Challenges in the Management of the Kidney Allograft: From Decline to Failure: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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ABSTRACT

In March 2022, KDIGO held a virtual controversies conference to address the important but rarely examined phase during which the kidney transplant is failing or has failed. In addition to discussing the definition of the failing allograft, four broad areas were considered in the context of a declining functioning graft: prognosis and kidney failure trajectory; immunosuppression strategies; management of medical and psychological complications, patient factors; and choice of kidney replacement therapy or supportive care following graft loss.

Identifying and paying special attention to individuals with failing allografts was felt to be important in order to prepare patients psychologically, manage immunosuppression, address complications, and prepare for dialysis and/or re-transplantation, or transition to supportive care. Accurate prognostication tools, though not widely available yet, were embraced as necessary to define allograft survival trajectories and the likelihood of allograft failure. The decision of whether to withdraw or continue immunosuppression after allograft failure was deemed most appropriately based on risk-benefit analysis and likelihood of re-transplantation within a few months. Psychological preparation and support was identified as a critical factor in patient adjustment to graft failure, as was early communication. Several models of care were noted that enabled a medically supportive transition back to dialysis or re-transplantation. Emphasis was placed on the importance of dialysis access readiness before initiation of dialysis in order to avoid use of central venous catheters. The centrality of the patient to all management decisions and discussions was prioritized as paramount. Patient activation, which can be defined as engaged agency, was seen as the most effective way to achieve success. Unresolved controversies, gaps in knowledge, and areas for research were also stressed in the conference deliberations.
THE FAILING KIDNEY ALLOGRAFT—DETERMINING PROGNOSIS AND KIDNEY FAILURE TRAJECTORY

Defining the failing allograft

What does it mean to have a failing allograft and how should it be defined? These concepts were debated by participants in the controversies conference as was the concern that using the term “failing” may unintentionally distress patients. Nevertheless, as better terminology was not found, “failing” was kept with the added caveat that providers should work with patients to address any unintended distress the term might cause. The American Society of Transplantation (AST) defined a failing kidney allograft as “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 kidney replacement therapy.” Without fully coming to consensus on the definition, KDIGO conference participants agreed that having a definition would be helpful. Whether the definition should include stable but low allograft function, as proposed by AST, was debated by conference participants in the context of recent efforts to decrease organ discards with transplantation of more kidneys that may have low but stable kidney function from the start, and may stay that way for some time. Nevertheless, with low but stable function there are risks including that there may be associated morbidities such as anemia; physicians and patients may be overly optimistic about prognosis despite that a sudden acute decline in kidney function more often leads to kidney failure than in someone with good kidney function.

Alternatively, the decline of GFR may take a steep negative slope leading to more rapid loss of function, and the kidney may indeed be failing. In agreement with AST, conference participants noted that “failing” implies a predicted need for dialysis or re-transplant within a relatively short period of time, i.e., less than a year. It may also mean that other sequelae of kidney failure are present. Failure means the graft is either no longer functioning at all or working so poorly that additional kidney replacement therapy is required and meaningful functional improvement is not possible. Defining clinical time points for the allograft with poor and declining function is important for patients and clinicians. The various phases of care during transplant, include not only immediate post-surgical care and management of
immunosuppression to minimize rejection or infection, but also management of the low and diminishing kidney function transplant (Figure 1).

Being able to predict when kidney transplant recipients (KTR) will need maintenance dialysis or re-transplantation will enable providers to identify patients with failing grafts, and more importantly will facilitate optimizing management and outcomes that matter to patients. A definition is only helpful if it prompts proper management of immunosuppressive medications, metabolic complications of low and decreasing kidney function, psychosocial issues, preparation and planning for dialysis and/or re-transplantation, or choosing supportive care. The definition of the failing kidney allograft should be based on an accurate and personalized prediction of allograft failure calculated from validated and clinically implementable prognostication systems. Prognostication includes estimating the trajectory of the decline in glomerular filtration rate (GFR) to estimate return to kidney replacement therapy, and accounts for other parameters that may influence that trajectory, e.g., allograft histology, donor age, circulating anti-HLA donor specific antibodies, and proteinuria.

During the conference, measures used to monitor graft health, were considered for their utility in identifying and monitoring patients with grafts that were at risk for failing, or actively failing. Interest centered on the emerging prognostication tools as means of predicting the kidney function course and a timeline for future graft failure and thus accurately identifying or diagnosing individuals with failing kidney grafts.

**Biomarkers**

Biomarkers play several roles in diagnosing patients with the potential for allograft failure. They can help identify those with failing or failed allografts; for example, eGFR and creatinine change when interpreted in the context of the clinical setting, may support the diagnosis while other biomarkers such as proteinuria and immunological markers can signal increased vulnerability for failure.

**GFR:** Measuring kidney function is useful. For reasons of cost, convenience and availability, serum creatinine-based formulas are most commonly used to estimate glomerular filtration rate (eGFR). The eGFR can help determine drug dosing, the likelihood of metabolic and other complications, as well as eligibility for re-transplantation. Measured serially over
time, eGFR can also estimate the rate of decline in GFR and impending graft failure. There are existing formulas to predict outcomes that are variably applied in the transplant setting. As these formulas were derived in non-transplant patients, their applicability to transplant recipients is uncertain. eGFR formulas should be improved for KTRs. Hence, there was a consensus that we need specific studies developing and validating eGFR equations for adult and pediatric KTR, and that they must perform better than existing equations. A kidney-recipient-specific eGFR equation should be promptly developed and tested in different countries and diverse populations and compared to the standard eGFR equations based on native kidneys. Formulas should avoid the use of race and ethnicity in ways that may deny access to care. A recent study validating the 2021 CKD-EPI eGFR equation in KTRs, found it performed well in comparison to cystatin C and isotope based GFR using radiolabeled diethylenetriaminepentaacetic acid, and older CKD-EPI formulas. Non-creatinine markers of kidney function such as cystatin C could play a role in monitoring grafts as well.

**Serum creatinine:** There are few studies of how often serum creatinine should be measured in stable KTR, let alone in those with failing grafts. The 2009 KDIGO guideline recommended that serum creatinine be measured every 2-3 months after the first post-transplant year, but rated the level of evidence for this recommendation to be low. The guideline did not specifically address the frequency of measuring serum creatinine in those with unstable or failing transplants. Some providers measure the serum creatinine more often as it makes intuitive sense that patients who have serum creatinine measured more frequently are more adherent to medications and have better graft survival, but few studies have addressed this. It is important that patients understand the reason for measuring serum creatinine and other laboratory values. However, serum creatinine is neither sensitive nor specific and thus not sufficient to use alone to monitor the graft post-transplant or to predict graft failure.

**Proteinuria:** Proteinuria is a strong predictor of kidney graft failure as highlighted in two large transplant studies, where proteinuria was a stronger predictor of allograft failure than circulating anti-human leukocyte antigen donor-specific antibodies (anti-HLA DSA) or histological parameters.
**Protocol Biopsies:** Protocol biopsies can detect treatable, subclinical, kidney allograft rejection. Studies demonstrating that benefits outweighed the risks of protocol biopsies were performed in an era when acute rejection occurred more frequently which may no longer be as relevant today.\textsuperscript{21,22} As with all screening tests, positive and negative predictive values are determined in part by the underlying incidence of the disorder being screened. Protocol biopsies may be of greatest value in high-risk populations. Their role in identifying individuals with failing grafts is to identify any reversible processes and in their absence to establish that the decline in graft function is irreversible.

**Immunologic markers:** There is substantial evidence that screening for *de novo* anti-HLA DSA can help detect antibody-mediated rejection (AMR).\textsuperscript{23} Donor-derived cell-free DNA is a promising biomarker. Additional studies are needed, including large unselected and well-phenotyped cohorts, to provide robust additional evidence for its clinical validity before widespread implementation as a patient monitoring test.\textsuperscript{24} It has a role in identifying individuals with subclinical immunologic injury and monitoring response to treatment. Gene-expression profiling of the allograft is not useful as a screening biomarker, and was not designed to address allograft prognosis, but may be helpful in interpreting histopathologic findings of biopsies.\textsuperscript{25}

Existing biomarkers, discussed above, are helpful but are limited by being neither sensitive nor specific enough to predict kidney failure, especially when used alone. There is a critical need for additional, non-invasive biomarkers. Because of the contrast between the very high number of biomarker studies published in the past years, and the very low number of biomarkers implemented in clinical practice studies, investigating the incremental value of biomarkers in terms of diagnostic and prognostic capacity over standard-of-care patient parameters is needed.

**Prognostication models**

Refined data on functional, structural and immunological parameters are needed to develop and validate accurate prognostication models for KTR outcomes.\textsuperscript{26,27} The iBox, which stands for “integrative box” is one such model.\textsuperscript{3,4} The iBox is promising as it appears to have the potential to predict short-, middle- and long-term allograft failure in many subpopulations of
transplant recipients and clinical scenario. The iBox potentially offers the opportunity to intervene earlier and create an environment that supports patient engagement with their care team. As one considers the use of prognostication systems in KTRs, it is critical to note that native-kidney-based prognostication models should not be used in kidney transplant recipients as they cannot capture the complexity and determinants specific to this population. The prognostication models should be kidney-transplant-specific.

Prognostication systems which accurately predict allograft failure, from the short-term to the long-term failure, have several roles and benefits: 1) Improving patient risk stratification and trajectory prediction; 2) capturing the response to treatment after rejection or change of immunosuppressive regimen;28-31 3) detecting and quantifying subclinical alterations to long-term allograft survival, at an early time point; 4) defining the future course of the allograft more accurately than repeated measurements of eGFR and proteinuria;3 and 5) optimizing patient management and psychological preparation. Recommendations for developing and establishing a kidney failure prediction system are outlined in Table 132-34 and a research agenda for this section is outlined in Table 2.
MANAGEMENT OF IMMUNOSUPPRESSION

The failing allograft

The management of immunosuppression in KTRs with declining GFRs should balance the potential risks (e.g., infection) and benefits (e.g., avoiding sensitization). In current practice, immunosuppression is usually reduced or discontinued, despite a gap in knowledge as to whether this is better or worse for the patient.\(^35\) A personalized approach taking the risks, potential benefits and personal preferences into account would be helpful for the individual, assessing their specific clinical needs in case of graft failure and their plans for management, and the side effects of immunosuppression (Figure 2). The lack of consensus makes this a relevant issue.\(^36\)

There are five important overarching considerations for immunosuppression therapy (IST) management as outlined in Table 3. The plan for re-transplantation is a key decision point and crucial in directing management.\(^2,37\) For example, if the patient with a failing allograft is a transplant candidate and there is an identified potential living donor, IST would be maintained to minimize development of DSA. Likewise, the presence of another transplanted organ such as a pancreas allograft dictates the need to maintain therapy. Personalized strategies are needed in the setting of common comorbidities or side effects as well as patient preferences. When there is no concern about preventing HLA sensitization, there are fewer potential benefits of maintaining IST. For patients who do not wish to resume kidney replacement therapy, the goal is to maximize their time with a functioning graft, e.g., by calcineurin inhibitor (CNI)-minimization.

Consensus points for management are shown in Table 4. Discussion focused on balancing the risks vs benefits of continued IST as noted in Supplementary Table S1. There was a general consensus that when IST management is changed, shared decision-making in terms of potential benefits, risks and next steps is important and drug adherence needs to be addressed.

In the discussion on IST management in the failing allograft, there remain areas of controversy (Supplementary Table S1). These included the extent of residual kidney function
or slope of change of function that would mandate a change. Additionally, there was a
discussion about care implementation (see below), and the role of CNI withdrawal with the goal
to prolong kidney function, e.g., using costimulatory blockade (belatacept). However, it was
understood that there are no data for clinical use, in this setting, beyond expert opinion and
clinical experience.

The failed allograft

Data on the efficacy of IST in the patient with a failed allograft are limited and
primarily derived from retrospective studies. Immunosuppression management in the patient
with the failed allograft differs conceptually from that in the failing allograft, in that the
expectation is that the immunosuppression will be tapered off at some point. However for some
time after graft failure, immunosuppression, albeit at low levels, may be continued. And for
some patients there are reasons to continue it for a while. For example, IST may prevent
sensitization, chronic inflammation, as well as the need for nephrectomy and has the
potential to maintain some residual kidney function and urine output. However, a prospective
observational study in Canada did not demonstrate benefit on prevention of sensitization in
patients who continued IST after graft failure, perhaps because participants were found to be
non-adherent to IST after graft loss. Other studies demonstrate the side effects of continued IST,
namely higher infection and malignancy rates, metabolic complications and cardiovascular
problems. Hence, a note of caution is needed to maintain IST without a clear endpoint as
noted in Tables 4 and Supplementary Table S2. In a recent survey of US transplant centers,
the estimated waiting time for re-transplantation was found to be an important consideration in
IST withdrawal. If the estimated wait-time was more than 3 years and there was no living
donor, nearly 50% of respondents recommended discontinuation of all IST.

When a decision to reduce immunosuppression is made, the method and protocol for
reducing and discontinuing immunosuppression are not consistent nor evidence based. Most commonly, discontinuation of antimetabolite occurs first, followed by CNI and
corticosteroids last. The decision to maintain, taper, or withdraw a particular IST after graft failure is based on personal experience, side effects (e.g., anemia, infection, tolerability), cost, and patient
preferences (**Supplementary Table S2**). Ideally, objective criteria should guide the risk stratification for maintaining IST. Potential criteria could be the previous history of rejection and sensitization, relisting and projected waiting times, as well as HLA match and perhaps high immunologic risk as defined by class II DR/DQ eplet mismatch. Some advocate for the importance and maintenance of residual function, which might be important for dialysis quality (especially in peritoneal dialysis) and quality of life because of higher fluid intake. Due to paucity of data, guidelines rely on expert opinion and various guidelines suggest different IST weaning strategies.¹ ² ⁵¹ For patients pursuing another kidney transplant (especially if likely to receive a pre-emptive re-transplant), all guidelines recommend maintaining IST. Alternatively, in the patient with BK viremia and impending graft loss, accelerated IST reduction is considered as based on clinical opinion. Some consider maintaining steroids to help preserve residual kidney function without good supporting evidence.⁴⁸ Many patients have received steroids for many years, and therefore steroids can only be tapered slowly in order to avoid hypocortisolism. In summary, there are no objective criteria to guide the order and timing of immunosuppressive withdrawal.

**Allograft nephrectomy**

Special consideration was given to the issues around allograft nephrectomy (**Supplementary Table S2**) and there may be deterrents including operative morbidity and mortality.⁵² The discussion noted concurrence regarding nephrectomy for “graft intolerance syndrome” associated with hematuria, abdominal pain, fever, failure to thrive, or source of infection or in the setting of renal vein or renal artery thrombosis and graft infarction with risk of allograft rupture as noted in the literature.⁵³-⁵⁵ Another situation requiring urgent nephrectomy is severe acute rejection that is unresponsive to bolus corticosteroids, with pain and hemorrhage.⁵⁶ The indication for severe anemia and other evidence of chronic inflammation were identified as potential reasons for nephrectomy, as noted in large retrospective studies.⁵⁷

With HLA antibodies developing after discontinuation of immunosuppression, the role of nephrectomy in exacerbating this issue was discussed. There are conflicting findings in the literature, and it is unclear if this is related to sensitizing events prior to graft removal.⁴¹ ⁴⁶ ⁵³ ⁵⁸-⁶² Likewise, there are limited and inconsistent data on the impact of “prophylactic” or “preemptive”
nephrectomy on HLA DSA development prior to IST withdrawal. Likewise, the indication for nephrectomy in patients with chronic allograft failure is unclear.
MANAGEMENT OF PSYCHOLOGICAL EFFECTS AND MEDICAL COMPLICATIONS IN KIDNEY TRANSPLANT RECIPIENTS WITH FAILING TRANSPLANTS

Communication

Preparing the patient with early discussions, even before the kidney is failing, improves planning and patient acceptance. Conversations concerning dialysis modality and form of access should begin at least 6 months before the anticipated dialysis start – determined by the GFR trajectory– especially in those individuals without a functional vascular access. The re-transplant evaluation process should be encouraged to begin at least 12 months before anticipated return to dialysis, and in those countries where preemptive listing for a deceased donor transplantation is permitted, patients should be relisted as soon as they meet eligibility criteria. Beginning the re-transplant evaluation process early increases the possibility of identifying a living kidney donor and preemptive re-transplantation.

From the initial interaction with the transplant team, patients should be fully informed of all transplant outcomes including the possibility of the need for future re-transplantation. While difficult to address, the potential for allograft loss should be discussed with the patient at every immunologic or non-immunologic event that has the potential to adversely affect kidney function. When biopsies are performed for diminished kidney function, the trajectory of potential further decline should be shared including some general idea of the time frame for graft survival.

Psychological management

Informing kidney transplant recipients that their allograft is failing elicits a range of emotions and reactions including shock, depression, anger, self-harm and grief. Transplant failure causes significant upheaval to a number of life domains including relationships (family planning, sexuality, role change), financial (reduced ability to work, insurance issues, etc.), social (reduced activities, travel, etc.), quality of life (fatigue), and for pediatric recipients a more difficult transition to adulthood. The medical and psychological consequences are particularly difficult
for individuals residing in low-income countries, who obtained paid kidney grafts in foreign
countries and/or for anyone for whom kidney replacement therapies are barely available.
Adapting to this new reality will be challenging for many and anticipating their psychological
needs is an important task for the transplant team. The conference participants identified mental
health as a priority and concluded that having the patient work with a mental health professional
is optimal though not always possible. It was also noted that improving provider literacy on the
key psychological concepts and competencies to help motivate, challenge and support patients
would be helpful. Strategies to strengthen self-management capacity may be needed to address
anxieties, minimize treatment fatigue and support decision making. Studies specific to this
cohort are limited.

Since periods of depression will be common for many and patients might be reluctant to
share their plight, the conference participants recommended routine screening for depression and
anxiety. Screening instruments that can be administered by nursing staff are available. Positive
screens can be further evaluated by social workers, and other mental health experts should be
available and consulted as necessary. For patients who are in the process of losing a live donor
allograft, additional support may not only be needed to help resolve guilt and depression in the
recipient but also depression in the donor. Importantly depression is associated with poor
patient outcomes, thus highlighting the need to screen and support. Given the psychological
impact, access to a clinical psychologist is most strongly recommended. This is a
psychologically vulnerable period for patients. Even if past behaviors such as medication non-
adherence may have contributed to the outcome, caregivers should avoid blaming patients for
graft failure, but rather be supportive.

The conference participants felt that adequate time was required to allow patients to
accept and prepare for the transition away from a functioning transplant health state. Better
educational tools (videos, webinars, brochures, etc.) should be developed to help patients grapple
with this transition and mark out the road ahead (Figure 3). The educational tools should
include peer support. Although peer support is strongly encouraged, engagement with this
resource has been low. Barriers include low provider referral rates, challenges matching
patients to support persons, and need for support person training. To overcome these barriers, patient peer support should be incorporated into the education tools.

**Medical management**

During the conference, communications guided by eGFR level were discussed (Table 5). If the transplant and dialysis teams are separate, identification and initial communication with the dialysis team should begin when the eGFR is 20 ml/min/1.73 m² or less, and/or if there is a rapid and apparently irreversible decline no matter the level of eGFR. Treatment has to be aligned with community physicians or general nephrologists managing CKD. Management of complications including anemia and CKD-MBD, should align with the severity of CKD for non-transplant patient. Patients will need modality counseling, which would ideally include different dialysis modalities, options for waitlisting (preemptive where permissible), and preemptive transplantation (if a living donor can be identified), and/or conservative therapy as appropriate (Table 6).

For reasons including denial as well as lack of planning, as many as 65% of patients with failed allografts have no established vascular access when returning to dialysis and the rate of preemptive re-transplantation or relisting is very low (around 15%-US transplant registry data). Taken together, this points to the needs for better coordination between the different factions of the patient’s health care providers. Whether the recipient has a failing or failed allograft will necessitate different coordination schemes. No evidence or guidelines exist, so we recommend a “common sense” approach that needs to be adapted according to national-regional-local health organization.

Another approach endorsed by conference participants is a multidisciplinary patient integrated care clinic (MDC). Patients with failing grafts should have ready access to multidisciplinary teams to allow a seamless transition of care determined by the subsequent modality of kidney replacement therapy. Nephrologists should partner with social workers, dieticians, healthcare navigators, and emotional support staff to support patients with failing allografts. Insurance policies, non-insurance-based financial resources, and strategies to address the financial burden of returning to dialysis should be provided. It is clear that more
comprehensive transplant insurance policies and financial coverage through this phase of transplant are needed worldwide. Since patients are at risk for needing dialysis, controversies and consensus for the failing transplant cohort parallels that of those with progressive CKD.\textsuperscript{78, 79} The entry criteria making patients most likely to benefit and the optimal provider composition (nurse, physician, dietician, social worker, transplant pharmacists, etc.) for CKD MDCs are unknown and may differ between centers and countries, thus constituting significant knowledge gaps.\textsuperscript{80} Analysis of cohort trials suggests significant benefit, however small randomized trials are equivocal.\textsuperscript{81, 82} Although it is not clear to what extent MDCs improve outcomes, there is no evidence of harm.

In sum, the potential options for those with advanced and deteriorating kidney transplant function are to refer to a general nephrology MDC with expertise in patients needing imminent dialysis/decisions of conservative care; or alternatively, to enrich the transplant clinic with providers capable of managing this select group of patients, helping them transition to the next treatment modality. Some transplant centers are already sending patients to a general nephrology CKD MDCs before dialysis is needed and others care for patients until the start of dialysis or conservative care is pursued.\textsuperscript{83} Although maintaining patients within the transplant programs has advantages, other issues such as geography, expertise and resources will dictate the model of care.

Given the complexity and scope of the medical and psychologic issues, spending more time with patients is needed. In-person (face-to-face conversations) may be a challenge for many, and alternative methods, such as telehealth, may help achieve medical targets and increase the likelihood of psychological adjustment.\textsuperscript{84-86} Several participants suggested the use of checklists at patient encounters to help achieve goals.\textsuperscript{71} Other clinic activities were discussed including routine screening for frailty and cognitive decline; however, the net benefits of these activities were uncertain.\textsuperscript{87, 88}

IST management is ideally integrated into the overall health care plan with interdisciplinary care clinics, or if available, MDC clinics, with a focus on optimization of adjunct CKD therapy.\textsuperscript{89} Discussion was held about the frequency of visits, target drug levels and assessment of immunosuppressant side effects. No evidence or guidelines exist on the extent of
monitoring during and after allograft failure, but expert opinions are available. Another question is whether the care can be expedited/integrated using telehealth approaches. Novel telehealth approaches may be one way to improve communication between transplant centers and local physicians and between transplant center and patients, but benefits need to be shown.

Monitoring strategies were also discussed, and the patients’ goals and desires must be considered. Physicians need clear guidance on the practical aspects of IST; specifically, how to monitor and adjust drug levels, lab values, side effects, diuresis, inflammation, panel reactive antibodies and other biomarkers. Patients starting dialysis with failed kidney transplants have worse anemia and serum albumin quality metrics than those starting dialysis with failed native kidneys, and the impact of IST is largely unknown.

Patients with failing allografts have higher rates of mortality and hospitalization compared to those with deteriorating native CKD. It is not clear if these findings relate to less-than-optimal care by transplant physicians, an inflammatory state caused by a failing allograft, the result of ongoing immunosuppression, and/or the unmeasured burden of kidney disease pre-dating transplantation. Hospitalization rates in the 6 months before dialysis initiation are especially high. The use of central venous catheters (CVC) for the initiation of dialysis is also high as is mortality in those starting dialysis urgently in hospital. Hospitalizations are associated with acute kidney injury that can precipitate the need for dialysis but also subsequent cardiovascular events.

KDIGO has published and updated numerous guidelines and controversies in the care of patients with kidney disease and transplantation. Much of the guideline evidence to support recommendations has not been studied specifically in kidney transplant recipients. Moreover, the benefits and safety of newer innovative therapies, that reduce cardiac events and kidney failure in the general CKD population such as SGLT2 inhibitors, has had limited examination in kidney transplant recipients. For the cohort with low and declining allograft function, it is also not clear when to stop potentially beneficial medications as the eGFR falls to <20 ml/min/1.73 m².
There are significant gaps in knowledge in this area and future studies are warranted in this population. Based on the extensive discussions, a number of research priorities were identified in order to begin to investigate and provide evidence for management recommendations. **Table 2** outlines areas of proposed research that could inform and improve care.
LISTING FOR RE-TRANSPLANTATION AND/OR RETURN TO DIALYSIS

Mental health and social support services should be provided for those individuals for whom kidney re-transplantation would be contraindicated. While transplant centers have their own eligibility criteria for re-transplantation, potential transplant candidates should be evaluated individually, and all criteria should be applied without bias. Centers should establish clear baseline criteria to provide certainty for patients and referring providers. Centers that decline listing a patient with a failing allograft should be required to direct these individuals to centers that may be willing to consider these individuals as candidates. All centers should ensure that transparency around both relisting criteria and access to the waitlist occurs (Table 6).

Patients should be encouraged to identify potential living donors to increase the potential for a pre-emptive transplant. However, listing for re-transplantation should not be conditional on the recipient candidate having potential living donors.

Considerations for optimal planning of kidney replacement therapy

While prior arteriovenous (AV) access often fails over time in transplant recipients, patients should be encouraged to protect their fistulas after transplantation. There are no data to suggest that ongoing dialysis access maintenance procedures (angioplasty, stenting, etc.) with the exposure to nephrotoxic dye are warranted or beneficial. A study examining using administrative data from 2011-2013 compared those recipients who underwent AV access ligation to those who did not was unable to demonstrate any association with either post-transplant allograft failure or reductions in all-cause mortality.

Ligation of AV access in those with well-functioning transplants should preferably be performed in patients who have disabling AV access complications such as venous hypertension, recurrent stenosis requiring intervention, and/or dialysis access associated steal syndrome. The return to dialysis following a failed first kidney transplant, without a functioning AVF is associated with a 22% increased risk of all-cause mortality, and lack of referral to a general nephrologist was a predictor of catheter use. There is a 3-fold greater risk of sepsis with CVC use 3-6 months after transplant failure which has been shown to increase mortality.
However the need to establish a functioning AVF does not apply to re-transplant candidates who have an established surgical date for living donor transplant who may initiate short-term dialysis with a tunneled catheter to optimize pre-surgical medical condition.

There are no specific guidelines for the timing of dialysis initiation based on eGFR. Studies in transplant-naive patients with CKD might not be generalizable to patients with failed kidney allografts. Unique factors associated with a failed allograft (i.e., immunosuppression, inflammation, sarcopenia) mean that the optimal timing of dialysis initiation in the setting of a failed transplant might differ from that of failed native kidneys. Filtration impairment and interstitial damage do not always progress in parallel – resulting in the potential for development of uremic symptoms and several complications of kidney disease appearing earlier or possibly later than expected by eGFR alone. In the absence of strong evidence suggesting that one dialysis modality is superior to another, the patient’s choice should be given priority.

We further recommend that timing of dialysis initiation be based on clinical factors and symptoms rather than eGFR evaluation alone. As patients transition back to dialysis, it is critical to communicate with the accepting dialysis unit and confirm that the patient understands the plan (Table 6). Clinicians should educate themselves about how conservative/palliative medical care options can assist patients through transitions of care (not simply at the end-of-life). Research recommendations are outlined in Table 2.
CONCLUSION

Post-transplant care should include not only immediate post-surgical care and management of immunosuppression but should also encompass management of the failing and failed kidney allograft. The complexity of managing patients with a failing and failed kidney transplant is multilayered. This phase of the transplant graft function trajectory (Figure 1) represents a high-risk period for patient outcomes. Firstly, identifying patients with a failing allograft is challenging as accurate prognostication tools that could support the clinician’s judgment and improve shared decision-making, though emerging, are still limited; and yet the importance of identifying these patients and starting early discussions is paramount not only for the patient’s psychological wellbeing but also to his/her medical care in order to prepare for graft failure through pre-emptive transplantation, optimal dialysis access placement or planning/referral for supportive care. Immunosuppression management is based on patient risks and potential plans for re-transplantation. Coordination of care between teams and communication is critical to ensure adequate preparation and maximum availability of options for such patients while being mindful of their values and preferences. Most important is putting the patient at the center of the care, supporting patient activation, and providing psychological support during this difficult period. Research is needed in order to more accurately define and identify patients with failing allografts, develop prognostication tools, formulate evidence-based approaches towards immunosuppression management, and focus on the implementation science of medical and psychological management for patients with failing and failed allografts. Key take home points from the conference are presented in Table 7.
TABLES

Table 1. Recommendations for establishing a kidney failure risk prediction system

Table 2. Research agenda

Table 3. Five key considerations for immunosuppressive management in recipients with allograft functional decline

Table 4. Consensus points for immunosuppression management

Table 5. Management based on eGFR

Table 6. Timeline of education, communication, and management in preparation for graft failure

Table 7. Key take home points

SUPPLEMENTARY TABLES

Supplementary Table S1. Controversies on immunosuppression management in the failing allograft

Supplementary Table S2. Controversies on immunosuppression management in the failed allograft
REFERENCES


Belcher JM. The Role of Telenephrology in the Management of CKD. *Kidney360* 2020; **1**: 1310-1315.


Figure headings and legends

Figure 1. Spectrum of kidney allograft function

Figure 2. Integrated management and shared-decision making for a declining and failed kidney allograft

eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy

Figure 3. The Road Ahead: The transplant recipient with low and deteriorating kidney transplant function (Adapted from Agrawal et al.71)
Table 1. Recommendations for establishing a kidney failure risk prediction system\textsuperscript{32-34}

<table>
<thead>
<tr>
<th>Domain</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Research purpose and clinical impact</td>
<td>The research purpose must be guided by the potential impact in clinical practice.</td>
</tr>
<tr>
<td></td>
<td>A precise literature search on what has been published on the topic should be conducted and reported.</td>
</tr>
<tr>
<td>2) Study design, participants, outcome(s) and data collection</td>
<td>Study design and population of interest as well as the outcome(s) measure and its timing should be precisely defined.</td>
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<tr>
<td></td>
<td>Sufficient sample size for the number of patients and number of events is critical and should be clearly justified.</td>
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<td></td>
<td>Data collection should include relevant candidate prognostic factors adapted to the population and outcome of interest.</td>
</tr>
<tr>
<td>3) Statistical analysis</td>
<td>The TRIPOD statement should be used when developing and validating a prediction model.</td>
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<tr>
<td></td>
<td>During parameters selection procedures, candidate predictors must be challenged with parameters already associated with the outcome and used in clinical practice. The additional value of a candidate predictor must be demonstrated over parameters routinely collected and used in standard of care.</td>
</tr>
<tr>
<td>4) Prediction model performances</td>
<td>Predictive performances should be assessed by at least two complementary methods adapted to the predictor-outcome associations, such as the discrimination and the calibration.</td>
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<tr>
<td></td>
<td>Model generalizability should be assessed on a population-based cohort and at least one external validation cohort.</td>
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<td></td>
<td>The new prediction model should be put in competition with other existing prediction models to show its superior prediction performances.</td>
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<tr>
<td>Domain</td>
<td>Consensus</td>
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<tr>
<td>-----------------</td>
<td>---------------------------------------------------------------------------</td>
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<tr>
<td>Research purpose</td>
<td>The study goal should be precisely defined.</td>
</tr>
<tr>
<td>Outcome</td>
<td>The outcome(s) to predict and its timing should be precisely defined.</td>
</tr>
<tr>
<td>Population</td>
<td>The population of interest should be precisely defined.</td>
</tr>
<tr>
<td>Parameters</td>
<td>The data collection should be based on the relevant candidate prognostic factors adapted to the population and outcome of interest.</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>The methods to evaluate the parameters collected should be reported.</td>
</tr>
<tr>
<td></td>
<td>The statistical model(s) used should be adapted to the outcome and the data.</td>
</tr>
<tr>
<td></td>
<td>The parameters included in the models should be prespecified before statistical analysis.</td>
</tr>
<tr>
<td></td>
<td>The methods used for parameters selection procedures should be reported.</td>
</tr>
</tbody>
</table>
Sufficient statistical power should be attained to interpret the models. For instance, for cohorts with a limited sample size, the rule of thumb of at least 10 events per parameter can be used.

<table>
<thead>
<tr>
<th><strong>If a prediction model is developed:</strong> transparent reporting</th>
<th>The number of patients and events in each analysis should be reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The TRIPOD statement should be used when developing and validating a prediction model.</td>
<td></td>
</tr>
<tr>
<td>In addition to the steps above, the key steps to develop and validate a prediction model are: 1) Univariate analysis (if the model is not a machine learning model), 2) Multivariable analysis, 3) Performance assessment in the development cohort with validated metrics and methods (at least discrimination and calibration), 4) Performance assessment in external validation cohort(s).</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Contextualization</strong></th>
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<tbody>
<tr>
<td>A literature search on what has been published so far on the topic should be conducted. Whether and how the model brings something new should be discussed.</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Impact in clinical practice</strong></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>The potential impact in clinical practice should be ideally demonstrated or at least discussed.</td>
<td></td>
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<tr>
<td>For instance, if a prediction model is validated, an online tool can be developed to facilitate the implementation in the real-life setting. A projection or simulation analysis to estimate the impact of the model in clinical practice can also be performed.</td>
<td></td>
</tr>
</tbody>
</table>

AMR, antibody-mediated rejection; anti-HLA DSA, anti-human leukocyte antigen donor-specific antibodies; eGFR, estimated glomerular filtration rate; TRIPOD, Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis.
Table 2. Research agenda

**Determining prognosis and kidney failure trajectory**
- Develop and validate eGFR equations for adult and pediatric KTR
- Evaluate whether biomarkers reflecting alterations in renal tubular function are predictive of kidney transplant outcomes
- Determine optimal frequency of monitoring serum creatinine after the 1st post-transplant year
- Investigate the incremental value of biomarkers in terms of diagnostic and prognostic capacity over standard-of-care patient parameters
- Evaluate gene profiling and other existing biomarkers (including Dickkopf-protein, suPAR) as an approach towards identifying failing allografts
- Develop and refine accurate prognostication systems for patient management
- Create database on allograft function in transplant follow-up before transplant graft failure

**Management of immunosuppression**
- Identify optimal approaches for immunosuppression adaptation in the settings of both the failing and failed allograft
- Develop a tool for risk stratification that includes assessment of recipient immune and medical risk that would guide immunosuppression management in this setting
- Identify the best time to modify immunosuppression
- Determine if CNI minimization/elimination slows progression of kidney allograft dysfunction in the failing allograft
- Consider randomized control trial or use of real world data to determine the risks and benefits of continued immunosuppression treatment (see supplemental table S1.)

**Management of psychological effects and medical complications in kidney transplant recipients**
- Comparison of CKD MDC versus Enhanced Transplant MDC with respect to outcomes and safety
- Identify the most important preventable complications that precipitate the need for dialysis or death in patients with failing transplants
- Test the safety and efficacy of SGLT2i, MRAs and GLP-1 RAs in adult and pediatric transplant recipients
- Examine integrated care pathways, integration of patient decision making, and telemedicine on improving communication and patient outcomes
- Institute patient-centered research on psychological impact of the failing and failed graft

**Listing for re-transplantation and/or return to dialysis**
- Should AV access function be preserved when the patient has good transplant function and asymptomatic access?
- What is the optimal dialysis therapy after transplant failure?
- Does AV graft ligation reduce mortality in the long term (> 5 years)?
- Is there an optimal eGFR to initiate dialysis after graft failure?
- Determine the impact of nephrectomy on HLA sensitization, procedural morbidity/mortality, and inflammation
- Does residual urine output affect endpoints and outcomes?
- When should the option of supportive care be introduced? Patient-centered research in PROMs and experiences after graft failure

AV, arteriovenous; CKD, chronic kidney disease; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HLA, human leukocyte antigen; KTR, kidney transplant recipient; MDC, multidisciplinary clinic; MRA, mineralocorticoid receptor antagonist; PROM, patient-reported outcome measure; SGLT2i, sodium–glucose cotransporter-2 inhibitor; suPAR, soluble urokinase plasminogen activator receptor
Table 3. Five key considerations for immunosuppressive management in recipients with allograft functional decline

<table>
<thead>
<tr>
<th>Circumstance</th>
<th>Intent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intended kidney replacement therapy mode following graft failure</strong></td>
<td></td>
</tr>
<tr>
<td>Pre-emptive transplantation</td>
<td>Avoid DSA to facilitate next transplant; retain IST to merge into induction for next allograft</td>
</tr>
<tr>
<td>Dialysis and waitlisting for re-transplantation</td>
<td>Need to balance dialysis safety, residual graft function and development of DSA; May be impacted by plans for graft nephrectomy</td>
</tr>
<tr>
<td>Dialysis but not candidate for re-transplantation</td>
<td>Imperative to minimize IST to reduce risks of infection, morbidity. Risk of allosensitization less a factor, balanced by need for graft nephrectomy</td>
</tr>
<tr>
<td>Supportive care</td>
<td>Need to maximize graft longevity and function</td>
</tr>
</tbody>
</table>

| Cause of graft failure                                                                 |
|------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Non-alloimmune cause                    |                                                                                                                                           |
| Recurrent glomerular disease             | Is there a role of IST in the recurrent disease management?                                                                            |
| BK polyomavirus nephropathy              | Need for IST reduction and /or graft nephrectomy                                                                                       |
| Interstitial fibrosis / tubular atrophy  | Concurrent comorbidities should be considered to tailor management                                                                       |
| Early surgical failure                   | Likely graft nephrectomy and IST withdrawal                                                                                             |
| Alloimmune cause                         | May require nephrectomy as IST failed                                                                                                    |
| Acute rejection                          | Complex decision about control of rejection versus safety                                                                               |
| Chronic rejection                        |                                                                                                                                           |

| Co-morbid considerations impacting safety of immunosuppression                |                                                                                                                                           |
| Sepsis, congestive heart failure, malignancy, diabetes, frailty, older age    | Tailor to condition                                                                                                                   |

| Past history of immunosuppression-associated adverse effects                 | Previous or ongoing adverse events may direct therapeutic management                                                                    |

| The other solid organ present                                                | Protection of the other allograft takes precedence for IST management                                                                   |

DSA, donor-specific antibodies; IST, immunosuppression treatment
Table 4. Consensus points for immunosuppression management

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Consensus Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maintain IST</strong></td>
<td>Continue IST in patients considered transplant candidates that have an identified living donor or expected short waiting time for a deceased donor organ (no consensus on what constitutes “short” waiting time)</td>
</tr>
<tr>
<td></td>
<td>Continue IST in patients with other solid organ transplants</td>
</tr>
<tr>
<td></td>
<td>Provide IST at a threshold level to prevent overt rejection, minimize sensitization and maintain residual function</td>
</tr>
<tr>
<td><strong>Taper IST (reduction to minimal or off)</strong></td>
<td>In patients not considered for re-transplantation</td>
</tr>
<tr>
<td></td>
<td>In patients with severe complications/side effects especially Infections and malignancies</td>
</tr>
<tr>
<td></td>
<td>On dialysis, once graft function ceases, corticosteroids should be maintained and the last medication to taper for those on corticosteroids maintenance (i.e., adrenal dependency)</td>
</tr>
<tr>
<td><strong>Allograft nephrectomy</strong></td>
<td>In patients with severe rejection or graft intolerance syndrome unresponsive to IST</td>
</tr>
</tbody>
</table>

IST, immunosuppression treatment
Table 5. Management based on eGFR

<table>
<thead>
<tr>
<th>eGFR</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Declining graft, if eGFR has consistently been above 20 ml/min/1.73 m²</td>
<td>Referral to transplant center for evaluation with consideration of biopsy to determine diagnosis and potential reversibility, and specific interventions to stabilize and potentially improve eGFR</td>
</tr>
</tbody>
</table>
| Low (approx. 20 ml/min/1.73 m²), but stable        | • Integration of care or co-management with communication between transplant center and nephrologist  
|                                                   | • Optimal CKD management including blood pressure control, anemia, proteinuria, metabolic acidosis, secondary hyperparathyroidism, cardiovascular issues, malignancy surveillance as per previous KDIGO guidelines  
|                                                   | • Close monitoring of levels of immunosuppressants and side effects |
| Low (approx. 20 ml/min/1.73 m²) and declining      | • Elicit life goals of patient; patient centered/shared decision making  
|                                                   | • Establish dialysis method and create appropriate dialysis access  
|                                                   | • Only candidates for re-transplantation with an established surgical date may initiate short-term dialysis with a tunneled catheter to optimize pre-surgical medical condition  
|                                                   | • If there is residual function of the allograft, evaluate maintaining low doses of immunosuppression unless there is a contraindication to its continuation  
|                                                   | • Monitor graft function, secondary complication of CKD and clinical symptoms in order to initiate dialysis at optimal time  
|                                                   | • Introduce conservative (palliative) medical care options, if re-transplantation is not an option |

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes;
Table 6. Timeline of education, communication, and management in preparation for graft failure

<table>
<thead>
<tr>
<th>Topic</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-transplant education</td>
<td>• Education about the potential for allograft loss should be discussed in the initial transplant evaluation process</td>
</tr>
</tbody>
</table>
| Post-transplant education                  | • Patients should be fully informed of all outcomes with transplant including the possibility of the need for re-transplantation in the future  
  • Potential for allograft loss should be discussed with the patient with every immunologic or non-immunologic event that has the potential to affect kidney function  
  • Discussions concerning the trajectory of potential accelerated decline should occur when the eGFR drops below 30 ml/min/1.73 m² and appears to be associated with rapidly declining function |
| Vascular access management                 | • Preserve functional AV access, in the absence of disabling AV access complications, especially in those with allografts with poor or declining function |
| Preparing for graft failure                | • Earlier conversations allow for improved planning and acceptance by the patient  
  • Patients with failing grafts should have ready access to multidisciplinary teams to allow a smooth transition to re-transplant listing and/or initiation of dialysis |
| Re-transplantation                         | • Pre-emptive transplantation should be the preferred approach  
  • Living donor transplantation should be offered in all instances when there is an acceptable living donor and no recipient related contraindications for re-transplantation |
| Standards for re-transplantation           | • Transplant centers are encouraged to develop their own guidelines for transplant consideration  
  • All guidelines such as the OPTN and KDIGO guidelines should be applied without bias.  
  • The need for a second transplant should not be regarded as the sole criterion either to restrict or promote candidacy |
| Non-adherence                              | • Medication non-adherence should be identified, fully investigated, and addressed to avoid recurrence. |
| Substance abuse                            | • Marijuana use should not be an absolute contraindication for re-transplantation.  
  • Clinicians should look for evidence for other modifiable risk factors that are often associated with dependence and attempt to address these issues prior to a second transplant. |

AV, arteriovenous; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; OPTN, Organ Procurement and Transplantation Network
Table 7. Key take home points

| Determining prognosis and kidney failure trajectory | Wider implementation of prognostication systems developed specifically for kidney transplant recipients which accurately predict allograft failure, from the short-term to the long-term failure is needed. The use of accurate kidney transplant specific prognostication systems would enable improved allograft management as well as activated patient engagement. |
| Management of immunosuppression | Immunosuppression management in the transplant recipient with a failing or failed kidney transplant must be individualized and based on risks vs benefits considerations. Decisions whether and how to taper and/or withdraw immunosuppression are consensus- or common sense-based, as there are no data to guide these decisions. |
| Management of psychological effects and medical complications in kidney transplant recipients | From a patient perspective, psychological support for patients with a failing or failed kidney transplant is paramount. Patient outcomes could be improved by better preparing patients and by minimizing adverse events during the transition phase. |
| Listing for re-transplantation and/or return to dialysis | Dialysis access preparation for individuals with failing allografts who will start dialysis improves outcomes. Psychological support is an integral part of managing patients with a failing and failed kidney transplant. |
Detection of graft dysfunction
Declining graft function
Failing allograft
Failed allograft

Kidney graft function
Kidney transplant recipient on immunosuppression treatment

Monitor and assess allograft with eGFR and/or other available biomarkers

Evidence for allograft dysfunction or injury

Refer to transplant center for potential biopsy, treatment, and immunosuppression treatment management

If unexpected worsening

Able to stabilize or treat – continue immunosuppression treatment accordingly

Slowly progressive – unlikely kidney failure within one year – consider immunosuppression treatment modification

Progressing and irreversible process with likely or “anticipated” graft failure within one year

Prepare for KRT

Supportive care and immunosuppression treatment management

Dialysis (access placement)

Pre-emptive transplant (continued immunosuppression treatment)

Dialysis as destination therapy (immunosuppression treatment taper and withdrawal)

Transplant following dialysis (immunosuppression treatment managed according to timing)
The kidney transplant recipient in transition

- Conservative care
- Medical and surgical management
- Psychological support
- Dialysis preparation
- Eligibility for re-transplantation
  - Pre-emptive
  - Live donor