

# 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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In March 2022, Kidney Disease: Improving Global Outcomes (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 a failing allograft, 4 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, and 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, prepare for dialysis and/or retransplantation, and transition to supportive care. Accurate prognostication tools, although not yet widely available, 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 to be based most appropriately on risk–benefit analysis

and likelihood of retransplantation 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 retransplantation. 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 deemed to be 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.

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What does it mean to have a failing allograft, and how should it be defined? These concepts were discussed by participants in the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference, as was the concern that using the term “failing” may unintentionally distress patients. Given that a better term was not determined, the use of “failing” was retained, with the added caveat that providers should work with patients to

address any unintended distress use of the term might cause. The American Society of Transplantation has defined a failing kidney allograft as being one that is characterized by “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.”<sup>1</sup> Without coming to full consensus on a 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 the American Society of Transplantation, was debated by conference participants in the context of recent efforts to decrease the volume of organs that were recovered but not transplanted, with transplantation of more kidneys that may have low but stable kidney function from the start and stay that way for some time. A state of low but stable function carries risks, including associated morbidities, such as anemia. Physicians and patients may also be overly optimistic about prognosis, given the fact that a sudden acute decline in kidney function leads to kidney failure more often in such cases than it does in those with good kidney function.

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

Being able to predict when kidney transplant recipients (KTRs) will need maintenance dialysis or retransplantation will enable providers to identify patients with failing grafts, and more importantly, it will facilitate the optimization of management and outcomes that matter to patients. A definition is only helpful if it prompts proper management of the following: immunosuppressive medications; metabolic complications of low and decreasing kidney function;

psychosocial issues; preparation and planning for dialysis and/or retransplantation; and the choice of supportive care.<sup>2</sup> 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.<sup>3,4</sup> Prognostication includes estimating the trajectory of the decline in GFR to estimate the point of return to kidney replacement therapy, and it accounts for other parameters that may influence that trajectory, such as allograft histology, donor age, circulating anti-human leukocyte antigen donor-specific antibodies (HLA-DSAs), and proteinuria.<sup>5</sup> During the conference, measures used to monitor graft health were considered in regard to their utility in identifying and monitoring patients with grafts that either are at risk for failing or are actively failing. Interest centered on use of the emerging prognostication tools as a means of predicting the course of kidney function decline and a timeline for future graft failure, thereby accurately identifying or diagnosing individuals with failing kidney grafts.

## DETERMINING PROGNOSIS AND KIDNEY FAILURE TRAJECTORY

### 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, estimated GFR (eGFR) and creatinine change, when interpreted in the context of the clinical setting, may support the diagnosis, and other biomarkers, such as proteinuria and immunologic markers, can signal increased vulnerability to failure.

**GFR.** Measuring kidney function is useful. For reasons of cost, convenience, and availability, serum creatinine-based formulas are used most commonly to estimate GFR. The eGFR can help determine drug dosing, the likelihood of metabolic and other complications, and eligibility for retransplantation. Measured serially over time, eGFR can also estimate the rate of decline in GFR and help predict impending graft failure. Existing formulas can be used to predict outcomes and are applied variably in the transplant setting.<sup>6</sup> As these formulas were derived in nontransplant patients, their applicability to transplant recipients is not clear. eGFR formulas should be improved for KTRs.<sup>7–12</sup> Hence, the consensus was that we need specific studies to develop and validate eGFR equations for adult and pediatric KTRs, and that they must perform better than the existing equations. A KTR-specific eGFR equation should be developed promptly, tested in various countries and diverse populations, and compared to the standard eGFR equations based on native kidneys.<sup>12a</sup> Formulas should avoid using race and ethnicity in ways that may limit access to care.<sup>13,14</sup> A recent study validating the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR equation in KTRs found that it performed well in comparison to cystatin C and isotope-based determinations of GFR using radiolabeled diethylenetriaminepentaacetic acid, and older Chronic Kidney Disease Epidemiology Collaboration

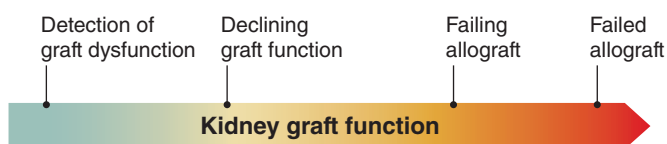


Figure 1 | Spectrum of kidney allograft function.

formulas.<sup>15</sup> Non-creatinine markers of kidney function, such as cystatin C, could play a role in monitoring grafts as well.<sup>16</sup>

**Serum creatinine.** Few studies have examined how often serum creatinine levels should be measured in stable KTRs, let alone in those with failing grafts. The 2009 KDIGO guideline recommended that serum creatinine levels be measured every 2–3 months after the first post-transplant year, but it rated the level of evidence for this recommendation as low.<sup>17</sup> The guideline did not specifically address the frequency of measuring serum creatinine levels in those with unstable or failing transplants. Some providers measure the serum creatinine level more often, as it makes intuitive sense that patients who have serum creatinine levels measured more frequently are more adherent to medications and have better graft survival, but few studies have addressed this point. The reason for measuring serum creatinine levels and other laboratory values is important for patients to understand. However, the serum creatinine level is neither sensitive nor specific, and thus is not sufficient to be used alone to monitor the graft post-transplant or predict graft failure.

**Proteinuria.** Proteinuria is a strong predictor of kidney graft failure,<sup>18–20</sup> as highlighted in 2 large transplant studies, in which proteinuria was a stronger predictor of allograft failure than circulating anti-HLA DSAs or histologic parameters.<sup>3,4</sup>

**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, an issue that may no longer be as relevant today.<sup>21,22</sup> 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.** Substantial evidence indicates that screening for *de novo* anti-HLA DSAs can help detect antibody-mediated rejection.<sup>23</sup> 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 prior to widespread implementation of its use as a patient-monitoring test.<sup>24</sup> This biomarker has a role in identifying individuals with subclinical immunologic injury and in 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 it may be helpful in interpreting histopathologic findings of biopsies.<sup>25</sup>

Existing biomarkers, discussed above, are helpful, but they are limited by being neither sensitive nor specific enough to predict kidney failure, especially when used alone. Therefore, a critical need exists for additional,

noninvasive biomarkers. Because of the contrast between the very high number of biomarker studies published in past years, and the very low number of biomarkers implemented in clinical practice studies, investigation of 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 immunologic parameters are needed to develop and validate accurate prognostication models for KTR outcomes.<sup>26,27</sup> The iBox, which stands for “integrative box,” is one such model.<sup>3,4</sup> 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 scenarios. 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, a critical point to note is that native kidney-based prognostication models should not be used for KTRs, as they cannot capture the complexity and determinants specific to this population. The prognostication models should be KTR-specific.

Prognostication systems that accurately predict allograft failure, from the short-term to the long-term, have the following roles and benefits: (i) improving patient risk stratification and trajectory prediction; (ii) capturing the response to treatment after rejection or change of immunosuppressive regimen<sup>28–31</sup>; (iii) detecting and quantifying subclinical alterations to long-term allograft survival, at an early time point; (iv) defining the future course of the allograft more accurately than repeated measurements of eGFR and proteinuria<sup>3</sup>; and (v) optimizing patient management and psychological preparation. Recommendations for developing and establishing a kidney failure prediction system are outlined in Table 1,<sup>32–34</sup> 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 the gap in knowledge as to whether this is better or worse for the patient.<sup>35</sup> A personalized approach that takes into account the risks, potential benefits, and personal preferences 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 on the appropriate approach to immunosuppression management makes this issue relevant.<sup>36</sup>

The 5 important overarching considerations for immunosuppression therapy (IST) management are outlined in

**Table 1 | Recommendations for establishing a kidney failure risk-prediction system<sup>32–34</sup>**

Domain	Recommendations	
(i) Research purpose and clinical impact	<ul style="list-style-type: none"> <li>The research purpose must be guided by the potential impact in clinical practice</li> <li>A precise literature search on what has been published on the topic should be conducted and reported</li> </ul>	
(ii) Study design, participants, outcome(s), and data collection	<ul style="list-style-type: none"> <li>Study design and population of interest, as well as the outcome(s) measure and its timing, should be precisely defined</li> <li>Sufficient sample size for the number of patients and number of events is critical and should be clearly justified</li> <li>Data collection should include relevant candidate prognostic factors adapted to the population and outcome of interest</li> </ul>	
(iii) Statistical analysis	<ul style="list-style-type: none"> <li>The TRIPOD statement should be used when developing and validating a prediction model</li> <li>During parameter-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</li> </ul>	
(iv) Prediction model performances	<ul style="list-style-type: none"> <li>Predictive performances should be assessed by at least 2 complementary methods adapted to the predictor–outcome associations, such as the discrimination and the calibration</li> <li>Model generalizability should be assessed on a population-based cohort and at least one external validation cohort</li> <li>The new prediction model should be put in competition with other existing prediction models to show its superior prediction performance</li> </ul>	
Subdomain	Consensus	Illustration
Research purpose	<ul style="list-style-type: none"> <li>The study goal should be precisely defined</li> </ul>	<ul style="list-style-type: none"> <li>To describe the association of a potential prognostic biomarker with allograft outcomes, to develop and validate a graft-survival prognostication system, to identify trajectories of patients based on the repeated measurements of a biomarker and their associations with outcomes, etc.</li> </ul>
Outcome	<ul style="list-style-type: none"> <li>The outcome(s) to predict and its timing should be precisely defined</li> </ul>	<ul style="list-style-type: none"> <li>Death-censored allograft failure, delayed graft function, antibody-mediated rejection, T-cell mediated rejection, all rejection, patient death, etc.</li> <li>For instance, the definition of any rejection type should be based on the Banff classification</li> </ul>
Population	<ul style="list-style-type: none"> <li>The population of interest should be precisely defined</li> </ul>	<ul style="list-style-type: none"> <li>Adult kidney recipients (e.g., recipients with kidney–pancreas combined transplantation, pediatric liver recipients, kidney recipients with AMR diagnosis at 1-year post-transplant, etc.)</li> </ul>
Parameters	<ul style="list-style-type: none"> <li>The data collection should be based on the relevant candidate prognostic factors adapted to the population and outcome of interest</li> <li>The methods to evaluate the parameters collected should be reported</li> </ul>	<ul style="list-style-type: none"> <li>For instance, to predict the allograft failure, functional (eGFR/proteinuria), histologic (Banff lesions), and immunologic data (anti-HLA DSA) are mandatory, in addition to basic characteristics of the recipient, donor, and transplant</li> </ul>
Statistical analysis	<ul style="list-style-type: none"> <li>The methods used to handle missing data should be reported</li> <li>The statistical model(s) used should be adapted to the outcome and the data</li> <li>The parameters included in the models should be prespecified before statistical analysis</li> <li>The methods used for parameters selection procedures should be reported</li> <li>Sufficient statistical power should be attained to interpret the models</li> <li>The number of patients and events in each analysis should be reported</li> </ul>	<ul style="list-style-type: none"> <li>For instance, multiple imputations by chained equation can be used, with continuous parameters imputed with random forest, and categorical parameters imputed with polynomial regressions</li> <li>Cox model, joint model, survival machine learning, logistic regression, latent class mixed model, etc.</li> <li>The parameters should be listed—for instance, in the study protocol or on <a href="https://clinicaltrials.gov">clinicaltrials.gov</a></li> <li>Such as backward elimination, Lasso selection, or elastic net selection</li> <li>For instance, for cohorts with a limited sample size, the rule of thumb of at least 10 events per parameter can be used</li> </ul>

(Continued on following page)

**Table 1 |** (Continued) **Recommendations for establishing a kidney failure risk-prediction system<sup>32–34</sup>**

Subdomain	Consensus	Illustration
If a prediction model is developed: transparent reporting	<ul style="list-style-type: none"> <li>The TRIPOD statement should be used when developing and validating a prediction model</li> </ul>	<ul style="list-style-type: none"> <li>In addition to the steps above, the key steps to develop and validate a prediction model are as follows: (i) univariate analysis (if the model is not a machine-learning model); (ii) multivariable analysis; (iii) performance assessment in the development cohort with validated metrics and methods (at least discrimination and calibration); and (iv) performance assessment in external validation cohort(s)</li> </ul>
Contextualization	<ul style="list-style-type: none"> <li>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</li> </ul>	
Impact in clinical practice	<ul style="list-style-type: none"> <li>The potential impact in clinical practice should be ideally demonstrated or at least discussed</li> </ul>	<ul style="list-style-type: none"> <li>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</li> </ul>

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 3.** The plan for retransplantation is a key decision point and is crucial in directing management.<sup>2,37</sup> For example, if a patient with a failing allograft is a transplant candidate, and a potential living donor has been identified, then IST would be maintained to minimize development of DSAs. Likewise, the presence of another transplanted organ, such as a pancreas

**Table 2 | Research agenda**

**Determining prognosis and kidney failure trajectory**

- Develop and validate eGFR equations for adult and pediatric KTR<sup>12a</sup>
- 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 toward 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 controlled trial or use of real-world data to determine the risks and benefits of continued immunosuppression treatment (see [Supplementary Table S1](#))

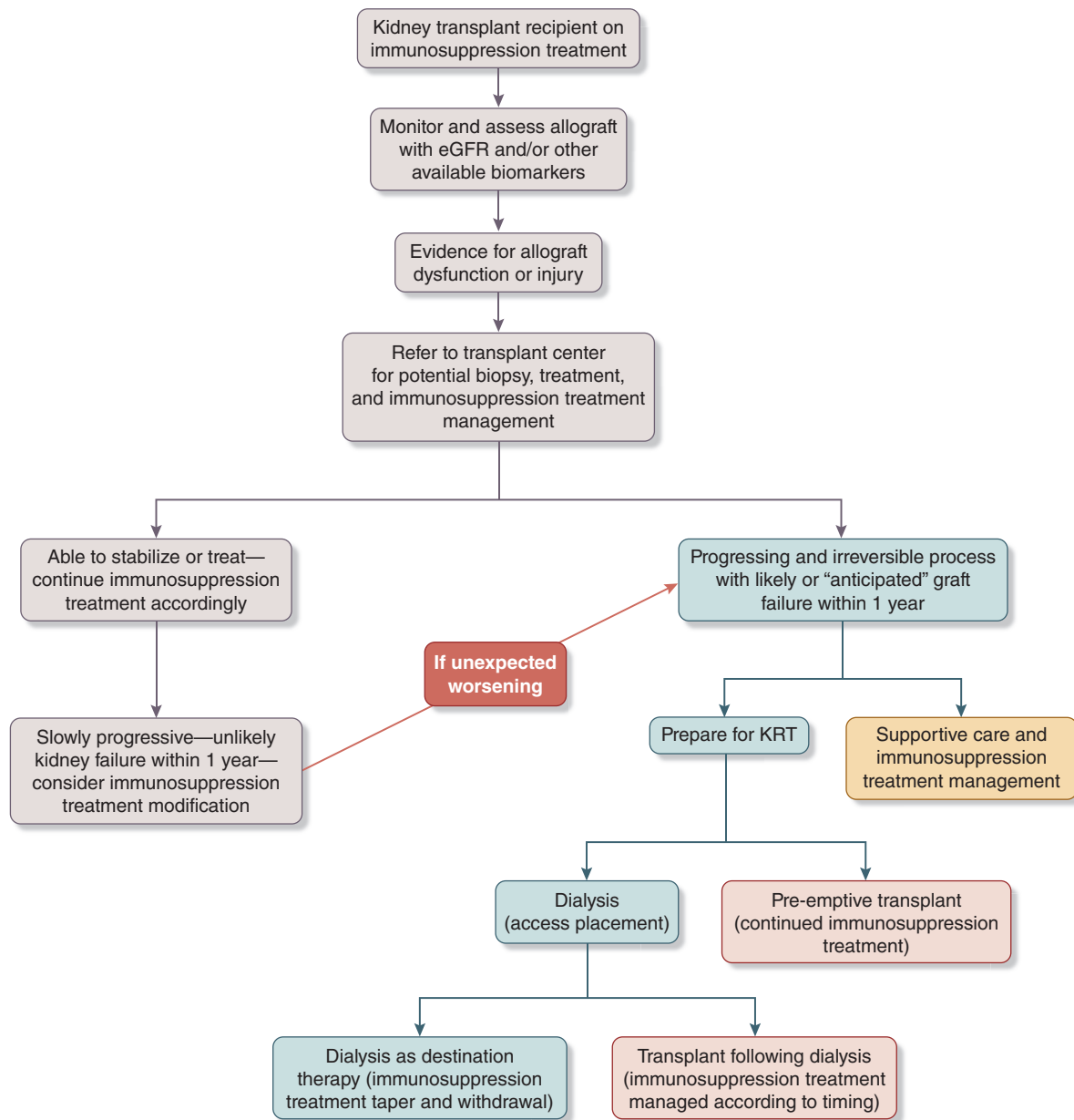
**Management of psychological effects and medical complications in kidney transplant recipients**

- Comparison of CKD MDC vs. Enhanced Transplant MDC with respect to outcomes and safety
- Identify the most important preventable complications that precipitate either 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 the psychological impact of the failing and failed graft

**Listing for retransplantation 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 yr)?
- Is there an optimal eGFR at which 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?
- Perform more 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; KTR, multidisciplinary clinic; MRA, mineralocorticoid receptor antagonist; PROM, patient-reported outcome measure; SGLT2i, sodium-glucose cotransporter-2 inhibitor(s); suPAR, soluble urokinase plasminogen activator receptor.



**Figure 2 | Integrated management and shared decision-making for a declining and failed kidney allograft.** eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy.

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. In the absence of concern about preventing HLA sensitization, maintaining IST has fewer potential benefits. For patients who do not wish to resume kidney replacement therapy, the goal is to maximize their time with a functioning graft—for example, by calcineurin-inhibitor minimization.

Points of consensus for management are shown in Table 4. The discussion focused on balancing the risks versus benefits of continued IST, as noted in Supplementary Table S1. The general consensus was 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, areas of controversy remain (Supplementary Table S1). These include the extent of residual kidney function or slope of change of function that would mandate a change. Additionally, care implementation was discussed (see below), as was the role of calcineurin-inhibitor withdrawal with the goal of prolonging kidney function, for example, by using costimulatory blockade (belatacept).<sup>38–40</sup> However, conference participants understood that no data for clinical use are available in this setting beyond expert opinion and clinical experience.

**Table 3 | Five key considerations for IST management in recipients with allograft functional decline**

Circumstance	Intent
<b>Intended kidney replacement therapy mode following graft failure</b>	
Preemptive transplantation	Avoid DSAs to facilitate next transplant; retain IST to merge into induction for next allograft
Dialysis and wait-listing for retransplantation	Need to balance dialysis safety, residual graft function, and development of DSAs; may be impacted by plans for graft nephrectomy
Dialysis, but not candidate for retransplantation	Imperative to minimize IST to reduce risks of infection and morbidity Risk of allosensitization less of a factor, balanced by need for graft nephrectomy
Supportive care	Need to maximize graft longevity and function
<b>Cause of graft failure</b>	
Non-alloimmune cause	
Recurrent glomerular disease	Does IST have a role 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	
Acute rejection	May require nephrectomy, as IST failed
Chronic rejection	Complex decision about control of rejection vs. safety
<b>Comorbid considerations impacting safety of IST</b>	
Sepsis, congestive heart failure, malignancy, diabetes, frailty, older age	Tailor to condition
<b>Past history of immunosuppression-associated adverse effects</b>	
	Previous or ongoing adverse events may direct therapeutic management
<b>Presence of another transplanted solid organ</b>	
	Protection of the other allograft takes precedence for IST management

DSA, donor-specific antibody; IST, immunosuppression treatment.

**The failed allograft**

Data on the efficacy of IST in the patient with a failed allograft<sup>41–43</sup> are limited and have been derived primarily from retrospective studies. Immunosuppression management with a failed allograft differs conceptually from that with a 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, reasons to continue it for a while are present. For example, IST may prevent sensitization,<sup>44,45</sup> chronic inflammation, as well as the need for nephrectomy and has

**Table 4 | Consensus points for immunosuppression management**

Strategy	Consensus points
Maintain IST	<ul style="list-style-type: none"> <li>Continue IST in patients considered transplantation candidates who have an identified living donor or a short expected waiting time for a deceased-donor organ (though there is no consensus on what constitutes a “short” waiting time)</li> <li>Continue IST in patients with other solid-organ transplants</li> <li>Provide IST at a threshold level to prevent overt rejection, minimize sensitization, and maintain residual function</li> </ul>
Taper IST (reduction to minimal or none)	<ul style="list-style-type: none"> <li>In patients not considered for retransplantation</li> <li>In patients with severe complications/side effects, especially infections and malignancies</li> <li>On dialysis, once graft function ceases, corticosteroids should be maintained and should be the last medication tapered for those on corticosteroids maintenance (i.e., adrenal dependency)</li> </ul>
Allograft nephrectomy	<ul style="list-style-type: none"> <li>In patients with severe rejection or graft-intolerance syndrome unresponsive to IST</li> </ul>

IST, immunosuppression treatment.

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,<sup>43</sup> 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.<sup>36,45–50</sup> Hence, a note of caution is needed when IST is maintained without a clear endpoint, as noted in Table 4 and Supplementary Table S2. In a recent survey of US transplantation centers, the estimated waiting time for retransplantation was found to be an important consideration in IST withdrawal.<sup>37</sup> If the estimated waiting time was more than 3 years, and no living donor was involved, nearly 50% of respondents recommended discontinuation of all IST.<sup>1,2,37,43</sup>

When a decision to reduce immunosuppression is made, the method and protocol for reducing and discontinuing immunosuppression are neither consistent nor evidence-based.<sup>1,2,37,43</sup> Most commonly, discontinuation of antimetabolites occurs first, followed by calcineurin inhibitor, and corticosteroids last.<sup>37</sup>

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 the paucity of data, guidelines rely on expert opinion, and various guidelines suggest different IST weaning strategies.<sup>1,2,51</sup> For patients pursuing another kidney transplant (especially if they are likely to receive a preemptive retransplant), 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, an approach without good supporting evidence.<sup>48</sup> Many patients have received steroids for many years, and therefore steroids can be tapered only slowly in order to avoid hypocortisolism. In summary, no objective criteria are available to guide the order and timing of IST withdrawal.

### Allograft nephrectomy

Special consideration was given to the issues around allograft nephrectomy (Supplementary Table S2), and possible deterrents include operative morbidity and mortality.<sup>52</sup> 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.<sup>53–55</sup> Another situation requiring urgent nephrectomy is severe acute rejection that is unresponsive to bolus corticosteroids, with pain and hemorrhage.<sup>56</sup> The indication for severe anemia and other evidence of chronic inflammation were identified as potential reasons for nephrectomy, as noted in large retrospective studies.<sup>57</sup>

With HLA antibodies developing after discontinuation of immunosuppression, the role of nephrectomy in exacerbating this issue was discussed. The findings in the literature are conflicting, and whether this development is related to sensitizing events prior to graft removal is unclear.<sup>41,46,53,58–62</sup> Likewise, the data are limited and inconsistent on the impact of “prophylactic” or “preemptive” nephrectomy on HLA-DSA development prior to IST withdrawal (<https://atcmeetingabstracts.com/abstract/elective-allograft-nephrectomy-after-transplant-failure/>).<sup>63,64</sup> 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 start of dialysis—determined by the GFR trajectory—especially in those individuals without functional vascular access. The retransplantation evaluation process should 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 retransplantation evaluation process early increases the possibility of identifying a living kidney donor and preemptive retransplantation.

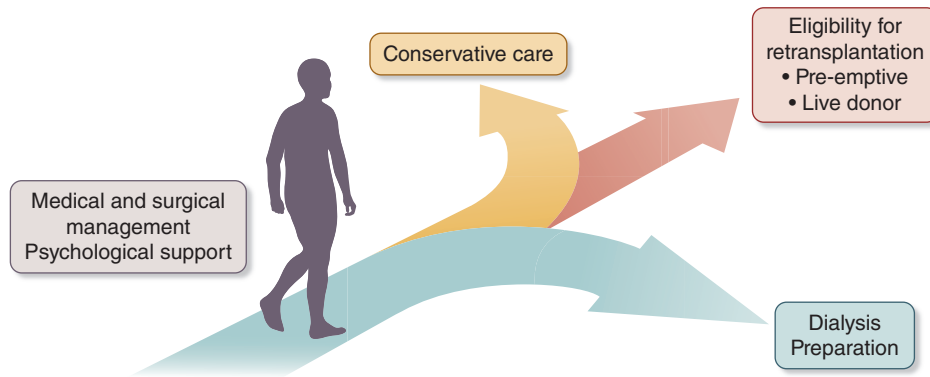
From the initial interaction with the transplantation team, patients should be fully informed of all possible transplantation outcomes, including the possibility of the need for future retransplantation. Although the issue is difficult to address, the potential for allograft loss should be discussed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

#### Psychological management

Informing KTRs that their allograft is failing can elicit a range of emotions and reactions, including shock, depression, anger, self-harm, and grief.<sup>65</sup> Transplant failure causes



The kidney transplant recipient in transition



**Figure 3 | The Road Ahead: The transplant recipient with low and deteriorating kidney transplant function.** Adapted with permission from Wolters Kluwer Health, Inc.: Agrawal N, Pavlakis M. Caring for the patient with a failing allograft: challenges and opportunities. *Curr Opin Organ Transplant.* 2019;24(4):416–423.<sup>71</sup> [https://journals.lww.com/co-transplantation/Fulltext/2019/08000/Caring\\_for\\_the\\_patient\\_with\\_a\\_failing\\_allograft\\_9.aspx](https://journals.lww.com/co-transplantation/Fulltext/2019/08000/Caring_for_the_patient_with_a_failing_allograft_9.aspx) Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved. The Creative Commons license does not apply to this content. Use of the material in any format is prohibited without written permission from the publisher, Wolters Kluwer Health, Inc. Please contact [permissions@lww.com](mailto:permissions@lww.com) for further information.

significant upheaval to a number of life domains, including relationships (family planning, sexuality, role change), finances (reduced ability to work, insurance issues, etc.), social interactions (reduced activities, travel, etc.), quality of life (fatigue), and for pediatric recipients, a more difficult transition to adulthood.<sup>65</sup> The medical and psychological consequences are particularly difficult to manage for individuals residing in low-income countries, those who obtained paid kidney grafts, and/or anyone for whom available kidney replacement therapies are minimal. Adapting to this new reality is challenging for many, and anticipating their

psychological needs is an important task for the transplantation 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. Also, participants noted that improving provider literacy on the key psychological concepts and competencies to help motivate, challenge, and support patients would be helpful.<sup>65</sup> Strategies to strengthen self-management capacity may be needed to address anxieties, minimize treatment fatigue, and support decision-making.<sup>65,66</sup> Studies specific to this cohort are limited.

**Table 5 | Management based on eGFR**

eGFR	Recommendation
Declining graft, if eGFR has consistently been >20 ml/min per 1.73 m <sup>2</sup>	<ul style="list-style-type: none"> <li>Referral to transplantation center for evaluation, with consideration of biopsy to determine diagnosis and potential reversibility, and specific interventions to stabilize and potentially improve eGFR</li> </ul>
Low (~20 ml/min per 1.73 m <sup>2</sup> ), but stable	<ul style="list-style-type: none"> <li>Integration of care or comanagement, with communication between transplantation center and nephrologist</li> <li>Optimal CKD management, including of blood pressure, anemia, proteinuria, metabolic acidosis, secondary hyperparathyroidism, cardiovascular issues, and malignancy surveillance, as per KDIGO guidelines</li> <li>Close monitoring of levels of immunosuppressants and side effects</li> </ul>
Low (~20 ml/min per 1.73 m <sup>2</sup> ) and declining	<ul style="list-style-type: none"> <li>Elicit life goals of patient and patient-centered/shared decision-making</li> <li>Establish dialysis modality and create appropriate dialysis access</li> <li>Only candidates for retransplantation with an established surgical date may initiate short-term dialysis with a tunneled catheter to optimize their presurgical medical condition</li> <li>If residual function of the allograft is present, evaluate whether to maintain low doses of immunosuppression, unless a contraindication to its continuation is present</li> <li>Monitor graft function, secondary complications of CKD, and clinical symptoms, in order to initiate dialysis at the optimal time</li> <li>Introduce conservative (supportive) medical care options, if retransplantation and dialysis are not options</li> </ul>

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**

Topic	Recommendation
Pre-transplantation education	<ul style="list-style-type: none"> <li>Education about the potential for allograft loss should be discussed in the initial transplantation evaluation process</li> </ul>
Post-transplantation education	<ul style="list-style-type: none"> <li>Patients should be fully informed of all possible outcomes with transplantation, including the possibility of the need for retransplantation in the future</li> <li>Potential for allograft loss should be discussed with the patient at the point of occurrence of every immunologic or nonimmunologic event that has the potential to affect kidney function</li> <li>Discussions concerning the trajectory of potential accelerated decline should occur when the eGFR drops below 30 ml/min per 1.73 m<sup>2</sup> and appears to be associated with rapidly declining function</li> </ul>
Vascular access management	<ul style="list-style-type: none"> <li>Preserve functional AV access, in the absence of disabling AV-access complications, especially in those with allografts with poor or declining function</li> </ul>
Preparing for graft failure	<ul style="list-style-type: none"> <li>Earlier conversations allow for improved planning and acceptance by the patient</li> <li>Patients with failing grafts should have ready access to multidisciplinary teams to allow a smooth transition to retransplantation listing and/or initiation of dialysis</li> </ul>
Retransplantation	<ul style="list-style-type: none"> <li>Preemptive transplantation should be the preferred approach</li> <li>Living-donor transplantation should be offered in all instances in which an acceptable living donor is available and no recipient-related contraindications for retransplantation are present</li> </ul>
Standards for retransplantation	<ul style="list-style-type: none"> <li>Transplantation centers are encouraged to develop their own guidelines for transplantation consideration</li> <li>All guidelines, such as the OPTN and KDIGO guidelines, should be applied without bias</li> <li>The need for a second transplant should not be regarded as the sole criterion to either restrict or promote candidacy</li> </ul>
Nonadherence	<ul style="list-style-type: none"> <li>Medication nonadherence should be identified, fully investigated, and addressed, to avoid recurrence</li> </ul>
Substance abuse	<ul style="list-style-type: none"> <li>Marijuana use should not be an absolute contraindication for retransplantation</li> <li>Clinicians should look for evidence of other modifiable risk factors that are often associated with dependence and attempt to address these issues prior to retransplantation</li> </ul>

AV, arteriovenous; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; OPTN, Organ Procurement and Transplantation Network.

Since periods of depression are common for many patients, and they 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 should be consulted as necessary.<sup>67</sup> For patients who are in the process of losing a live-donor allograft, additional support may be needed to help resolve guilt and depression in not only the recipient but also the donor.<sup>68,69</sup> Important to note is that depression is associated with poor patient outcomes, thus highlighting the need to screen and support.<sup>70</sup> Given the psychological impact, access to a clinical psychologist is most strongly recommended. This period is one of psychological vulnerability for patients. Even if past behaviors, such as medication nonadherence, may have contributed to the outcome, caregivers should avoid blaming patients for graft failure, but rather should be supportive.

The conference participants felt that patients need to be allowed adequate time 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<sup>71</sup>). The educational tools

should include peer support. Although peer support is strongly encouraged, the level of engagement with this resource has been low.<sup>72,73</sup> Barriers include low provider referral rates, challenges in matching patients to support persons, and the need for support-person training. To overcome these barriers, patient peer support should be incorporated into the educational tools.

### Medical management

During the conference, communications guided by eGFR level were discussed (Table 5). If the transplantation and dialysis teams are separate, identification and initial communication with the dialysis team should begin when the eGFR is  $\leq 20$  ml/min per 1.73 m<sup>2</sup>, and/or if a rapid and apparently irreversible decline occurs, no matter the level of eGFR. Treatment has to be aligned with community physicians or general nephrologists who are managing the CKD. Management of complications, including anemia and CKD–mineral bone disease, should align with the severity of CKD for the nontransplant patient. Patients will need modality counseling, which ideally would include different dialysis modalities, options for wait-listing (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 they return to dialysis,<sup>54,74,75</sup> and the rate of preemptive retransplantation or relisting is very low (around 15%, per US transplant registry data).<sup>41,54,76,77</sup> Taken together, this finding points to the need for better coordination among the various factions of the patient's healthcare providers. Whether the recipient has a failing versus a failed allograft will necessitate different coordination schemes. No evidence or guidelines in this regard exist, so we recommend a "common sense" approach that needs to be adapted according to the national–regional–local healthcare 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, dietitians, 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. The worldwide need for more comprehensive transplant insurance policies and financial coverage through this phase of transplant is clear. Given that patients are at risk for needing dialysis, controversies and consensus regarding the failing transplant cohort parallel those regarding patients with progressive CKD.<sup>78,79</sup> The entry criteria making patients most likely to benefit, and the optimal provider composition (nurse, physician, dietician, social worker, transplant pharmacist, etc.) for CKD MDCs, are unknown and may differ among centers and countries, thus constituting significant knowledge gaps.<sup>80</sup> Analysis of cohort trials suggests significant benefit, but results of small randomized trials are equivocal.<sup>81,82</sup> Although the extent to which MDCs improve outcomes is not clear, no evidence indicates harm.

In sum, the potential options for those with advanced and deteriorating kidney transplant function are to either refer them to a general nephrology MDC with expertise in patients needing imminent dialysis and/or decisions to pursue conservative care, or alternatively, enrich the transplant clinic with providers capable of managing this select group of patients, helping them transition to the next treatment modality. Some transplantation centers are already sending patients to a general nephrology CKD MDC before dialysis is needed, and others care for patients until the start of dialysis or conservative care is pursued.<sup>83</sup> Although maintaining patients within the transplantation 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 psychological 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.<sup>84–86</sup> Several participants suggested the

use of checklists at patient encounters, to help achieve goals.<sup>71</sup> Other clinic activities were discussed, including routine screening for frailty and cognitive decline; however, these activities do not have clear net benefits.<sup>87,88</sup>

Ideally, IST management is integrated into the overall healthcare plan with interdisciplinary care clinics, or if available, MDC clinics, with a focus on optimization of adjunct CKD therapy.<sup>89</sup> 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.<sup>2,37</sup> Another question is whether the care can be expedited/integrated using telehealth approaches. Novel telehealth approaches may be one way to improve communication between transplantation centers and local physicians and between transplantation centers and patients, but benefits need to be shown.<sup>90–92</sup>

Monitoring strategies were also discussed, and the patients' goals and desires must be considered.<sup>93,94</sup> 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<sup>95</sup> 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.<sup>96</sup> What is not clear is whether these findings relate to less-than-optimal care by transplant physicians, an inflammatory state caused by a failing allograft, ongoing immunosuppression, and/or the unmeasured burden of kidney disease predating transplantation. Hospitalization rates in the 6 months before dialysis initiation are especially high.<sup>97</sup> The use of central venous catheters for the initiation of dialysis is also high, as is the mortality incidence in those starting dialysis urgently in the hospital.<sup>75,97</sup> Hospitalizations are associated with acute kidney injury that can precipitate the need for dialysis but also subsequent cardiovascular events.<sup>96,98,99</sup>

KDIGO has published and updated numerous guidelines addressing controversies in the care of patients with kidney disease and transplantation.<sup>100</sup> 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 sodium–glucose cotransporter-2 inhibitors, has had limited examination in kidney transplant recipients.<sup>101</sup> For the cohort with low and declining allograft function, when to stop potentially beneficial medications as the eGFR falls to <20 ml/min per 1.73 m<sup>2</sup> is also unclear.<sup>101</sup>

Significant gaps in knowledge in this area remain, and future studies are warranted in this population. Based on

**Table 7 | Key takeaway points**

Determining prognosis and kidney failure trajectory	<ul style="list-style-type: none"> <li>• Wider implementation is needed of prognostication systems developed specifically for kidney transplant recipients that accurately predict allograft failure, across the range of short-term to long-term failure</li> <li>• The use of accurate kidney transplant-specific prognostication systems would enable improved allograft management as well as activated patient engagement</li> </ul>
Management of immunosuppression	<ul style="list-style-type: none"> <li>• Immunosuppression management in the transplant recipient with a failing or failed kidney transplant must be individualized and based on risk-vs.-benefit considerations</li> <li>• Decisions on whether and how to taper and/or withdraw immunosuppression are based on consensus or common sense, as no data are available to guide these decisions</li> </ul>
Management of psychological effects and medical complications in kidney transplant recipients	<ul style="list-style-type: none"> <li>• From a patient perspective, psychological support for patients with a failing or failed kidney transplant is paramount</li> <li>• Patient outcomes could be improved by better preparing patients and minimizing adverse events during the transition phase</li> </ul>
Listing for retransplantation and/or return to dialysis	<ul style="list-style-type: none"> <li>• Dialysis access preparation for individuals with failing allografts who will start dialysis improves outcomes</li> <li>• Psychological support is an integral part of managing patients with a failing or failed kidney transplant</li> </ul>

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 RETRANSPLANTATION AND/OR RETURN TO DIALYSIS**

Mental health and social support services should be provided for those individuals for whom kidney retransplantation is contraindicated. Although transplantation centers have their own eligibility criteria for retransplantation, 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 to list a patient with a failing allograft should be required to direct these individuals to centers that might be willing to consider these individuals as candidates. All centers should ensure that transparency around both relisting criteria and access to the wait list occurs ([Table 6](#)).

Patients should be encouraged to identify potential living donors to increase the potential that they can receive a preemptive transplant. However, listing for retransplantation should not be made conditional on the recipient candidate having potential living donors.

#### **Considerations for optimal planning of kidney replacement therapy**

Although prior arteriovenous (AV) access often fails over time in transplant recipients, patients should be encouraged to protect their fistulas after undergoing transplantation. No data suggest that ongoing dialysis access maintenance procedures (angioplasty, stenting, etc.), with the patient's exposure to nephrotoxic dye, are warranted or beneficial. A study examining the use of administrative data from 2011–2013, comparing those recipients who

underwent AV access ligation to those who did not, was unable to demonstrate any association of the procedure with either post-transplant allograft failure or reductions in all-cause mortality.<sup>102</sup>

Ligation of AV access in those with well-functioning transplants preferably should 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 AV fistula, is associated with a 22% increased risk of all-cause mortality,<sup>103</sup> and lack of referral to a general nephrologist is a predictor of catheter use.<sup>75</sup> A 3-fold greater risk of sepsis occurs with central venous catheter use 3–6 months after transplant failure, which has been shown to increase mortality.<sup>75,103,104</sup> However, the need to establish a functioning AV fistula does not apply to retransplant candidates who have an established surgical date for receiving a living-donor transplant, who may initiate short-term dialysis with a tunneled catheter to optimize their presurgical medical condition.

No specific guidelines have been developed for the timing of dialysis initiation based on eGFR. Results of studies in transplant-naïve 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 in the setting 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 the timing of dialysis initiation be based on clinical factors and symptoms rather than on eGFR evaluation alone. As patients transition back to dialysis, communication with the accepting dialysis unit and confirmation that the patient understands the plan are critical (Table 6). Clinicians should educate themselves about how conservative/palliative medical care options can assist patients through periods of transition of care (not simply at the end of life). Research recommendations are outlined in Table 2.

## CONCLUSION

Post-transplant care should not only include immediate post-surgical care and management of immunosuppression but also encompass management of the failing and failed kidney allograft. The complexity of managing patients with a failing or failed kidney transplant is multilayered. This phase of the transplant graft function trajectory (Figure 1) represents a high-risk period for patient outcomes. First, 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. Yet the importance of identifying these patients and starting early discussions is paramount for not only the patient's psychological well-being but also the patient's medical care, in order to prepare for graft failure through preemptive transplantation, optimal dialysis access placement, or planning/referral for supportive care. Immunosuppression management is based on patient risks and potential plans for retransplantation. Coordination of care and communication among teams are 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 to more accurately define and identify patients with failing allografts, develop prognostication tools, formulate evidence-based approaches toward immunosuppression management, and focus on the implementation science of medical and psychological management for patients with failing and failed allografts. Key takeaway points from the conference are presented in Table 7.

## APPENDIX

### Other Conference Participants

Curie Ahn (Korea), Josefina Alberú (Mexico), Mary Baliker (USA), Eburn L. Bamgboye (Nigeria), Thelma Barber (USA), Melissa Bensouda (USA), Steve J. Chadban (Australia), Darshana M. Dadhanania (USA), Alicja Dębska-Słizień (Poland), Arnaud Devresse (Belgium), Beate Ditzgen (Germany), Kevin Fowler (USA), John S. Gill (Canada), Vivekanand Jha (India), Pascale Khairallah (USA), Greg A. Knoll (Canada), Uwe Korst (Germany), Austin Lee (USA), Christophe Legendre (France), Krista L. Lentine (USA), Edgar V. Lerma (USA), Elizabeth C. Lorenz (USA), Arthur J. Matas (USA), Sumit Mohan (USA), Sławomir Nazarewski (Poland), Irene L. Noronha (Brazil), Gregorio T. Obrador (Mexico), Rulan S. Parekh (Canada), Martha Pavlakis (USA), Julio Pascual (Spain), Helen L. Pilmore (New Zealand), Alexander R. Rosenkranz (Austria), Benaya Rozen-Zvi (Israel), Prabir Roy-Chaudhury (USA), Kazunari Tanabe (Japan), Christoph Wanner (Germany), Haimanot Wasse (USA), and Chul-Woo Yang (Korea).

## DISCLOSURE

MAJ has declared receiving grants from Apollo and Gift of Hope; consulting fees from Exosome Diagnostics, Immucor, Otsuka, UBC Pharmaceuticals, and Vera Therapeutics; speaker honoraria from Advanced Renal Education Program, American Society of Nephrology (ASN), Platform Q Health Education, University of Minnesota, and Weill Cornell; and travel support from Japanese Society of Nephrology. She has also declared participating on data safety monitoring for Thinker Study: University of Pennsylvania; holding a leadership role at ASN; and holding stock or stock options from Seagen. YB has declared receiving consulting fees from Transplant Solutions and speaker honoraria from Osmosis Editor via Elsevier. She has also declared participating on a data safety monitoring or advisory board for Savor Health (unpaid) and serving on the Board of Directors for Enduring Hearts (unpaid). KB has declared receiving the following payments to his institution: grants from Alexion, Astellas, Chiesi, CSL Behring, and MSD. He has also declared receiving consulting fees from Aicuris, Alexion, Carealytics, CareDx, CSL Behring, MSD, Natera, Neovii, Paladin, Pirche, Stada, Takeda, Veloxis, and Vifor; speaker honoraria from Alexion, MSD, Natera, Neovii, Paladin, Takeda, and Vifor; and travel support from and serving on data safety monitoring board for Aicuris, Alexion, Carealytics, CareDx, CSL Behring, MSD, Natera, Neovii, Paladin, Stada, Takeda, Veloxis, and Vifor. AL has declared receiving grants from KTDinnov, EU-TRAIN, Fondation pour la Recherche Médicale, INSERM, and the MSD Avenir Foundation; he has also declared patents pending on allograft failure monitoring. RBM has declared receiving grants from Verici Dx; consulting fees from Chinook Therapeutics, CSL Behring, Olaris Inc., and Verici Dx; participating on data safety monitoring boards for the National Institutes of Health (NIH) and advisory board for Natera; and holding a leadership role at ASN Policy and Advocacy Committee and Scientific Registry of Transplant Recipients Review Committee. BT has declared receiving grants from Astellas, Chiesi, and Novartis; consulting fees from Bristol-Myers Squibb, Chiesi, CSL Behring Biotherapies for Life, and Vifor; and holding a leadership role at Eurotransplant Kidney Advisory Board and Council of the International Pediatric Transplant Association (IPTA). MJ has declared receiving the following payments to his institution: grants from AstraZeneca; consulting fees from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, CSL Vifor, GSK, and Vertex Pharmaceuticals; speaker honoraria from AstraZeneca, Bayer, and Boehringer Ingelheim; and payment for expert testimony from Astellas and STADA-Eurogenerics. MJ has also disclosed receiving travel support from AstraZeneca and Boehringer Ingelheim, and serving as volunteer co-chair for KDIGO. WCV has declared receiving grants or contracts from the NIH; speaker honoraria from GSK, Pharmacosmos, and multiple universities and medical schools; participating on data safety monitoring or advisory boards for Akebia/Otsuka, Ardelyx, AstraZeneca, Bayer, Boehringer Ingelheim/Lilly, GSK, Merck Sharp & Dohme, Reata Pharmaceuticals, Unicycive, and Zydus Lifesciences; and serving as co-chair of KDIGO and associate editor of the *Journal of the American Medical Association*. All other authors declared no competing interests.

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## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

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

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

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