and had some residual renal function.[15] The model suggested that life expectancy was increased from 5.3 to 5.8 years in patients who remained on immunosuppression.[15] In their model, there was additional survival benefit for higher levels of preserved GFR in kidney transplant patients who returned to DAGL. Therefore, although patients who return to DAGL are at high mortality risk, for patients with residual renal function, there may be survival benefit from remaining on immunosuppression.

5.3 | Potential complications from overimmunosuppressed state: mortality, infection risk, and malignancy

Mortality risk is extremely high during the first few months after transition to dialysis in patients with or without kidney transplants.[2,16] In the first week and the first month after allograft failure, the mortality risk is more than 13 times and almost 7 times higher in patients with transplant failure compared with their transplant naïve counterparts.[2] A large meta-analysis also confirmed that the first year on dialysis shows significantly higher mortality in failed transplant recipients compared with subsequent years.[17] The mortality risk of patients with transplant failure is quite different in different countries.[18] Canadian Dialysis registry data from the early 1990s indicated similar mortality risk in transplant-naïve and transplant failure patients.[19] An analysis from the French Renal Epidemiology and Information Network similarly demonstrated equivalent survival between the two groups.[20] By contrast, data from US Dialysis Outcomes and Practice Patterns Study (DOPPS)[21] and Scientific Registry of Transplant Recipients (SRTR)[2] indicate higher mortality risk in transplant failure patients when compared with transplant-naïve, but transplant-eligible patients. The reasons for this increased mortality are unclear, but likely include potential side effects from immunosuppression such as infection and malignancy, as well as the possible increased cardiac and metabolic risks from specific immunosuppressive agents. There is a need for national research to help clarify which modifiable and non-modifiable risk factors are associated with mortality risk with return to dialysis and which patients may benefit from either more rapid withdrawal of immunosuppression or conversely remain on low-dose immunosuppression. A potential group of patients to determine effects of long-standing immunosuppression after a failed allograft would be those with dual-organ transplants, where the kidney transplant has failed, but the patient remains

on immunosuppression for protection of an additional organ (pancreas and liver). Such patients may provide improved insight into this important issue.

It is well known that immunosuppression in the setting of transplantation carries an increased risk of both infections and malignancies. Infections have been shown to be strongly associated with death after allograft loss, and several studies illustrate the increased risk of infection when returning to dialysis.[3] A retrospective cohort study of 197 patients demonstrated that patients who remained on immunosuppression after returning to dialysis had 3.4-times the risk of infection (95% CI 2.5–4.5) as the patients who were off immunosuppression.[22] This study also demonstrated that remaining on immunosuppression was associated with a similar increased risk of mortality (OR 3.4, 95% CI 1.8–6.3). This study, however, was limited in that it represented patients transplanted from 1975 to 1995 and may not represent the most current immunosuppressive regimens used today. Additionally, in this cohort, most patients were offered nephrectomy when their allograft failed, and thus, sicker patients (who did not undergo nephrectomy) likely were maintained on immunosuppression longer. The follow up period was also shorter in those who remained on immunosuppression. Other studies have found increased rates of sepsis in the first months after returning to dialysis. Johnston et al. examined sepsis rates among three groups: transplant recipients within 3–6 months after transplantation, new dialysis patients without prior transplant, and kidney transplant patients returning to DAGL and demonstrated that during the same time period sepsis rates were 5.4, 7.8, and 19.7 events per 100 patient years, respectively.[23] Similarly, another study by Woodside et al. demonstrated that in patients who remained on immunosuppression in the first 6 months after allograft failure had significantly higher rates of documented infections (88% of patients had documented infection as compared with only 38%, $p < .001$).[24] For the patients with documented infections, mortality rates were also significantly higher.[24]

Malignancy after return to dialysis is less well described. In a large retrospective study of over 8000 Australian kidney transplant recipients, rates of Kaposi sarcoma, non-Hodgkin's lymphoma, lip cancer, and melanoma were all higher during transplantation than after return to DAGL; however, rates of leukemia, lung cancer, kidney, urinary tract, and thyroid cancers were significantly higher in patients with failed transplants who return to DAGL.[25] The rates were highest with thyroid cancers, with an incidence rate ratio of 6.7. The authors concluded that malignancies, especially those with potentially infectious origin, seemed to decrease with return to dialysis; however, cancers associated with end-stage kidney disease continued to have increased rates after return to DAGL. Of note, there was no data on how immunosuppression was tapered in these patients and if patients who return to dialysis were on any immunosuppression. Currently, guidelines outlined by the British Transplant Society (BTS) maintain that in patients with a history of skin cancers, immunosuppression should be withdrawn upon return to DAGL.[26]

6 | POTENTIAL IMMUNOSUPPRESSION MANAGEMENT FOR FAILING ALLOGRAFT

In summary, for patients with an anticipated long waiting time for subsequent kidney transplantation but still with residual renal allograft function, we recommend that immunosuppressive medications may be continued with close follow up and management at the transplant center. Patients who are not candidates for re-transplantation may continue immunosuppressive medications as long as residual renal allograft function remains, and there are no significant complications to overimmunosuppression. In anuric kidney transplant recipients returning to dialysis after graft loss with a long anticipated waiting time for subsequent kidney transplantation, tapering off all immunosuppressive medications or keeping immunosuppression at a minimum should be considered. Our recommended clinical and multi-disciplinary management of the failing allograft are shown in Table 1.

In terms of choice of agents to withdraw and schedule of tapering, based on the currently available data, we recommend that anti-proliferative agents such as MMF or AZA should be stopped before other agents as patients start dialysis. Next, we recommended a personalized approach to tapering the CNI based on factors such as perceived infection risk, residual renal function, availability of repeat transplantation, and expected waiting time. There is little guidance as to the tapering of prednisone. We recommend tapering to the minimal dose necessary over the first 6 months after graft failure. Decision and timing of prednisone withdrawal should be done slowly and based upon individual needs of each patient. mTOR inhibitors can be tapered slowly in a similar manner as CNI; however, much less data exists on the best approach to withdrawal of this agent. This approach is similar to that taken by the British Transplantation Society, which recommends tailoring and tapering of immunosuppression based upon availability of repeat transplantation within 1 year, infection and cancer risk, while monitoring for the development of sensitization.[26] The British Transplantation Society also recommends the use of “low clearance transplant clinics” (LCTC) or “failing allograft clinics” where available to help guide the transition for repeat transplant or to go back to dialysis. A proposed strategy to manage immunosuppressive medications for kidney transplant recipients with a failing allograft is shown in Figure 2 and described in the subsequent paragraphs. Given the lack of data on withdrawal of newer agents such as belatacept, we have not included it in this flowchart.

6.1 | Failed allograft with residual renal function (CKD 5)

For patients with a failing allograft who have residual renal function (not yet requiring dialysis), the goal of continued immunosuppression is to maintain the urine output. As discussed above, CNI is the main immunosuppressive medication to minimize the risk of new DSA

TABLE 1 Management of the failing allograft

	Candidate for re-transplant	Not a candidate for re-transplant
Stable transplant function, eGFR >20 cc/ml/m^2	• Close monitoring of levels of immunosuppression and side effects • Optimize CKD management including BP control, anemia, proteinuria, secondary hyperparathyroidism • Routine malignancy surveillance	• Establish joint management approach with general nephrologist • Continue close monitoring at transplant center • Close monitoring of levels of immunosuppression and side effects • Optimize CKD management including BP control, anemia, proteinuria, secondary hyperparathyroidism • Routine malignancy surveillance
Failing transplant with declining function	• Refer for re-listing when eGFR approaches 20 • Establish baseline PRA value • Living Donor Champion • Optimize wait-list management • Discuss options for decreasing time to transplantation • Referral for vascular access if there is no living donor • Referral to General Nephrology for preparation for dialysis • Consider reduction in immunosuppression to decrease side effects and complications • Maintain CNI trough in the low therapeutic range	• Establish vascular access • Continue transition of care to general nephrology • Coordinate reduction in immunosuppression over time • Reduction in anti-metabolite by 50% • Maintain CNI ± low dose prednisone • Monitor for graft intolerance syndrome
Failed allograft with return to dialysis[a]	• Primary management with general nephrology • Monitor CPRA every 3–6 months • Taper of immunosuppression: • Reduction in anti-metabolite by 50%, maintain CNI ± low dose prednisone • 3 months post dialysis initiation: stop anti-metabolite, maintain low dose CNI ± low dose prednisone • 6 months post dialysis initiation: reduce CNI by 50% ± low dose prednisone • 9 months consider additional reduction in CNI or maintenance of prednisone 5 mg • 12 months consider cessation of all immunosuppression if no signs of graft intolerance syndrome and no significant increase in CPRA value • Continue to monitor for sensitization while wait-listed and signs of toxicity from immunosuppression	• Primary management with general nephrology • Taper of immunosuppression: • Stop anti-metabolite • Taper CNI by 50% • Maintain on low dose CNI and/or low dose prednisone therapy for 6–12 months in coordination with transplant nephrology • Monitor for graft intolerance syndrome • Monitor patient every 3–6 months until patient is off immunosuppression

[a]These immunosuppression management strategies represent a general guideline from the consensus committee; however, all changes in immunosuppression and the decision to stop all immunosuppression should be done on an individualized basis in consideration of balancing the risks of sensitization and potential complications from prolonged immunosuppression and in coordination with both transplant and general nephrology.

formation as well as acute and chronic rejection of the allograft. We recommend tapering off MMF first followed by steroids. CNIs should be lowered to minimize potential complications from excess immunosuppression but still maintained to suppress immune reactivation and maintain urine output.

6.2 | Failed allograft without residual renal function (CKD 5 on dialysis)

Patients whose allografts decline to the point that they need dialysis initiation eventually progress to having low residual renal urine output. Similar to patients who do not require dialysis, the goal of immunosuppressive medication management in patients who need dialysis is to maintain residual renal allograft function as long as reasonable. However, the overall dose of immunosuppression may be higher or lower depending on not just urine output but also other complications from the failing allograft.

6.3 | Graft intolerance syndrome on dialysis

Patients who need dialysis initiation while requiring a high level of immunosuppression such as those with acute rejection or GIS should maintain the high level of immunosuppression for acute management of these complications.Some cases may benefit from a pulse of intravenous steroids. Subsequently, MMF should be tapered off, whereas steroids and CNIs are maintained at moderate doses before being tapered down.

The above recommendations are meant to serve as a guide. Tapering of immunosuppression should be personalized as sequences and dosage of each immunosuppressive medication may

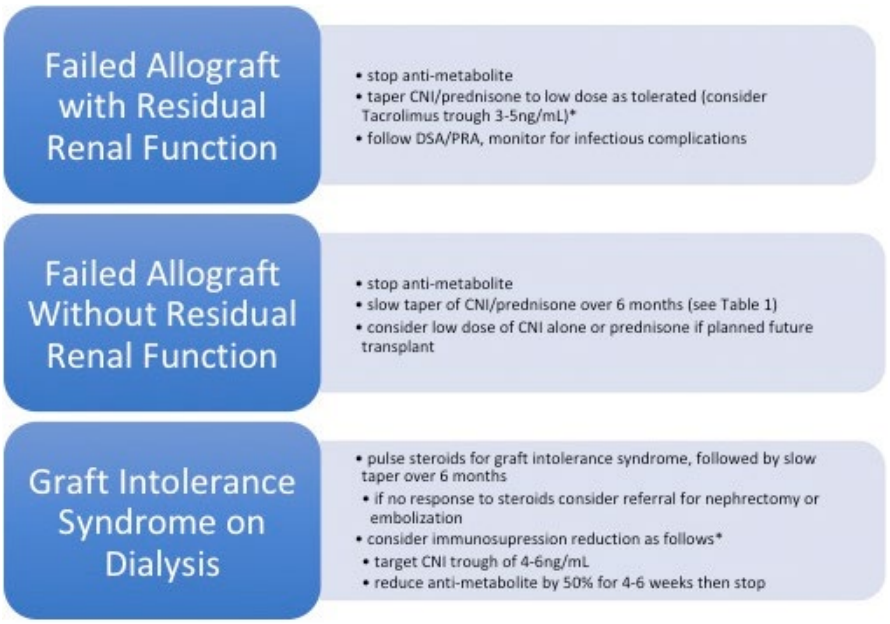

FIGURE 2 Suggested immunosuppression tapering based on allograft function. This figure outlines immunosuppression management strategies based upon allograft function, including failed allograft with residual function, failed allograft without residual function, and failed allograft with graft intolerance syndrome

TABLE 2 Symptoms and signs of graft intolerance syndrome

Common clinical findings	Less common clinical findings
• Fever	• Malaise
• Gross hematuria	• Weight loss
• Allograft enlargement and localized edema	• Hematological findings: thrombocytopenia, ESA resistant anemia
• Allograft tenderness	• Elevated inflammatory markers: ferritin, CRP, ESR

Abbreviations: CRP, C-reactive protein; ESA, erythropoietin stimulating agents; ESR, erythrocyte sedimentation rate.

vary depending on patients' conditions during the period of allograft failure including their dialysis requirement, current immunosuppressive medication regimens and their side effects, and complications from the failing allograft.

7 | SIGNS AND SYMPTOMS OF REJECTION AND GRAFT INTOLERANCE SYNDROME

Immunosuppression withdrawal may result in a state of chronic inflammation related to the rejection of the failed allograft left in situ. This chronic inflammatory state due to immunological intolerance is referred to as GIS.[27] GIS or symptomatic rejection has been reported in up to 30%–50% of patients within 1 year of allograft failure and dialysis initiation in some series, regardless of the immunosuppression withdrawal protocol used.[28] Fever, gross hematuria, allograft enlargement, or graft tenderness are all well recognized symptoms associated with GIS.[24,28,29,30,31,32,33] Other subtle findings have also been reported in this cohort (Table 2).

GIS presentation varies widely, making the diagnosis challenging. Infections or malignancies need to be ruled out before the diagnosis of GIS is made. A single center study highlighted a 7-fold higher risk of hospital admissions in the setting of febrile illnesses without an identified infection source, within 6 months following immunosuppression withdrawal.[24]The majority of patients with failed grafts presenting with fever after immunosuppression weaning had rejection as their source of fever (62%); however, it is important to note that not all fevers in patients with a failing allograft are due to rejection. In failed allograft patients who presented with fever, 38% were found to have an infection, with the most common infection being associated with a dialysis catheter.[24]

8 | MEDICAL MANAGEMENT OF GRAFT INTOLERANCE SYNDROME

Options for medical management of symptomatic rejection of the failed allograft are relatively limited. In adults, high dose steroids are

the mainstay for treatment of symptomatic rejection. The steroid dosage and duration for treatment vary across transplant centers in the United States. The number of cycles of pulse steroids that should be attempted prior to proceeding with a surgical intervention is unclear. In the absence of guidelines, the decision is left to the discretion of individual transplant practitioners. Despite medical management, most individuals with symptoms ultimately require surgical intervention.

9 | SURGICAL MANAGEMENT OF A FAILED ALLOGRAFT: RISKS, BENEFITS, AND IMPACT ON HLA SENSITIZATION

When options for medical management of a symptomatic failed allograft have been exhausted, surgical management with transplant nephrectomy or graft embolization should be considered. The most significant indications for transplant nephrectomy are hemorrhage (ongoing hematuria, or more urgently, intra-abdominal bleeding), unrelenting pain, malignancy, or a persistent source of sepsis.[28,34] Early post-transplant renal artery/vein thrombosis or graft infarction prompts allograft removal in the vast majority of cases given the increased risk for allograft vessel or parenchymal rupture.[35] Other, less salient, but important arguments for surgical intervention include opportunities to minimize immunosuppression (and its side effects, i.e., infectious or neoplastic risks), HLA sensitization, and recurrent hospital admissions.[24,28,36] Operative mortality from transplant nephrectomy varies widely in the literature, with some variance based on whether the nephrectomy was done prophylactically or for worsening clinical status.[27]

Allograft nephrectomy has been associated with improved mortality,[37] suggesting that avoidance of the chronic inflammatory state from the failed allograft and/or the potential side effects of prolonged immunosuppression required to avoid acute on chronic rejection, such as infection, are beneficial. There is conflicting literature about the effects of transplant nephrectomy on sensitization. In the majority of these studies, transplant nephrectomy is often performed after the failed kidney has suffered acute and/or chronic rejection due to weaning of immunosuppression, which results in the sensitizing event occurring prior to the nephrectomy. [9,23,24,28,38,39] Furthermore, patients with end-stage kidney disease may receive transfusions causing additional sensitizing events, either as part of the transplant nephrectomy (which can be a blood operation due to chronic allograft scarring and acute inflammation from GIS), in response to anemia driven by CKD and/or a chronic inflammatory state from the failed kidney, or for other medical conditions after the surgical hospitalization.[36] Few studies have reported prophylactic nephrectomy prior to immunosuppression weaning, although these offer support for the hypothesis that it is the events around the nephrectomy, rather than the nephrectomy itself, that cause sensitization to HLA antigens not associated with the failed allograft.[40] Given that the goal of prophylactic nephrectomy is to avoid both the risks of chronic immunosuppression and chronic inflammation, it is reasonable that such nephrectomies occur relatively soon after dialysis initiation, while still on full (or near-full) maintenance immunosuppression, to avoid the risk of acute rejection.[27] However, prophylactic transplant nephrectomy can deprive the patient of beneficial residual renal function that provides a survival benefit on dialysis and this consideration should be weighed in the non-oliguric patient.[41]

There are a number of surgical considerations for transplant nephrectomy, depending on indication, current inflammatory state, failed allograft perfusion or ischemia, anatomic location, and future transplant candidacy. It is vital to appreciate that, even though the allograft has failed, most failed allografts still have significant blood flow and can be the source of significant hemorrhage either during nephrectomy or with spontaneous allograft rupture. Most transplant nephrectomies are performed for symptomatic or problematic failed kidney transplants. The approach to removing these kidneys is often subcapsular, with vascular control and ligation of the renal vessels in the renal hilum, allowing a margin of safety for the recipient iliac vessels, as well as adherent peritoneal structures such as bowel.[42] In the case of allograft rupture, emergent exploration and/or embolization is warranted, depending on the level of acuity and local resources. Transplant nephrectomies for oncological purposes can be more complicated, as a more complete resection is desirable, but often difficult, because transplant kidneys are often surrounded by scarring from the transplant engraftment that a native kidney does not have. Figure 3 illustrates the considerations for surgical management of the allograft with graft intolerance as well as gross pathology and histology of a nephrectomy specimen.

The timing of transplant nephrectomy for a failed allograft with acute-on-chronic rejection requires clinical judgment and can be controversial. If the allograft has significant swelling, it is at risk of rupture and should be removed. There can be significant scarring and inflammation around a failed allograft, which is difficult to predict, resulting in a highly variable level of intraoperative blood loss and risk to nearby structures such as bowel and the iliac vessels. Because of this unpredictable risk, if the failed allograft is not overly edematous, symptoms are reasonably controlled, and there is not refractory anemia or risk of transfusion, pulse steroids can be given to "cool down" the "hot kidney" and allow nephrectomy under more controlled conditions. A course of steroids reduces inflammation and may reduce risk of intraoperative hemorrhage.

Embolization of the allograft renal artery is an alternative to transplant nephrectomy. Embolization is accomplished by the injection of ethanol followed by stainless steel coils into the branches of the renal artery.[43] Data on the efficacy and safety of this procedure compared with graft nephrectomy are limited, but a recent systematic review and meta-analysis suggested that renal artery embolization may pose lower risks to patients with a failed allograft.[44] In this review, renal artery embolization successfully treated graft intolerance syndrome in the majority of cases, but 20% required follow-up nephrectomy. Mortality associated with renal artery embolization was much lower at 0.1%, compared with 4% in patients who underwent nephrectomy. Procedure-related morbidity was likewise much lower with renal artery embolization.[43,45] Another study by Al Badaai and colleagues demonstrated less complications and an 84% success rate with embolization

in this setting over nephrectomy.[31] There are some caveats to this approach; allograft renal artery embolization can be complicated by a post-embolization syndrome, characterized by fever 24–48 h after the procedure in the absence of infection. The use of pulse steroids pre-procedure may mitigate the risk of this syndrome.[45]

Overall, the decision for medical versus surgical management of failed allograft should be individualized based on the severity of patient symptoms, potential for medical management and future risk of sensitization.

10 | THE ROLES OF THE TRANSPLANT PROGRAM AND GENERAL NEPHROLOGISTS

Efficient transitions of care between different providers are an ongoing challenge in CKD.[16] After the first 6 –12 months of transplantation, referring nephrologists are usually encouraged to take responsibility and participate in the care of their transplant recipients.[46] The timing of this transition is generally based on local expectations, patients' needs and the transplant program's relationship with the referring provider. When the allograft begins to fail, there are many more opportunities and need for improved communication and coordination of care. Given the increased mortality seen in patients returning to DAGL, it is imperative that referring and transplant nephrologists work together to improve these transitions. Unfortunately, many patients with a failing allograft are not optimally prepared for dialysis, with 65% resuming dialysis using a central venous catheter based on a large registry study.[47] Data are similar to what was shown in a Canadian study where despite being overall younger and healthier, most transplant patients did not have AV access placed prior to starting dialysis.[48] The use of central venous catheters increases the risk of infection, particularly in the setting of ongoing immunosuppressive medications.[24] Additional registry data have demonstrated benefit for later initiation of dialysis in patients with failed allografts.[1] Dialysis modality is also an important consideration. A study by Perl and colleagues demonstrated no difference between outcomes in patients who returned to dialysis with either peritoneal or hemodialysis.[49] Given that both are viable options, this is another opportunity where transplant nephrologists can coordinate with general nephrologists to ensure all dialysis modalities are available. Similar to non-transplant settings, general and transplant nephrologists should coordinate so that patients are followed for clinical indications for dialysis initiation as well as timely evaluation for dialysis access and CKD follow-up care.

11 | REFERRAL FOR RE-TRANSPLANTATION: EVALUATION, EDUCATION, AND COORDINATION WITH GENERAL NEPHROLOGY

Acceptance that an allograft is failing can be a difficult process for patients and transplant professionals, as it requires a change in focus from preservation of graft function to optimal transitions of care, including preparation for dialysis or re-transplantation. Evans et al. recently described creation of low clearance transplant clinics (LCTC) to facilitate such transitions, using an eGFR threshold of <30 ml/min per 1.73 m^2 for referral.[50] Patients in the LCTC were primarily managed by nephrologists but also had access to transplant nurses specifically trained in the management of the complications of advanced CKD, renal dieticians, and specialist renal pharmacists. The authors found that that dedicated LCTC improved renal replacement counseling and re-transplant evaluation, although re-transplant rates during the study period were not impacted. The BTS endorses provision of access to a LCTC for all patients with a failing allograft.[26]

Previous authors have recommended timely attention to referral of the patient with a failing allograft for re-transplantation—for example, when allograft GFR is between 25–30 ml/min per 1.73 m^2, to facilitate preparation for listing when the GFR reaches 20 ml/min per 1.73 m^2.[51] We recommend all patients who do not meet clear exclusion criteria for repeat transplant be referred for evaluation when their eGFR approaches 20 ml/min per 1.73 m^2. Timely referral is vitally important, as the time to re-transplantation may be longer than for first time transplant candidates due to sensitization, which can increase the complexity of identifying a compatible organ. That said, a limitation to this approach is that all insurance

FIGURE 3 Management of graft intolerance syndrome and pathology. (A) Symptoms of graft intolerance syndrome signaling the need for allograft nephrectomy. (B) Gross pathology of nephrectomy specimen showing thrombosis and necrosis (image courtesy of Dr. Surya Seshan Weill Cornell Medical College Division of Pathology). (C) Kidney allograft biopsy core with diffuse interstitial inflammation in a background of severe global glomerulosclerosis and interstitial fibrosis (image courtesy of Dr. Parker Willson Washington University School of Medicine Division of Pathology)

TABLE 3 Summary and recommendations for future study

Take home points	Areas for future research/study
1. Early recognition of kidney transplant recipients with failing allograft is critical to appropriately plan for transition of care, dialysis initiation, and listing for re-transplantation.	• Create composite score of failing allograft to predict kidney allograft failure and graft intolerance syndrome. • The composite score could be composed of clinical variables routinely used in clinical practice, biomarkers, or gene signatures.
2. The top three factors determining immunosuppressive medication management for patients with failing kidney allograft are candidacy for subsequent kidney transplantation, residual kidney allograft function, and complications from an overimmunosuppressed state.	• Identify clinical outcomes and survival benefits of maintaining residual kidney allograft function and risks for complications of continued immunosuppressive medications during and after failing kidney allograft.
3. Optimal practice for tapering immunosuppressive medications is unknown. Recommendation is to taper off mycophenolate mofetil (MMF) first. Lowering of CNI trough and tapering of steroids should to be individualized to minimize potential complications from overimmunosuppression but still suppress immune reactivation and maintain urine output.	• Examine the appropriate doses, trough levels, and durations of tapering immunosuppressive medications to preserve residual kidney allograft function, prevent allosensitization, and avoid overimmunosuppression. • Determine the clinical significance, utility, and frequency of HLA monitoring during process of failing allograft and while waiting for re-transplantation. • Data are needed to explore the best practice for tapering of newer immunosuppression agents such as belatacept.
4. Graft intolerance syndrome commonly presents with gross hematuria and allograft tenderness. Treatment consists with pulse steroids followed by steroid taper.	• Identify risk factors for graft intolerance syndrome.
5. Patients with recurrent graft intolerance syndrome are managed by graft nephrectomy or embolization.	• Examine surgical therapy including indications and appropriate time for transplant nephrectomy or allograft embolization.
6. Care collaboration between transplant programs and general nephrologists improves patient outcomes in terms of dialysis transition and timely referral for re-transplantation.	• Determine factors that affect collaboration of care between the transplant program and general nephrologists during and after failing kidney allograft.

carriers may not cover evaluation at this stage of GFR; this should be considered at the time of referral and represents an area for future advocacy within the transplant community. It is also important to state the equation used for estimating GFR may differ from center to center and the basis for the use of race in the equation for estimating GFR is not well defined (M. D. Doshi, N. Singh, B. E. Hippen, et al., unpublished data, 2021).[52] The use of the Black race variable in eGFR equations may result in delayed referral for re-transplantation and thus should be given careful consideration. Additionally, some patients, particularly those with early graft failure in their original transplant, may have increased risk of graft failure in re-transplantation and this should be reviewed by a multidisciplinary team.[53] The 2014 BTS "Guidelines for the Management of Failing Kidney Transplant" recommend that patients suitable for re-transplantation be evaluated for repeat transplantation when graft survival is anticipated to be less than 1 year, in an effort to facilitate re-transplantation when eGFR falls to <10–15 ml/min per 1.73 m^2,[26] ideally before the need for dialysis initiation.

In addition to pursuit of listing for deceased donor transplantation, patients with a failing allograft should be educated about the benefits of living donor transplantation as a re-transplantation strategy. If no living donors are available, they should be educated about resources such as living donor champion programs, to help in finding living donors and overcome some of the barriers that exist to living donor transplantation. Again, because the presence of preformed anti-HLA antibodies may challenge identification of a biologically compatible living donor, these discussions should include education on the option of kidney-paired donation.[54] Such

practice is consistent with a general recommendation of the 2020 Kidney Disease: Improving Global Outcomes (KDIGO) transplant candidate guideline to refer potential kidney transplant candidates for evaluation at least 6–12 months before anticipated dialysis initiation to facilitate identification and evaluation of living donors and plan for possible pre-emptive transplantation.[55]

The importance of timely education and referral is exemplified in recent data demonstrating variation and disparities in rates of preemptive relisting or transplantation (PRLT) after allograft failure. Based on analysis of US transplant registry data from 2007 to 2018, Schold et al. found that the overall incidence of PRLT was 15% and rates of relisting declined over time.[56] PRLT was significantly *lower* among patients who were African American, Hispanic, male, older, obese, publicly insured, had lower educational attainment, were diabetic, had longer dialysis time prior to initial transplant, shorter graft survival, longer distance to transplant center, and resided in "distressed" communities. Rates of PLRT varied substantially across transplant centers (10th percentile, 6%; 90th percentile, 24%). During re-listing, consideration for patients that may need evaluations for extra-renal transplants can also occur. Overall improved coordination between transplant and referring nephrologists is an integral part to managing the failing allograft and ensuring that both CKD management, initiation of dialysis and timely referral for re-transplantation are patient-centered and best address the needs of each individual patient.

12 | FUTURE DIRECTIONS

In this review, we presented data on immunosuppression management of the failing allograft and discuss the risks of sensitization, infection, morbidity and mortality in this population. Yet in evaluating the current literature, there are many knowledge gaps and areas for future study to best manage this complex transition. A summary of our review and areas for future research are outlined in Table 3.

13 | CONCLUSIONS

The failing allograft can pose a management challenge for both the transplant and referring nephrologists. Return to dialysis is associated with increased mortality due to multi-factorial causes. Overall, we recommend a coordinated approach between transplant and general nephrologists to tailor immunosuppression weaning to the individual needs of each patient, minimize sensitization in candidates for repeat transplantation, improve management of GIS, and to better prepare patients for return to dialysis and/or re-transplantation, with a focus on maximizing opportunities for pre-emptive re-listing and repeat transplantation..

DATA AVAILABILITY STATEMENT

Data sharing not applicable.

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ORCID

Michelle Lubetzky https://orcid.org/0000-0003-1076-7953
Ekamol Tantisattamo https://orcid.org/0000-0003-0883-6892
Miklos Z. Molnar https://orcid.org/0000-0002-9665-330X
Krista L. Lentine https://orcid.org/0000-0002-9423-4849
Arpita Basu https://orcid.org/0000-0002-0533-4582
Ronald F. Parsons https://orcid.org/0000-0002-9243-1582
Kenneth J. Woodside https://orcid.org/0000-0002-7495-3758
Christopher D. Blosser https://orcid.org/0000-0001-8368-6682
Neeraj Singh https://orcid.org/0000-0002-3814-1920
Beatrice P. Concepcion https://orcid.org/0000-0002-0576-6756
Gaurav Gupta https://orcid.org/0000-0003-1919-1970
Song Ong https://orcid.org/0000-0002-4972-0776
Leonardo V. Riella https://orcid.org/0000-0002-7636-3196
John Friedewald https://orcid.org/0000-0002-9344-9928
Alex Wiseman https://orcid.org/0000-0002-8619-0938
Darshana M. Dadhania https://orcid.org/0000-0002-7973-1521
Tarek Alhamad https://orcid.org/0000-0003-4289-0817

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