

Management of a Recipient with a Failed Kidney Transplant

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Disclosures

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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 (was treated with pulse steroids in the last few weeks)

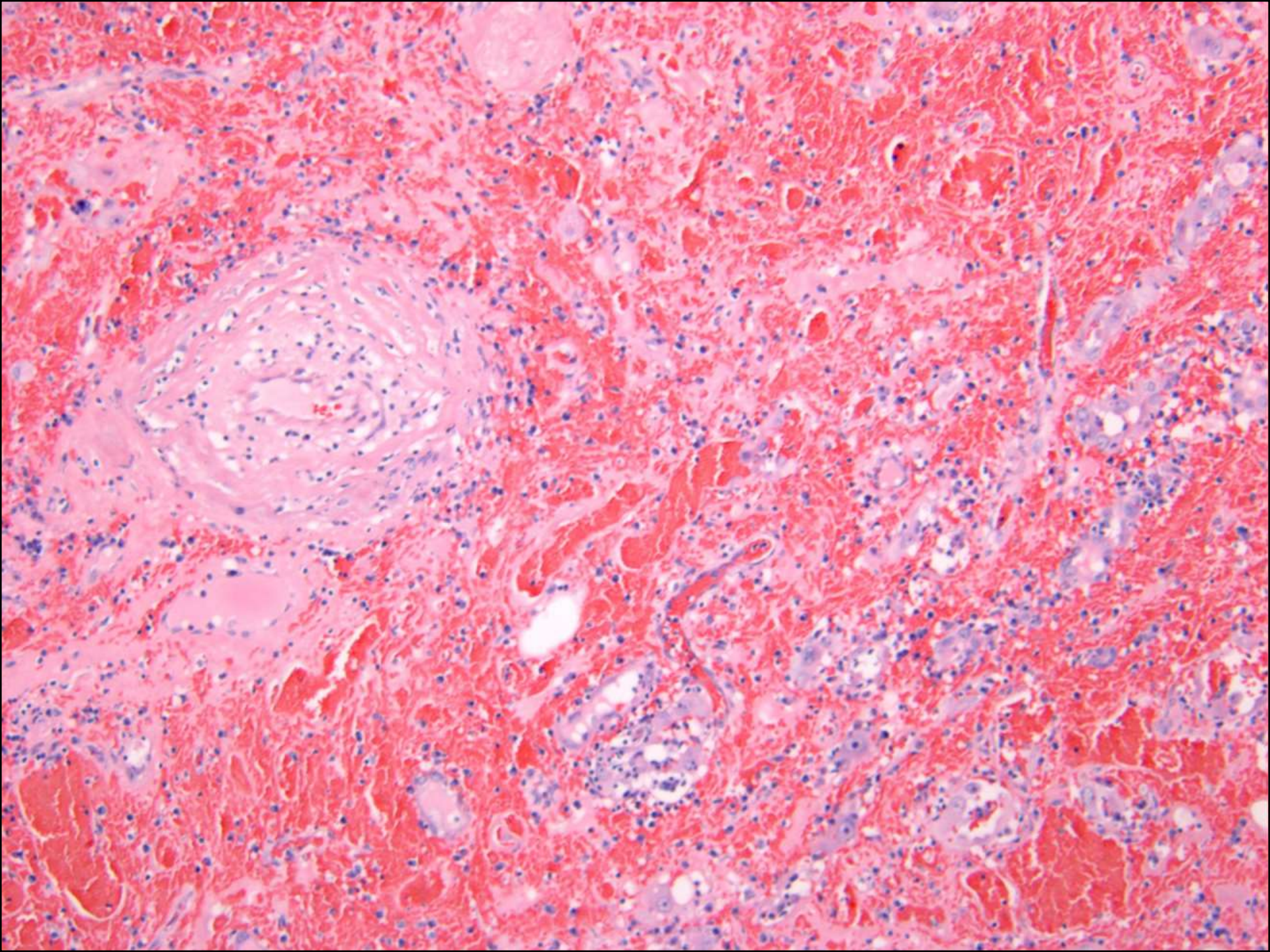


- Transplant with scattered foci of dystrophic calcification; there has been an interval increase in degree of **inflammatory stranding** surrounding the kidney; several nearby enhancing lymph nodes and increased free fluid within the pelvis; **kidney itself appears more edematous, and has enlarged significantly**

Case Discussion

- Transplant nephrectomy done on 12/13/2012
- The last blood sample 5/16/13: has high levels of both class I and II antibodies—CPRA = 99%; has strong DSA to all mismatched antigens from the 2001 transplant (A3, 30, B13, 47, DR7, 53, DQ2) and also many other specificities

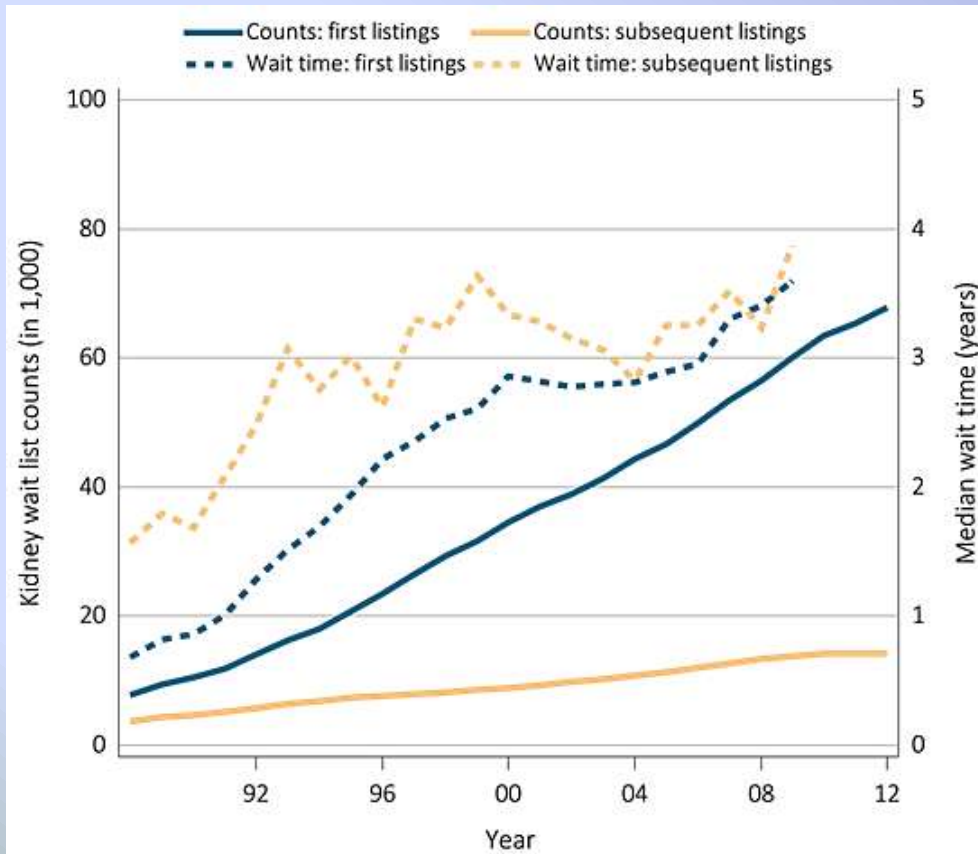




Objectives

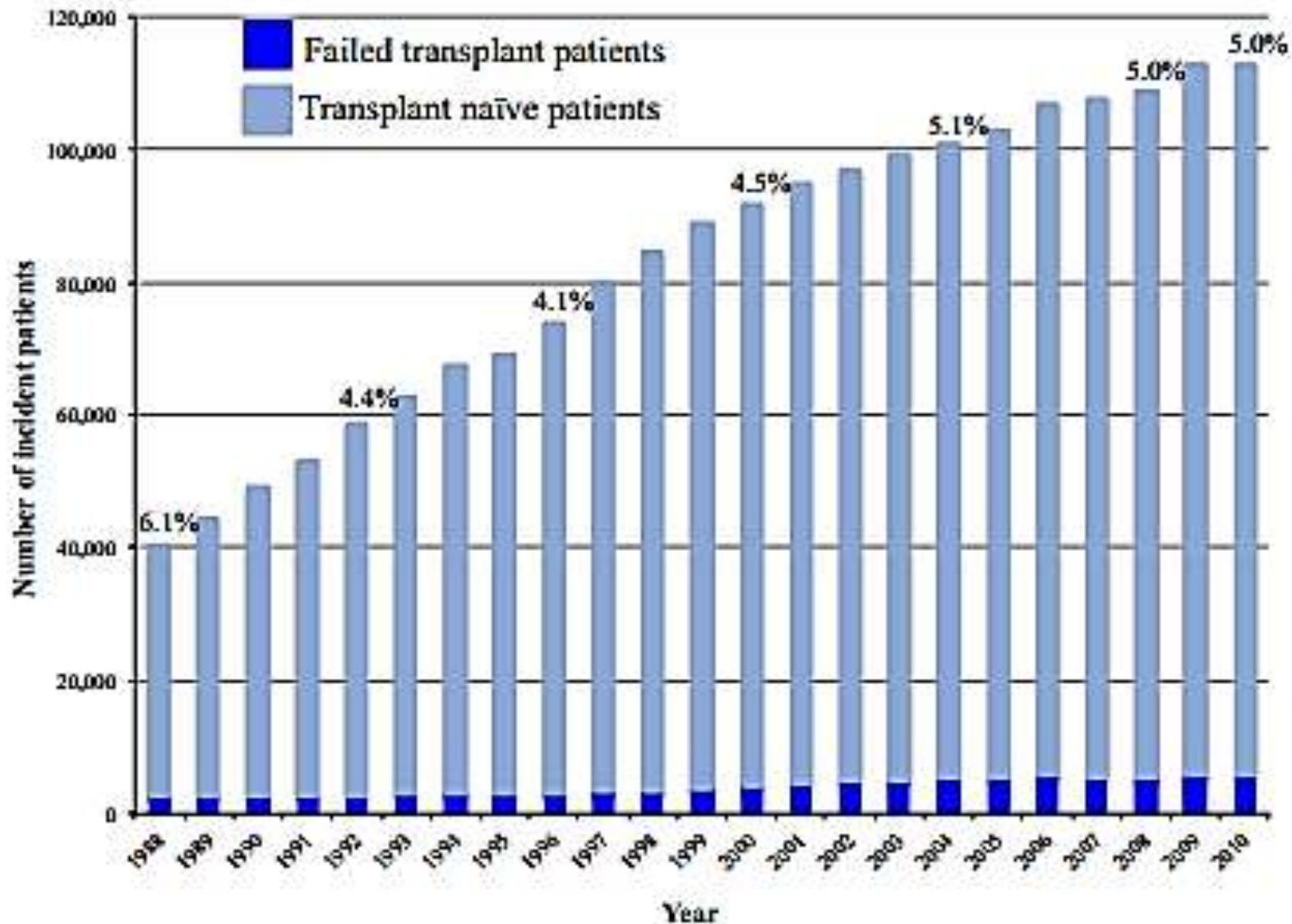
- Epidemiology of transplant failure
- Timing of dialysis initiation
- Survival on dialysis after graft failure/Cause of death
- Dialysis access
- Dialysis modality
- Immunosuppression withdrawal
- Chronic inflammation/transplant nephrectomy

Waiting List



- Continues to grow
- 83% awaiting their first transplant and **17% awaiting re-transplant**
- **Prior transplants wait longer**

U.S. Renal Data System, USRDS 2014 Annual Data Report



•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
 - 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

Dialysis Patient With Failed Graft

- USRDS data on 4,741 patients; between April 1995 and September 1998
- Patients with failed grafts have **high mortality on dialysis** (one, two and three year patient mortality from all causes: 16%, 25%, and 33%, respectively)-much higher
- Cause of death: **cardiac (36%), infectious (17%),** cerebrovascular disorders (6%) and malignancies (2%)

Survival of Patients Returning to Dialysis after Graft Loss

- **Era of first kidney transplant failure:** improved survival-between 2001-2005 (reference) compared with 1996-2000 and between 1991-1995 (Canadian)
- **Length of allograft function** was inversely proportional to survival: >5 years and between 1-5 years had poorer survival compared with patients with allograft loss within the first year posttransplant

Survival of Patients Returning to Dialysis after Graft Loss

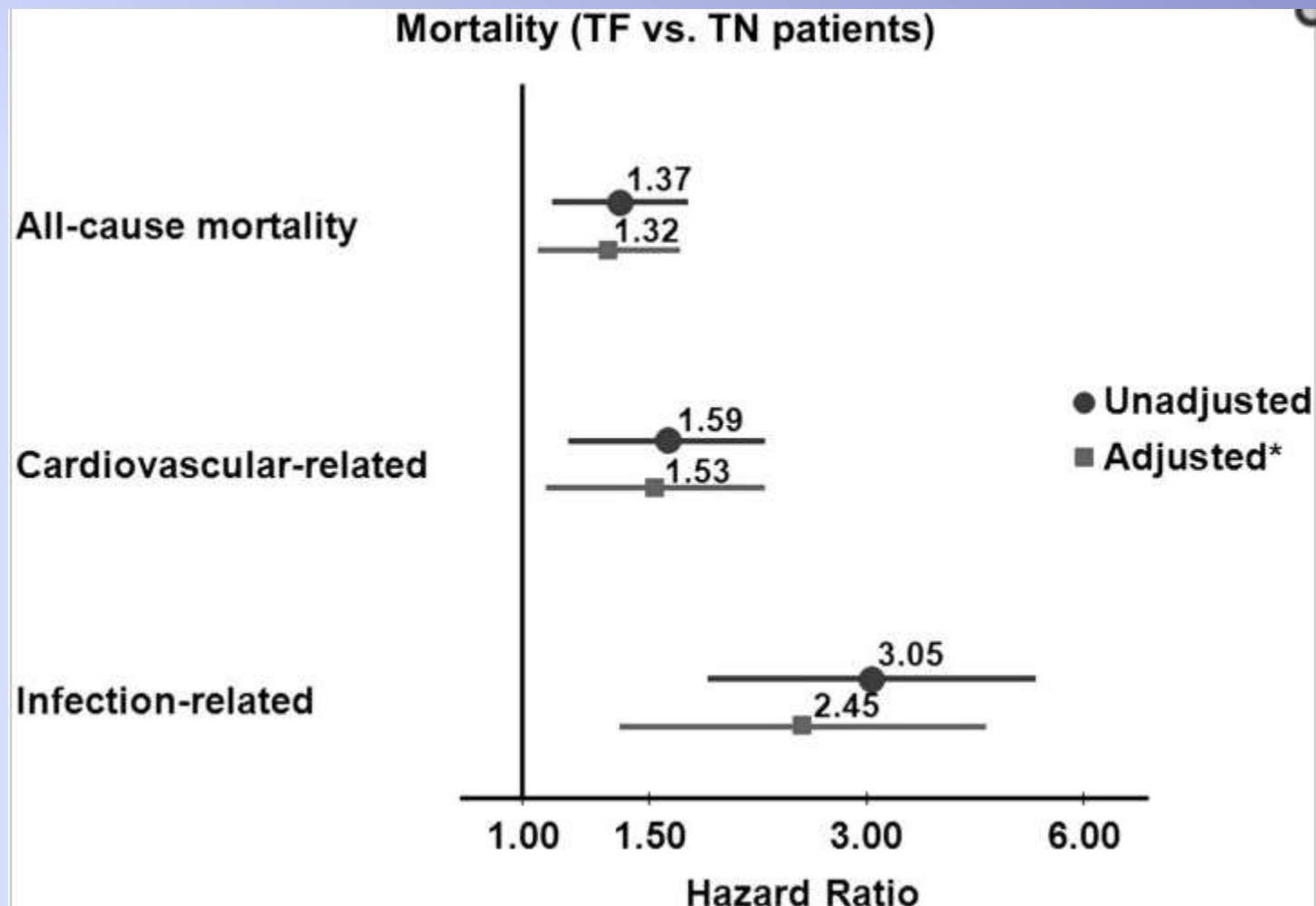
- **Increased duration of ESRD exposure** before transplantation: associated with a trend toward reduced survival
- Patients treated with **preemptive transplantation** had superior survival compared with patients treated with dialysis before kidney transplantation

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



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

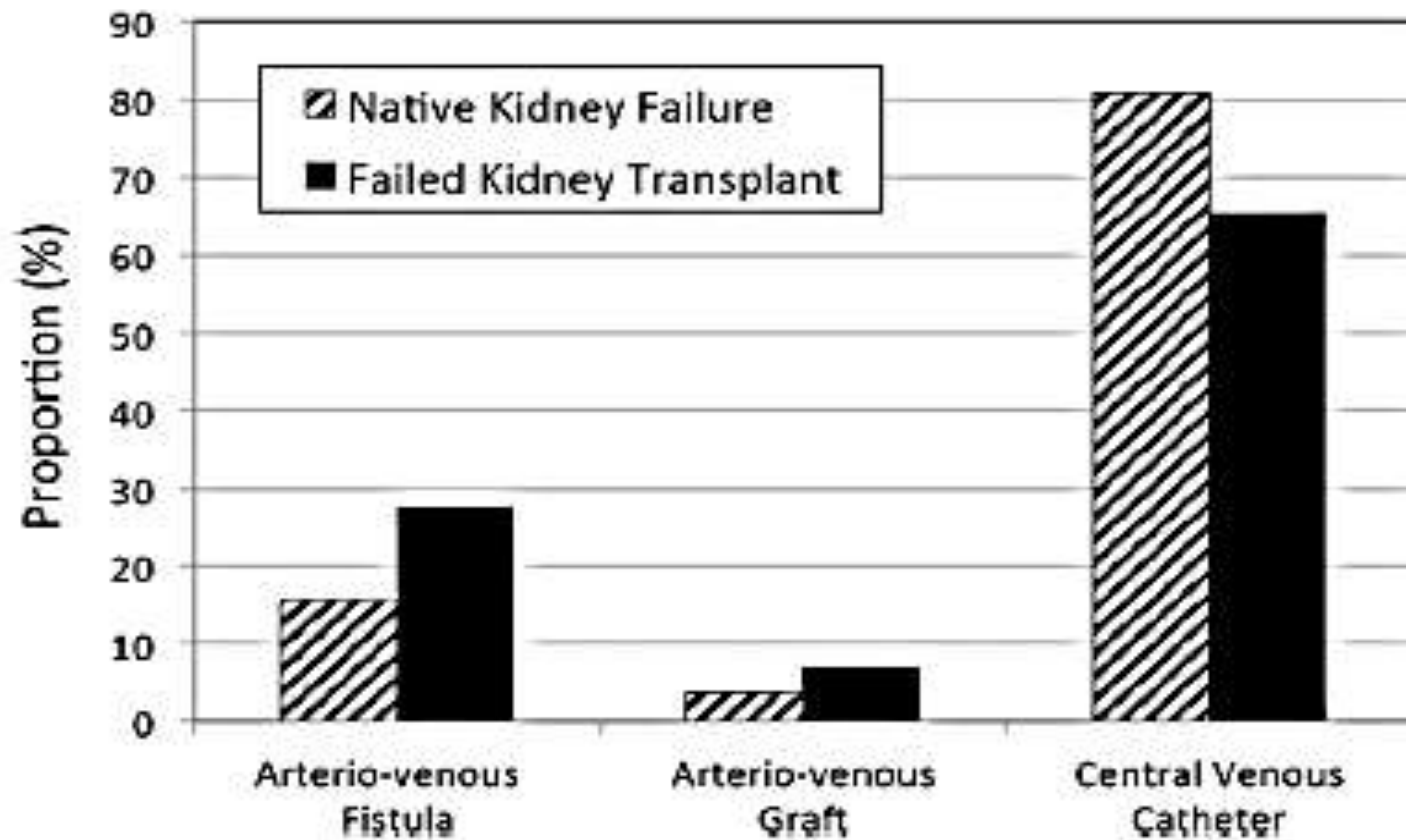
Perl J, et al. Nephrol Dial Transplant 2012

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**



- 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

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

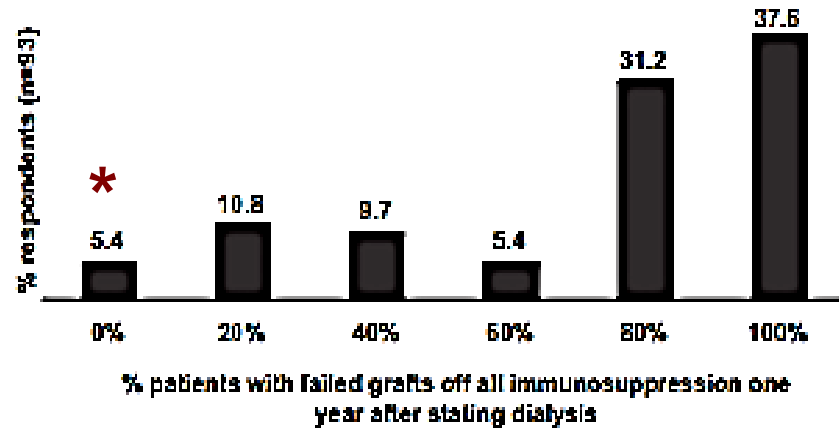


Fig. 1. Approximately what percentage of your centers' patients with failed grafts is off all immunosuppression one yr after starting on dialysis?

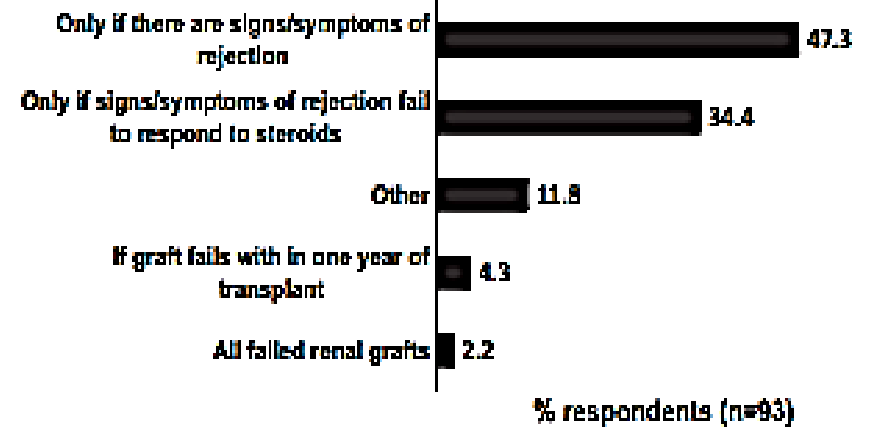


Fig. 2. When does your program perform a nephrectomy of a failed renal graft?

	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	35.5	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%.

Immunosuppression

- No consensus; lack of data
- Might continue some meds-low dose CNI and or steroids if there is a plan to retransplant 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 retransplant or in the event of serious infection

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

Chronic Inflammation in Dialysis Patients

- Linked to increased mortality and morbidity as well as poor cardiovascular outcomes
- “Silent” infection in clotted HD vascular accesses, even the presence of 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*

Chronic Inflammatory State

- Between 1997 and 2000, 43 patients (group A) started HD after graft failure; compared with incident HD patients from the same unit (group B)
- Group A patients required higher EPO doses and had lower levels of serum albumin ($P < 0.001$) and serum prealbumin ($P < 0.001$) and a higher CRP ($P < 0.001$) compared to group B.

Chronic Inflammatory State

- Group A: 29 patients had transplant nephrectomy due to clinical symptoms; these patients had significantly higher ferritin, CRP levels, and ESR
- Significant improvement in serum albumin, prealbumin, ferritin, plasma fibrinogen, ESR, and CRP levels were seen after transplant nephrectomy

	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 $P < 0.001$;

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

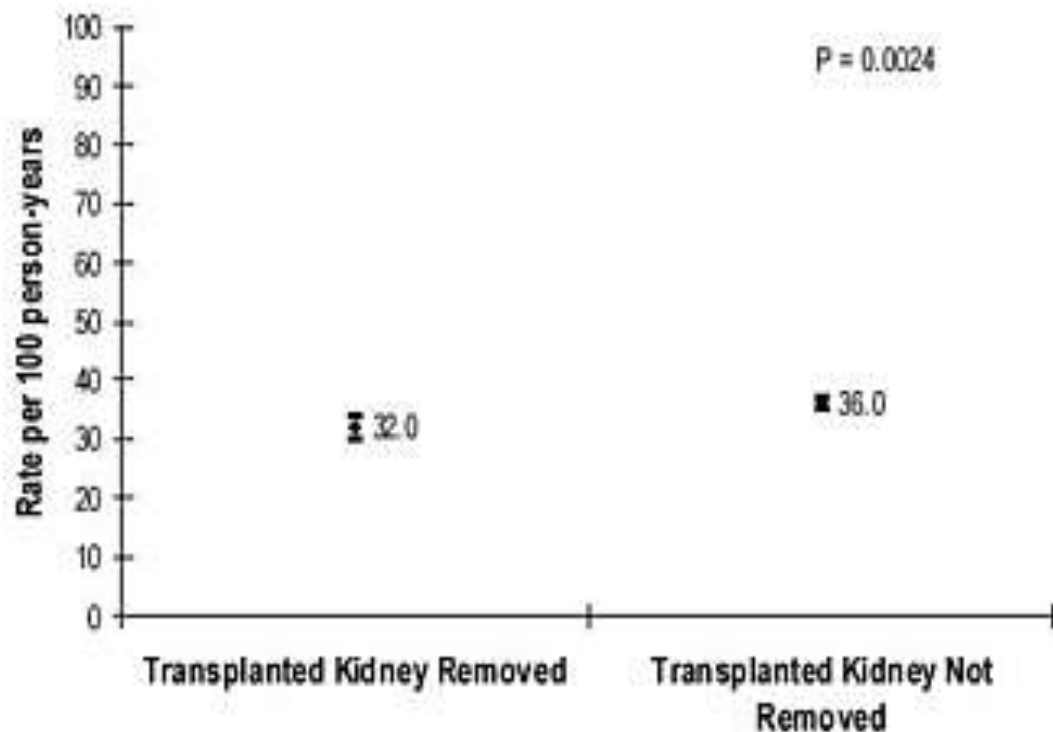


Figure 2. Unadjusted rate of death from any cause associated with or without receipt of renal allograft nephrectomy in 10,951 patients returning to maintenance dialysis after a failed kidney transplant between January 1, 1994, and December 31, 2004, is shown.

- 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
- Divided patients into 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)

Transplant Nephrectomy-A Single Center Study at UPenn

- All nephrectomy slides were retrieved from the archives and re-evaluated
- C4d staining was not performed
- Specimens were graded according to the Banff 2005 diagnostic update
- Anti-HLA antibodies were detected using Flow bead and Luminex bead platforms in the majority of cases (79%)

Characteristics of the Patient Cohort

- During the observation period, a total of 592 grafts failed, including 73 grafts that were removed at our institution
- The transplants had been performed between 1985 and 2005
- The mean duration between the restart of dialysis and TN was 132 days (range 0-658 days) for the whole cohort

	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 changes consistent with acute rejection: **grade 2B (21%) and grade 3 (43%)**
- 32 patients (60%) also had extensive interstitial hemorrhage raising the possibility of significant vascular involvement and antibody-mediated rejection

Results-Late TN

- Only 4 patients had TN with the purpose of creating “space” for the new transplant
- All had grade 3 IF/TA; one also had 2B AR; one had grade 3 AR and one had grade 1A AR, **suggesting ongoing inflammation despite not being clinically symptomatic**
- Three of these 4 patients also had extensive infarction and interstitial hemorrhage

Anti-HLA Antibody Testing

- Only 22 patients (38%) were tested both pre- and post-TN
 - 12 patients (54%) had DSAs at both time points
 - **7 patients (32%) did not have DSAs pre-TN but developed DSAs post-TN**
 - The remaining 3 patients (14%) had no DSAs pre-TN or post-TN

Findings-Late TN

- Extensive inflammation and ongoing immunologic activity, specifically high-grade acute rejection, as well as advanced IFTA changes in patients who had nephrectomy late in their clinical course
 - Supporting the concept of chronic inflammatory state
- Found not only in symptomatic patients but also in patients who had their grafts removed to create space for the transplant

Findings-Late TN

- Significant increase in DSAs after transplant nephrectomy-not only in our patients but also in the literature
 - Mostly class I antibodies and some appearing as soon as 5 days after the surgery (*Del Bello A, et al. CJASN 2012*)
- More inflammation and immunological activity on histopathological exam in patients who had DSAs either pre-or post nephrectomy

Recommendations-Late TN

- Grafts in patients with symptoms should not be left in place but removed quickly
- There is **no clear evidence** that routine nephrectomy in clinically asymptomatic patients is beneficial; though these patients might have undiagnosed chronic inflammation

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

- Patient education and counseling
- Dialysis modality selection
- Early dialysis access planning
- Timely initiation of dialysis before uremic symptoms
- Appropriate treatment of CKD-related issues-bone disease, hyperkalemia, acidosis, and anemia
- Discontinuation of immunosuppression-over 6-month period

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.

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)

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