Management of patients with a failed transplant

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UCLA Health

Management of patients with a failed transplant

Epidemiology of graft failure

Literature overview

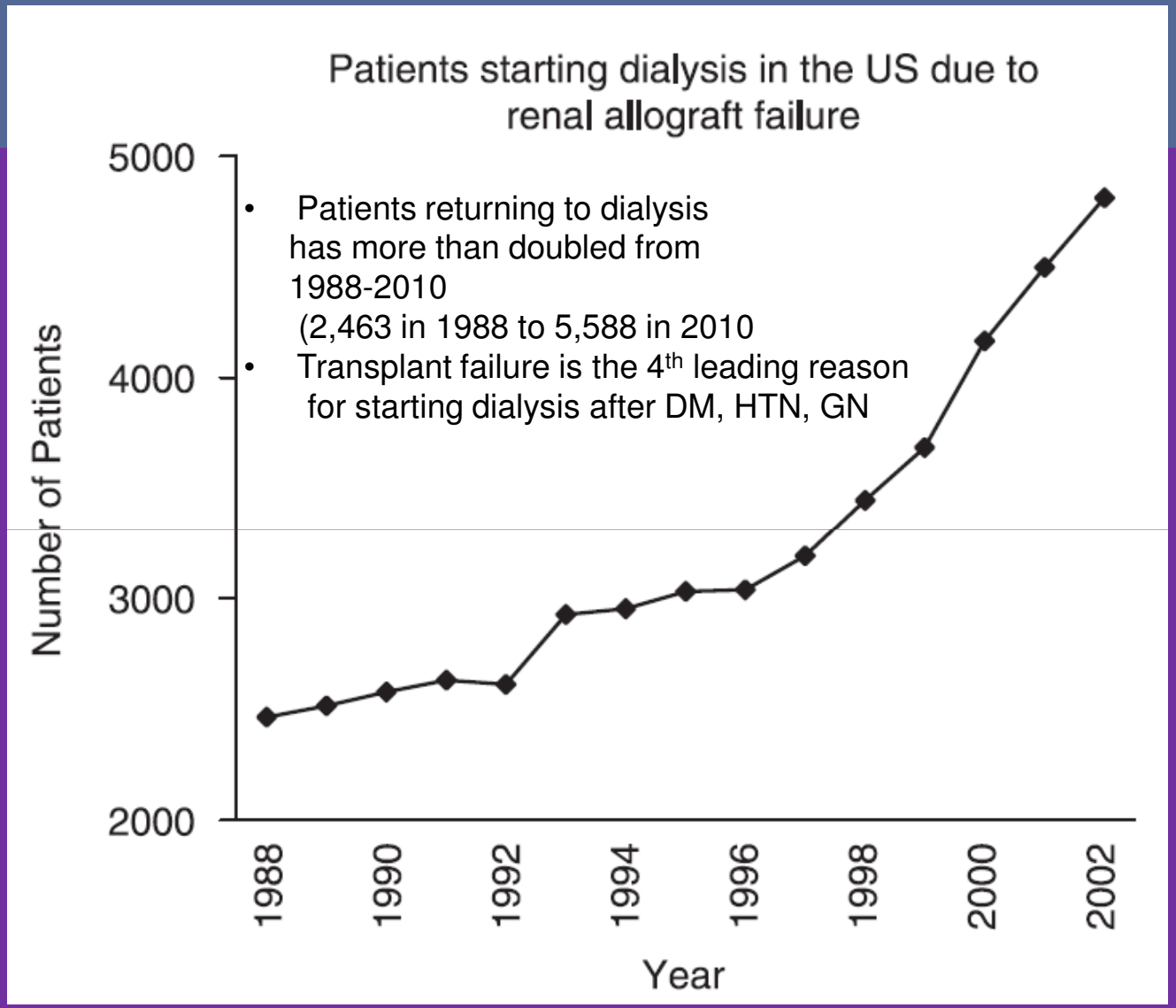
- Immunosuppression weaning after graft failure
- Allograft nephrectomy (indications)
- Timing of dialysis re-initiation after transplant failure

Personal perspectives

- Immunosuppression weaning
- Allograft nephrectomy
- Timing of dialysis re-initiation

Epidemiology of allograft failure

- In the US ~ 5000 patients with graft failure require renal replacement therapy annually
- > 90% will return to dialysis, ~ 8% to 10% undergo repeat transplant.
- Patients returning to dialysis after a failed transplant comprised of 4-5% of the annual number of dialysis initiations in US



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Semin Dial 18(3): 185-187, 2005.

Mortality after allograft failure

- The **USRDS** database revealed a > 3 fold ↑ in the annual adjusted death rates for patients returning to dialysis after graft loss c/w those with a functioning graft (9.4% *vs.* 2.8%, respectively)

- The **Canadian Organ Replacement Registry** database similarly demonstrated a > 3 fold ↑ in the risk of death among patients with a failed allograft c/w those with a functioning graft (aHR 3.39; p< 0.0001)

Mortality after graft failure

Despite the significant # of patients requiring re-initiation of renal replacement therapy after a failed transplant & the increasing evidence suggesting their high mortality rates, management of the failed allograft in these patients has received little attention

Riks and Benefits

- Continuation of low dose immunosuppression *vs.* discontinuation of immmunosuppression
- Allograft nephrectomy
- Timing of reinitiation of dialysis (early *vs.* late) after transplant failure

Continuation of low-dose immunosuppression

Benefits

- Preservation of residual kidney function
- Minimization of allosensitization
- Prevention of graft intolerance syndrome
- Prevention of adrenal insufficiency syndrome & reactivation of systemic disease (SLE,vasculitis)

Risks

- Metabolic complications

(diabetes, HTN, dyslipidemia)

- Long-term effects of steroids
- Cardiovascular complications
- Infection
- Malignancy

Continuation of low-dose immunosuppression

Potential Benefits

Preservation of renal function

Background

- Peritoneal & hemodialyis patients with preserved kidney function have been shown to have higher survival rates than their oliguric or anuric counterparts

- Similar to the transplant naïve ESKD population, patient with a failed allograft and preserved residual function has been shown to have survival advantage over those who lost residual kidney function.

Continuation of immunosuppression & preservation of residual renal function

Continued transplant immunosuppression may prolong survival after return to peritoneal dialysis:

Results of a Decision Analysis

Jassal *et al*. AJKD 2002

Decision analytic model

Assumptions:

1. The survival benefit in patients with a transplant kidney was the same as that expected from a native kidney with a similar GFR and
2. The risks of cancer & opportunistic infections were equal to that of the general population if immunosuppressive therapy was discontinued

Decision analytic model: Results

Continuation of immunosuppression therapy after return to PD

- Prolong life expectancy **from 5.3 yrs to 5.8 yrs**
- A survival benefit in patients who had > 2.97 mL/min of additional residual renal function
- A survival benefit was apparent even at marginal GFR (additional GFR of 1.48 ml/min)
- An incremental survival benefit @ higher GFR

- It is speculated that the loss of residual kidney function may have a negative impact on survival in patients returning to PD after graft loss

Decision analytic model: limitations

- The decision analytic model was based on the assumptions that continued use of immunosuppressive therapy would preserve residual kidney function

- The model did not assess the effect of immunosuppression on diabetes mellitus and cardiovascular risks

Decision analytic model limitations

- Whether a mathematical model represents true clinical scenario remains to be studied

- USRDS registry analysis demonstrated that c/w hemodialysis, PD was associated with greater survival within the 1st yr after initiation of dialysis after kidney transplant failure, but lower after 2 years (Perl *et al.* Perit Dial Int 2014)
- It is tempted to speculate that the early survival benefit of PD over HD was due to greater preservation of residual kidney function

Continuation of immunosuppression & preservation of residual kidney function: Summary

- Current evidence supporting a benefit of residual renal function with continued IS is solely based on a decision model in PD patients and cannot be routinely recommended
- Whether continuing maintenance IS to preserve residual renal function in patients returning to PD confers an early survival advantage over immunosuppressant withdrawal after allograft failure remains to be studied

- Data for any potential survival benefits of continuation of maintenance IS among patients returning to HD are lacking

Continuation of immunosuppression
Prevention of allosensitization

Background

- Allograft nephrectomy was previously shown to correlate with sensitization after transplant failure

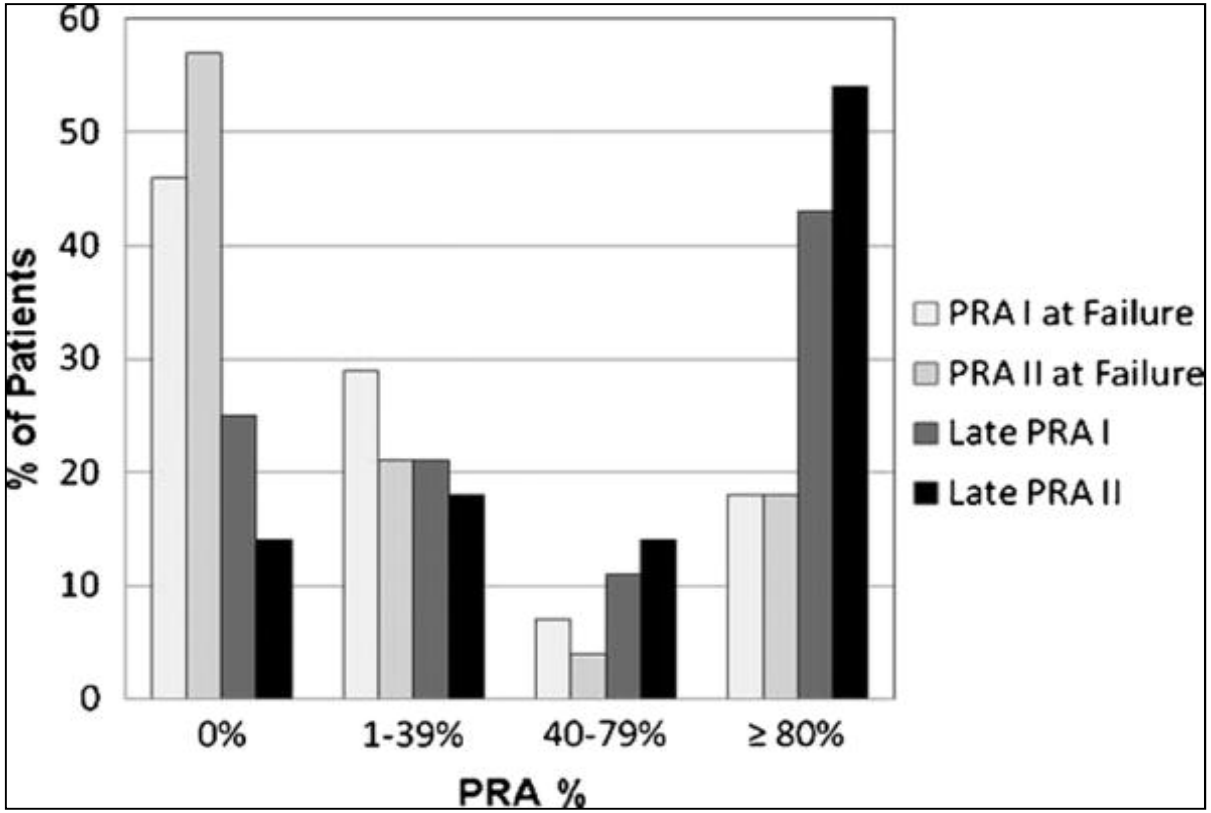
- A number of studies have shown that even in the absence of nephrectomy, most patients who were weaned from immunosuppression became highly sensitized

Continuation of immunosuppression
Prevention of allosensitization

Independent of nephrectomy, weaning immunosuppression leads to late sensitization after kidney transplant failure

Augustine *et al.,* Transplantation 2012

Percentages of class I and II panel reactive antibodies (PRA) in 28 patients stratified by PRA @ the time of graft failure on IS (lighter bars) vs. PRA after IS weaning (darker bars)



> 40-50% of pts became highly sensitized after IS weaning c/w only 8% of those who were maintained on IS (2/24)

Late PRA (PRA testing at 6 to 24 months after failure)

Prevention of allosensitization

Human leukocyte antigen sensitization after transplant loss: timing of antibody detection and implications for prevention

Scornik JC *et al*., Hum Immunol 2011

Continuation of immunosuppression & prevention of allosensitization

- Single-center study
- N=69 unsensitized patients at the time of graft loss
- Follow up (months to years after graft loss)

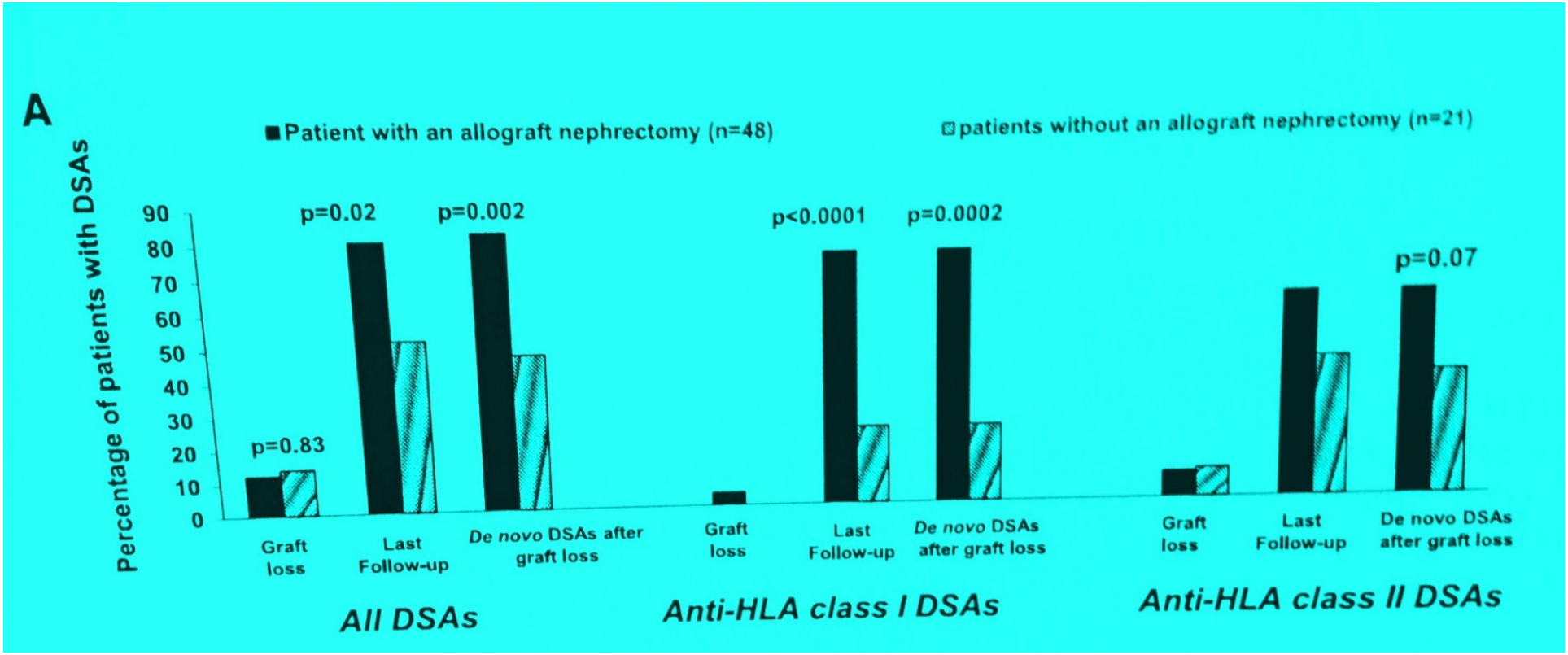
- 4/15 without nephrectomy or transfusion developed *de novo* class I and/or class II anti-HLA antibodies when immunosuppression was discontinued
- In contrast, none of the eleven patients who continued immunosuppressants developed antibodies although 7/11 had a nephrectomy or blood transfusion

Continuation of immunosuppression
Prevention of allosensitization

Donor-specific antibodies after ceasing immunosuppressive therapy with or without an allograft nephrectomy

Del Bello *et al.* CJASN 2012

Donor specific antibodies (DSAs) after discontinuation of IS with (n=48) or without (n=21) graft nephrectomy



De novo DSAs appeared in 47.6% of patients w/o Nx when immunosuppressive therapy was d/c

Nx @ 150 days, f/u 538 ± 347 days

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Prevention of Graft Intolerance Syndrome

Graft intolerance syndrome: Clinical features



- Fevers, malaise, gross hematuria, graft enlargement or tenderness, and flu-like symptoms
- Commonly occurs within the 1st year of returning to dialysis
- May occur in 30% to 50% of patients despite different immunosuppression withdrawal protocols

Prevention of Graft Intolerance Syndrome

Fever, infection, and rejection after kidney transplant failure

Woodside KJ *et al.* Transplantation 2013

Prevention of graft intolerance syndrome

	Weaned N=143	Maintained N=43	P
Age at failure			NS
Female			NS
African American	84 (59%)	9 (21%)	< 0.001
Median graft survival	72 (1-306)	92 (1-276)	NS
Pancreas transplant	7 (5%)	24 (56%)	< 0.001
Hospitalization (6 mo.)	65%	65%	NS
Hospitalization w/ fever	45%	40%	NS
Hospitalization w/ infection	25 (17%)	15 (35%)	0.015
Graft nephrectomy	60 (42%)	11 (26%)	0.053

Indications for Nx: fever in the absence of infection. Nx led to resolution of fever in all patients

Continuation of IS:
Avoid the need for nephrectomy

Determinants of late allograft nephrectomy

Madore *et al.* Clin Nephrology 1995

Determinants of late allograft nephrectomy

- Aim: identify risk factors for the subsequent need for graft nephrectomy
- Inclusion criteria: loss of graft function $\geq$ 6 months after transplantation, resumption of dialysis and initiation of weaning from immunosuppression

Results

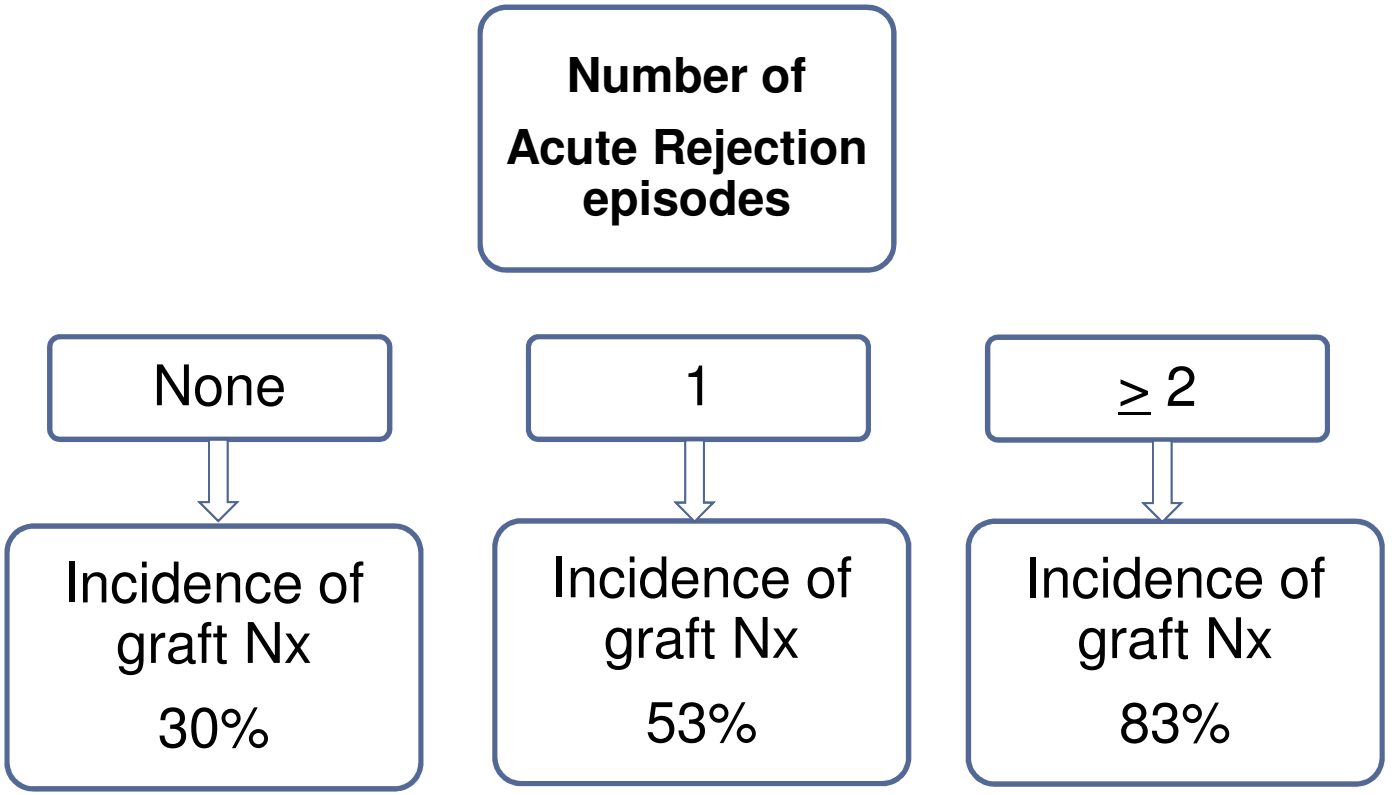
- N=41
- Immunosuppression:

  CSA + AZA + Prednisone, n=30

  AZA + Prednisone, n=11
- Mean follow-up: 17.8 months (6 months to 6.1 years)

- Multivariate analysis showed that the number of previous rejection episodes was a significant predictor for graft nephrectomy

Results



p= 0.03

Symptoms: graft tenderness (61%); fever (47%); hematuria (43%); uncontrolled HTN (14%)

Gradual tapering of IS or continuation of low-dose IS indefinitely may reduce the need for graft Nx

Continuation of low-dose immunosuppression

Potential Risks

Infectious, metabolic complications & CV risks

Immunosuppression should be stopped in patients with renal allograft failure

Smak Gregoor *et al*. Clin Transplant 2001

Infectious, metabolic complications & CV risks

- Retrospective single-center study
- 197 failed transplants

	Continuation of IS	IS withdrawal	P-value 95% CI
Infectious complications	1.7%	0.51%	P < 0.001
Mortality (infectious)	OR 2.8		95% CI:1.1-7.0
Mortality (CV)	OR 4.9		95% CI: 1.8-13.5
Acute rejection rates			P= 0.3

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→ Immunosuppression should be stopped after transplant failure

Smak Gregoor *et al.*

Infectious, metabolic complications & CV risks

Fever, infection, and rejection after kidney transplant failure

Woodside KJ *et al.* Transplantation 2013

Infectious, metabolic complications & CV risks

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Infectious, metabolic complications & CV risks

	Weaned N=143	Maintained N=43	P
Age at failure			NS
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Median graft survival	72 (1-306)	92 (1-276)	NS
Pancreas transplant	7 (5%)	24 (56%)	< 0.001
Hospitalization (6 mo.)	65%	65%	NS
Hospitalization w/ fever	45%	40%	NS
Febrile patients w/ documented infection	38%	88%	
Mortality risk	↑ with infection	↑ with infection	

Continuation of immunosuppression
Malignancy risk

Background

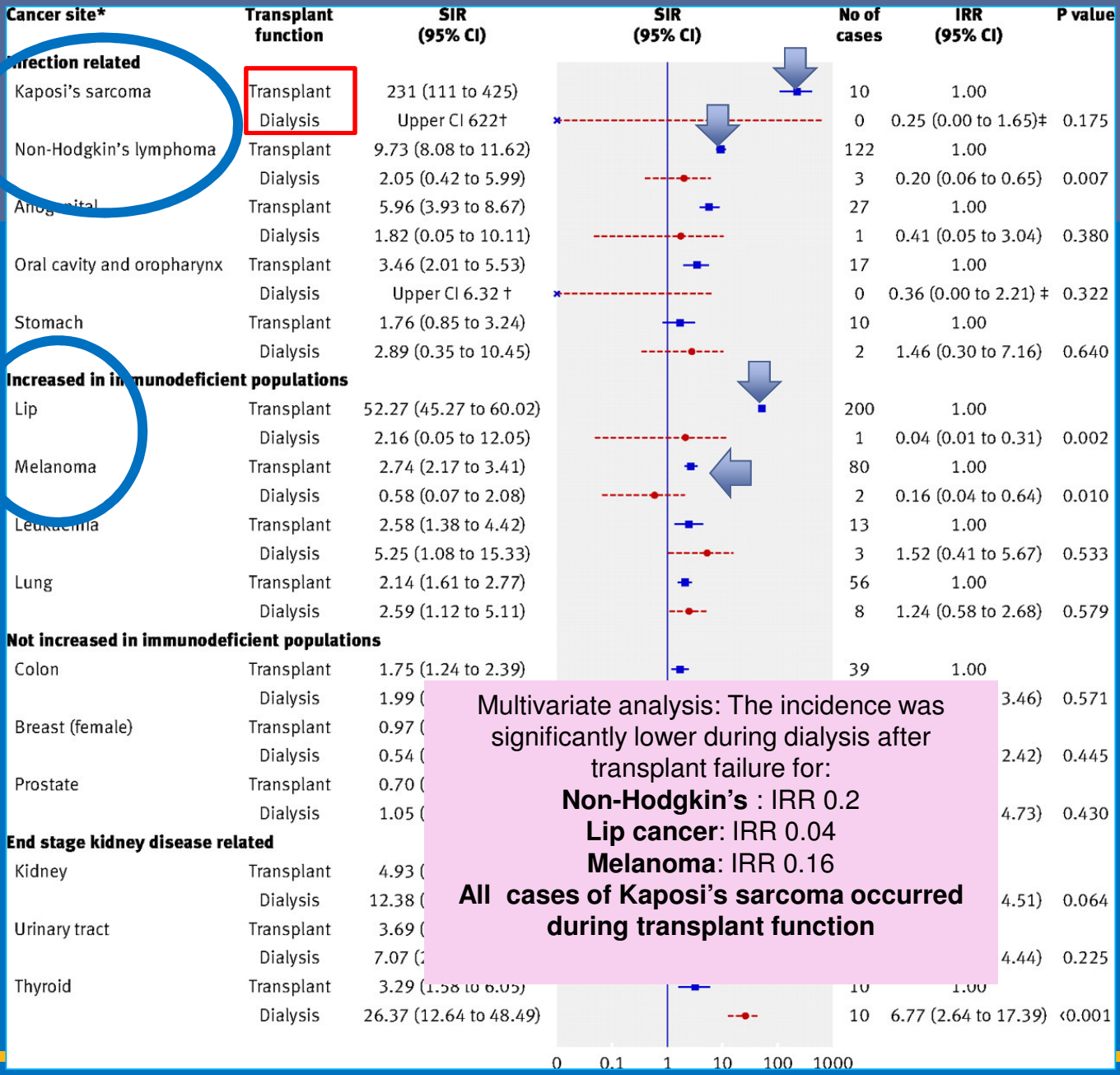
- Recipients of organ transplants are at increased risk for developing certain neoplasms c/w the general population
- Patients receiving “low-dose” CSA was shown to have a lower overall frequency of cancers ($p<0.03$) & a lower incidence of virus-associated cancers ($p=0.05$) c/w their “normal-dose” CSA counterparts (Dental *et al.* Lancet 1998)
- The intensity and duration of IS and the ability of these agents to promote replication of various oncogenic viruses have been suggested to be important risk factors for the development of certain cancers in kidney transplant recipients

Malignancy

Effect of reduced immunosuppression after kidney transplant failure on risk of cancer: population based retrospective cohort study

Van Leeuwen *et al.* BMJ 2010

Data source: The Australian and New Zealand Dialysis and Transplantation (ANZDATA) Registry



Cancer site*	Transplant function	SIR (95% CI)	No of cases	IRR (95% CI)	P value
Infection related					
Kaposi's sarcoma	Transplant	231 (111 to 425)	10	1.00	
	Dialysis	Upper CI 622†	0	0.25 (0.00 to 1.65)‡	0.175
Non-Hodgkin's lymphoma	Transplant	9.73 (8.08 to 11.62)	122	1.00	
	Dialysis	2.05 (0.42 to 5.99)	3	0.20 (0.06 to 0.65)	0.007
Anogenital	Transplant	5.96 (3.93 to 8.67)	27	1.00	
	Dialysis	1.82 (0.05 to 10.11)	1	0.41 (0.05 to 3.04)	0.380
Oral cavity and oropharynx	Transplant	3.46 (2.01 to 5.53)	17	1.00	
	Dialysis	Upper CI 6.32 †	0	0.36 (0.00 to 2.21) ‡	0.322
Stomach	Transplant	1.76 (0.85 to 3.24)	10	1.00	
	Dialysis	2.89 (0.35 to 10.45)	2	1.46 (0.30 to 7.16)	0.640
Increased in immunodeficient populations					
Lip	Transplant	52.27 (45.27 to 60.02)	200	1.00	
	Dialysis	2.16 (0.05 to 12.05)	1	0.04 (0.01 to 0.31)	0.002
Melanoma	Transplant	2.74 (2.17 to 3.41)	80	1.00	
	Dialysis	0.58 (0.07 to 2.08)	2	0.16 (0.04 to 0.64)	0.010
Leukaemia	Transplant	2.58 (1.38 to 4.42)	13	1.00	
	Dialysis	5.25 (1.08 to 15.33)	3	1.52 (0.41 to 5.67)	0.533
Lung	Transplant	2.14 (1.61 to 2.77)	56	1.00	
	Dialysis	2.59 (1.12 to 5.11)	8	1.24 (0.58 to 2.68)	0.579
Not increased in immunodeficient populations					
Colon	Transplant	1.75 (1.24 to 2.39)	39	1.00	
	Dialysis	1.99 (		3.46)	0.571
Breast (female)	Transplant	0.97 (			
	Dialysis	0.54 (		2.42)	0.445
Prostate	Transplant	0.70 (			
	Dialysis	1.05 (		4.73)	0.430
End stage kidney disease related					
Kidney	Transplant	4.93 (			
	Dialysis	12.38 (		4.51)	0.064
Urinary tract	Transplant	3.69 (			
	Dialysis	7.07 (		4.44)	0.225
Thyroid	Transplant	3.29 (1.58 to 6.05)	10	1.00	
	Dialysis	26.37 (12.64 to 48.49)	10	6.77 (2.64 to 17.39)	<0.001

0 0.1 1 10 100 1000

Multivariate analysis: The incidence was significantly lower during dialysis after transplant failure for:
Non-Hodgkin's : IRR 0.2
Lip cancer: IRR 0.04
Melanoma: IRR 0.16
All cases of Kaposi's sarcoma occurred during transplant function

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SIR: standardized incidence ratios
IRR: incidence rate ratios

Malignancy

- Increased cancer risk is rapidly reversible on reduction of IS after transplant failure for some, but not all cancer types
- For Kaposi's sarcoma, non-Hodgkin's lymphoma, melanoma, and lip cancer, the oncogenic effect of IS was rapidly reverse when IS was discontinued
- For leukemia, lung cancer, and cancers related to ESKD, the risk remained significantly elevated after transplant failure

Malignancy

- The literature on cancer risk reversal after graft failure and return to dialysis is limited

- Although it is tempting to speculate that IS withdrawal has no effect on risk reversal of “non-immune deficiency-related” cancers, most clinicians advocate IS withdrawal in patients with a history of malignancy regardless of cancer types

- In immune deficiency-related cancers, the risks of continuation of immunosuppression after graft failure likely outweigh the benefits

Indications for nephrectomy of a failed graft

Absolute indications (commonly accepted)

- Primary nonfunction
- Hyperacute rejection
- Arterial or venous graft thrombosis
- Early recalcitrant acute rejection
- Early graft failure (< 12 months)

Late graft failure (≥12 months)

- No consensus guidelines

Indications for allograft nephrectomy (Nx)

Nephrectomy for early graft failure

- USRDS registry study: Nx was nearly twice as common in patients w/ early (<12 mo.) c/w late (> 12 mo.) graft failure

- Single-center study: children w/ graft failure w/in 1 year (n=34) were 4-fold more likely to require transplant Nx than those w/ graft failure after 1 year (fever, graft tenderness, elevated CRP more common in those who subsequently underwent Nx)

Indications for allograft nephrectomy (Nx)

- Although practices vary among centers, most favor allograft nephrectomy in patients whose graft failed within 1-2 years post-transplantation

- Controversies exist regarding allograft nephrectomy when graft failure occurs late (defined by most centers as grafts that function > 12 months)

- In general, the decision to perform a failed graft nephrectomy requires careful consideration of potential risks and benefits

Allograft nephrectomy

Benefits

- Failing graft is a focus of a chronic inflammatory state
- USRDS: Nx assoc with ↓ all cause mortality
- Graft Nx assoc with ↓ mortality in patients with late transplant failure (>12 month) but not in those with early transplant failure

Risks (or disadvantages)

- Residual renal function may allow less stringent fluid restriction
- Surgery-related morbidity (17% -60%) and mortality (1.5%-14%)
- Allosensitization and the potential for future prolonged wait times for a compatible crossmatch kidney

Failing graft: focus of chronic inflammatory state

Presence of a Failed Kidney Transplant in Patients Who Are on Hemodialysis Is Associated with Chronic Inflammatory State and Erythropoietin Resistance

JUAN M. LÓPEZ-GÓMEZ,* ISABEL PÉREZ-FLORES,* ROSA JOFRÉ,* DIANA CARRETERO,* PATROCINIO RODRÍGUEZ-BENITEZ,* MAITE VILLAVERDE,* RAFAEL PÉREZ-GARCÍA,* GEORGE M. NASSAR,† ENRIQUE NIEMBRO,‡ and JUAN CARLOS AYUS§

*Departments of *Nephrology and ‡Pathology, Hospital General Universitario Gregorio Marañón, Madrid, Spain; †Department of Nephrology, Baylor College of Medicine, and Renal Research Inc., The Kidney Institute, Houston, Texas; and §Department of Nephrology, University of Texas Health Sciences Center at San Antonio, San Antonio, Texas*

Prospective, non-randomized single-center study looking at the biomarkers of chronic inflammation in patients with a failed TX who did and those who did not undergo TX nephrectomy

Failing graft: focus of chronic inflammatory state

Prospective, non-randomized, single-center study

Group A: pts started on HD after a failed TX

A1: graft nephrectomy (fever, ↓ appetite, weight loss, malaise), n=29

A2: No Nephrectomy, n=14

Group B: incident HD patients: n=121

All patients screened for the presence of chronic inflammatory state:
Hemoglobin, ferritin, erythropoeitin resistive index, CRP, ESR, albumin)

Follow up: 6 months

Failing graft: focus of chronic inflammatory state

Table 1. Baseline demographic, clinical, and laboratory data of group A and group B[a]

	Group A (Pts w/ a failed graft on HD)	Group B (TX naive HD pts)
N	43	121
Age (yr)	48.6 ± 14.6[b]	62.9 ± 13.8
Gender (% male)	55.8	63.2
Cause of chronic renal failure	GN (32.5%), DN (14%), CIN (11.6%), APCD (20.9%)	GN (22.6%), DN (19.5%), CIN (20.3%), APCD (16.5%)
Hb (g/dl)	10.4 ± 1.9[b]	12.7 ± 1.4
rHu-EPO dose (U/wk)	8862 ± 3924[b]	6380 ± 3706
ERI (U/kg per wk per g/dl)	16.1 ± 9.0[b]	8.3 ± 5.5
Ferritin (μg/L)	469 ± 382[NS]	412 ± 320
TSI (%)	26.7 ± 10.7[NS]	34.5 ± 15
Albumin (g/dl)	3.2 ± 0.6[b]	3.8 ± 0.4
Prealbumin (mg/dl)	25.3 ± 12.1[b]	32.3 ± 7.8
Cholesterol (mg/dl)	181.3 ± 42.7[NS]	191.4 ± 39.5
CRP (mg/dl)	4.1 ± 4.7[b]	1.3 ± 1.9
iPTH (pg/ml)	258.3 ± 271.3[c]	386 ± 400

[a] Data from group A were obtained within 1 wk before transplant nephrectomy. Data are mean ± SD. GN, glomerulonephritis; DN, diabetic nephropathy; CIN, chronic interstitial nephropathy; APCD, adult polycystic disease; Hb, hemoglobin; ERI, erythropoietin resistance index; TSI, transferring saturation index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; iPTH, intact parathyroid hormone; NS, no significance.

Significance between groups A and B at baseline: [b] $P < 0.001$; [c] $P < 0.05$.

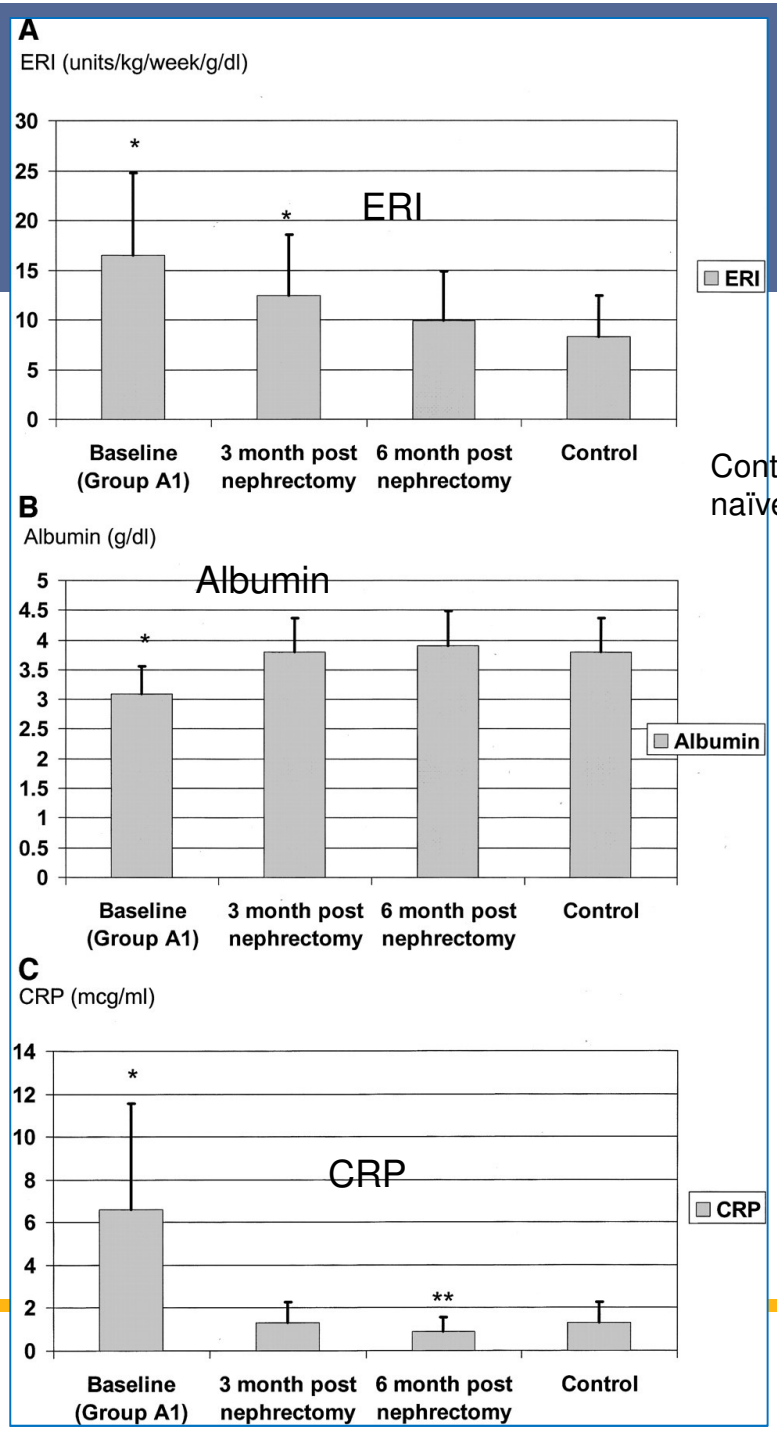
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JASN 15: 2494-2501, 2004

After graft nephrectomy

Transplant nephrectomy, group A1

Control (transplant naïve HD patients, group B)



*Significantly worse than group B ($P < 0.01$); **significantly better than group B

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After transplant nephrectomy…

Table 3. Baseline and follow-up laboratory data of group A1[a]

	Baseline	+3 Months	+6 Months
Hb (g/dl)	9.8 ± 1.8	12.2 ± 2.0[b]	12.7 ± 1.1[b]
rHu-EPO dose (U/wk)	8448 ± 2599	7655 ± 2525[NS]	6925 ± 3173[NS]
ERI (U/kg per wk per g/dl)	16.5 ± 7.9	12.4 ± 5.9[b]	9.9 ± 5.5[b]
Ferritin (μg/L)	594.3 ± 400.7	365.2 ± 343.1[NS]	356.7 ± 268.6[e]
TSI (%)	23.5 ± 8.0	39.5 ± 19.8[c]	37.9 ± 14.3[b]
Albumin (g/dl)	3.1 ± 0.7	3.8 ± 0.6[b]	3.9 ± 0.6[b]
Prealbumin (mg/dl)	26.0 ± 13.5	29.6 ± 8.2[NS]	30.8 ± 8.6[d]
CRP (mg/dl)	6.6 ± 5.2	1.3 ± 1.0[d]	0.9 ± 0.5[d]
Fibrinogen (mg/dl)	535.3 ± 218.6	354.8 ± 65.5[NS]	400.2 ± 107.9[b]
ESR (mm first h)	88.4 ± 40.4	35.9 ± 22.8[d]	29.2 ± 14.4[d]
iPTH (pg/ml)	234.9 ± 250.2	379.4 ± 504.0[NS]	526.4 ± 630.3[NS]

[a] Follow-up data were obtained at 3 and 6 mo after transplant nephrectomy. Data are mean ± SD.
Significance with respect to baseline: [b] $P < 0.001$; [c] $P < 0.005$; [d] $P < 0.01$; [e] $P < 0.05$.

JASN 15: 2494-2501, 2004

Comparison of hematologic & biochemical data between groups A1 and A2 @ 6 mo. f/u

	Group A1 After transplant Nephrectomy	Group A2 retained failed graft
N	29	14
Hb (g/dl)	12.7 ± 1.1[c]	10.9 ± 1.4[c]
rHu-EPO dose (U/wk)	6925 ± 3173[c]	12714 ± 8693[c]
ERI (U/kg per wk per g/dl)	9.9 ± 5.5[c]	20.2 ± 12.3[c]
Ferritin (µg/L)	356.7 ± 268.6[NS]	235 ± 119[NS]
TSI (%)	37.9 ± 14.3[NS]	38.7 ± 18.1[NS]
Albumin (g/dl)	3.9 ± 0.6[b]	3.3 ± 0.4[b]
Prealbumin (mg/dl)	30.8 ± 8.6[c]	27.6 ± 7.9[c]
CRP (mg/dl)	0.9 ± 0.5[b]	3.6 ± 6.0[b]

b < 0.001 c < 0.005

CLINICAL RESEARCH www.jasn.org

Transplant Nephrectomy Improves Survival following a Failed Renal Allograft

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Design:	Year	n	Period	Database
Retrospective	2010	10,951	1994-2004	USRDS

- Purpose: Determine the impact of Tx nephrectomy on mortality in patients with failed allografts returning to HD or PD
- 3451 (31.5%) received allograft nephrectomy

Results

- Allograft nephrectomy → 32% reduction in adjusted relative risk for all-cause death
- Perioperative mortality risk (<30 d.) was 1.5% vs. historically reported 6-37%

- Limitations: Patients who underwent nephrectomy were healthier (younger, less DM, smoking), unclear reasons for nephrectomy, unclear comorbid conditions

JASN 21: 374-380, 2010.

American Journal of Transplantation 2007; 7: 1961–1967
Blackwell Munksgaard

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doi: 10.1111/j.1600-6143.2007.01884.x

Nephrectomy After Transplant Failure: Current Practice and Outcomes

Design:	Year	n	Period	Database
Retrospective	2007	19,107	1995-2003	USRDS

- Johnston *et al.*
- Aim: Look at outcomes of transplant nephrectomy in patients on dialysis after allograft failure: death, sepsis, repeat Tx failure.
- Two groups: Early graft failure (<12 mo.) and late graft failure (> 12 mo.)

Effect on mortality

Table 4: Association of nephrectomy with death and hospitalized sepsis in patients with early and late graft loss[1]

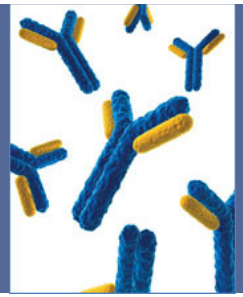
	Patients with early graft failure		Patients with late graft failure	
	Death	Sepsis	Death	Sepsis
Hazard ratio	1.13	1.09	0.89	0.88
95% confidence interval[2]	1.01–1.26	0.95–1.24	0.83–0.95	0.81–0.96

- Why difference in mortality risk with Tx nephrectomy of early vs. late graft loss?

  Indications for nephrectomy not known (done electively vs. for symptoms- likely worse outcomes if done for urgent or symptomatic indications—more likely in early graft loss)

- Further studies are needed to determine whether graft nephrectomy after late graft failure confers a survival advantage over leaving the graft *in situ*

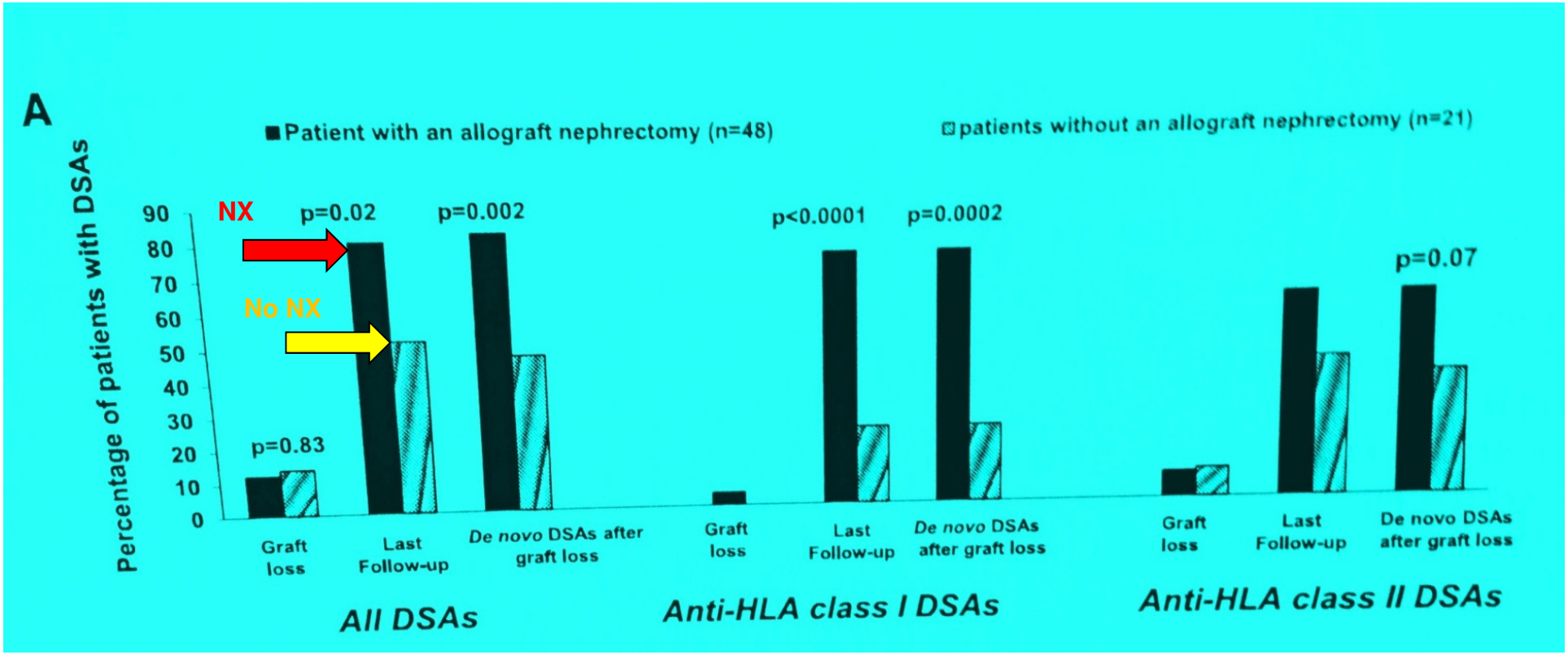
Effect of allograft nephrectomy and allosensitization



There has been ample literature showing that graft nephrectomy leads to an increase in class I/II panel reactive antibodies (PRAs), and donor specific antibodies (DSAs) and non-DSAs to variable extent

→Prolonged wait times for a potential compatible donor

Donor specific antibodies (DSAs) after discontiuation of IS with (n=48) or without (n=21) graft nephrectomy (NX)



Nephrectomy @ 150 days, f/u 538 ± 347 days

Allograft nephrectomy and allosensitization

Suggested mechanisms





- The failed allograft serves as a sponge
- Rapid withdrawal of immunosuppression
- Injury caused by the nephrectomy may stimulate pro-inflammatory cytokine and upregulation of HLA alloantibodies
- Sensitization may occur due to the persistence of antigen-presenting cell or residual donor tissues and vessels

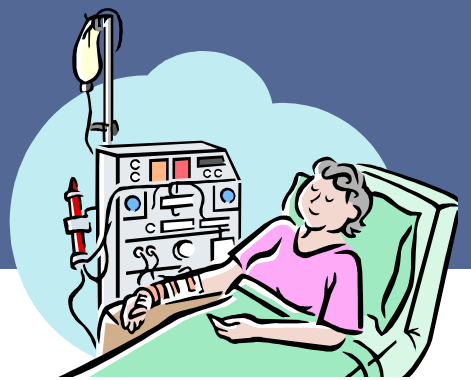
Allograft nephrectomy and allosensitization

- The mechanisms or predominant mechanisms of *de novo* development of anti-HLA alloantibodies after Nx is currently not fully understood

- Whether immunosuppression weaning over a prolonged period after graft Nx may reduce the risk of *de novo* anti-HLA alloantibodies development is unknown and warrants further exploration.



Timing of dialysis re-initiation



- Current guidelines for transplant naïve patients with progressive CKD advocate late-start dialysis (defined as dialysis initiation at an eGFR between 6-9mL/min)

- Studies on the optimal timing of dialysis reinitiation after a failed transplant are limited

Timing of dialysis re-initiation

≥

Mortality after kidney transplant failure: the impact of non-immunologic factors

Gill *et al*, Kidney Int 2002

Timing of dialysis re-initiation

- Retrospective study
- Data source: USRDS
- Aim: To determine the effect of immunologic or transplant related factors and non-immunologic factors on mortality in patients who initiated dialysis after kidney transplant failure in the US between April 1995 and September 1998

- N= 4741 patients who initiated dialysis after transplant failure
- Median follow-up: 15 $\pm$ 11 months

Timing of dialysis re-initiation

Predictors of all cause mortality after kidney transplant failure[a] (Cox multivariate regression)

	Hazard ratio	95% CI	P
Age at graft failure per year higher	1.04	1.03–1.04	<0.01
Female gender	1.31	1.10–1.56	<0.01
Race reference other			
White	1.94	1.32–2.84	<0.01
Black	1.45	0.96–2.17	0.08
Cause of ESRD reference glomerulonephritis			
Diabetes	1.76	1.43–2.16	<0.01
Polycystic kidney disease	0.85	0.57–1.26	0.42
Other	1.01	0.82–1.25	0.93
Peripheral vascular disease	1.94	1.54–2.43	<0.01
Congestive heart failure	1.26	1.05–1.53	0.01
Drug use	2.23	1.08–4.60	0.03
Smoking	1.35	1.01–1.81	0.04
Medicare only	1.06	0.83–1.35	0.64
Both Medicare and private		0.74–1.36	0.43
GFR at dialysis initiation per mL/min higher	1.04	1.02–1.06	<0.01
Serum albumin at dialysis initiation per g/dL higher		0.64–0.83	<0.01

It is speculated that the sickest patients tended to require initiation of dialysis at higher levels of renal function

It is speculated that the sickest patients tended to require initiation of dialysis at higher levels of renal function

UCLA

Timing of dialysis re-initiation

Estimated glomerular filtration rate at reinitiation of dialysis and mortality in failed kidney transplant recipients

Molnar *et al*, Nephrol Dial Transplant 2012

Timing of dialysis re-initiation (early vs. late)
eGFR > 10.5 ml/min vs. eGFR ≤ 10.5 ml/min

Death HR using eGFR at dialysis reinitiation in 747 failed kidney transplant patients[a]

	Unadjusted model		Adjusted model[b]		Fully adjusted model[c]	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
eGFR (each 1 mL/min/1.73m^2 higher)	1.06 (1.01–1.11)	0.02	1.03 (0.98–1.09)	0.22	1.02 (0.97–1.07)	0.54
Early versus late reinitiation of dialysis	1.27 (0.93–1.74)	0.14	1.03 (0.74–1.43)	0.86	0.95 (0.68–1.33)	0.77
HR of death for other covariates in the above model						
Age (each 1 year increase)	N/A	N/A	1.03 (1.02–1.04)	<0.001	1.03 (1.01–1.04)	<0.001
Gender (male versus female)	N/A	N/A	1.11 (0.82–1.50)	0.50	1.24 (0.91–1.69)	0.18
Presence of diabetes	N/A	N/A	1.86 (1.36–2.55)	<0.001	1.66 (1.20–2.29)	0.002
Serum albumin (each 1 g/dL increase)	N/A	N/A	N/A	N/A	0.44 (0.33–0.59)	<0.001
BMI (each 1 kg/m^2 increase)	N/A	N/A	N/A	N/A	0.99 (0.96–1.02)	0.38
Presence atherosclerotic heart disease	N/A	N/A	N/A	N/A	2.23 (1.44–3.46)	<0.001

[a]The early versus late dialysis reinitiation dichotomy is based on eGFR >10.5 versus ≤10.5 mL/min/1.73m^2. N/A, not applicable.
[b]Model adjusted for age, gender and diabetes.
[c]Model adjusted for age, gender, diabetes, serum albumin, BMI and presence atherosclerotic heart disease.

Timing of dialysis re-initiation

- Based on available data, a number of investigators feel that reinitiation of dialysis in patients with failed kidney transplants based on eGFR alone is not justified and could be harmful in some cases

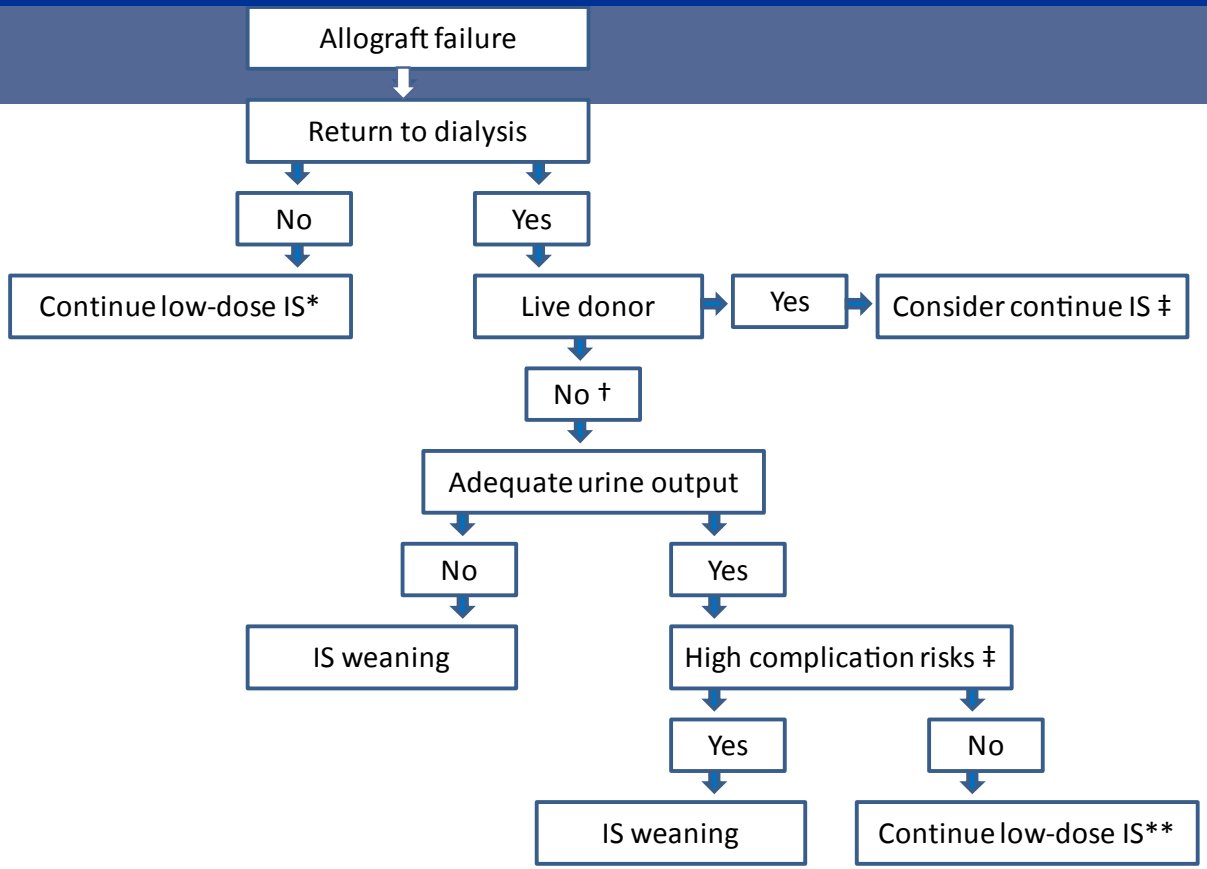
- Dialysis reinitiation in patients with a failed allograft may rely on eGFR as a rough guide that must be redefined by patients' comorbidities, nutritional status, and overall wellness

Management of patients with a failed transplant
Conclusions and personal perspectives

- Continued low-dose IS should be reserved for:
  - Pre-dialysis patients
  - Patients with live donor
  - Those with rejection sxs to serve as a bridge to graft Nx, or
  - Those with adequate residual UO (> 500-1,000 cc/day)

- IS should probably be discontinued in high risk patients (e.g. advanced age, DM, obesity or other comorbid conditions, neurogenic bladder, recurrent UTIs or urosepsis, or history of malignancy)

Suggested algorithm for the management of immunosuppression after allograft failure



*Continue antimetabolite and low-dose prednisone (usually 5 mg daily), calcineurin inhibitor dose reduction (or mTOR inh dose reduction if used as based-therapy),
† No live donor or not a re-allograft candidate; ‡ See text; ** Usually prednisone 5 mg daily ± low-dose calcineurin inhibitor or mTOR inh
Abbreviations: IS: immunosuppression; mTOR inh: mammalian target of rapamycin inhibitor

Suggested immunosuppressive withdrawal protocols

CNI + antimetabolite[a] + prednisone	CNI + mTOR inh + prednisone	mTOR inh + prednisone
• Discontinue antimetabolite at initiation of dialysis • Taper CNI over 4-6 weeks[b] • Maintain same steroid dose at initiation of dialysis x 2-4 weeks, then taper by 1 mg/month (starting from 5 mg daily) until off	• Discontinue mTOR inh at initiation of dialysis • Taper CNI over 4-6 weeks[b] • Maintain same steroid dose at initiation of dialysis x 2-4 weeks, then taper by 1 mg/month (starting from 5 mg daily) until off	• Taper mTOR inh over 4-6 weeks[b] • Maintain same steroid dose at initiation of dialysis x 2-4 weeks, then taper by 1 mg/month (starting from 5 mg daily) until off

Allograft Nephrectomy
CONCLUSIONS

Absolute indications (or commonly accepted)	Relative indications (controversial)
• Primary nonfunction • Hyperacute rejection • Early recalcitrant acute rejection • Early graft loss (generally defined as graft loss within the first year) • Arterial or venous thrombosis • Graft intolerance syndrome • Recurrent UTIs or sepsis/urosepsis • Multiple retained failed transplants prior to a repeat transplant	• The presence of hematologic or biochemical markers of the chronic inflammatory state EPO resistance anemia ↑ Ferritin level ↑ C reactive protein ↑ ESR ↓ Prealbumin/albumin • Graft loss due to BK nephropathy and high level BK viremia

Re-initiation of dialysis after a failed transplant
Personal perspectives

- Reinitiation of dialysis should not be based solely on an absolute level of residual kidney function.
- However, dialysis reinitiation when eGFR reaches < 6-9 mL/min seems reasonable
- In patients with higher level of residual kidney function, dialysis reinitiation should be based on clinical and/or laboratory parameters (e.g. symptomatic uremia, volume overload or hyperkalemia refractory to medical therapy)
- In patients with significant comorbid conditions such as long-standing DM, infectious or urological complications, weaning of IS and early return to dialysis seem justifiable


Thank You
for your Attention!