Management of a Recipient with a Failed Kidney Transplant

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Objectives

- Epidemiology of transplant failure
- Timing of dialysis initiation
- Survival on dialysis after graft failure/Cause of death
- Dialysis access and modality
- Immunosuppression withdrawal
- Chronic inflammation/transplant nephrectomy
- Relisting for a subsequent transplant

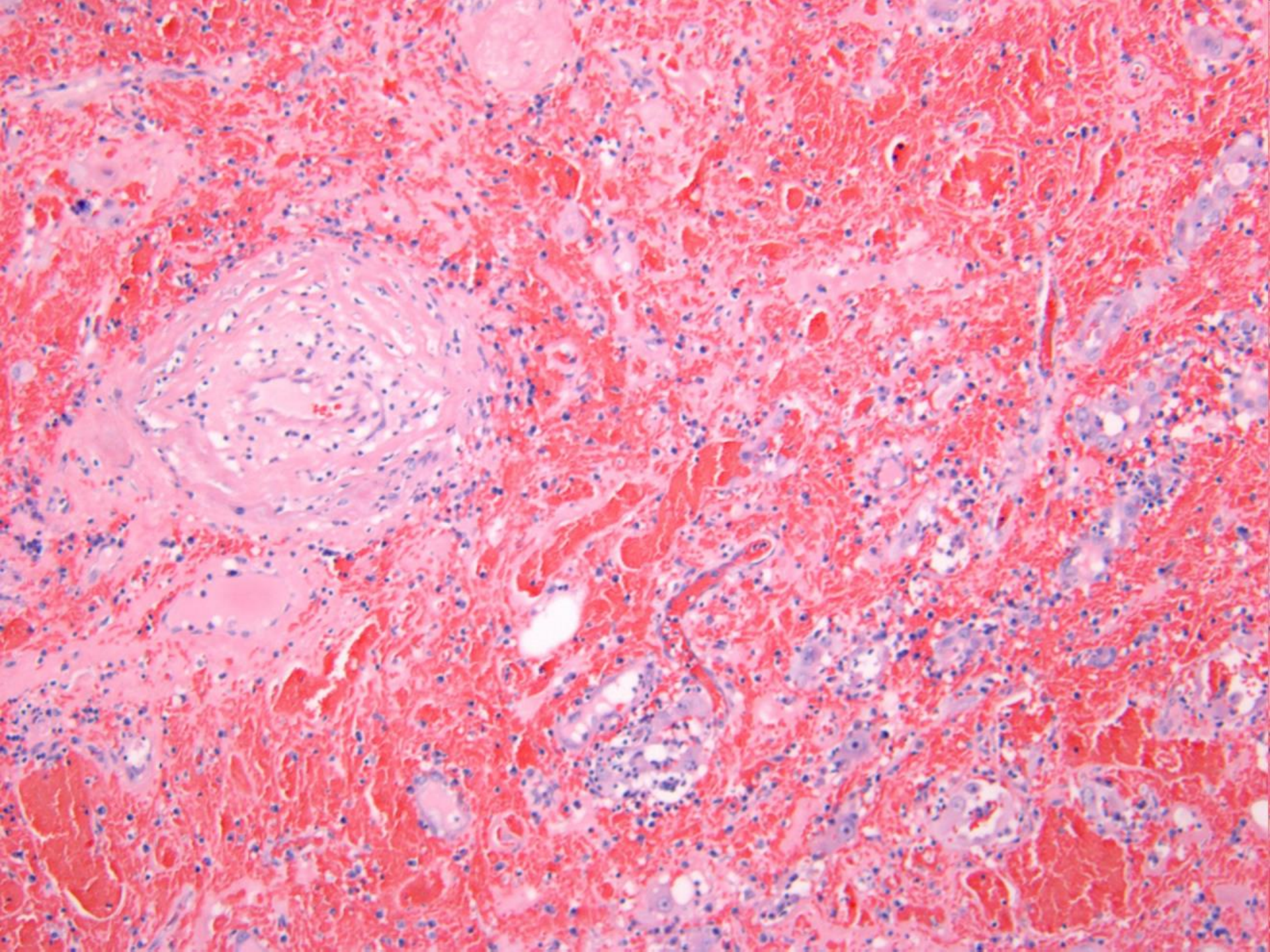
Case Discussion

- 26 year old female with ESRD due to FSGS/nephrotic syndrome-diagnosed at age 13
- DD kidney transplant in 2009 (#1); graft failure due to combination of noncompliance and recurrent FSGS-restarted HD in 12/2011
- DD kidney transplant (#2) in 2015; graft failure due to recurrent FSGS and multiple rejection episodes; restarted HD in 12/2018
- Admitted in 2/2019 with hematuria, low-grade fever, and graft tenderness

•“Compared to the prior CT, the transplant kidney appears **swollen/edematous** with mild surrounding edema in the right lower quadrant”

Case Discussion

- Transplant nephrectomy done in 2/2019
- Readmitted 2 weeks later with anterior pelvic wall fluid collection and right lower quadrant/pelvic fluid collection/infection in the nephrectomy bed
- High levels of **class II DSA; PRA 100%**
- Would like to be re-listed for a 3rd transplant



Waiting List-on 7/30/2024

- Continues to grow (89,575 on the waiting list for kidney transplant, 2,185 for SPK)
- Kidney transplants do not last forever
- 89% awaiting their first transplant and **11% awaiting re-transplant (prior failed graft)**
- **1/5 patients will lose their kidney within 5 years and over half will experience graft loss by 10 years**
- **Prior transplants wait longer**
- Number of patients returning to dialysis after graft failure up to 7000 annually, or 3-5 % of the incident dialysis population

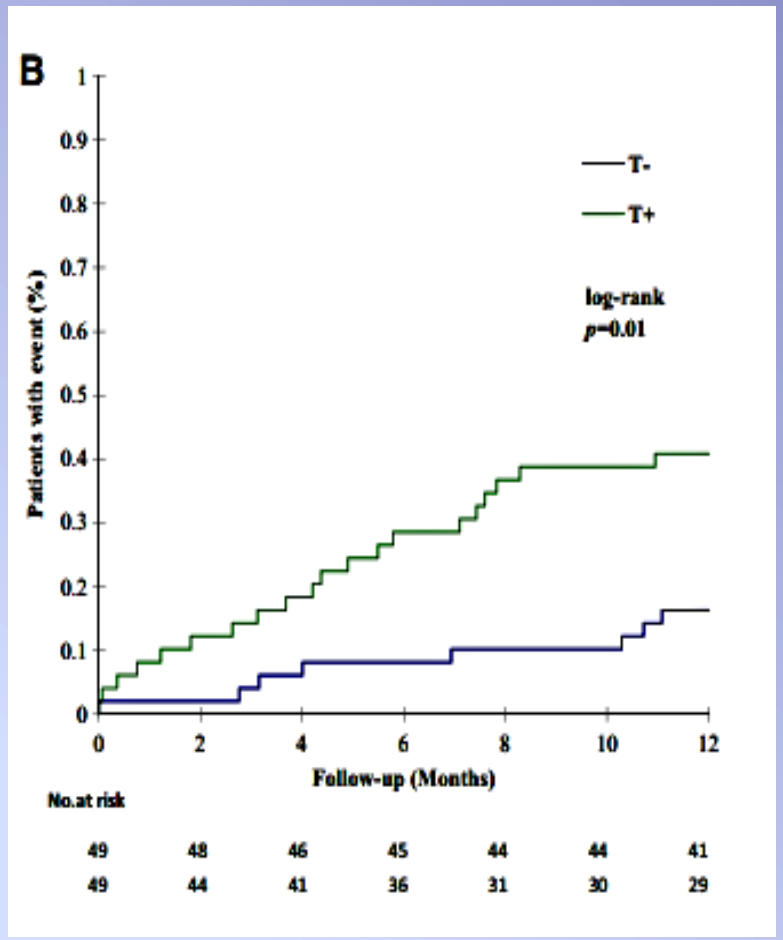
OPTN/SRTR Data

Return to Dialysis

- Over 90% of patients with failed graft will return to dialysis; approximately 10% will undergo preemptive repeat transplantation
- Physical and emotional consequences
- **10-15% of patients listed for DD kidney transplantation had prior allograft failure; in Eurotransplant system between 17.9-18.9%**
- Fragmented transitions of care among providers and health systems; unclear how best to care for patients with failed grafts who return to dialysis

Ansell D, et al. Am J Transplant 2007, Pham PT, et al. World J Nephrol 2015, Clark S, et al. CJASN 2019, Assfalg V, et al. Transplant Int 2020

- Clinical practice targets are less likely to be met compared to transplant-naïve dialysis patients
- **Worse blood pressure control, higher serum phosphorus, lower bicarbonate and lower hemoglobin** (less EPO use)
- T+ patients were more likely to have BMI less than 23, and **lower serum albumin**
- **Cumulative incidence of first hospitalization for a CV event/cancer/infection-higher in T+ patients** in the year following dialysis initiation



Ansell D, et al. Am J Transplant 2007

Gill JS, et al. Kidney Int 2002

Aniort J, et al. J Nephrol 2018

Patients with Failed Allograft

- Difficult transition
- Medically complicated; high burden of depression
- Estimated mortality rate 16% in the first year following graft failure
- Many years of dialysis, multiple comorbidities, long-term immunosuppression and side effects
- Difficulty with management of immunosuppression after the graft fails
- Indications for initiating maintenance dialysis-similar to nontransplant patients

Survival of Patients Returning to Dialysis after Graft Loss

- Many kidney transplant patients require **urgent** re-initiation of dialysis due to acute graft loss: sepsis, cardiac events, or acute rejection
- Efforts are concentrated on attempting to **salvage the transplant** rather than optimizing predialysis care
- Patient with diabetes at the time of graft loss have a significant survival disadvantage

Molnar MZ, et al. Semin Dial 2013

Perl J, et al. Nephrol Dial Transplant 2012

Samarasinghe A, et al. Clin Kidney J 2024

Patients with Failed Allograft

- Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) between 1996-2008
- **All-cause mortality is 32% higher** for transplant failure (TF) patients on dialysis than for transplant-naïve (TN) patients, with **a hazard ratio for death from infection-2.45** **(***Perl J, et al. Nephrol Dial Transplant 2012)*
- Data from USRD between 2003-2008; follow-up 30.9±22.6 months after graft failure
- **Cause of death: cardiac (47%), infectious (16.8%), vascular disease (6%)**
- Adjusted hazards ratio (AHR) for death was increased with lack of AV fistula at initiation of dialysis, albumin <3.5 g/dl and being underweight *(Brar A, et al. Am J Nephrol 2017)*

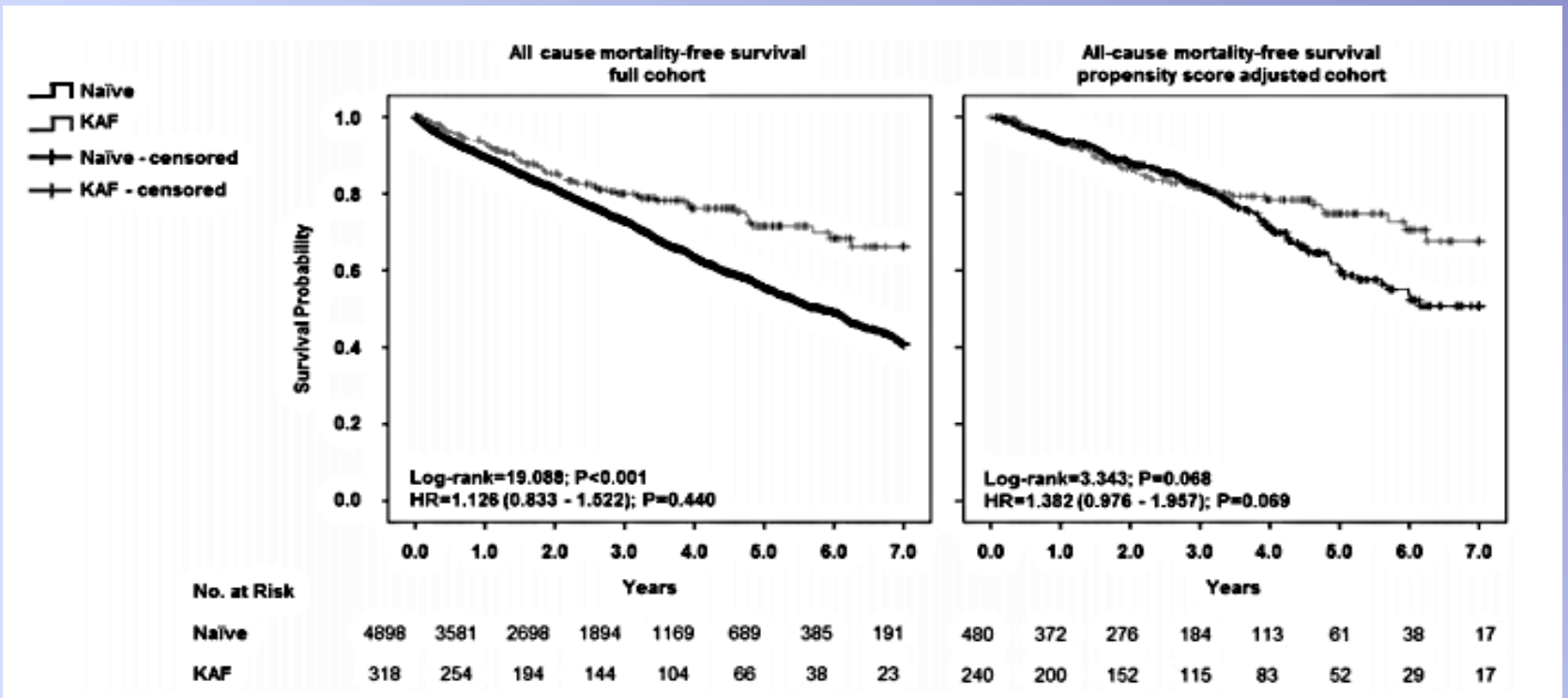


FIGURE 1: Kaplan–Meier survival plots for all-cause mortality in the entire study population (left panel) and after PSM adjustment (right panel). Grey lines represent survival curves for patients who returned to dialysis after KAF. Black lines represent survival curves for transplant-naïve incident HD patients. The corresponding log-rank test results and survival tables are also shown.

- 5216 patients from 65 different FMC clinics in Spain between 2009 and 2014
- Propensity Score Matching-adjusted population: 480 naive and 240 KAF patients
- When comparing properly matched patient groups, **patients who return to HD after KAF present similar survival with transplant-naive incident patients (were older with more comorbidities and catheters)-small sample size and retrospective**
- Very early mortality (during the inpatient stay) was not registered though

Varas J et al. Nephrol Dial Transplant 2019

Vascular Access

- Retrospective observational cohort of 138 patients; dialysis after kidney transplant failure 1995-2014
- 53 (**38.4 %**) patients-**no access planning**
- **Increased mortality** in patients with **dialysis catheters** (hazard ratio 5.90)
- Use of AVF at initiation of HD 11.7% of the cohort

Laham G, et al. Transplantation 2017

Brar A, et al. Am J Nephrol 2017

Dialysis Modality: Hemodialysis vs Peritoneal Dialysis

Authors/year	Cohort size	Groups	Follow-up time	Main results
Davies/2001 [43]	45	PD compared to HD	Up to 125 months	PD and HD groups had similar outcome
Sasal et al./2001 [39]	85 (42 failed kidney Tx patients)	Kidney failed PD compared to Tx naïve PD	Up to 100 months	Failed kidney transplant patients reported higher mortality and complication risk
Duman et al./2004 [40]	116 (34 failed kidney Tx patients)	Kidney failed PD compared to Tx naïve PD	Up to 5 years	Similar patients and technique survival
Rao et al./2005 [41]	25,362 (675 failed kidney Tx patients)	Compared transplant-naïve dialysis, deceased/living kidney transplant, failed kidney transplant dialysis and retransplant	Up to 8 years	The transplant-naïve and failed kidney transplant dialysis patients have equivalent mortality risk and that mortality is significantly reduced upon retransplantation
De Jonge et al./2006 [44]	60	PD compared to HD	Up to 60 months	PD and HD groups had similar outcome
Mujais and Story/2006 [77]	1464 (494 failed kidney Tx patients)	Failed kidney transplant patients on PD compared to new dialysis initiation or transfer from HD	Up to 4 years	Similar outcome between the groups; however, the retransplant rate was lower in failed kidney transplant group
Perl et al./2011 [3]	2110	HD compared to PD and preemptive transplant	Median of 2.9 years	Patients had preemptive transplant had better outcome; however, the PD and HD outcome was similar

- **No difference between modalities**
- **Similar survival**

Molnar MZ, et al. Semin Dial 2013

PD after Transplant Failure- French PD Registry

- Retrospective 2002-2012
- 328 patients on PD after transplant failure (Tx group) vs 656 matched never-transplanted patients (control group)
- Similar patient survival and peritonitis rate
- **Higher PD technique failure in Tx group**
- The main cause of switch to HD: adequacy and/or ultrafiltration failure
- Transplant 29% vs 40% (less transplant in failed group)

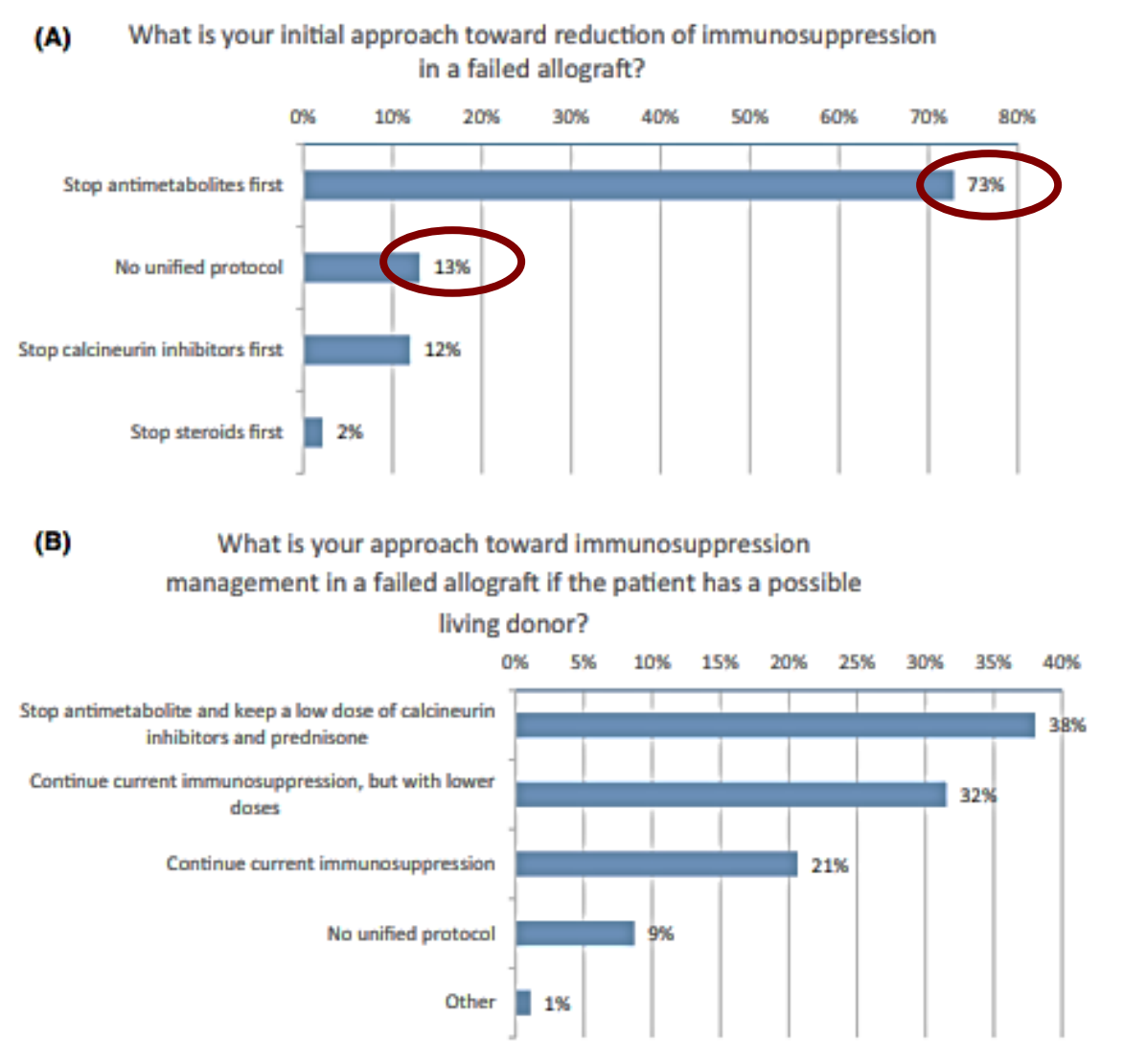
Benomar M, et al. Nephrol Dial Transplant 2019

Immunosuppression: Balancing the Potential Risks and Benefits

Immunosuppression-What to Do?

- No consensus; lack of data
- Considerations:
  - Cause of graft failure
  - Plans for preemptive retransplantation
  - Dialysis and waitlisting for DD retransplantation
  - Dialysis-not a candidate for retransplantation
  - Presence of other solid organ transplants such as pancreas, heart or lung

Josephson MA, et al. KDIGO Controversies Conference, Kidney Int 2023



-92 kidney transplant centers
-If no living donor and waiting time >3 years: 47% tapered all immunos within 2-6 months, 21% kept prednisone and tapered the rest, 10% kept low-dose CNI and tapered the rest, 5% kept CNI and pred, 3% kept low doses of all, and 2% kept only a low dose antimetabolite

A practice survey developed by AST Kidney Pancreas Community of Practice; US transplant practitioners

Alhamad T et al, AJT 2021

Reasons to Continue Immunosuppressive Drugs

- To avoid rejection
- Prevention of “graft intolerance” syndrome
- Prevention/minimization of sensitization
- Preservation of residual renal function
- Prevention of adrenal insufficiency
- Prevention of reactivation of systemic diseases such as lupus or vasculitis
- Plans for a living donor transplant

Reasons to Stop Immunosuppressive Drugs

- Metabolic and cardiovascular complications (diabetes, hypertension, hyperlipidemia, etc)
- Complications related to steroids (cataract, myopathy, osteoporosis, avascular necrosis, DM)
- Increased susceptibility to infections (**dialysis catheter-related infections-the most common)**
- Malignancy (skin cancers, lymphoma etc)
- Increased/ongoing cost

Graft Failure-Risk of Cancer

- The Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry data: 7809 patients (4628 males, 3181 females); failure of the first transplant necessitating dialysis in 1820 (23%) patients; 668 (9%) underwent a second transplantation
- Increased cancer risk is rapidly reversible on reduction of immunosuppression after graft failure **for Kaposi's sarcoma, non-Hodgkin's lymphoma, melanoma, and lip cancer (malignancies with potentially infectious origin-viral like HHV8, HPV and EBV)**
- For **leukemia, lung cancer, and cancers related to ESRD (urinary tract,** kidney, thyroid) risk remained significantly elevated after transplant failure

van Leeuwen MT, et al. BMJ 2010

Management of Immunosuppressive Therapy after Allograft Failure

- French National database: 121 patients returning to dialysis after graft failure between 1/2008 and 12/2019; 2 groups, IT continuation (35 patients) or IT discontinuation
- **HLA-sensitizations higher in the IT discontinuation group** (57% vs 38%)
- IT continuation was associated with a lower incidence in incompatible graft rate; no association with patient mortality (*Ferrari K, et al. Clin Transplant 2024)*
- Failed allograft with residual renal function: consider tacrolimus trough 3-5 ng/mL *(Lubetzky M, et al. AJT 2021)*

Prospective Multicenter Canadian Cohort Study

- 269 patients; was followed 21 days of starting dialysis after transplant failure; follow-up median 558 days
- 65% continued immunos, 20% continued only prednisone, and 12% stopped all immunos
- Prolonged use of immunos after graft failure was not associated with a higher risk of death or hospitalized infection but NOT sufficient to prevent higher anti-HLA antibodies or rejection (possibly inadequate drug exposure; no drug levels)
- Randomized controlled trial is needed

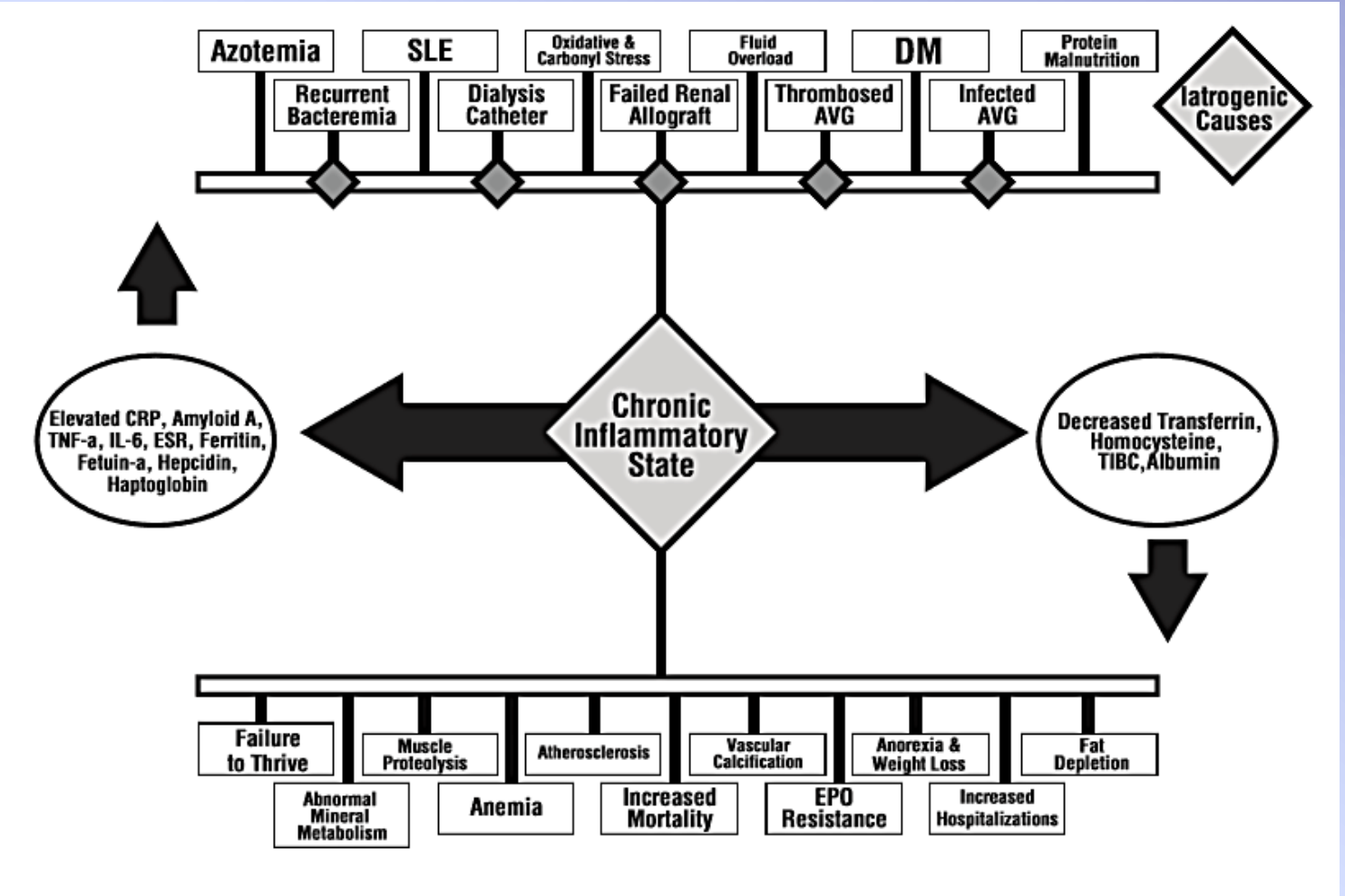
Knoll G, et al. JASN 2022

British Transplantation Society Guidelines

- Immunosuppressive therapy **be continued to avoid immunologic sensitization if a living kidney donor is available** and there is the prospect of **retransplantation preemptively or within 1 year of starting dialysis**. (2C)
- Immunosuppressive treatment be withdrawn after graft failure when there are immunosuppression-related complications such **as skin cancer and an anticipated delay in retransplantation**. (2C)

Andrews PA, et al. Transplantation 2014

Chronic Inflammation in Dialysis Patients-Hiding in Plain Sight



Achinger SG, et al. Seminars in Dialysis 2019

Chronic Inflammation in Dialysis Patients-Hiding in Plain Sight

- Linked to increased mortality and morbidity as well as poor CV outcomes
- **Graft intolerance syndrome: fever, malaise, weight loss, gross hematuria, anemia-EPO resistant, elevated ESR, CRP and ferritin, flank or graft pain, and low albumin**

Cachofeiro V, et al. Kidney Int 2008

Wasse H, et al. Nephrol Dial Transplant 2013

Achinger SG, et al. Seminars in Dialysis 2019

Lubetzky M, et al. Am J Transplant 2021

Transplant Nephrectomy

- Reported ranging from 5% to 35%; **more likely to be performed** in patients who had graft failure **within 12 months** posttransplant
- Rates of TN in patients undergoing retransplantation: 43%
- Morbidity: 10-68%; Mortality: 1.2-38% (old data); USRDS data (published in 2007)-perioperative mortality 1%; sepsis rate was high in the early TN group
- Complications: blood loss, need for transfusion, wound infections, surgical complications

O'Sullivan DC, et al. J of Urol 1994
Zargar MA, et al. Transplant Proc 2001
Mazzucchi E, et al. J of Urol 2003
Johnston O, et al. AJT 2007
Ghyselen L, et al. Transplant Reviews 2019

Reasons for Transplant Nephrectomy

- Center's protocol
- To make room for a new transplant
- Vascular thrombosis/primary nonfunction
- Clinically symptomatic patient-hematuria/severe rejection resistant to immunosuppression
- Presence of chronic inflammatory state
  - Refractory "Graft intolerance syndrome"
- PTLD in the graft
- To decrease and stop immunosuppression

Concerns Related to Nephrectomy

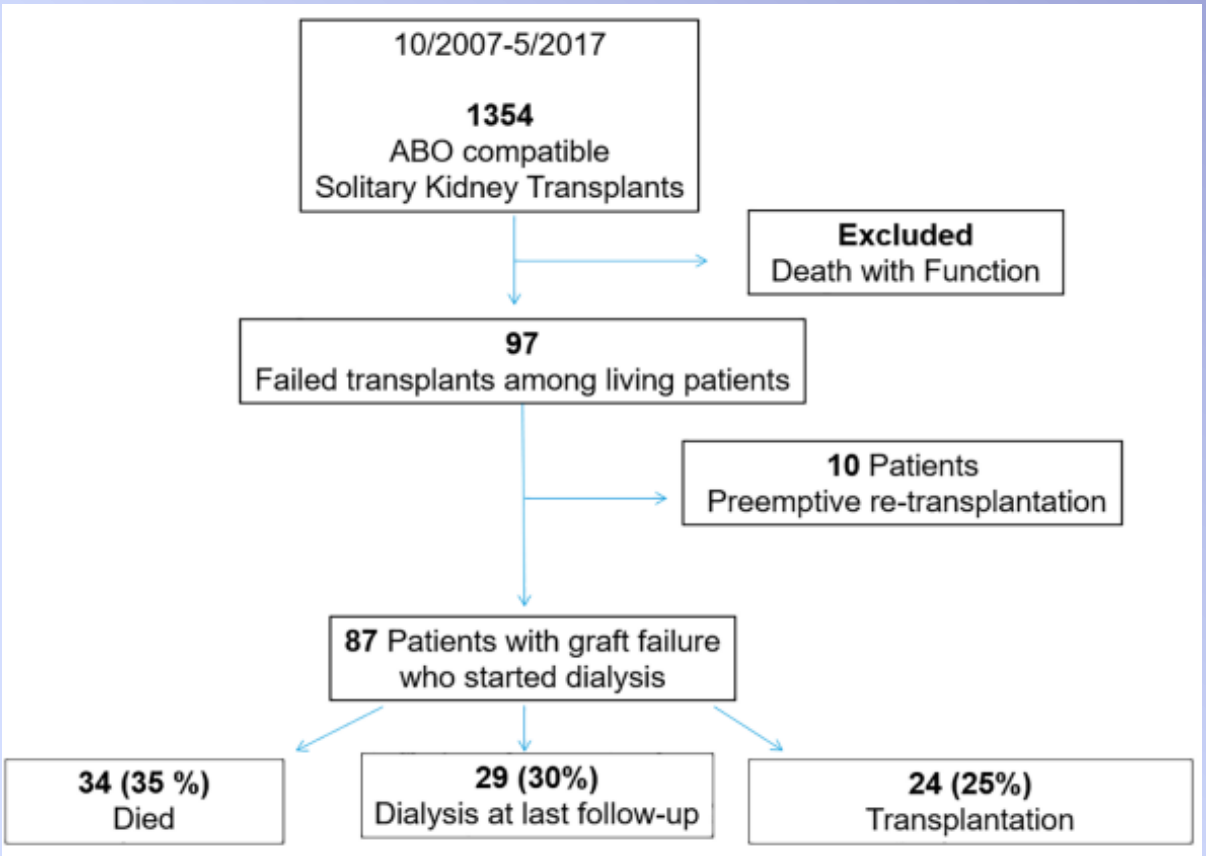
- Major surgery with potential morbidity and mortality; technically challenging
  - No data on mortality in asymptomatic patients who had nephrectomy
- Loss of residual kidney function/diuresis
- Need for blood transfusions
- Possibility of worse outcomes after re-transplantation
- Increased sensitization (32% did not have DSAs pre-TN but developed DSAs post-TN) (*Goral S, et al. Am J Nephrol 2014)*

Maintaining Immunosuppression Does Not Reduce Sensitization

- 33 patients with early graft loss/rapid nephrectomy (within first week)
- 11 patients continued immunosuppression for 3 more months after the nephrectomy
- At 1 year post-TN, anti-class I, II, and I+II DSAs were present, respectively, in 5 (45%), 2 (18%), and 2 (18%) patients who had continued immunosuppressive treatment and in 4 (19%), 2 (9%), and 8 (38%) of the controls
- More infections noted

Del Bello A, et al. Transpl Int 2015

Mayo Clinic Data-Single Center

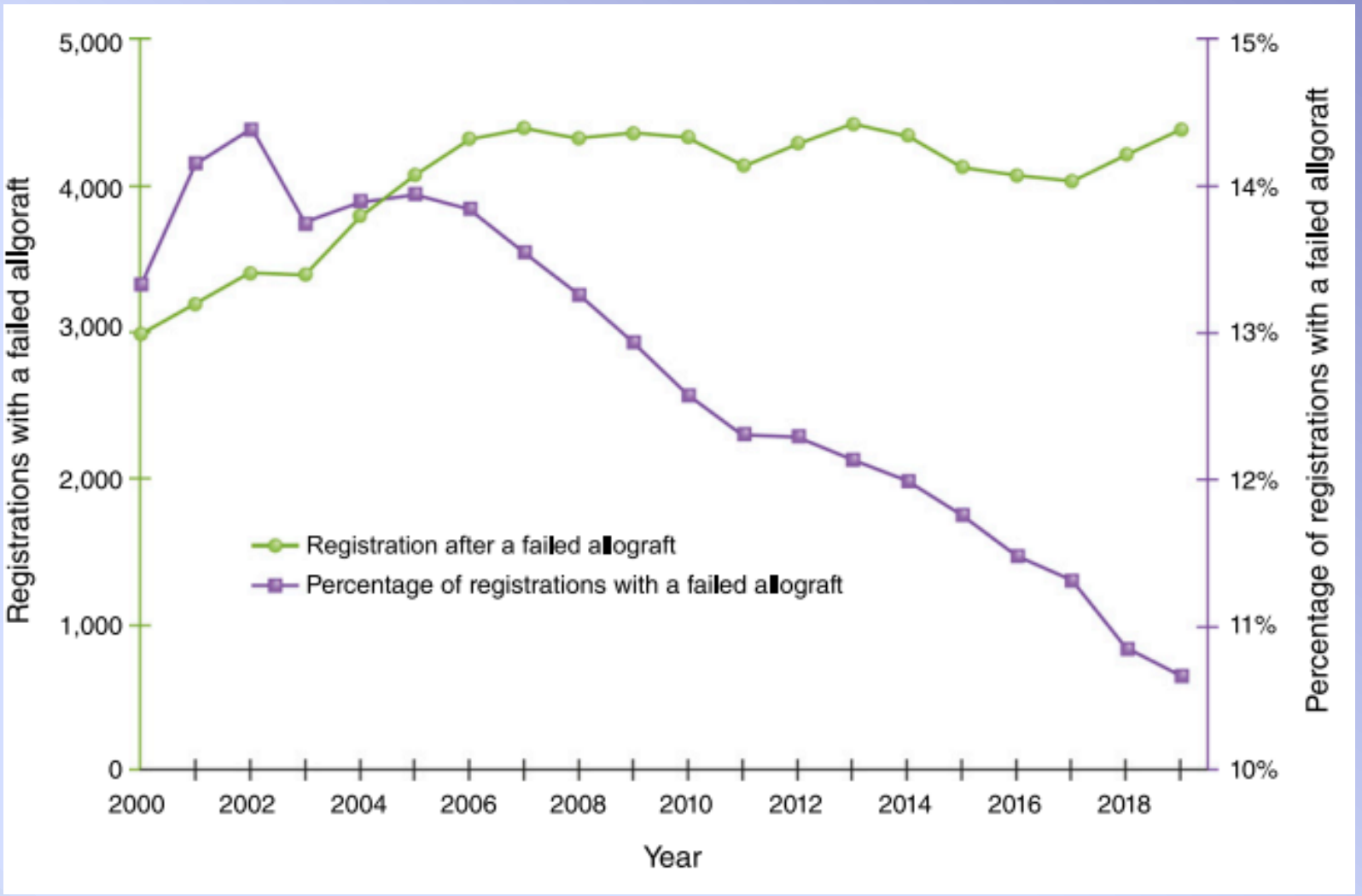


-46% discontinued immunosuppression-associated with increased cPRA
-Age at failure and CV disease were associated with death
-Immunosuppression withdrawal was not associated with reduced transplantation; maintenance was not associated with increased death or retransplantation

Balakrishnan S, et al. Transplant Direct 2022

Recommendations-TN

- Grafts in patients with symptoms-to be removed quickly
- **No clear evidence** that routine nephrectomy in clinically asymptomatic patients is beneficial; though these patients might have undiagnosed chronic inflammation
- No indication for nephrectomy in patients with BK viremia or BK nephropathy
- Embolization of the graft renal artery-an alternative; minimally invasive-complications such as abscess formation, migration of embolization coils, postembolization syndrome-need more/better data



-Percentage of waitlist registrations for candidates with failing or failed allografts have decreased over time

Davis S and Mohan S. CJASN 2022

Retransplantation

- Likely to be more sensitized
- More comorbidities-diabetes and cancers
- Lower graft survival rate compared to primary transplants-old data
- About 15% of patients with a failing kidney transplant undergo preemptive placement on a waiting list or are retransplanted in the US *(Schold JD, et al. AJT 2020)*
- To be referred when eGFR is around 20 cc/min
- Significant life expectancy benefit and improvement in survival compared to patients on dialysis; a covariate-adjusted **20-88% reduction in mortality**, depending on comorbidities and transplant era; most pronounced in the 18- to 59-year age group-Canadian patients (*Rao P, et al. Transplantation 2006 and Clark S, et al. CJASN 2019)*

	N		Median survival time	95% confidence interval of median survival time	1-year survival rate	5-year survival rate	10-year survival rate
Primary Kidney	178,947	Graft Survival	10.7	10.6-10.8	93%	76%	53%
		Patient Survival	12.2	12.1-12.3	96%	84%	61%
Repeat Kidney	17,819	Graft Survival	10.5	10.2-10.7	92%	74%	51%
		Patient Survival	13.2	12.9-13.5	97%	86%	67%

- Kidney **allograft** outcomes and **patient survival comparable** in primary and repeat kidney transplant recipients (UNOS database, 2000-2014)
- Graft survival was significantly lower for patients who received more than 2 kidney transplants *(El-Husseini A, et al. Clin Transplant 2017)*
- Patients with multiple transplants: younger with less DM, fewer CV risk factors, requiring induction therapy *(Bielopolski D, et al. Ann Transplant 2024)*

A systematic Review by Updated Meta-Analysis Allograft Nephrectomy vs No Nephrectomy

- 16 studies; retrospective, mostly single centers, follow-up period varied widely
- The incidences of PRA, acute rejection, primary nonfunction and DGF significantly higher in TN group
- **5-year graft and patient survival not different after re-transplantation between groups**

Gavriilidis P, et al. Transplant Int 2021

Summary

- Patients with failed grafts are different from transplant-naïve patients
  - They have increased mortality, mostly due cardiovascular diseases and infections
  - They usually do not have adequate preparation before the initiation of dialysis such as a permanent dialysis access, education or transplant listing
  - They are not usually followed at the transplant center
  - Specific issues: immunosuppression withdrawal and decision for allograft nephrectomy (ongoing study with tocilizumab-anti-IL6 receptor ab use-France)
  - OK to continue immunos, at least temporarily, if a patients has potential living donors and timely retransplantation is possible

Recommendations

- Excess mortality may be lessened by facilitating access to **high-quality transitional care and integrated services (CKD and dialysis care)**
- **Partnership between transplant team and general nephrologist-very important; specific clinics at some transplant centers for patients with failing allograft**
- Plan for appropriate treatment of CKD-related issues (bone disease, acidosis, and anemia)
- Patient education/counseling on dialysis modality, access planning-vein mapping, and timely initiation of dialysis-no good data for guidance

Recommendations

- Careful assessment of individual patient's risks and likelihood of retransplantation
- Planning and relisting for transplantation when GFR is around 20 cc/min
- Encourage for living donor transplantation
- No prospective data to guide the discontinuation of immunosuppression-slow taper over 6-month period, if no plans for living donation in the near future, all to be done in connection with patient's CKD/dialysis team
- How to taper/stop belatacept is not very clear
- There is still need for standardization of immunosuppressive management