Global Science. Local Change.

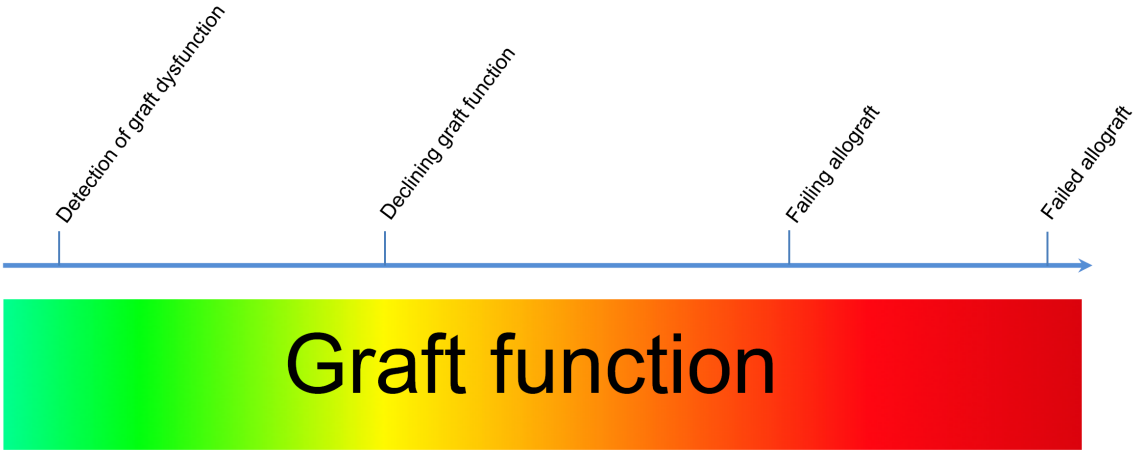
KDIGO Controversies Conference on Challenges in Management of the Kidney Allograft: From Decline to Failure

Scope of Work

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences on topics of importance to patients with kidney disease. These conferences are designed to review the state of the art on a focused subject and set priorities for improving patient care and outcomes. In addition to highlighting areas for which additional research is needed, sometimes the conferences lead to KDIGO guideline development efforts.

CONFERENCE BACKGROUND AND RELEVANCE

Kidney allograft survival has improved over the past several decades. In 1989, the half-life of an allograft from a deceased donor was 6.6 years while the current median half-life has now extended to about 12 years.[1, 2] Still, approximately 6000 allografts are lost every year just in the United States alone (*Dr. Rita McGill, personal communication*). Despite the increase in kidney longevity, kidney allografts do not survive as long as the recipients, usually failing after a course of deteriorating kidney function. The factors causing the transplants' demise are many, and may be immunological, infectious or metabolic in nature.[3] With declining allograft function, the associated morbidities of chronic kidney disease require additional medical monitoring and management.[4]



We are undertaking this Controversies Conference to explore the important but rarely examined clinical considerations of the management of declining allograft function as well as to address the poorly understood associated care gaps for such kidney transplant recipients (above figure). A patient with declining kidney transplant function is not only subjected to the specific side-effects of immunosuppression but he/she also faces a variety of other challenges. When the allograft fails and dialysis is reinstituted the patient is medically as well as psychologically vulnerable, and this transition period is associated with increased mortality for which little is known regarding how best to optimize his or her management and outcome.[5] The potential loss of a kidney transplant is a traumatic experience which both the nephrologist and patient may have difficulty facing. Furthermore, a return to dialysis may bring with it a loss of independence, escalating demands on family members, decreased income, and lifestyle infringements, as well as increased costs to payers and elevated risk of death. Additional counseling and other psychological support are often needed and should be a standard part of care. At present, the clinical care provided to these patients has remained variable and suboptimal.[6] Therefore, it is critically important for members of the nephrology and transplant health care teams to recognize and understand the specific needs for this group of patients by identifying key controversial issues and knowledge gaps in care management. The intent of this conference is to seek expert consensus where possible and to ascertain whether the current evidence base is sufficiently robust to establish a clinical practice guideline in this area and to determine what additional clinical research may be needed. Some aspects of care often encountered in this patient population include:

1. Prognosis and kidney failure trajectory

Understanding how quickly an allograft is failing is clinically important for the practitioner and the patient. Current kidney function equations, including both MDRD and Chronic Kidney Disease Epidemiology Collaboration Equation may not be optimal for use in kidney transplant recipients (KTRs). Analyses evaluating cystatin C-based equations, previously hindered by a lack of standardized assay, cost, and limited availability, have not consistently demonstrated superiority, and are not widely used.[7] The estimation of residual GFR in KTRs is an important research task. In addition, novel biomarkers such as KIM-1, suPAR, Dickkopf may provide insights into remaining kidney function.[8-10] The combination of several markers, with the potential use of artificial intelligence, may improve the future estimation of allograft function and help to stabilize GFR at least for a certain amount of time.[11-13] Liquid biopsies (e.g., cell free-DNA) and/or gene expression assessment in kidney allografts could provide earlier detection of and delay allograft dysfunction. These are innovative techniques and assays which deserve further consideration.[14]

2. Immunosuppression

The management of immunosuppression in KTRs with a declining GFR 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 it is better or worse for the patient.[15] A personalized immunosuppression approach would be helpful for the individual patient who returns to dialysis, taking into account his or her specific clinical course and side effects of immunosuppression. The lack of consensus makes this a relevant issue to examine closely.[16]

3. Management of complications

Patients with failing allografts who return to dialysis have high mortality rates.[17] Cardiovascular, malignancy, and infectious complications top the list of causes leading to death in this group. The risk of infection for KTRs is particularly high for patients who continue immunosuppression after allograft loss.[18] Despite the reduction in risk with

transplantation relative to dialysis, cardiovascular disease remains the most common cause of death in KTRs[19] just as in CKD patients. Beside the classical etiological risk factors such as smoking, dyslipidemias, hypertension and diabetes, studies show that compromised GFR from preexisting cardiovascular disease and obesity are superimposed risks that may further affect the kidney.[20] There are now pharmacotherapies (e.g., SGLT2i) with demonstrated organ-protective benefits for patients with CKD. Whether such improved outcomes are applicable in KTRs remain to be shown.

4. Transition to ensuing KRT (kidney replacement therapy)

The optimal time for a KTR with a failing allograft to transition to dialysis is not well defined despite a number of retrospective studies (registry data). One study indicated that for every 1 ml/min loss in eGFR, mortality is increased by 4%.[21] The identification of optimal timing and approach to transition of care from a functioning allograft to dialysis is therefore an important task since there are several medical challenges. When to initiate a discussion regarding transition to dialysis, the appropriate time for access placement, as well as the choice of modality are not well defined and understood. Other critical aspects to consider are proper timing of re-listing for kidney transplantation and when to initiate a search for a potential living donor.

Just as residual kidney function is important in both hemodialysis and peritoneal dialysis patients, attempts at preserving allograft residual kidney function in the transplant recipient returning to dialysis may be reasonable based on the manifold benefits seen in dialysis patients with residual native kidney function.[22]

Considerations for graft nephrectomy and its associated implications for sensitization, immunosuppression management, and optimal timing are also issues to be fully examined.[23]

Death with function (largely due to cardiovascular disease, malignancy and infections) and death censored graft failure each accounted for approximately half of allograft losses.[24] With an expected increase in incidence of patients with failed allografts returning to dialysis, it has been estimated that failed allograft patients in the US who are relisted on waiting list already comprised 14% of all prevalent patients on the list.[15] It is imperative to define elements of optimal management and outline research areas

that require further study so as to prolong that gift of life as much as possible and to provide the best quality of life for the transplant recipient.

CONFERENCE OVERVIEW

Drs. Michelle Josephson (University of Chicago, USA) and Martin Zeier (Heidelberg University, Germany) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full group for consensus building. This highly interactive conference will invite key thought leaders and relevant stakeholders in nephrology and other related disciplines, including patients, who will comprehensively review the literature and current state of understanding in this area and address clinical issues as outlined in the **Appendix: Scope of Coverage**. The conference output will include publication of a position statement that will help guide KDIGO and others on the optimal management and future research in this patient population.

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APPENDIX: SCOPE OF COVERAGE

Breakout Group 1: Prognosis and Kidney Failure Trajectory

1. What should be the definition of a "failing kidney allograft"? Also, should we be using KDIGO nomenclature and definitions: e.g. GFR rather than "kidney function" or "allograft function"?

2. How often should serum creatinine be measured in stable patients more than one year after transplant? Does more frequent monitoring increase adherence to immunosuppressive medications?

3. Does the eGFR formula used affect management of a transplant recipient? Are current eGFR formulas adequate in kidney transplant patients and if not why not?

4. What is the accuracy of 2021 new eGFR formula derived from native kidneys and is there any evidence on how they perform in transplanted kidneys?

5. Anti-HLA DSA screening is the currently most predictive and used "biomarker" used for screening patients for de novo DSA appearance. Is monitoring of any biomarker more effective than monitoring serum creatinine? What is the role of cell-free DNA? Gene expression profiling? Protocol biopsy?

6. Which transplanted populations should be screened for subclinical rejection?

7. What is the evidence that treating chronic active AMR is safe and effective? What is the evidence that treating chronic TCMR and/or subclinical TCMR is safe and effective?

8. Is "death with function" a premature death with stable kidney function?

9. What is the role of proteinuria for prognostication?

10. Is AI-based multimodality combination of functional, structural, immunological parameters able to achieve high performance for allograft outcome prognostication?

11. Strategies for preserving residual kidney function: What is the evidence that novel therapies that slow CKD progression (e.g., SGLT2i, MRAs) are safe and effective in kidney transplant recipients? Role of metformin?

12. What should be the role of iBox and other pronosticators?

Breakout Group 2: Immunosuppression Strategies

1. What are the critical overarching considerations regarding immunosuppressive (IS) treatment in this patient population?
    a. What are the considerations for a patient with a failing allograft in terms of IS management?
        - Residual allograft function? Side effects and toxicities such as infection and malignancy? Development of chronic inflammation and need for nephrectomy? Risks of nephrectomy? Candidacy for next transplant? Availability of a living donor? Sensitization status?
    b. Should the timing of detection of failure be a major consideration?
        - Early versus late, or as defined by an eGFR threshold
    c. Does age play a role: Should there be different considerations for pediatrics vs adults vs elderly adults?

2. How do we consider specific immunosuppression management?
    a. Can we prevent HLA sensitization and/or nephrectomy by continuing IS?
        - What IS (type, dosage, and level) is needed to prevent sensitization?
    b. Is it safe to maintain IS after graft failure? Is there an increased frequency of infection and malignancy?
    c. What are the risks of IS withdrawal? Is there an increased frequency of rejection, chronic inflammation or need for nephrectomy?
        - How should IS treatment decisions affected by transplant nephrectomy?

d. Are there specific agents that may be more harmful (or more effective) in failing allografts?
e. What criteria (e.g., age, transplant history, presence of donor specific antibodies, re-transplant candidacy, availability of living donor, residual function, diuresis, timing after return to dialysis, type of dialysis modality) can guide risk stratification for maintaining IS?
f. What criteria (eGFR, diuresis, transplant history, can guide order and timing of immunosuppressive withdrawal?
g. Are patients adherent to IS treatment after graft failure?
h. What monitoring strategies are needed to guide and adjust IS (drug levels, lab values, side effects, diuresis, inflammation, PRA, biomarkers)?

3. How may clinical IS management in this patient population be facilitated?
   a. Who should be taking the lead for management?
   b. How is integration with community physician or general nephrologist managing CKD occur?
   c. How is this management plan integrated into their health care?
   d. How frequently should the visits be for IS management? When should drug levels be checked?
   e. Can care be expedited/integrated using telehealth approaches?

Breakout Group 3: Management of Medical and Psychological Complications in Kidney Transplant Recipients

1) What is the preferred model of care to manage these complex patients? Refer to general nephrology multidisciplinary (MDC) clinics, routine transplant care or create special MDC transplant clinics for failing transplant recipients?
   a) Are patients managed by the transplant team until graft loss and beyond?
   b) Do transplant teams have the expertise and time to reach recommended CKD/CVD and diabetes care targets?
   c) Do they refer patients to back to primary nephrologist/dialysis center before graft loss?

d) What level of renal function (who should be referred) trigger referral to an MDC? What disciplines are required for an effective MDC?

2) Scope of Care for an MDC
   a) Would an increase in clinic patient visits/frequent nurse contact help prevent AKI/hospitalizations and reduce mortality and improve psychologic wellbeing?
   b) Would increase patient contact help facilitate patient decision making for transition to dialysis/modality choice/conservative care/palliative care?
   c) Can telehealth or other platforms help deliver care to these complex patients?

3) What are the different potential MDC models?
   a) What are their benefits and limitations?
   b) Should there be a shared coordinated care with other specialty clinics in selected patients (for example heart failure clinics, diabetes clinics) or should these MDCs broaden their scope of practice?

4) What types of psychological problems are experienced by this cohort and what types of interventions should be considered?

5) Are there unique challenges facing patients and physicians with a failing transplant compared to a cohort with progressive native kidney disease?

6) Is there a role for additional training to the providers on how to take care of patients with a failing graft?
   a) How should peer support interactions be facilitated by the MDC?
   b) What type of care should be included? Role of ancillary testing? What would routine screening for depression, frailty, and cognitive decline in performance provide for these patients and their health care team?

7) Goals of Care
   a) Is there new evidence to challenge standard guidelines recommendations for the management of CKD (anemia, blood pressure, cardiovascular disease) in the general population?

8) How do you measure performance of MDCs in transplantation?

Breakout Group 4: Recognizing Graft Loss: Patient Factors and Kidney Replacement Therapy

1. How do we define the "failing graft"?
    a. Is this defined as a specific percentage rise in creatinine alone or is there a better marker to define when to increase follow-up?
    b. If a graft is defined as failing, should the patient return to the transplant center if in the community or how does the patient transfer back to the original referring nephrologist?
    c. What is optimal schedule for follow-up and what specific tests should be ordered? Biopsy, imaging, CKD labs?
    d. Are there ways to delay the onset of failure or to slow the progress to failure?

2. How do we prepare the patient for a relisting and/or return to dialysis?
    a. Should there be ongoing education about the potential for graft loss even immediately after transplant?
    b. What should patients be told about saving dialysis access sites after transplant?
    c. Are there services to assist patients with their loss? Social workers, healthcare navigators, emotional support staff, insurance and financial coordinators? How are patients put in touch with these resources? Who will pay for these services?
    d. Who should initiate the conversations about the need to return to dialysis? Is CrCl of 20 an appropriate marker for listing for re-transplant?

3. What are the ways to assess patients for retransplant in a fair, transparent and uniform way?
    a. With the legalization of marijuana, is it appropriate to list or relist patients with significant marijuana use? What defines "significant"?
    b. Are there different ways to address patients who recognize the role of non-adherence vs those that do not?
    c. Prior studies have shown high failure rates in patients who are re-transplanted who had documented non-adherence. Should the

transplant centers have special requirements and how would they be applied fairly?

d. Should there be uniform standards considered for re-transplantation?
e. Should patients be encouraged to seek out a living donor or be required to find a living donor for retransplant?

4. What are the considerations for optimal KRT planning? Factors to consider include: re-transplant listing criteria or return to dialysis (e.g., timing of initiation, modality selection; optimal dialysis access and fistula creation; role of residual kidney function?

5. When do we consider conservative care as the appropriate option? How can we optimize the provision of supportive care, social care (e.g., workplace, etc.)?

6. Should transplant nephrologists be involved in monitoring graft function after return to dialysis, or are we "giving up" on the graft at that point? How often should the graft be monitored after return to dialysis? Should dialysis prescription be altered based on degree of graft function?

7. Are there specialized needs required in specific populations such as older adults, pediatrics, women?