

Management of a Recipient with a Failed Kidney Transplant

Simin Goral MD

University of Pennsylvania Medical Center
Philadelphia, Pennsylvania

Objectives

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

Case Discussion

- 20 year old female with ESRD due to nephrotic syndrome
- DD kidney transplant in 2001-failed in 2010-restarted dialysis in 8/2010; off immunosuppression
- Admitted with hematuria and graft tenderness in 12/2012

Case Discussion

Which test (most helpful) would you like to order?

- A. Serum creatinine
- B. CT abdomen and pelvis
- C. C reactive protein
- D. Lactate dehydrogenase
- E. Angiogram

Case Discussion

Which test (most helpful) would you like to order?

- A. Serum creatinine
- **B. CT abdomen and pelvis**
- C. C reactive protein
- D. Lactate dehydrogenase
- E. Angiogram



- Transplant with scattered foci of dystrophic calcification; there has been an interval increase in degree of **inflammatory stranding** surrounding the kidney; several nearby enhancing lymph nodes and increased free fluid within the pelvis; **kidney itself appears more edematous, and has enlarged significantly**

Case Discussion

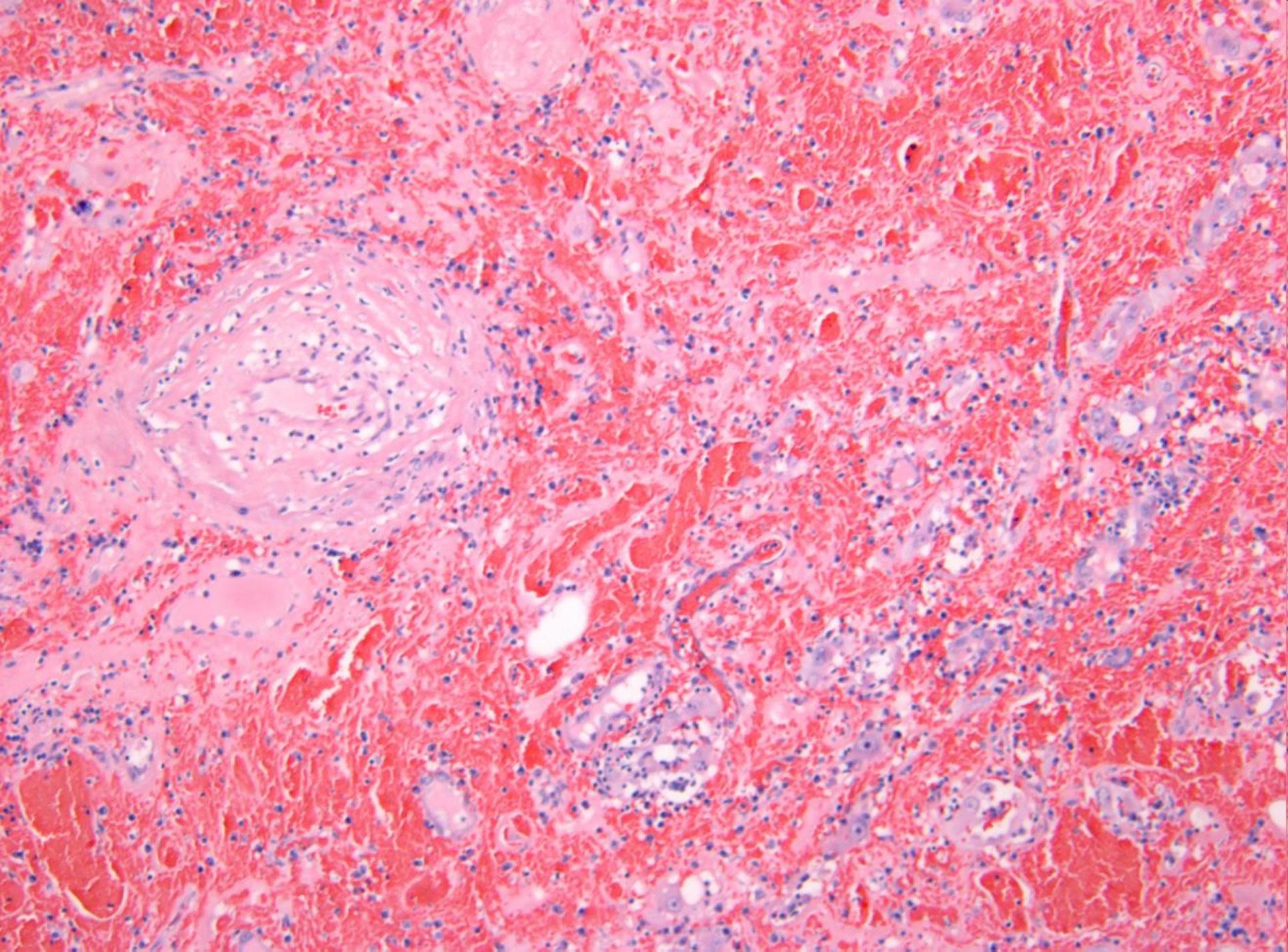
- Transplant nephrectomy done 12/2012
- The last blood sample 5/2013: has high levels of **both class I and II antibodies—CPRA = 99%**; has strong DSA to all mismatched antigens from the 2001 transplant and also many other specificities
- Still on the list for another transplant



Case Discussion

Which of the following is most likely to be seen on the path report?

- A) Intranuclear inclusion bodies
- B) Acute tubular necrosis
- C) Grade 3 IFTA only
- D) Interstitial hemorrhage and infarction
- E) Acute cellular rejection

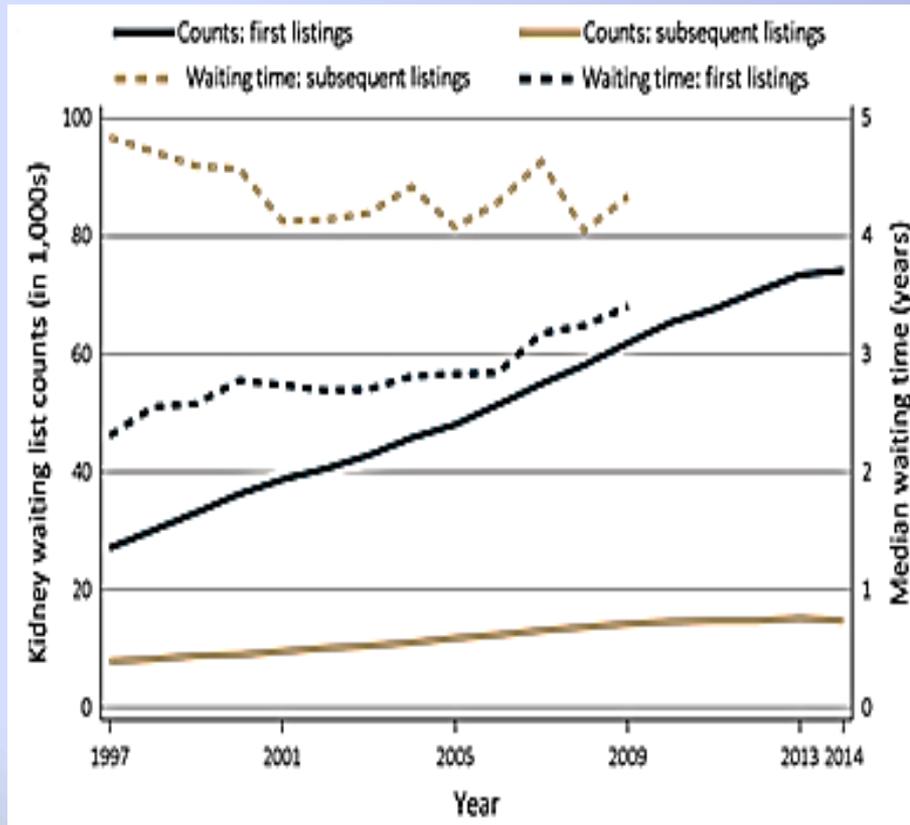


Case Discussion

Which of the following is most likely to be seen on the path report?

- A) Intranuclear inclusion bodies
- B) Acute tubular necrosis
- C) Grade 3 IFTA only
- **D) Interstitial hemorrhage and infarction**
- E) Acute cellular rejection

Waiting List-on 12/31/2014



- Continues to grow (88,231 candidates-on dialysis)
- 83% awaiting their first transplant and **17% awaiting re-transplant**
- **Prior transplants wait longer**

Table 4.5(i) Active Eurotransplant waiting lists at year end, from 2012 to 2016

Waiting list type	Composition	2012	2013	2014	2015	2016	2015/2016
Kidney	kidney	10151	10757	10689	10400	10476	8.5%
	kidney + heart	25	17	12	14	19	35.7%
	kidney + lung	1	1	1	0	1	--
	kidney + liver	67	57	55	62	57	3.6%
	kidney + liver + pancreas	1	1	1	1	1	0.0%
	kidney + pancreas	280	287	322	320	347	12.3%
Kidney	Total	10525	11120	11080	10797	10901	8.6 %

Re-registration events	2012	2013	2014	2015	2016	2015/2016
Kidney	884	817	862	813	866	6.5 %
Heart	25	18	11	20	15	-25.0 %
Lungs	49	38	40	46	38	-17.4 %
Liver	349	284	304	306	281	-8.2 %
Pancreas	51	48	38	33	34	3.0 %
Total events	1358	1205	1255	1218	1234	1.3 %
Total patients	1310	1173	1227	1189	1195	0.5 %

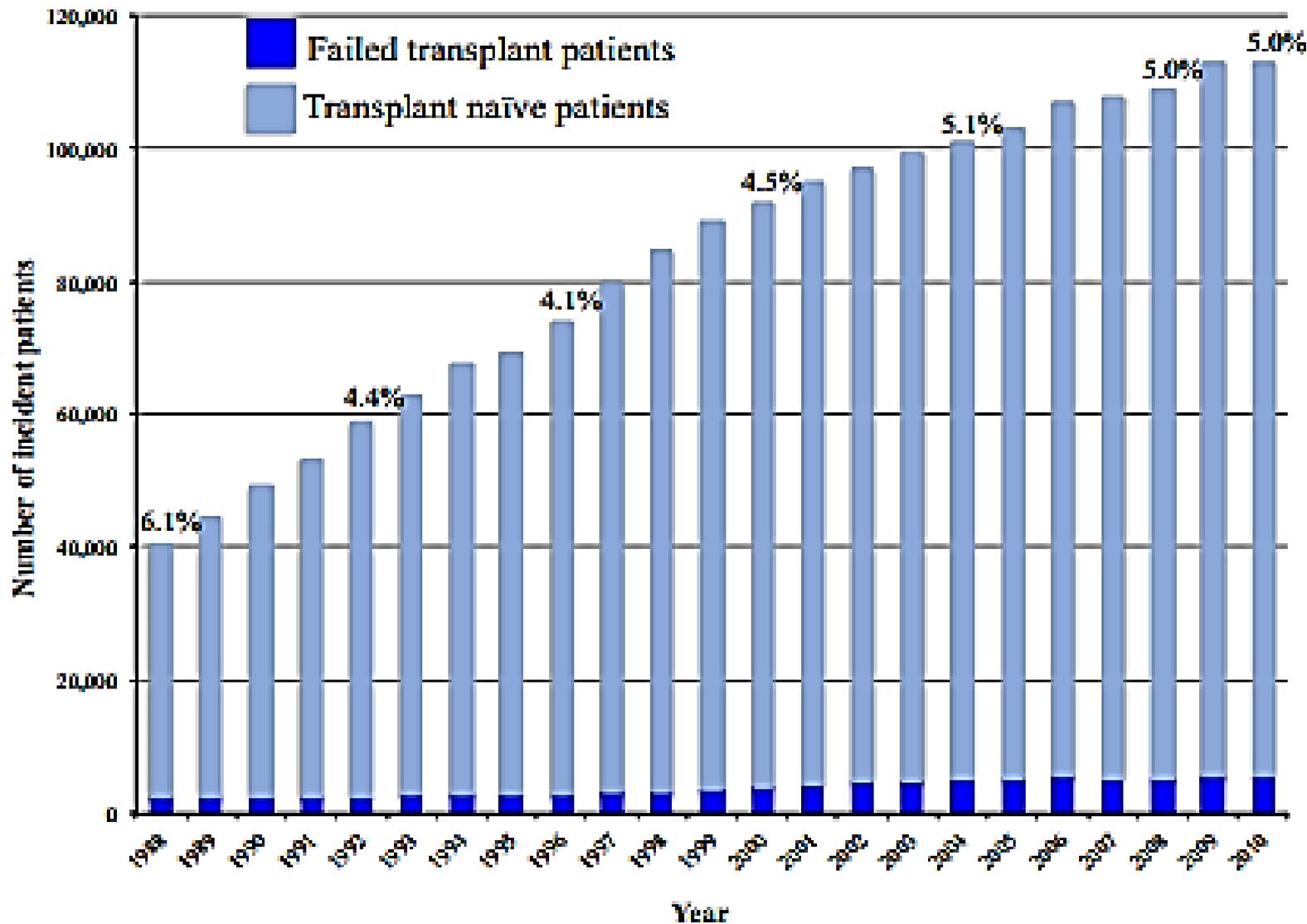
Patient registrations for multiple organs are counted for each organ separately. Re-registrations are where a patient has previously received a transplant for the same organ, new registrations are all other patient registration events. Registrations for both deceased and living donor transplants are included.

Table 5.3(i) Active kidney-only transplant waiting list at year end, from 2012 to 2016 - characteristics

Blood group	2012	2013	2014	2015	2016	2015/2016
A	3488	3838	3734	3614	3551	-1.7 %
AB	236	272	336	344	370	7.6 %
B	1357	1523	1553	1598	1664	4.1 %
O	5070	5124	5066	4844	4891	1.0 %
Total	10151	10757	10689	10400	10476	0.7 %

% PRA current	2012	2013	2014	2015	2016	2015/2016
0-5 %	8500	8792	8762	8424	8478	0.6 %
6-84 %	1346	1599	1547	1517	1482	-2.3 %
85-100 %	232	299	369	449	502	11.8 %
Not reported	73	67	11	10	14	40.0 %
Total	10151	10757	10689	10400	10476	0.7 %

Sequence	2012	2013	2014	2015	2016	2015/2016
First	8233	8828	8708	8500	8618	1.4 %
Repeat	1918	1929	1981	1900	1858	-2.2 %
Total	10151	10757	10689	10400	10476	0.7 %



•Proportion of failed kidney transplant patients in all incident dialysis patients

Molnar MZ, et al. Semin Dial 2013

Timing of Return to Dialysis

- Number of patients returning to dialysis after graft failure about 5000 annually, or 4-5% of the incident dialysis population
- Over 90% of patients with failed graft will return to dialysis; approximately 10% will undergo preemptive repeat transplantation

Ansell D, et al. Am J Transplant 2007

Gill JS, et al. Kidney Int 2002

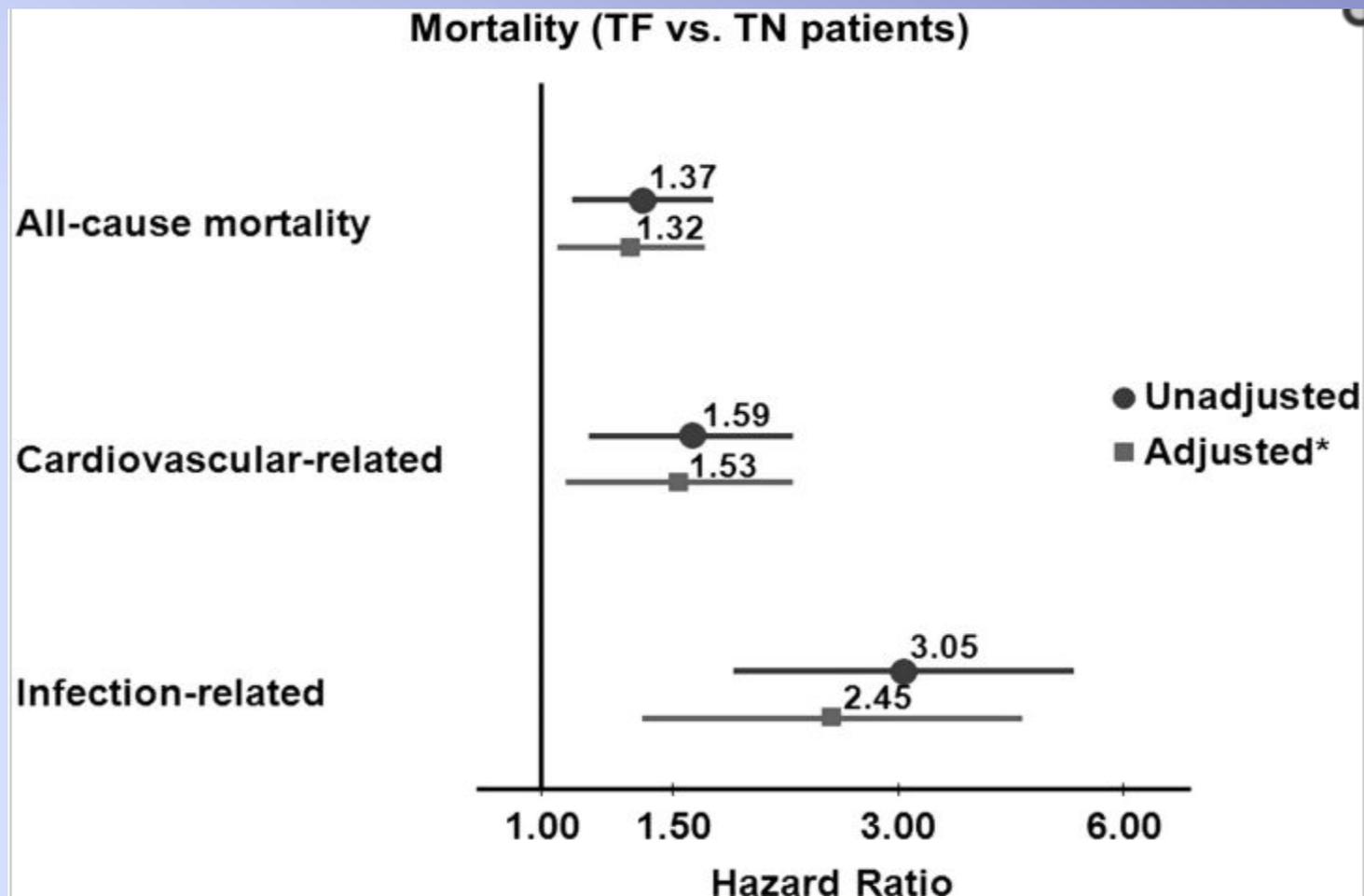
Pham PT, et al. World J Nephrol 2015

Timing of Return to Dialysis

- Clinical practice targets are less likely to be met in these patients compared to transplant-naïve dialysis patients
- Worse blood pressure control, higher serum phosphorus, lower bicarbonate and lower hemoglobin (less EPO use)

Ansell D, et al. Am J Transplant 2007

Gill JS, et al. Kidney Int 2002

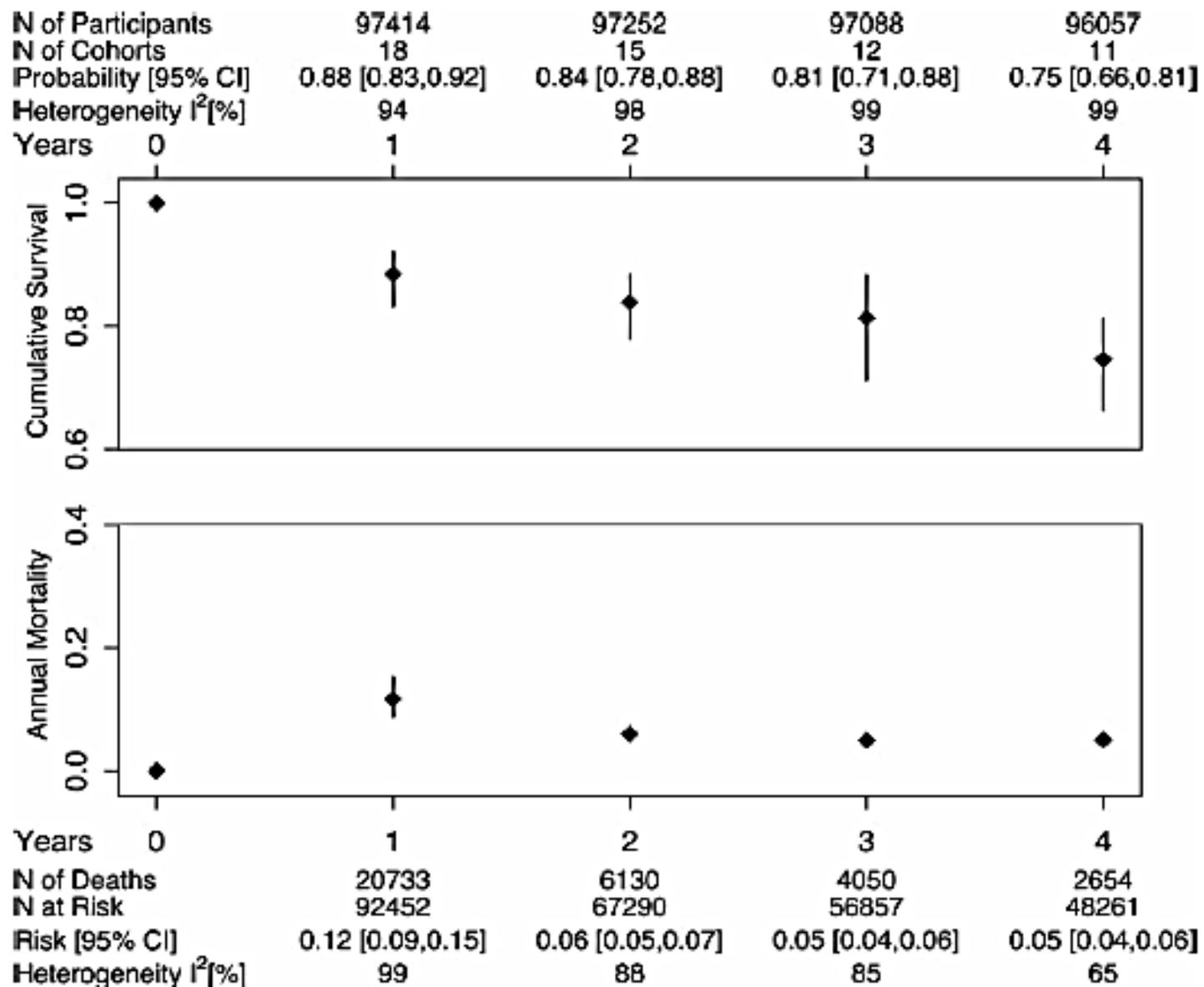


- Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) between 1996-2008
- **All-cause mortality is 32% higher** for transplant failure (TF) patients on dialysis than for transplant-naïve (TN) patients, with **a hazard ratio for death from infection-2.45**

Perl J, et al. Nephrol Dial Transplant 2012

Risk of Death After Graft Failure

- Meta-analysis: 40 cohort studies-between 1975 and 2013 (20 of them based on registry data; large between-study heterogeneity); 249,716 patients with allograft failure; cause of death is unknown for > 20% patients
- **The first year of dialysis therapy was associated with the highest mortality (12%)** and decreases in subsequent years- from 6% in the 2nd year to 5% thereafter
- Insufficient data to assess factors (previous transplants or dialysis modality) or interventions-impacting prognosis following graft failure (such as nephrectomy or stopping immunos)



Patient Survival after Graft Failure

- Patients who resumed dialysis after graft failure 2007–2009-French registry database; all returned to HD (<65 years); 11% had diabetes
- Case–control analysis, the observed mortality rates in 778 graft failure and 778 transplant-naïve HD patients were 11.8 and 10.8%, respectively, f/u to 3 years
- Significant amount of missing data; short term follow-up

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

Molnar MZ, et al. Semin Dial 2013

Perl J, et al. Nephrol Dial Transplant 2012

What is the Percentage of Dialysis Catheter Use in Patients with Failed Graft?

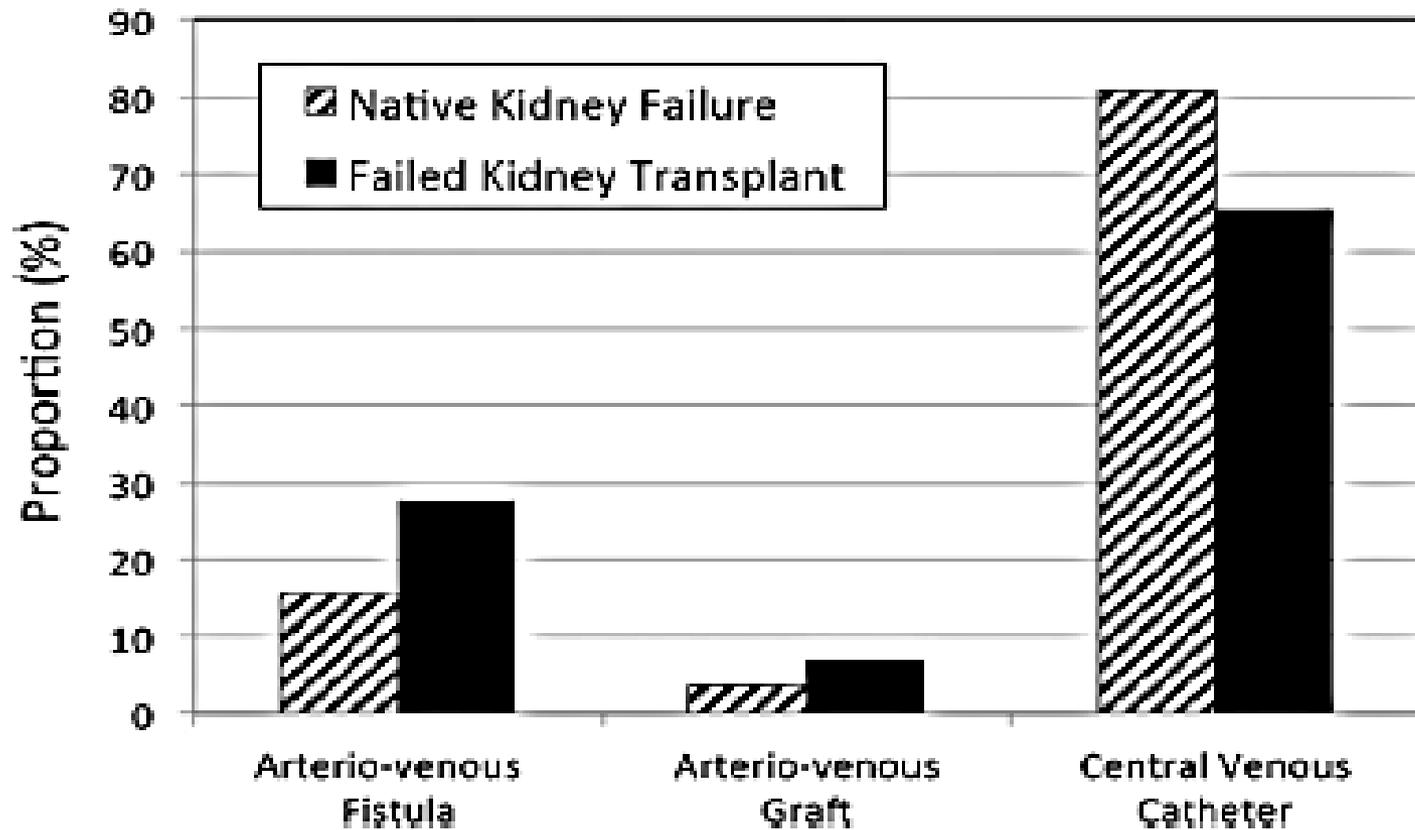
- A) Less than 10 percent
- B) 15-25%
- C) 30-40%
- D) 50-60%
- E) 60-70%
- F) More than 80%

Patients Returning to Dialysis

- US Renal Data System database; 16,728 patients with a failed renal transplant and 509,643 patients with native kidney failure-initiated dialysis between January 1, 2006, and September 30, 2011
- In patients with a failed transplant, 27.7% (n=4636) used an AV fistula, 6.9% (n=1146) used an AV graft, and **65.4% (n=10,946) used a central venous catheter**

What is the Percentage of Dialysis Catheter Use in Patients with Failed Graft?

- A) Less than 10 percent
- B) 15-25%
- C) 30-40%
- D) 50-60%
- **E) 60-70%**
- F) More than 80%



•93.5% of patients with a failed transplant (vs 63.7% of transplant naïve patients) had been under the care of a nephrologist

•Lack of referral, women, diabetes, and peripheral vascular disease were associated with use of a CVC

Vascular Access

- Retrospective observational cohort of 138 patients; dialysis after kidney transplant failure between 1995 and 2014
- 53 (38.4 %) patients-no access planning
- Increased mortality in patients with dialysis catheters ((hazard ratio 5.90)

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

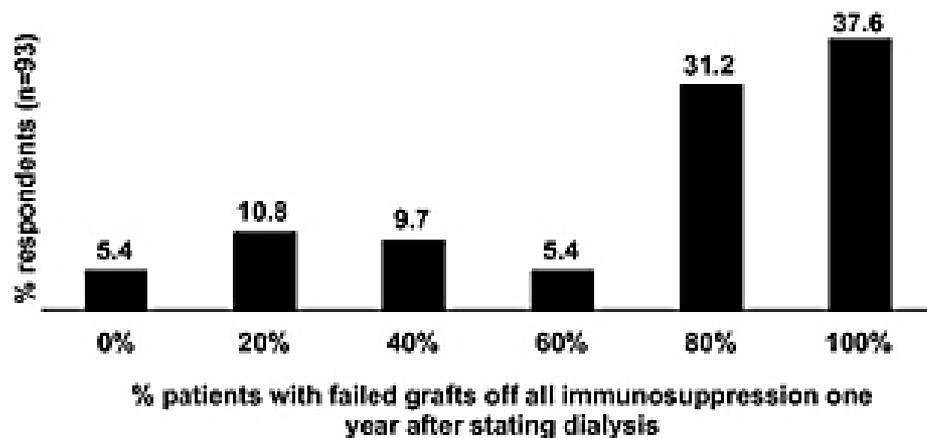
•No difference between modalities *Molnar MZ, et al. Semin Dial 2013*

Immunosuppression

Immunosuppression after Graft Failure

Do you continue immunosuppression after the graft fails (patient is back on dialysis)?

- A-Yes
- B-No
- C-Sometimes



•Approximately what percentage of your center's patients with failed grafts is off all immunos 1 year after starting on dialysis?

	MMF/AZA %	Tacro/CSA%	Sirolimus %	Prednisone %	None %
What drugs do you use in your standard immunosuppression regimen? n = 93	95.7/8.6	95.7/17.2	15.1	74.2	NA
If a patient's transplant fails, which drug do you wean off first? n = 92	57.6	38.0	0.0	4.3	0
Which drug do you usually wean next? n = 93	33.3	55.9	2.2	6.5	0
Which drugs do you leave patients on indefinitely after graft failure and return to dialysis? n = 93 ^a	5.4	5.4	0.0	21.5	71.0

AZA, azathioprine; CSA, cyclosporine; MMF, mycophenolate mofetil; Tacro, tacrolimus.

^aThree respondents said they leave patients on both prednisone and an antimetabolite, so the percentages add up to over 100%.

Reasons to Continue Immunosuppressive Drugs

- To avoid rejection
- Minimization of systemic inflammation
- Prevention/minimization of sensitization
- Preservation of residual renal function
- Concerns 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, avascular necrosis, etc)
- Increased susceptibility to infections
- Malignancy (skin cancers, lymphoma etc)
- Increased/ongoing cost

Infections/Nephrectomy

- 186 patients with failed kidney transplants; rates of hospitalization with fever within 6 months of graft failure (overall 44%)
- 88% of patients maintained on immunos had documented infection vs 38% weaned off of immunos before admission ($P < 0.001$)-**dialysis catheter-related infections-the most common**
- Nephrectomy-done in 81% of hospitalized patients with no infection, compared to 30% of patients with documented infection ($P < 0.001$)

Immunosuppression-What to Do?

- No consensus; lack of data
- Might continue some meds-low dose CNI and/or steroids if there is a plan to re-transplant relatively soon after graft failure
- Taper and stop immunosuppression entirely over some period of time (up to 6 months) if there is no plan to re-transplant or in the event of serious infection

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)

Table 1.

Immunosuppression weaning protocol following kidney transplant failure and return to dialysis

1. Stop cyclosporine/tacrolimus or sirolimus immediately.
2. Wean azathioprine or mycophenolate mofetil/mycophenolic acid off over 3 months; stop immediately with acute infection requiring hospitalization or IV antibiotics and do not resume.
3. Maintain prednisone 5 mg daily if plans to retransplant within 1 year of transplant failure or if residual renal function on 24-h urine provides for ≥ 0.5 mL/min urea clearance.
4. Wean prednisone 1 mg/day per month to off if no plans to retransplant, no residual renal function or still on dialysis 6 months after kidney failure.
5. Surgical consult for nephrectomy if signs/symptoms of acute rejection after immunosuppression stopped (pain, redness, swelling over graft) or if signs/symptoms of rejection fail to respond to oral steroids.
6. Stop all immunosuppression after nephrectomy.
7. Check PRA immediately upon return to dialysis and monthly if plans to retransplant.

Chronic Inflammation in Dialysis Patients

- Linked to increased mortality and morbidity as well as poor cardiovascular outcomes
- “Silent” infection in clotted HD vascular accesses, non-infected HD catheters, or **failed transplants left in place**

Ayus JC, et al. JASN 1998

Wanner C, et al. Kidney Int 2002

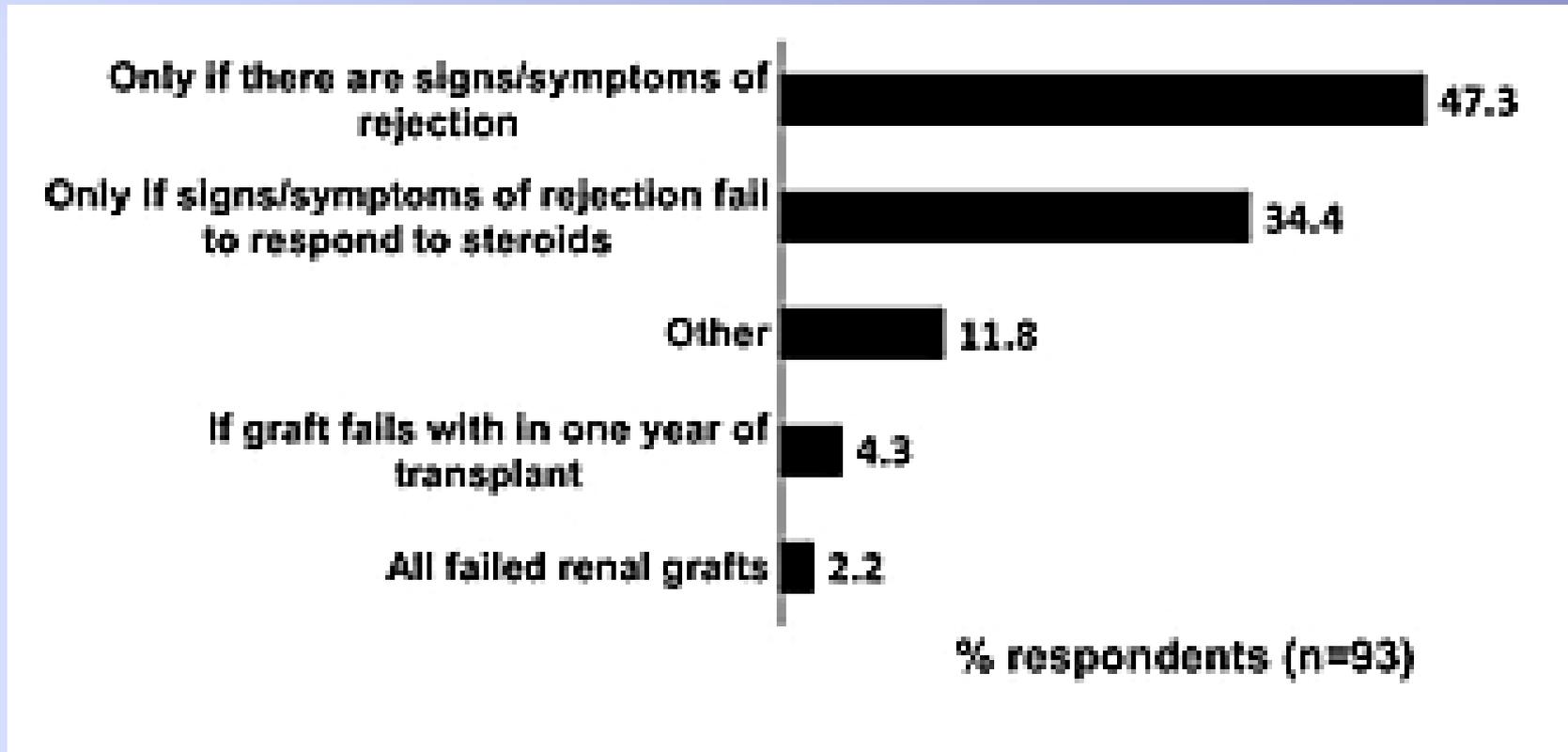
Cachofeiro V, et al. Kidney Int 2008

Wasse H, et al. Nephrol Dial Transplant 2013

Transplant Nephrectomy

When would you perform a transplant nephrectomy?

- A-Only if there are symptoms/signs of rejection
- B-Only if signs/symptoms of rejection fail to respond to steroids
- C-If graft fails within 1 year of transplant
- D-After dialysis initiation on all failed grafts



- When would you perform a transplant nephrectomy?

- **A-Only if signs/symptoms of rejection**

Transplant Nephrectomy-Survival

- 10,951 transplant recipients who returned to dialysis between 1/1994 and 12/2004 (US Renal Data System); 3,451 (31.5%) had allograft nephrectomy during follow-up
- Transplant nephrectomy was associated with a 32% lower adjusted relative risk for all-cause mortality

Ayus JS, et al. JASN 2010

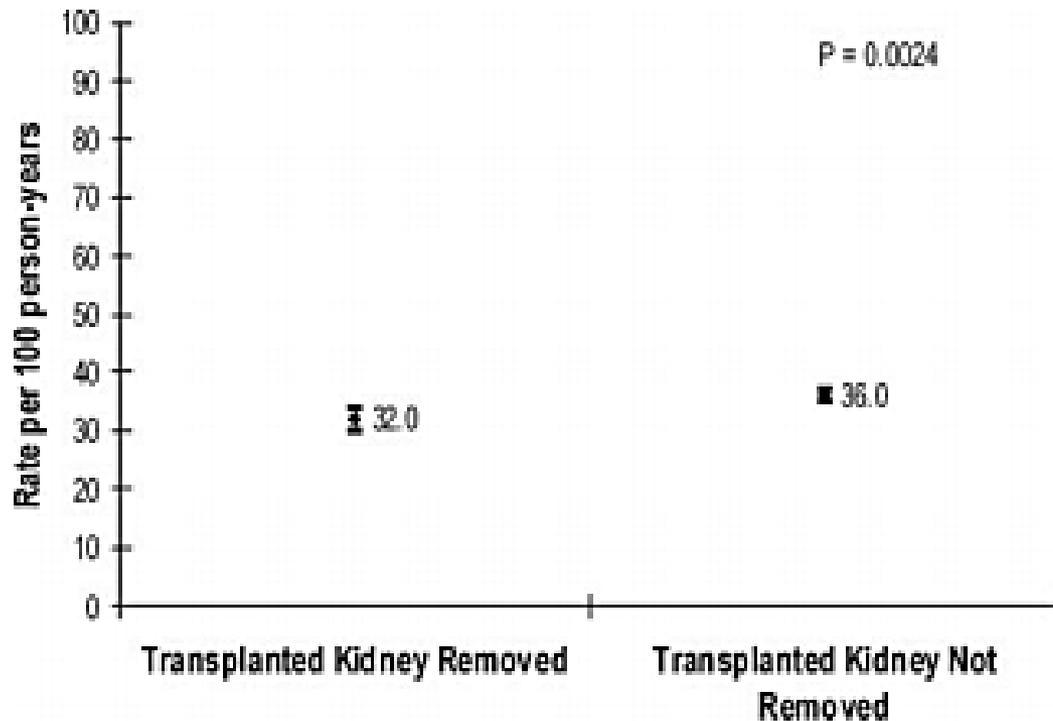


Figure 2. Unadjusted rate of death from any cause associated with or without receipt of renal allograft nephrectomy in 10,951 patients returning to maintenance dialysis after a failed kidney transplant between January 1, 1994, and December 31, 2004, is shown.

- Large observational study
- Cause of nephrectomy or symptoms-not known
- Significant differences in comorbidities
- No info on concomitant therapies or histology
- No longitudinal comorbidity data

Transplant Nephrectomy

- Reported ranging from 5% to 35%; **more likely to be performed** in patients who had graft failure **within 12 months** posttransplant
- Morbidity: 10-68%; Mortality: 1.2-38%
- Complications: blood loss/need for transfusion, wound infections, surgical complications (especially late in the course)

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

Reasons for Transplant Nephrectomy

- Center's protocol
- To make room for subsequent transplant
- Vascular thrombosis/primary nonfunction
- Clinically symptomatic patient
- Presence of chronic inflammatory state
- To improve outcomes after the failed graft

Concerns Related to Nephrectomy

- Another major surgery with potential morbidity and mortality
 - No data on mortality in asymptomatic patients who had nephrectomy
- Need for blood transfusions
- Possibility of worse outcomes after re-transplantation
- Increased sensitization

Transplant Nephrectomy

- No standard approach on how to manage the failed graft
- Paucity of data on the histologic examination of nephrectomy specimens in regards to ongoing inflammation and the extent of lesions

Transplant Nephrectomy-A Single Center Study at UPenn

- 73 transplant nephrectomies (TN)-performed between 04/1999 and 01/2007 at UPenn
- Retrospectively collected data
- Two groups according to the timing of the nephrectomy after transplantation: **early graft removal** (≤ 3 months after transplantation, n=20); and **late graft removal** (> 3 months after transplantation, n=53)

	TN ≤ 3 months (n=20)	TN > 3 months (n=53)
Median age at the time of transplant, years (range)	41 (24-61)	39 (10-73)
Median age at the time of nephrectomy, years (range)	41 (24-61)	45 (19-74)
Male/Female	8/12	31/22
Ethnicity		
White, n (%)	11 (55)	27 (51)
Black, n (%)	9 (45)	24 (45)
Other, n (%)	0	2 (4)
Clinical presentation		
Decreased/absent flow on renal scan or decreased urine output, n (%)	20 (100)	0
Hematuria, n (%)	0	17 (32)
Graft tenderness/pain, n (%)	0	27 (51)
Fever/failure to thrive/weight loss, n (%)	0	13 (25)
Unknown, n (%)	0	11 (2)
Median time from transplant to nephrectomy (range)	4 days (0-75 days)	67 months (4.4-185 months)

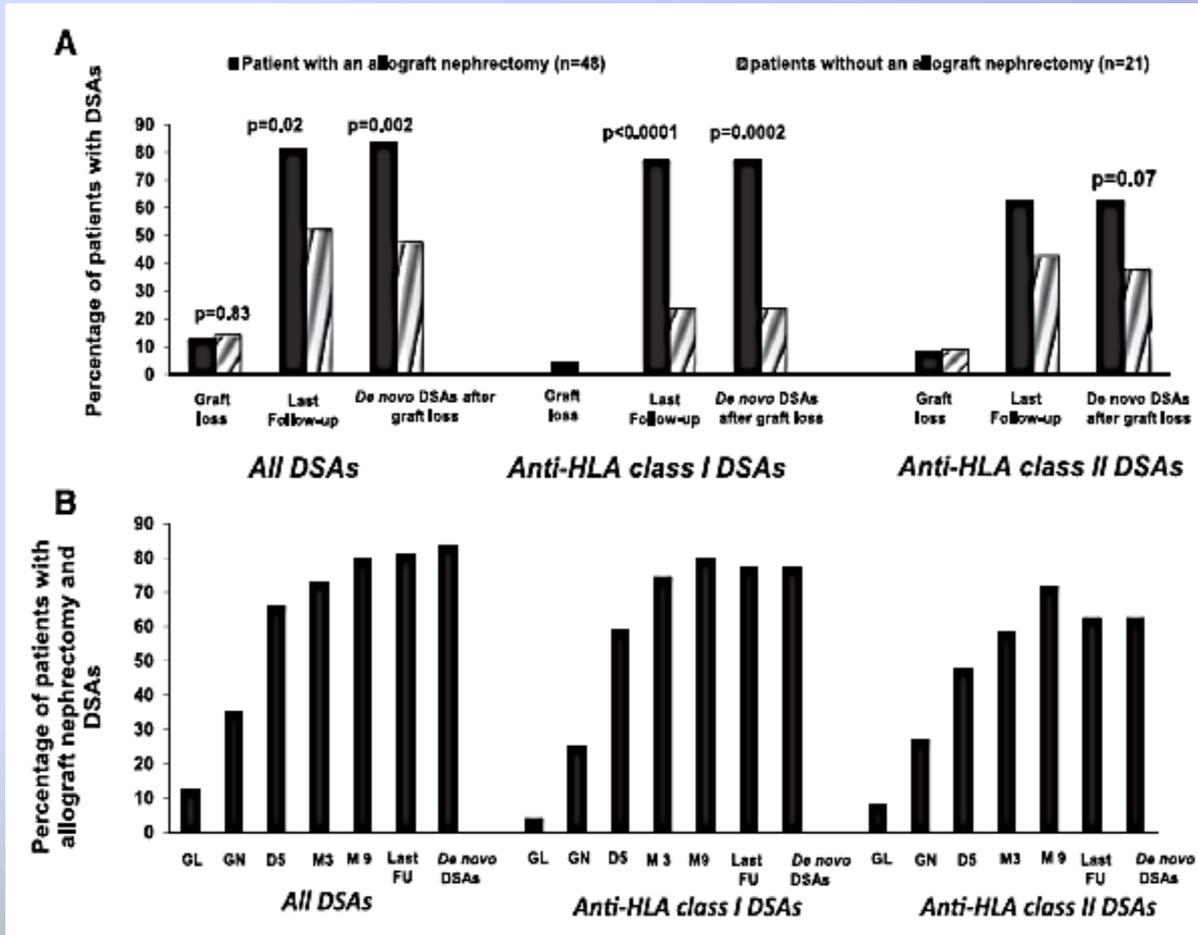
Histopathologic Findings of Acute Rejection

Histopathologic category	All n=73	TN ≤ 3 months n=20	TN > 3 months n=53
Grade 0	19 (26%)	13 (65%)	6 (11%)
Grade 1			
Grade 1A	4 (5.5%)	0	4 (8%)
Grade 1B	5 (7%)	0	5 (9%)
Grade 2			
Grade 2A	4 (5.5%)	0	4 (8%)
Grade 2B	11 (15%)	0	11 (21%)
Grade 3	30 (41%)	7 (35%)	23 (43%)
TCMR	48 (66%)	1 (5%)	47 (89%)

Results-Late TN

- 47 patients (89%): had acute rejection-**grade 2B (21%) and grade 3 (43%)**
- 32 patients (60%): had interstitial hemorrhage
- 4 patients had TN to create “space” for the new transplant; all had grade 3 IF/TA; one 2B AR; one grade 3 AR and one grade 1A AR, **suggesting ongoing inflammation despite not being clinically symptomatic**
- **7 patients (32%) did not have DSAs pre-TN but developed DSAs post-TN**

DSA and Transplant Nephrectomy



- 2 groups (48 patients with nephrectomy-done 150 days after graft loss- vs 21 patients without nephrectomy)
- More DSAs in patients with nephrectomy (as soon as 5 days postop)
- Predictive factors for the appearance of DSAs after graft failure: the number of HLA class I mismatches and having a nephrectomy

DSA and Transplant Nephrectomy

- *de novo* DSAs in 47.6% of patients without allograft nephrectomy when immunosuppression was stopped
- In patients who had an nephrectomy, the incidence of *de novo* DSAs increased from 35.4% after cessation of immunosuppressive therapy and before a nephrectomy to 83.3% (P=0.002)
- The incidence of *de novo* DSA class I antibodies was significantly higher in patients who had an allograft nephrectomy
- Complication rate was relatively high at 30%

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

Recommendations-Late TN

- Grafts in patients with symptoms should be removed quickly
- There is **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

Summary

- Patients with failed grafts are different from transplant-naïve patients
- Increased mortality mostly due cardiovascular diseases and infections
- May not receive adequate preparation before the initiation of dialysis
- Also have specific issues such as immunosuppression withdrawal or the need for allograft nephrectomy

Recommendations

- Appropriate treatment of CKD-related issues- bone disease, hyperkalemia, acidosis, and anemia
- **Relisting for transplantation when GFR is around 20 cc/min**
- **Preemptive transplant planning**
- **Encourage for living donor transplantation**
- **Discontinuation of immunosuppression- over 6-month period if no plans for living donation in the near future**

Recommendations

- Excess mortality may be lessened by facilitating access to **high-quality transitional care and integrated services (CKD and dialysis care)**
- Improve the **coordination between transplant and pre-dialysis teams**
- **Partnership between transplant team and general nephrologist-very important**
- Intensive patient education and counseling/Dialysis modality selection/Early dialysis access planning/Vein mapping/Timely initiation of dialysis

