Managing the patient with failing kidney allograft

Terms and Conditions

HOW SHOULD WE DEFINE "FAILING KIDNEY ALLOGRAFT"?

- Overall, the failing allograft is a continuous process and we should take this into account in the definition.
- Avoid "*failing*" and its negative connotations, use:
  - "*low function & stable*" or "*low function & declining*"
  - "*transition period*"
- GFR is currently the most used measure of allograft function but alone its performance is insufficient for predicting the long term allograft failure. Multiple factors should be taken into account (functional, histological, immunological, etc.) to accurately predict allograft failure and then define what a failing allograft is.
- Two key elements in the definition:
  - Predicting return to dialysis or re-transplant
  - Estimating time to dialysis or re-transplant
- Importance of managing:
  - Immunosuppression, metabolic changes, psychosocial issues, preparation & planning for dialysis, re-transplant, palliative care

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?

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?

- Failing allograft/ Allograft at risk for failure is defined:
  - Absence of an acute rejection
  - eGFR <= 30 ml/min/1.73 m^2
  - Rapid progression in eGFR defined as a sustained decline in eGFR of more than 5 ml/min/1.73 m^2 /year.
  - IFTA >50% and/or Glomerulosclerosis >50% on kidney biopsy

- Kidney biopsy should be done at an eGFR below 30 ml/min/1.73 m^2 for prognostication and possible immunosuppression adjustment.

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?

- Patients with failing allografts should be followed closely by a nephrologist/transplant nephrologist.
  - Conversations should be initiated by the nephrologist following the patient at the time the graft is determined to be at risk for failure.
  - Patients with declining kidney function need to have an acute rejection ruled out.
  - Improved communication between transplant general nephrologists (when distinct as in the US) is essential to prolong allograft function and optimize management of CKD complications and goals of care.
  - Patients will need modality counseling, preparation for relisting or conservative therapy as appropriate.

c. What is optimal schedule for follow-up and what specific tests should be ordered? Biopsy, imaging, CKD labs?

- Using KDIGO CKD, anemia and MBD guidelines, follow-up is recommended as follows:
  - Follow up at intervals of 3–6 months for CKD stage 3A, 3 months for stage 3B, 1–3 months for stage 4, and 1 month for stage 5
  - For CKD patients with anemia not being treated with an ESA, measure Hb concentration when clinically indicated and at least every 3 months in patients with CKD 3–5
  - Serum levels of calcium, phosphate, PTH levels to be measured every 6-12 months in CKD G3a–G3b, every 3–6 months in CKD 4 (PTH every 6-12 months); and every 1–3 months in CKD5 (PTH every 3–6 months).
- We recommend a kidney biopsy when eGFR <=30 ml/min/1.73 m^2 for prognostication and potentially findings that might alter immunosuppression management - such as CNI avoidance or increasing immunuosuppression for chronic active AMR. [1,2]

1. Durr, M et al.Transplant Proc 2017
2. Schulte, K et al. J Nephrol 2017

d. Are there ways to delay the onset of failure or to slow the progress to failure?

- Recommend the KDIGO 2012 CKD management and evaluation guidelines, section on Prevention of CKD progression:
  - BP and RAAS interruption
  - Protein intake
  - Glycemic control
  - Salt intake
  - Lifestyle

- CNI minimization/elimination when clinical situation allows. [1,2]

1. Durr, M et al.Transplant Proc 2017
2. Schulte, K et al. J Nephrol 2017

What is a failing allograft ?

Allografts with different degrees of dysfunction including chronic kidney disease (CKD) stage 4 and CKD stage 5 may be perceived as failing.

the failing allograft should be broadly defined to include all of the following:

- stable but low allograft function,

- declining function (when there is irreversible and progressive decline in kidney function with anticipated allograft survival of less than 1 year), and return to renal replacement therapy.

<u>+ laboratory symptoms (low Hb, acidosis, K/Na, Ca/P disturbances) and clinical symptoms (blood pressure control, oedema)</u>

- **Lubetzky 2021** *Am J Transplant*. 2021;21:2937–2949.

How frequently should the visits be for IST management? When should drug levels be checked? In the specific context of allograft failure

- In a stable KT recipient, monitoring is required every 3-6 months (Baker *BMC Nephrol* 2017) or 2-3 months (*KDIGO*) after one year of transplantation.
- **When allograft fails…no evidence/guidelines**
- **Monitoring strategies needed to guide and adjust IS**
  - Role of drug levels, lab values (i.e. refractory anemia, hypoalbuminemia), side effects, inflammation, PRA, other biomarkers?
  - Patients on dialysis with failed kidney transplants have worse anemia and albumin– impact of IST? (Huml Am J Neph 2019)

How frequently should the visits be for IST management*? When should drug levels be checked? In the specific context of allograft failure

Allograft failure

« Intense» monitoring*
- Acute rejection
- Severe BKV
- Active malignancy
- IS side effect
- Non-adherence
- Polymedication-interaction
- Candidate for early retransplantation (*e.g.* living donor)
- High cPRA?

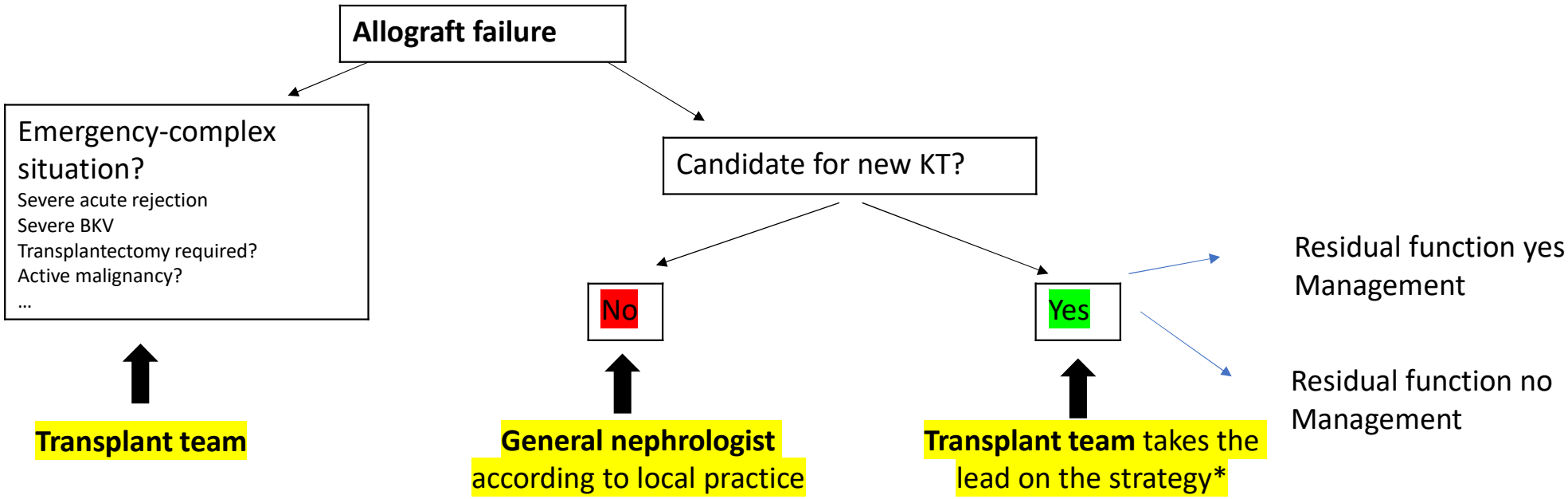
« Regular» monitoring*
- No rejection
- No IS complication
- Not candidate for retransplantation

Geography
Insurance
Culture

Issues to address:
- Cost-effectiveness
- Logistics
- Which « IS » target depending of clinical situation?

*Optimal frequency is unknown and deserves further investigations.

Who should be taking the lead for management in the specific context of allograft failure?



In all cases, the patient must closely be informed.

*Depending on living donor availability, PRA, expected time on WL, comorbidities, etc…

Is it safe to maintain IST after graft failure?

- **Yes, but…..**

- **Retrospective studies also suggest an increased risk of both infections and malignancy with continued immunosuppression.**
  - Higher CV mortality
  - More frequent opportunistic infections
  - Higher infectious mortality

Smak-Gregoor P, *Transplantation* 1997
Rao P, *AJKD* 2007
Woodside K, *Transplantation* 2014
Casey M, *Transplantation* 2014

What are the risks of IS withdrawal? Is there an increased frequency of rejection, chronic inflammation or need for nephrectomy?

- **YES – retrospective studies suggest an increased risk of rejection, chronic graft intolerance syndrome and nephrectomy after withdrawal, but data on frequency are less clear.**

Smak-Gregoor P, *Transplantation* 1997
Rao P, *AJKD* 2007
Woodside K, *Transplantation* 2014
Casey M, *Transplantation* 2014

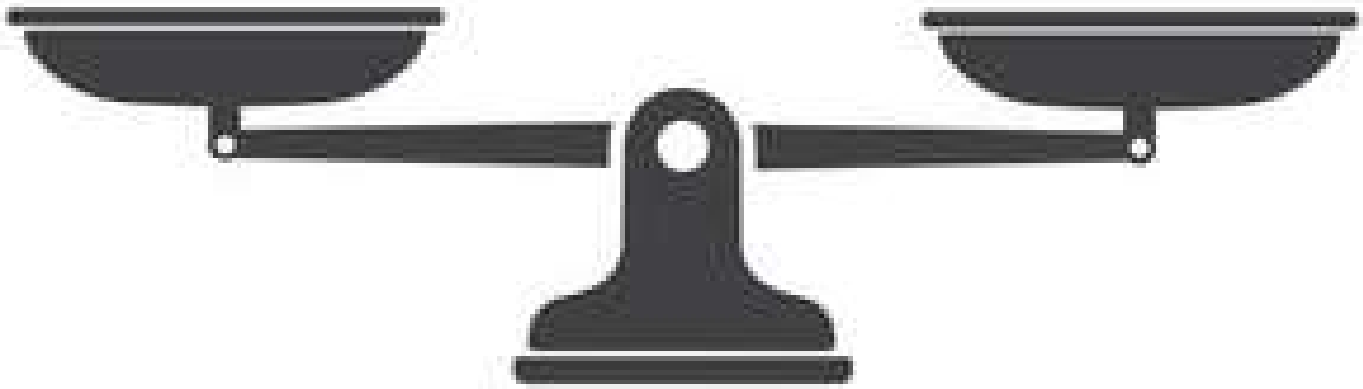
Pros and cons of maintaining IS after graft failure

PROS

- Less sensitization
- Preservation of residual renal function
- Decreased graft intolerance syndrome
- Prevention of adrenal insufficiency or systemic disease flares

CONS

- More infections *(Woodside Transplantation 2014; Gregoor Clin Transplant 2001; Gregoor Transplantation 1997)*
- More malignancies *(van Leeuwen BMJ 2010)*
- Increased mortality from infection and cardiovascular disease *(Smak Gregoor Clin Transplant 2001)*



Role of allograft nephrectomy

- **Advantages of nephrectomy**
  - Eliminates inflammation *(Lopez Gomez JASN 2004)*
  - May be associated with higher rates of retransplantation *(Ayus JASN 2010)*
  - Associated with improved survival following allograft failure *(Ayus JASN 2010)*
- **Disadvantages of nephrectomy**
  - DSA and non-DSA anti-HLA antibodies may develop if IS stopped after allograft nephrectomy *(Del Bello Transplantation 2012; Abouljoud Transplantation 1995; Schleicher Transplant Int 2011)*
  - Operative morbidity
- **Alternatives to nephrectomy**
  - Consider embolization if graft fails after 1 year *(Spanish guideline Nefrologia 2009)*

Are there specific agents that may be more harmful or more effective in failing allograft recipients?

- **Failing allograft – "do not harm"**
  - **before intensifying IST weigh potential benefits and risks,**
  - **communicate and manage expectations**
  - **include different perspectives into shared decision making**
  - **consider CNI Withdrawal e.g. double therapy, Belatacept as a potential "rescue therapy"**

- **Failed allograft –**
  - **less clear, decisions to withdraw /maintain mainly driven by side effects, e.g. anemia, infection, tolerability, cost, patient preferences….**

KDIGO KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES

How does integration with community physician or general nephrologist managing CKD occur?

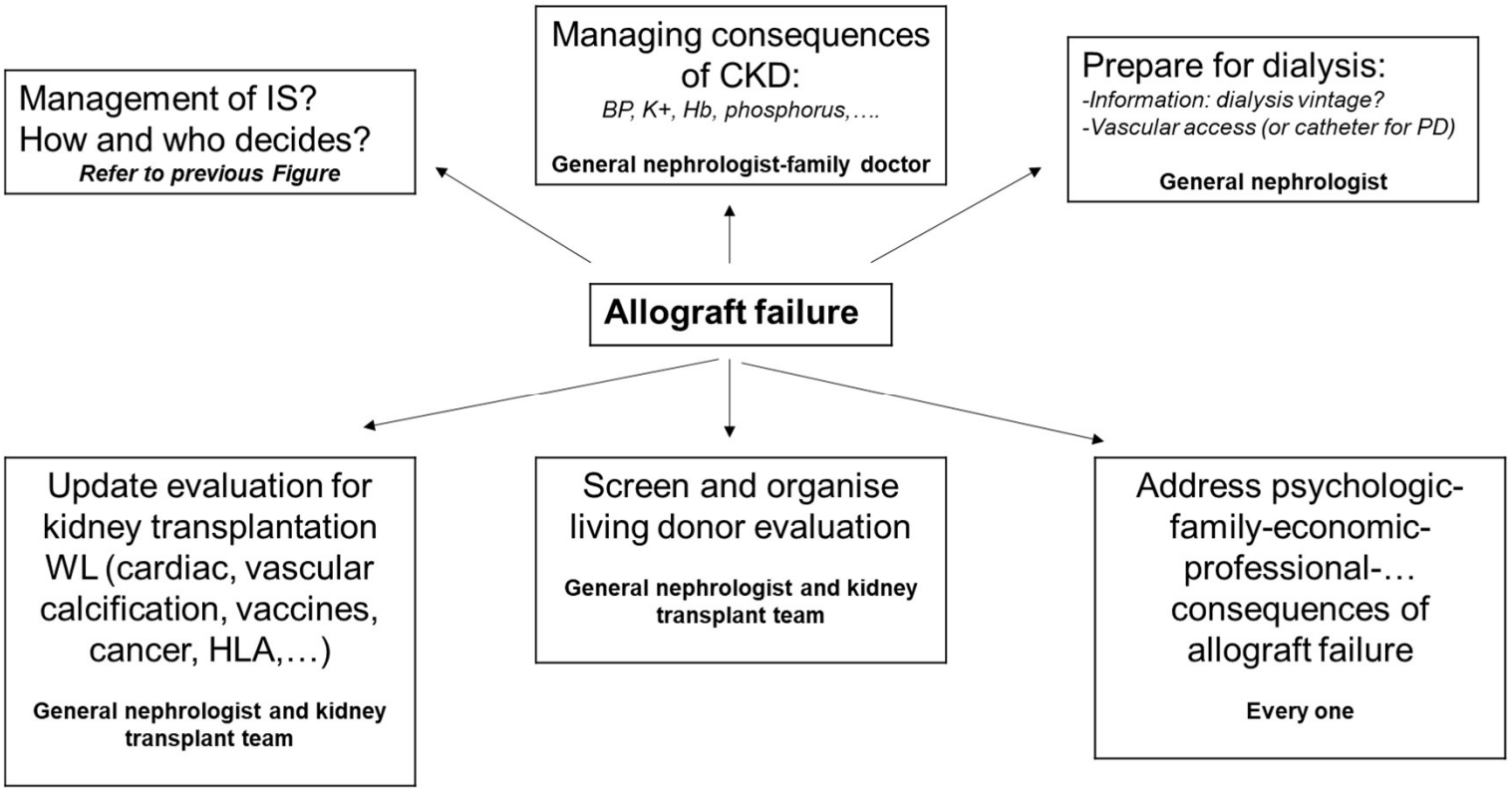
- Evidence/guidelines? No

- **Current situation is not optimal in many centers:**
  - 65% of patients with failed allograft have no vascular access when returning to dialysis (*Chan CJASN 2014, Zhang AJKD 2015*)
  - Rate of preemptive re-transplantation or relisting is very low (around 15%-US transplant registry data) (*Schold AJT 2020; Vinson 2022*)

Taking together, it suggests that the coordination between the different actors of the patient's health care needs to be improved. The next slide shows such a model and summarizes the challenges to the recipient.

KIDNEY DISEASE · KDIGO · IMPROVING GLOBAL OUTCOMES

How does integration with community physician or general nephrologist managing CKD occur?



How is this management plan integrated into their health care?

Johns *et al. BMC Nephrology* (2015) 16:161
DOI 10.1186/s12882-015-0158-6

REVIEW **Open Access**

Interdisciplinary care clinics in chronic kidney disease

Tanya S. Johns[1*], Jerry Yee[2], Terrian Smith-Jules[3], Ruth C. Campbell[4] and Carolyn Bauer[1]

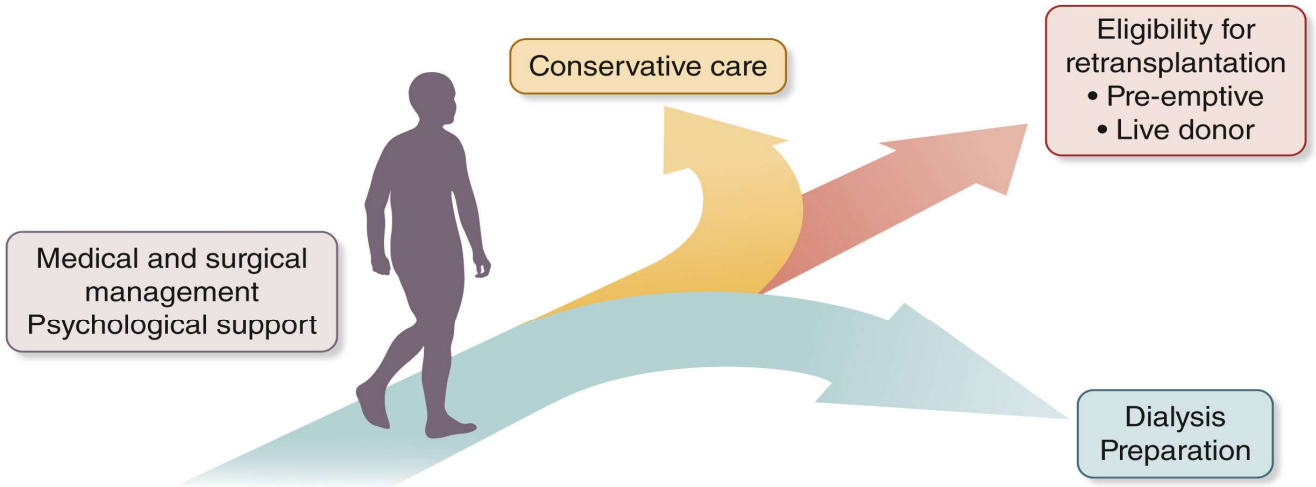
Abstract

The burden of chronic kidney disease (CKD) is substantial, and is associated with high hospitalization rates, premature deaths, and considerable health care costs. These factors provide strong rationale for quality improvement initiatives in CKD care. The interdisciplinary care clinic (IDC) has emerged as one solution to improving CKD care. The IDC team may include other physicians, advanced practice providers, nurses, dietitians, pharmacists, and social workers—all working together to provide effective care to patients with chronic kidney disease. Studies suggest that IDCs may improve patient education and preparedness prior to kidney failure, both of which have been associated with improved health outcomes. Interdisciplinary care may also delay the progression to end-stage renal disease and reduce mortality. While most studies suggest that IDC services are likely cost-effective, financing IDCs is challenging and many insurance providers do not pay for all of the services. There are also no robust long-term studies demonstrating the cost-effectiveness of IDCs. This review discusses IDC models and its potential impact on CKD care as well as some of the challenges that may be associated with implementing these clinics.

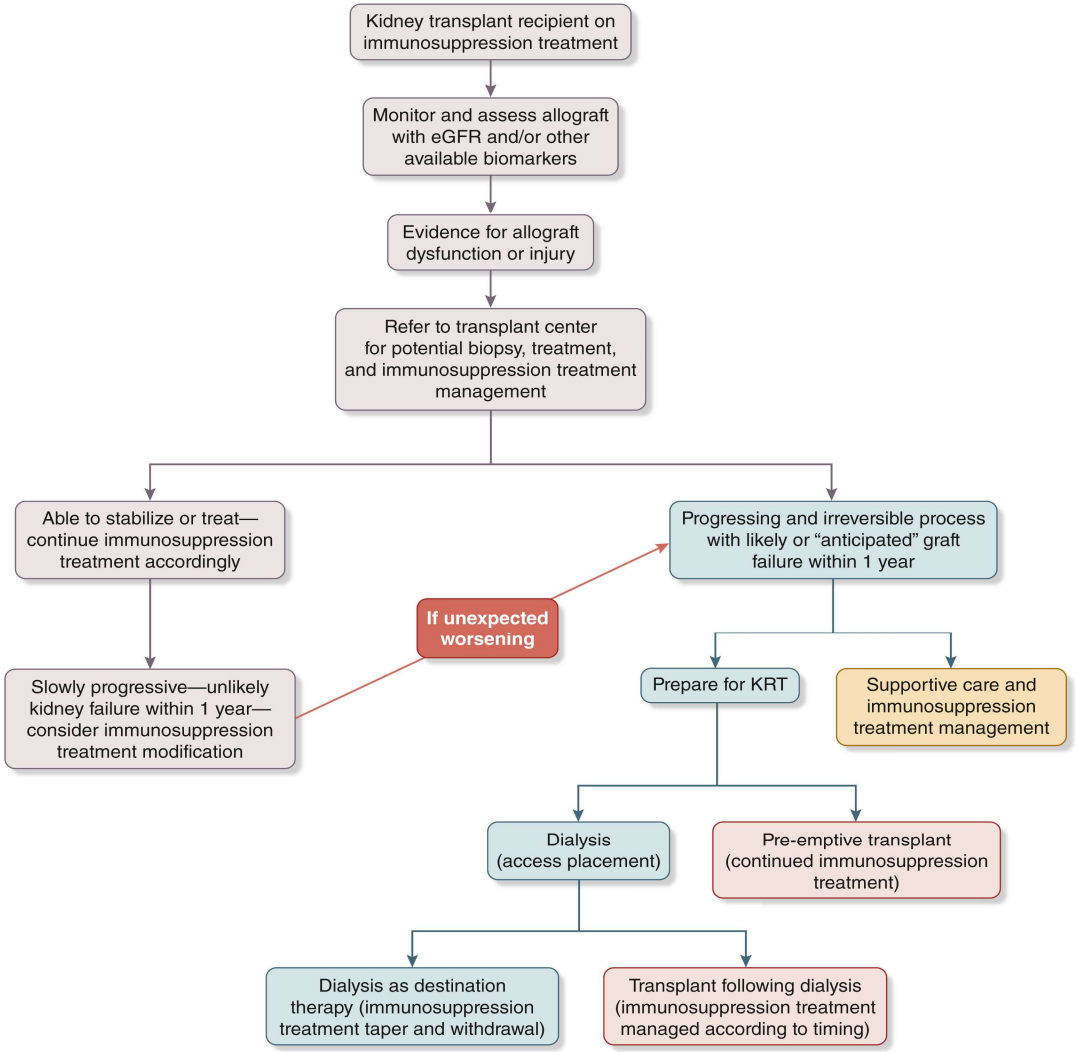
Keywords: Interdisciplinary care, Patient-centered, Quality improvement, Clinical outcomes

https://bmcnephrol.biomedcentral.com/articles/10.1186/s12882-015-0158-6

The kidney transplant recipient in transition



Terms and Conditions



Terms and Conditions

Summary

American Journal of TRANSPLANTATION

AST AMERICAN SOCIETY OF TRANSPLANTATION ASTS

COMPREHENSIVE REVIEW

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

Michelle Lubetzky, Ekamol Tantisattamo, Miklos Z. Molnar, Krista L. Lentine, Arpita Basu
... See all authors

First published: 11 June 2021 | https://doi.org/10.1111/ajt.16717 | Citations: 1

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

AST KPCOP KRAFT Recommendations

Failing allograft with declining function

Candidate for re-transplantation

- Refer for relisting when eGFR approaches 20 *mL/min/1.73 m²*
- Establish baseline PRA value
- Living donor champion
- Discuss options for decreasing time to transplantation
- Referral to general nephrology *(for preparation for dialysis)*
- Consider reduction in immunosuppression *(to decrease side effects and complications)*
- Maintain calcineurin inhibitor (CNI) trough *(in the low therapeutic range)*

Not a candidate for re-transplantation

- Establish vascular access
- Continue transition of care to general nephrology
- Coordinate reduction in immunosuppression over time
- Reduction in anti-metabolite by 50%
- Maintain CNI ± low dose prednisone
- Monitor for graft intolerance syndrome

The authors propose a shared-care model in which there is improved coordination between transplant providers and general nephrologists so that immunosuppression management and preparation for renal replacement therapy and/ or repeat transplantation can be conducted with the goal of improved outcomes and decreased morbidity.

Lubetzky M, Tantisattamo E, Molnar MZ, et al. The failing kidney allograft: ***A review and recommendations for the case and management of a complex group of patients.*** Am J Transplant. Jun 2021. doi: 10.1111/ajt.16717
Visual Graphic by Edgar Lerma, MD, FASN

Failed allograft with return to dialysis

Candidate for re-transplantation

- Primary management with general nephrology
- Monitor CPRA every 3-6 months
- ***Taper off immunosuppression***
  - *Reduction in anti-metabolite by 50%, maintain CNI ± low dose prednisone*
  - ***3 months post-dialysis initiation:*** *stop anti-metabolite, maintain low dose CNI ± low dose prednisone*
  - ***6 months post-dialysis initiation:*** *reduce CNI by 50% ± low dose prednisone*
  - ***9 months:*** *consider additional reduction in CNI or maintenance of prednisone 5 mg*
  - ***12 months:*** *consider cessation of all immunosuppression if no signs of graft intolerance syndrome and no significant increase in CPRA value*
  - *Continue to monitor for sensitization while wait-listed and signs of toxicity from immunosuppression*

Not a candidate for re-transplantation

- Primary management with general nephrology
- ***Taper off immunosuppression***
  - *Stop anti-metabolite*
  - *Taper CNI and/or low-dose prednisone therapy for 6-12 months in coordination with transplant nephrology*
  - *Monitor for graft intolerance syndrome*
  - *Monitor patient every 3-6 months until patient is off immunosuppression*

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

The authors propose a shared-care model in which there is improved coordination between transplant providers and general nephrologists so that immunosuppression management and preparation for renal replacement therapy and/ or repeat transplantation can be conducted with the goal of improved outcomes and decreased morbidity.

Lubetzky M, Tantisattamo E, Molnar MZ, et al. The failing kidney allograft: ***A review and recommendations for the case and management of a complex group of patients.*** Am J Transplant. Jun 2021. doi: 10.1111/ajt.16717
Visual Graphic by Edgar Lerma, MD, FASN

KDIGO — Kidney Disease: Improving Global Outcomes