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The Failing Allograft: Updates from The KDIGO Challenges Conference

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A continued challenge in kidney transplantation is late allograft failure, which includes both death of the recipient with a functioning allograft as well as failure of allograft function. The KDIGO Challenges Conference was on 4 issues: the definition, management of immunosuppression, goals of care of the recipient, and developing practices to facilitate re-transplantation. This talk will summarize the discussion and opinions from the 4 working groups.

1. **Definition of allograft failure**. The patients participating in the conference recommended removing the term "failure" as this was interpreted to mean that they (the patient) had somehow 'failed". Although the term "failing" my unavoidably causing guilt and distress for patients, there may not be better terminology. The definition implies a predicted need for dialysis or transplant within a relatively short period of time, i.e., in weeks or months and not years. Prognostication includes not only estimating the trajectory of the decline in glomerular filtration rate (GFR), but also other parameters that may influence that trajectory, e.g., allograft histology and albuminuria [Raynaud M et al*. Kidney Int* 2021; 99: 186-197]. A definition of a failing kidney allograft is helpful if and only if it prompts proper management of immunosuppressive medications, metabolic complications of low kidney function, psychosocial issues, preparation and planning for dialysis and/or re-transplantation, or supportive care [Davis S, Mohan S. *Clin J Am Soc Nephrol* 2022; 17: 444-451]. 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 [Raynaud M, et al. *Lancet Digit Health* 2021; 3: e795-e805; Loupy A, et al. *BMJ* 2019; 366: l4923]. Projecting the timing of allograft failure is complex. The working group identified that includes multiple features such as histology, function and immunological responses. Such multi-composite models must be well studied and validated. One such example is the iBOX [Loupy A, et al. *BMJ* 2019; 366: l4923] that includes kidney function, proteinuria, donor specific HLA antibody and histology. Overall, comprehensive methodology and

transparent reporting should be encouraged. Importantly, the group recognizes that native-kidney-based prognostication models should not be used in kidney recipients as they cannot capture the complexity and determinants specific to this population. The prognostication models thus should be kidney-transplant-specific.

2. **Immunosuppressive management.** This was one of the more complicated discussions with wide ranging opinions but limited clinical data. Five overarching considerations for immunosuppressive therapy (IST) management include:
    a. The intended mode of renal replacement therapy following graft failure;
    b. The cause of Graft Failure: immunologic or nonimmunologic;
    c. The presence of co morbidities that may impact the safety of continued IST;
    d. Any past history of IST adverse events;
    e. The presence of another solid organ allograft

An overarching consideration is for those with expected re-transplantation within a year, and to mitigate the development of HLA donor specific antibody. On the other hand, exacerbation of comorbities such as congestive heart failure or in the setting of sepsis, may argue for IST reductions to preserve recipient life and other organ function. Strategies considered include IST tapering and while there is no consensus on which class and how quickly, a number of groups have made practice recommendations, even in the absence of data (Davis and Mohan, *CJSAN* 2022; Lubetsky M et al. *Am Jnl Transplant* 2021; 21:2937-2949]. Alternatively, conversion to a less nephrotoxic agent was discussed, and finally allograft nephrectomy in extreme cases. Data on the efficacy of IST in the patient with a failed allograft are limited and primarily derived from retrospective studies [Schrezenmeier E, et al. *Transpl Int* 2021; 34: 732-742; Garg N, et al. *Clin Transplant* 2022]. A recent prospective observational study in Canada did not demonstrate benefit on prevention of sensitization in patients who continued IST after graft failure [Knoll G, et al. *J Am Soc Nephrol* 2022; 33: 1182-1192], perhaps due to the unexpected finding in which participants were found to be nonadherent to IST after graft loss. Other studies demonstrate the side effects of continued IST, namely higher infection and malignancy rates, metabolic and cardiovascular complications

3. **Goals of care and management:** For all patients, a health care plan should include interdisciplinary care clinics, with a focus on optimization of adjunct CKD therapy as shown in the table [Johns TS, Yet al. *BMC Nephrol* 2015; 16: 161]. There was no consistent opinion about frequency of visits, collection of drug levels and assessment of immunosuppressant side effects. No evidence or guidelines exist on the extent of monitoring after allograft failure but have been suggested by expert opinion [Davis and Mohan CJASN 2022; Lubetsky M et al. *Am Jnl Transplant* 2021] .Care may be expedited/integrated using telehealth approaches. Importantly, communication between transplant center and local physicians and between transplant center and patients are important in this management. Care is needed to attend to the unique psychological features of loss of function coupled with sociological and economical impact to these patients as well.

Considerations for optimal planning of kidney replacement therapy

Residual kidney allograft function	Recommendation
eGFR low (approx. 20 ml/min/1.73 m²), but stable	• Establish co-management with nephrologist • Optimal CKD management including blood pressure control, anemia, proteinuria, secondary hyperparathyroidism, cardiovascular issues, malignancy surveillance as per previous KDOQI guidelines • Close monitoring of levels of immunosuppressants and side effects
eGFR low (approx. 20 ml/min/1.73 m²) and declining (loss of > 5 ml/min/1.73 m² per year)	• 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