

Recurrent Diseases After Transplantation

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Editorial

Recurrent Disease after Kidney Transplantation—It Is Time to Unite to Address This Problem!

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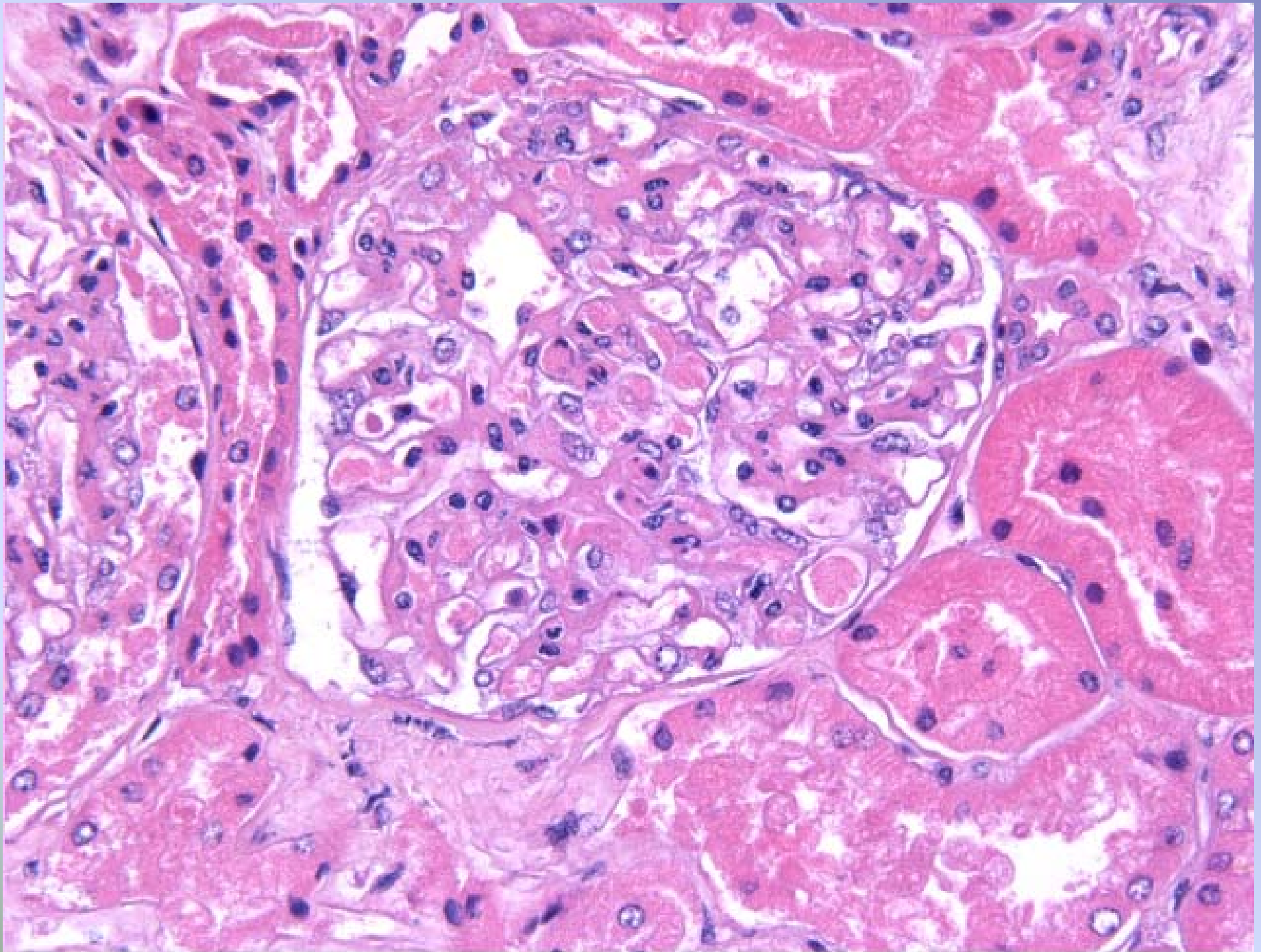
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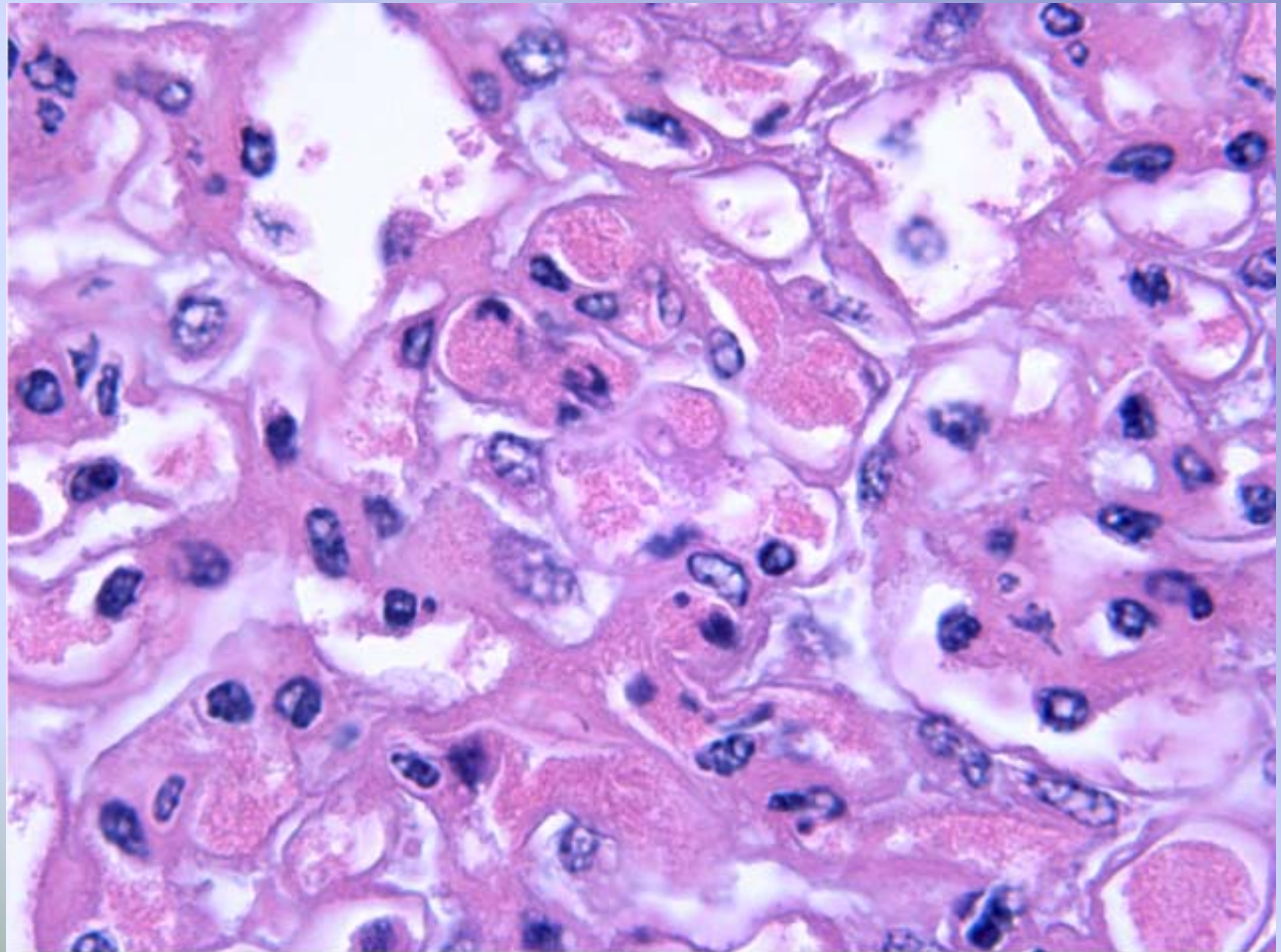
rates. Late graft loss has become one of the leading causes of end-stage renal disease (ESRD).

There are multiple causes of late kidney allograft loss. Each must be addressed if we are to improve outcomes. Most attention is paid to the two commonest causes—death

Case #1

- 21-year-old male, was on hemodialysis since September 2005
- History of nephrotic range proteinuria and hematuria at the age of 3
- Kidney biopsy (native): FSGS, treated with high dose steroids and Cytoxan
- Living-related kidney transplant 3/14/2006, Scr down to 1.7 mg/dl
- 3/27/06: On 6 mg three times a day of Prograf, Scr 2.0 mg/dl, spot urine protein/creat ratio 2.2, platelets 120,000
- Transplant biopsy done





Case #1

- Kidney biopsy:
 - Small numbers of glomerular capillary platelet thrombi consistent with thrombotic microangiopathy
 - Acute tubular necrosis
 - No evidence for rejection
 - Extensive visceral epithelial foot process effacement, most likely early recurrence of a sclerosing glomerulopathy

Case #1

- Clinical course:
 - Prograf dose decreased to a level around 4 (TAC 4 mg bid), also on MMF, prednisone
 - Plasmapheresisx10 treatment
 - Urine protein/creat ratio is down to 0.2, platelets >150,000
 - Repeat kidney biopsy 6/1/06: no rejection, no TMA, early FSGS
 - Last clinic visit (3.5 years after surgery): on valsartan, could not tolerate lisinopril and spironolactone (hyperkalemia), Scr 2.0 mg/dl, spot urine prot/creat ratio: 4

Case #2

- 37 yo male, biopsy-proven FSGS, treated with high dose steroids, Cytoxan, azathioprine, and cyclosporine in the past
- Started PD in January 2002
- Received a DD kidney transplant in August 2004-never worked
- Transplant nephrectomy in October 2005
- Second DD kidney transplant on 11/30/2005

Case #2

- Two months after surgery: spot urine protein/creat ratio: 5.8
- Kidney biopsy 2/1/2006:
 - Banff "Borderline changes", suspicious for early acute cellular rejection and mild mesangial proliferative glomerulopathy with significant effacement of the visceral epithelial foot processes as a background lesion for early FSGS

Case #2

- Clinical course:
 - Steroidsx3 (500 mg, IV)
 - Plasmapheresisx10
 - Initial decrease in proteinuria to 1.7 g/d, then increased to 7.5 g/d
 - Patient did not want to continue PE
 - On Valsartan and ramipril, Scr 1.6-1.8 mg/dl, protein/creatinine ratio: 11, kidney function worsened and started dialysis 14 months after surgery
 - Still on dialysis; listed for a 3rd kidney but inactive

Case #3

- 21 year old African American woman
- ESRD due to biopsy-proven lupus nephritis (class V) and h/o anti-cardiolipin antibody syndrome
- Living-unrelated kidney transplant from her husband
- ATS induction, on Neoral + Cellcept + Prednisone for maintenance

Case #3

- Microscopic hematuria, proteinuria (2.7 g/day) and worsening kidney function (Scr 2.5 mg/d)
- Kidney biopsy: Focal proliferative GN with crescents and immune complexes (WHO class III, SLE)
- Solu-Medrol pulses (250 mg x 3), prednisone 60 mg/d

Case # 3

- Severe herpes esophagitis and CMV infection
- ACE inhibitor, good blood pressure control, on 1000 mg twice a day Cellcept
- Returned to dialysis 8 years after transplantation

Case # 4

- 19 year-old male, on dialysis since March 2008; evaluated for kidney transplantation in May 2008-serum albumin 1.9 g/dl
- Biopsy-proven FSGS-diagnosed at the age of 14, treated with steroids, cyclosporine, tacrolimus, CellCept and Cytoxan in the past
- Started on NSAIDs and ACE inhibitor to decrease the proteinuria and increase his serum albumin

Case #4

- Living-related kidney transplant from his father in August 7th, 2008; immediately started on plasmapheresis + low dose ACE inhibitor
- Kidney biopsy on August 11th 2008: diffuse effacement of foot processes over 80-90% of the capillary loop surfaces as well as mild mesangial proliferation c/w early recurrence of FSGS

Case #4

- One year after transplantation, still on plasmapheresis twice a week; on cyclosporine, mycophenolate mofetil, prednisone, and warfarin
- Participated in a clinical trial of galactose use to decrease the “circulating factor”
- Admitted with bacteremia due to a dialysis catheter-used for plasmapheresis
- Anemic on high-dose EPO
- Serum albumin 1.9 g/dl, spot urine p/c ratio: 14, serum creatinine 3.6 mg/dl

Recurrent Disease (True Recurrence): Diagnosis

Biopsy proven disease on native kidney



Posttransplant proteinuria or hematuria or elevated creatinine



Same biopsy proven disease on kidney transplant

Recurrent Glomerular Diseases

- Recurrence of primary GN (such as FSGS, MPGN, IgA nephropathy)
- Recurrence of secondary GN (such as SLE, Henoch-Schonlein, HUS/TTP, anti-GBM disease)
- Recurrence of metabolic or systemic disease (such as diabetic nephropathy, amyloidosis, scleroderma, oxalosis, Fabry disease)

Recurrent GN in the Transplant

- Native kidney biopsy: in approximately 25% of patients with ESRD (registry data)
- The prevalence of GN as the cause of ESRD: 10-25%, higher prevalence in children and white patients
- Lower prevalence of reported GN in black patients: paucity of info on renal biopsy, higher prevalence of hypertensive nephrosclerosis and diabetic nephropathy
- The prevalence of recurrent GN: 1.9%-31% in different series

Recurrent GN in the Transplant

- True prevalence of recurrent GN: patients who lost their grafts due to recurrence + patients who have recurrence with a functioning graft
- Higher prevalence in patients with ESRD due to biopsy-proven GN
- Higher recurrence: younger age, male gender, re-transplants, use of antilymphocytic serum for induction
- 1-8.4% of all graft failures are due to recurrent disease
- **Recurrence is an important cause of allograft loss for those with ESRD due to GN**

Table 3. Epidemiology of native glomerulonephritides reported through various registries^a

Registry	Prevalence of GN as the Cause of ESRD (%)	FSGS (%)	IgAN (%)	MPGN (%)	MN (%)	SLE (%)	HUS/TTP (%)
NAPRTCS 2006	25.9	11.7	1.3	2.7	0.5	1.6	2.7
USRDS 2000 to 2004	10.3	2.0	0.7	0.3	0.4	1.0	0.1
ANZDATA 2005	25.0 ^b	4.0	22.0	4.0	5.0	4.0	–
RADR 1998 to 2001	14.0	4.0	4.0	2.0	0.6	0.2	0.3

^aANZDATA, Australia New Zealand Dialysis Transplant Data System; NAPRTCS, North American Pediatric Renal Transplant Collaborative Study; RADR, Renal Allograft Disease Registry; USRDS, US Renal Data System

^bData for 2002 through 2005; all other ANZDATA refers to year 2005 only.

Table 4. Epidemiology of recurrent glomerulonephritis reported through various registries

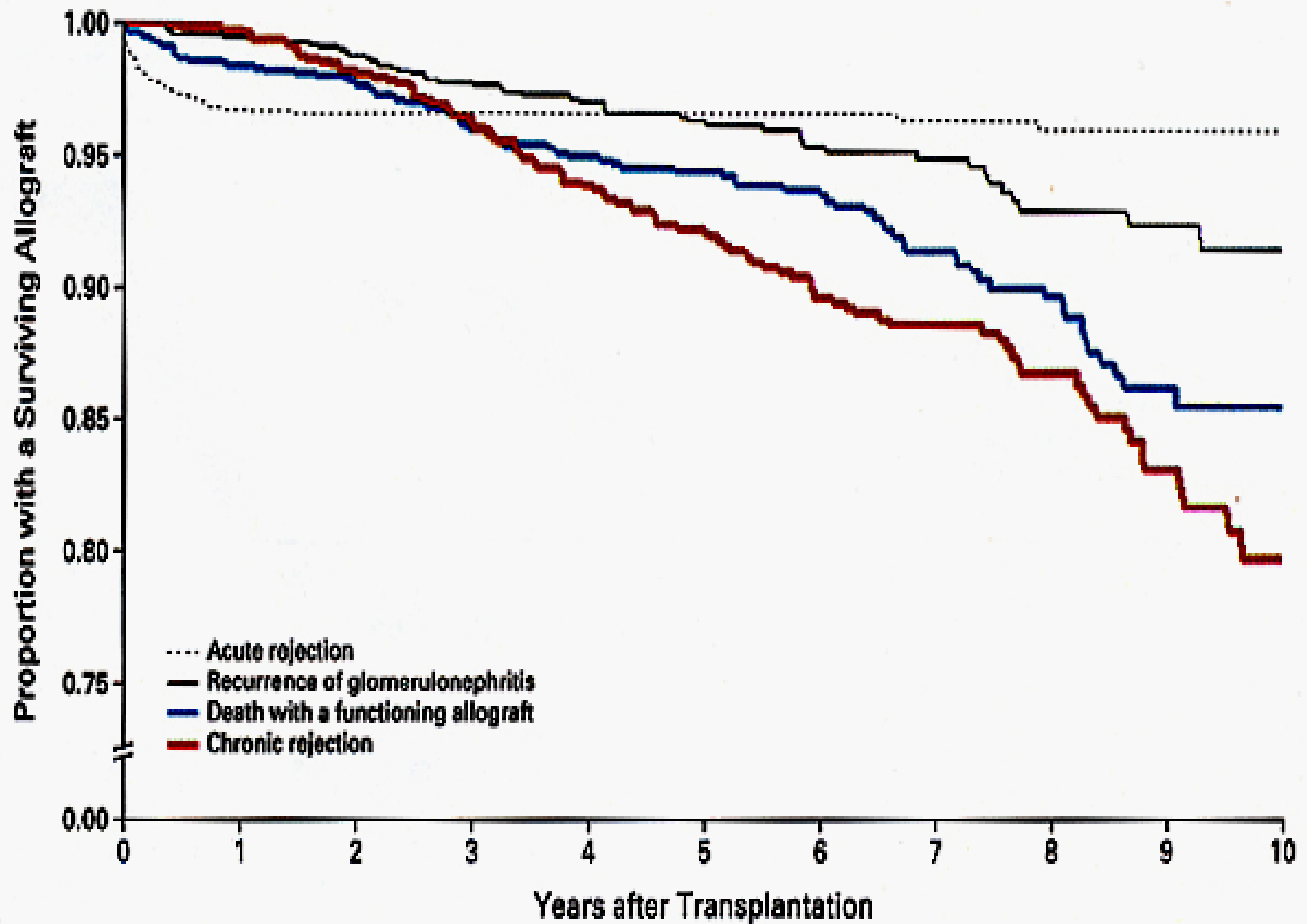
Registry	Prevalence of Recurrent GN after Transplantation (%)	FSGS (%)	IgAN (%)	MPGN (%)	MN (%)	SLE (%)	HUS/TTP (%)
NAPRTCS 2006	12.0	5.5	–	0.8	–	–	1.1
ANZDATA 1996 to 2005	4.0	–	–	–	–	–	–
RADR 1998 to 2001	2.9	1.0	0.1	0.1	0.1	0.1	0.2

Golgert W, et al. CJASN 2008

Risk of Graft Loss From Recurrent GN

- 1505 patients with biopsy-proven GN from Australia (1988-1997)
- The incidence of allograft loss due to recurrence at 10 years was 8.4% and increased overtime
- Most frequent causes of allograft loss at 10 years: **1. Chronic rejection, 2. Death with a functioning graft, 3. Recurrence**
- Recurrence is more frequent than acute rejection as a cause of allograft loss during first 10 years after transplant

Briganti EM, et al NEJM 2002



No. at Risk

1505

1287

1091

872

717

612

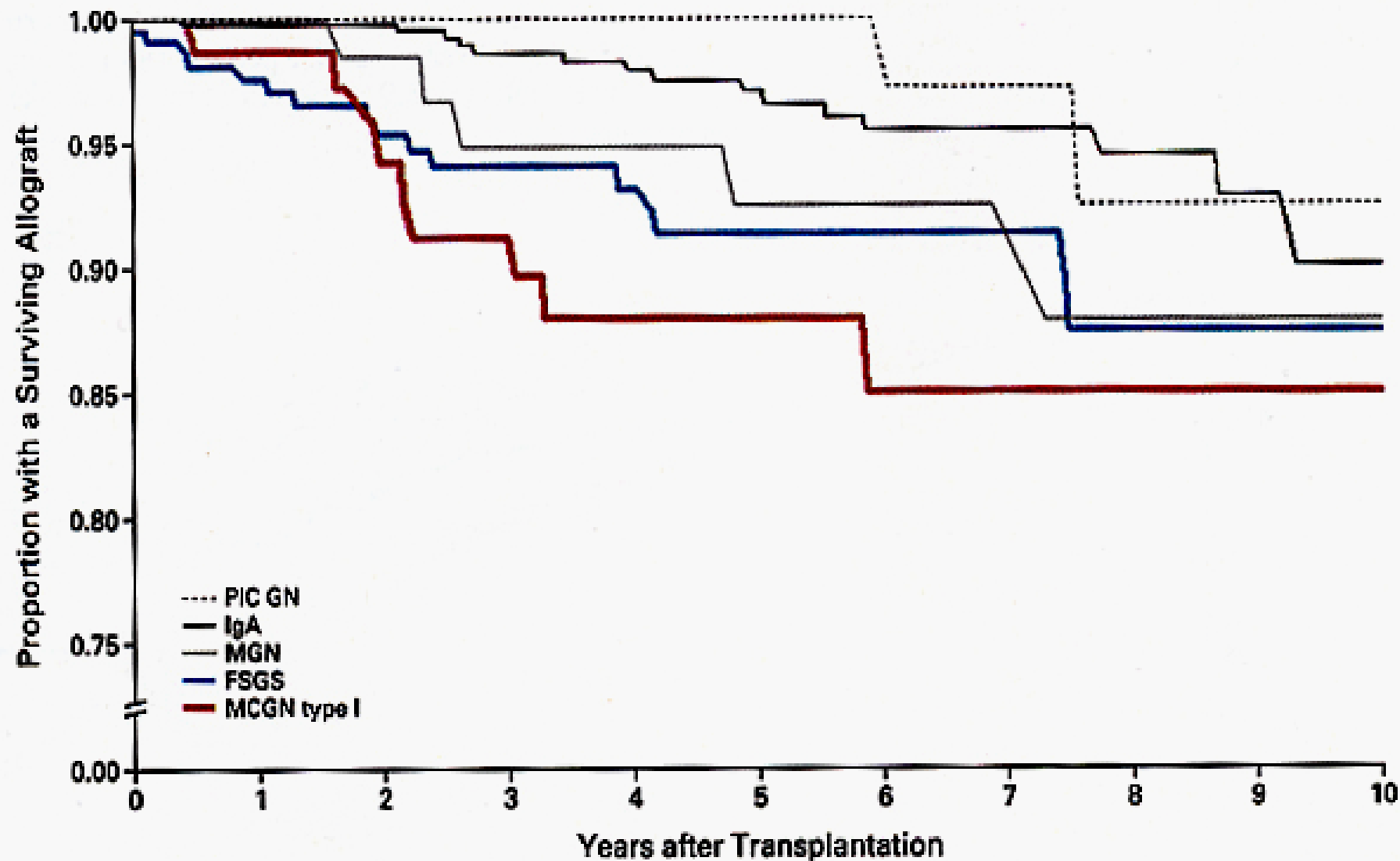
459

350

245

137

48



NO. AT RISK

PIC GN	102	90	74	62	56	48	36	26	16	5	2
IgA	532	462	398	312	253	217	153	119	87	47	15
MGN	81	70	60	49	44	40	31	20	15	9	5
FSGS	221	189	156	124	103	91	65	54	36	19	5
MCGN type I	88	75	64	57	48	40	28	25	16	12	4

Causes of Graft Loss (Living Kidney Transplantation from HLA- identical Sibling Donors)

Table 2 Cause of graft loss, by time post-transplant

	<1 years		>1 years	
	Non-identical	Identical	Non-identical	Identical
Acute rejection	5 (41.7%)	0 (0%)		
CAN with/without CR	2 (16.7%)	0 (0%)	16 (31.4%)	5 (23.8%)
CNI nephrotoxicity	0 (0%)	0 (0%)	2 (3.9%)	1 (4.8%)
→ Recurrence of original disease	1 (8.3%)	0 (0%)	10 (19.6%)	6 (28.6%)
Death with functioning graft	2 (16.7%)	1 (50%)	19 (37.3%)	7 (33.3%)
Discontinuation of immunosuppressant	0 (0%)	1 (50%)	4 (7.8%)	1 (4.8%)
Non-compliance	1 (8.3%)	0 (0%)	0 (0%)	1 (4.8%)
Others	1 (8.3%)	0 (0%)	0 (0%)	0 (0%)
<i>P</i>	0.2002		0.6158	

CAN, chronic allograft nephropathy; CNI, calcineurin inhibitor; CR, chronic rejection.

Causes of Graft Loss

Table 3 Cause of recurrent disease in graft loss recipients

	Non-identical	Identical
IgA nephropathy	7 (63.6%)	5 (83.3%)
FGS	3 (27.3%)	1 (16.7%)
MPGN	1 (9.1%)	0 (0.0%)

FGS, focal glomerulosclerosis; IgA, immunoglobulin A; MPGN, membranoproliferative glomerulonephritis.

Shimmura H, et al. Int J Urol 2006

Recurrent GN in the Transplant

- Renal Allograft Disease Registry (RADR):
 - 167 cases (3.4%) of recurrent and de novo diseases in 4913 renal transplants from 6 U.S. centers (1987-1996)
 - More men and a higher number of re-transplants in this group
 - No difference according to the transplant type (LRD vs CAD)
 - **More graft failures (55% vs 25%, $p < 0.001$) and shorter half-life in the recurrent disease group**

Hariharan S et al, Transplantation 1999

Risk Factors for Allograft Failure

- Cadaveric transplants
- Prolonged cold ischemia time (>20 hours)
- Elevated panel reactive antibody (>20%)
- The relative risk for graft failure because of recurrent and de novo disease was 1.9
- **The highest RR for graft failure:
HUS/TTP (5.36), MPGN (2.37) and FSGS
(2.25)**

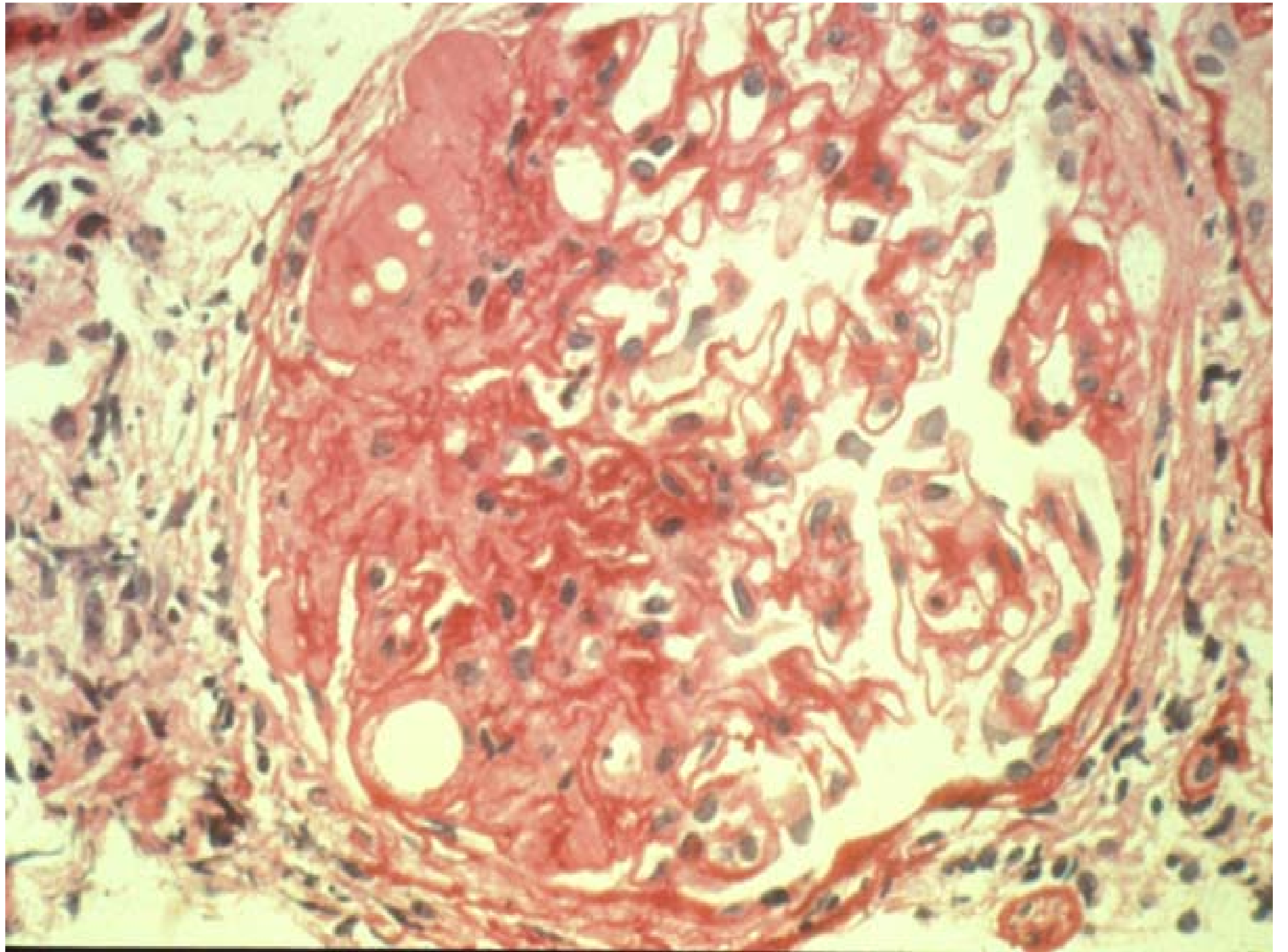
Hariharan S et al, Transplantation 1999

Graft Loss due to Recurrent GN

- 1-8.4% of all graft failures are due to recurrent disease
- More recurrence is studies with longer follow-up
- **Recurrence is an important cause of allograft loss for those with ESRD due to GN**

	Clinically relevant ¹ recurrent risk ²	Risk of graft loss due to recurrence 5–10 years post- transplant ²
IgAN	13–46%	2–16%
FSGS	20–50%	13–20%
MPGN		
Type I	20–25%	~15%
Type II	80–100%	15–30%
Membranous nephropathy	10–30%	10–15%
ANCA-associated glomerulonephritis	~17%	6–8%
SLE	2–8%	2–4%
Anti-GBM	Rare	Rare

Choy BY, et al. Am J Transplant 2006



Recurrent FSGS

- Recurrence rate: 20-50% (difficult because of the focal nature of the distribution of lesions and possible sampling error)
 - Primary vs secondary vs *de novo*-rapamycin related?
 - Familial forms do not recur after transplantation (linked to genes encoding various podocyte-related proteins, such as podocin, alpha-actinin 4 and nephrin)
- In series with primary FSGS and including pediatric patients and young adults: the incidence of recurrence is as high as 50%

Recurrent FSGS

- Recurrence of primary FSGS: early in the posttransplant period with heavy proteinuria, progressive kidney dysfunction and graft failure
- Graft loss: in ~50% of recurrent cases

Factors Contributing to Recurrence of FSGS

- Early onset (<15 years) of nephrotic syndrome
- Rapidly progressive FSGS in the native kidneys
- Race (more in African Americans), African-American kidney in a white recipient
- Diffuse mesangial proliferation on original kidney biopsy and collapsing variant of FSGS
- History of recurrence in a previous transplant (up to 80%)

Factors Contributing to Recurrence of FSGS

- Circulating protein that alters glomerular capillary permeability?
(Savin V, et al, NEJM 1996)
- Induction therapy with ALS (more with ATGAM)
(Raafat R et al, Pediatr Nephrol 2000)
- Increased intra-graft NF-kappaB expression and intra-graft angiotensinogen gene expression (role in recurrence is not clear, potential marker for recurrence?)
(Schachter AD et al, Transplantation 2000)
- Patients with active FSGS or with posttx recurrence had oxidized plasma albumin-Free radical involvement in FSGS
Musante L, et al. J AM Soc Nephrol 2007

Recurrent FSGS

- NAPRTCS database, age 13-17 year
- Clinical: malignant, diagnosis to dialysis is usually <3 years, nephrotic range proteinuria, ~75-80 % recurrence in the second graft
- Waiting 1-2 years between transplants
- **Living-related vs cadaveric renal transplantation** (controversial): Graft loss due to recurrent disease, no difference between LD (17%) or CAD (13.8%) grafts in NAPRTCS data

Baum MA et al, Pediatr Transplantation 2002

Recurrent FSGS

- USRDS and US Scientific Renal Transplant Registry, 1988-1997
- 2,414 patients in 19,259 adult primary renal transplant recipients
- Death-censored graft survival rates among FSGS patients

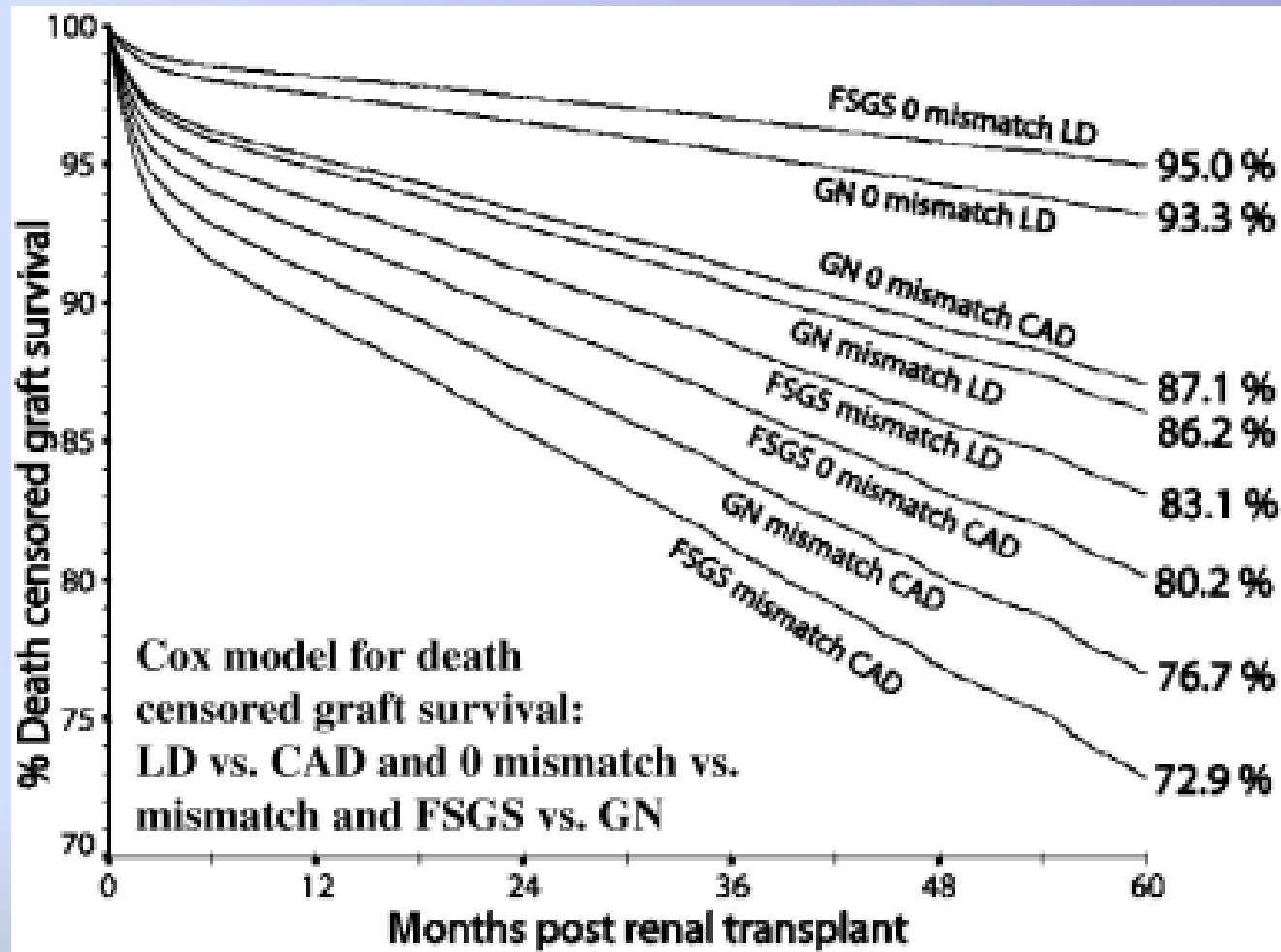
*Cibrik DM, Kaplan B, Campbell DA,
Meier Kriesche H, AJT 2003*

Recurrent FSGS

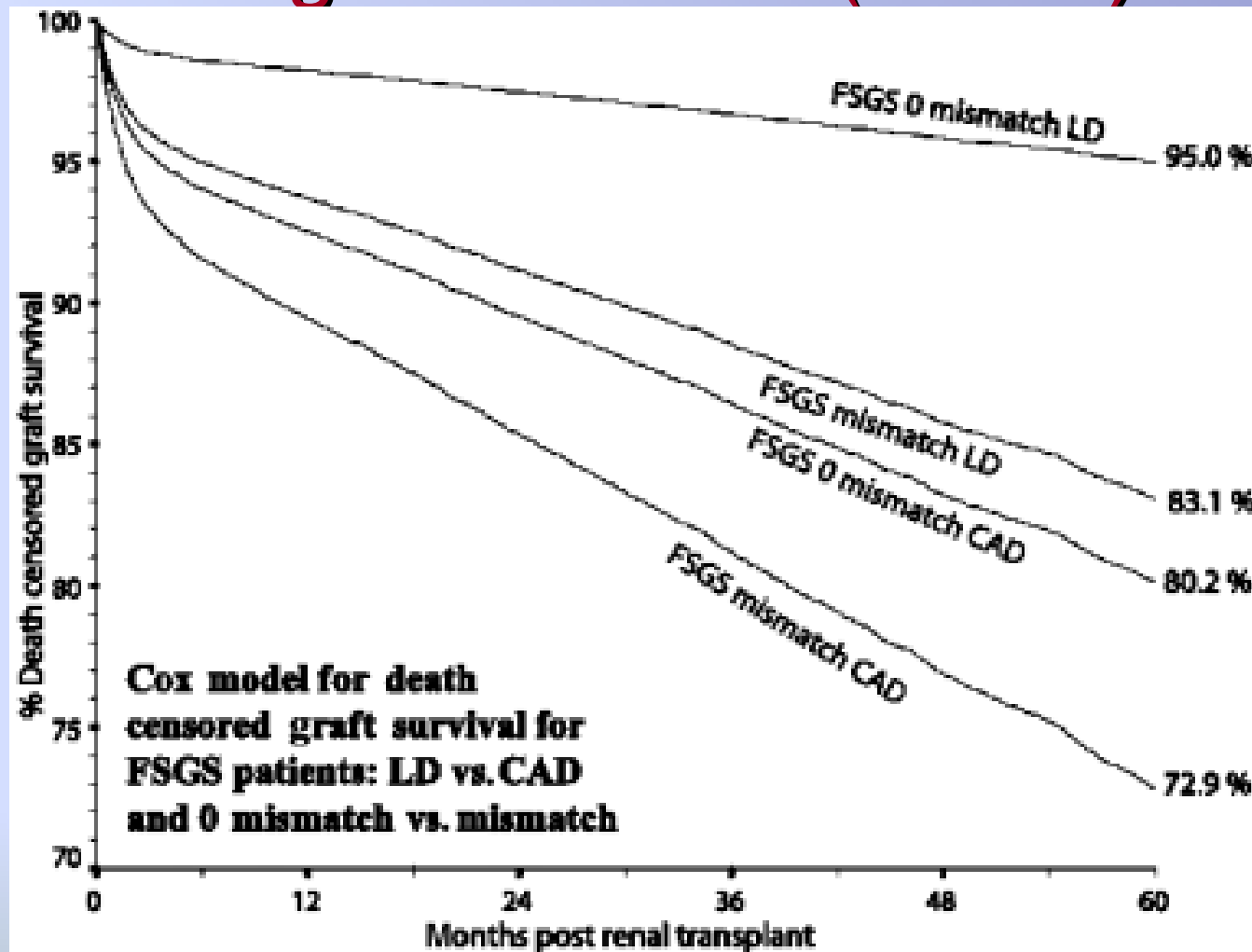
- Superior death-censored graft survival for FSGS patients who received a zero mismatch LD kidney vs HLA-mismatched CAD kidney
- Similar results in FSGS patients vs patients with other GN (zero mismatch LD kidney)

*Cibrik DM, Kaplan B, Campbell DA,
Meier Kriesche H, AJT 2003*

Five-year Death-censored Renal Allograft Survival (FSGS Vs Other GN)



Five-year Death-censored Renal Allograft Survival (FSGS)



Recurrent FSGS

- Limitations: retrospective, diagnosis of FSGS (biopsy-proven?), secondary causes of FSGS, incidence of recurrence
- Zero-mismatch LR transplant is NOT a risk factor for graft loss in FSGS, associated with significantly better death-censored renal allograft survival

*Cibrik DM, Kaplan B, Campbell DA,
Meier Kriesche H, AJT 2003*

Treatment for Recurrent FSGS

- No prospective randomized studies
- Plasmapheresis ± dipyridamole (pre-or post transplant), ~50% relapse after stopping plasmapheresis, nonresponders: sclerosis on biopsy, less effective in adults
- Pre-transplant plasmapheresis in children
- Plasma protein adsorption
- High-dose cyclosporine, cyclophosphamide
- ACE inhibitors, NSAIDs, rapamycin use (controversial)

Treatment for Recurrent FSGS

- Combination of ACE-inhibitor, an AT 1 receptor blocker and the direct renin inhibitor aliskiren (*Freiberger W, et al. Transpl Int 2009*)
- Combination of plasmapheresis and rituximab
- Anti-TNF alpha treatment (infliximab then etanercept)
- Galactose (oral or IV)
- High dose of oral steroids, 14 days of IV cyclosporine (2 mg/kg, target blood level: 200–400 ng/mL) followed by oral treatment, targeting C2 levels 1200–1400 ng/mL and PE with 5% albumin replacement until month 9 and ramipril

**Resolution of Recurrent Focal Segmental Glomerulosclerosis
Proteinuria after Rituximab Treatment**

Pescovitz MD, Book BK, Sidner RA

N ENGL J MED 354;18 WWW.NEJM.ORG MAY 4, 2006

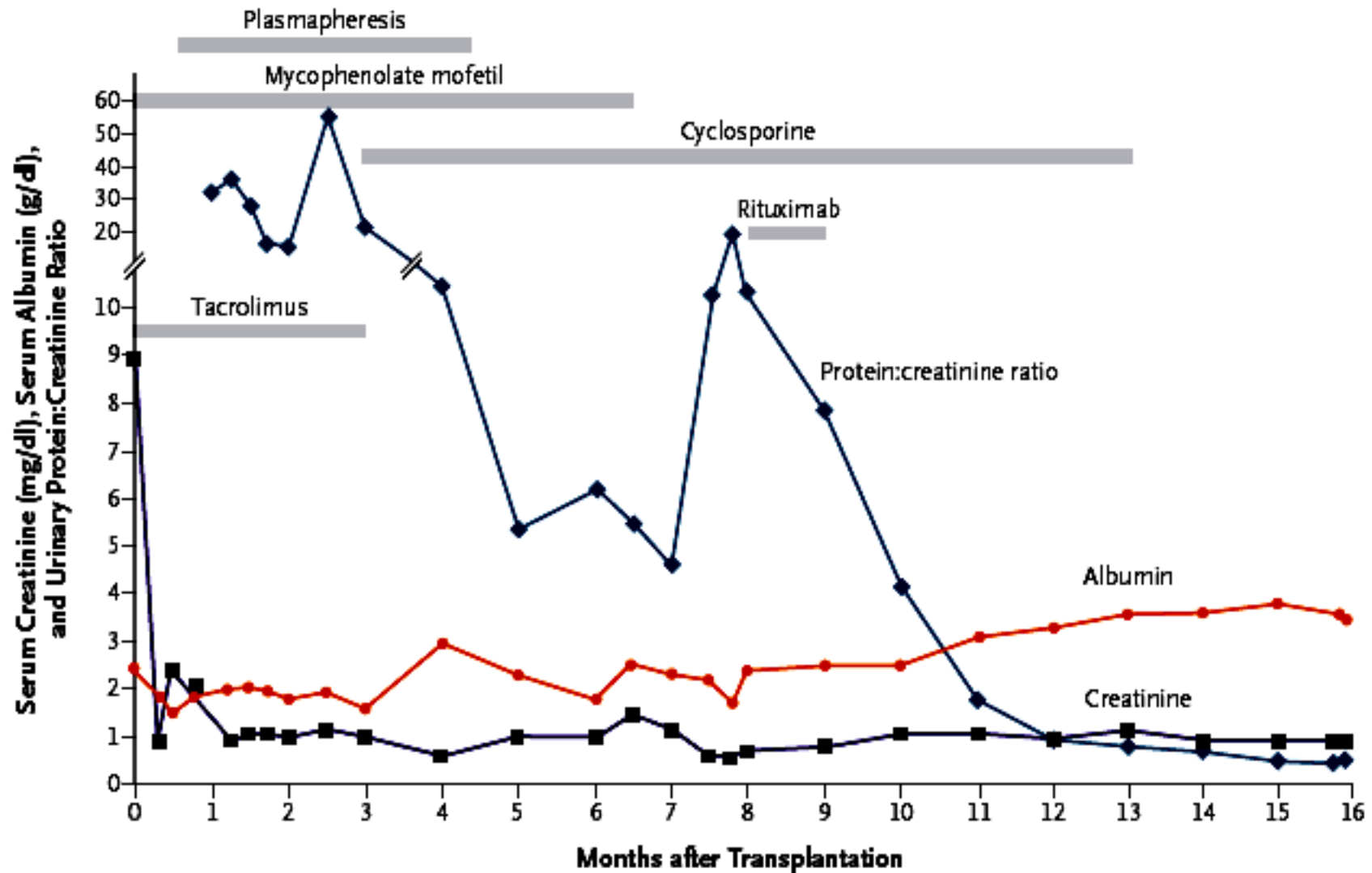


Figure 1. Serum Levels of Creatinine and Albumin and the Urinary Protein:Creatinine Ratio in the Index Patient after the Initiation of Treatment.

Treatment for Recurrent FSGS

- Glomerular capillary permeability (P_{alb}) is increased by sera from patients with recurrent FSGS and that administration of plasma fractions causes proteinuria in rats
- FS permeability factor (FSPF) consists of low-molecular anionic proteins or proteins that alter phosphorylation of several glomerular proteins; phosphatase inhibition blocks the permeability activity

Treatment for Recurrent FSGS

- Thirty paired samples from 22 FSGS patients before and after PP were studied
- Repeated samples from 27 patients who did not receive plasmapheresis were also studied
- Galactose is a sugar that has been shown to have a high *in vitro* affinity for FSPF in chromatographic studies; a trace amount of galactose blocks or reverses the increase in P_{alb} .
- Galactose inactivates FSPF in the circulation and seems to lead to its clearance from the plasma.

Savin VJ et al. Translational Research 2008

Treatment for Recurrent FSGS

- A 30-year-old man: lost a prior transplant to recurrent FSGS received 1 PP before transplant and additional PP as well as infusion of FFP immediately after transplantation
- This intensive therapy at the time of transplantation lowered $P_{alb} < 0.2$
- Proteinuria returned within 2 weeks, and additional PPs were performed on multiple occasions, usually weekly
- Galactose infusion was performed about 3 months after transplantation
- P_{alb} was undetectable immediately after galactose infusion and 48 h later. P_{alb} decreased progressively during the 4 weeks of ingestion and remained low 4 weeks after galactose was discontinued

Savin VJ et al. Translational Research 2008

FSGS Permeability Factor-Associated Nephrotic Syndrome: Remission after Oral Galactose Therapy

Eric De Smet, Jean-Philippe Rioux, H el ene Ammann, Cl ement D eziel and Serge Qu erin

Nephrology Dialysis Transplantation June 2009

- 48-year-old male with a nephrotic syndrome found to be resistant to corticosteroids, immunosuppression and plasmapheresis
- The patient was given oral galactose (10 g oral twice a day) as a last resort treatment
- Remission of his nephrotic syndrome that correlated with a reduction of FSPF activity-follow-up at 13 months, on galactose 15 g BID, proteinuria at 1.14 g/24 h and serum creatinine at 1.75 mg/dL
- No side effects of prolonged treatment

Pilot Trial

- Oral galactose use in patients with resistant FSGS
- Phase I trial
- Galactose: 0.2 g/kg body weight/dose twice daily
- The duration of treatment: 28 days
- ClinicalTrials.gov: NCT00816478

FSGS and Transplantation

- Assay for a serum factor to predict recurrent FSGS have not been standardized or validated for clinical practice
- There are not yet sufficient data for or against the use of prophylactic plasma exchange or other measure to prevent recurrent FSGS
- Native nephrectomy is not useful as a prevention

FSGS and Transplantation

- FSGS can recur in minutes after transplantation
- Massive proteinuria→massive edema
- Posttransplant acute renal failure mimicking delayed graft function (DGF)
- Allograft biopsy-needed for diagnosis

FSGS and Transplantation

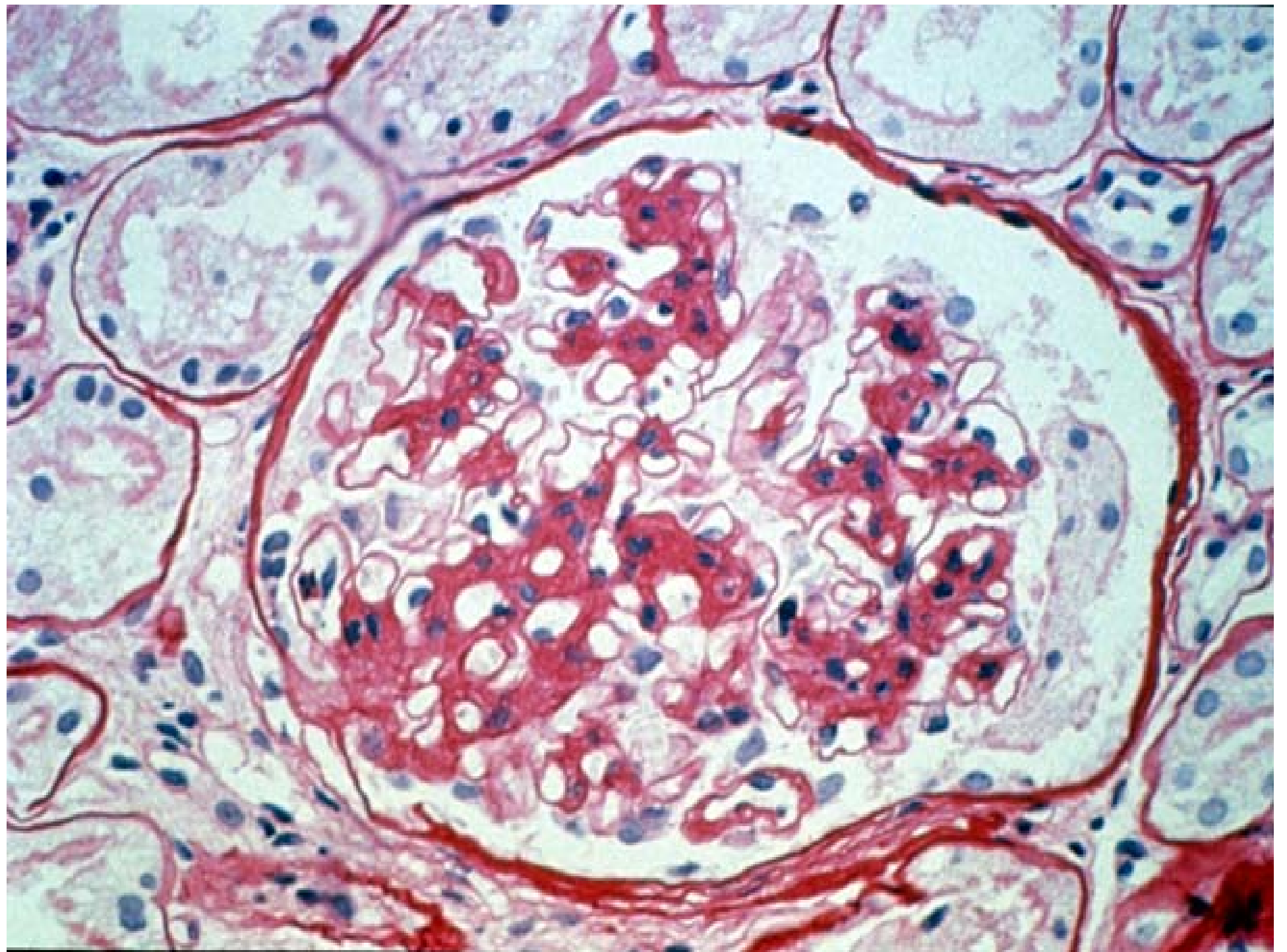
- Candidates with FSGS should be warned about the 30-50% risk of recurrence
- The risk of recurrence should not preclude transplantation
- Cadaveric versus LRD transplant (ethical issues)
- Should prior history of graft loss from recurrent FSGS be considered a relative contraindication to living donor transplantation (recurrence up to 80%)?

Recurrent IgA Nephropathy

- Recurrence rate: 21-58%-the true risk is not known
- Predictor for recurrence: longer time after transplantation
- Risk factors:
 - Younger age, HLA B35 and DR4 antigen
 - Living-related transplantation: conflicting data; no contraindication
 - High titers of serum IgA concentrations
 - Short interval between onset and ESRD

Recurrent IgA Nephropathy

- Risk factors:
 - Glomerular crescents on original biopsy
 - Better donor/recipient HLA matching?: decrease in graft survival with better HLA-DR matching
 - Greater number of rejections, previous h/o recurrence
 - IL-10 gene G-1082A polymorphism: associated with an increased recurrence rate (n=16 patients) (*Bantis C, et al. J Nephrol 2008*)



Recurrent IgA Nephropathy

- Graft loss: eventual graft loss 46-71%
- Clinical: microscopic hematuria ± proteinuria, worsening renal function, usually late recurrence, progression to ESRD is very slow
- Treatment: tonsillectomy (case reports from Japan), use of anti-thymocyte globulin for induction-less recurrence, mycophenolate mofetil, high-dose fish oil
- A trend toward improved 5-year and 10-year graft survival seen in those prescribed ACEi/ARBs (n=39) (*Courtney AE, et al. Nephrol Dial Transplant 2006*)

Recurrent Membranous Nephropathy (MN)

- Recurrence rate: 5%-42%
- Most cases are idiopathic, can be secondary to infectious agents (hepatitis B and C) or to SLE
- De novo MN is more frequent than recurrent MN
- 23 patients with MN had surveillance biopsies (time zero, 4 months, 12 mo, 24 mo, 5 yrs): recurrent MN in 8/19 patients (42%); histologic evidence of recurrence by 5 years, in most cases by 1-year post-tx.
Progression of proteinuria and also interstitial fibrosis; minor clinical manifestations at diagnosis-Mayo Clinic experience

Dabade TS, et al. Am J Transplant 2008

Recurrent Membranous Nephropathy

- Graft loss: rare-30%
- Risk factors: male gender, rejection, HLA-identical living-related transplants
- Clinical: nephrotic range proteinuria, venous thrombosis of the allograft
- Treatment: Protein A immunoadsorption, pulse methylprednisolone and high-dose alternate day steroids, ACE inhibitors and MMF, early use of rituximab (*Weclawiak H, et al. Clin Nephrol 2008*)

Recurrent MPGN

- Recurrence rate: 20-30 % in type I, 80-100 % in type II
- Graft loss: 40 % in type I, 10-20 % in type II
- Risk factors: male gender, rapid progression to ESRD, massive proteinuria, identical LRD, recurrence on the first graft, HLA haplotype B8DR3 (*Andresdottir et al, Transplantation 1997*)
- *May mimic chronic allograft nephropathy

Recurrent MPGN

- Clinical: in secondary MPGN positive serology for hepatitis C \pm cryoglobulinemia, low complement levels and rheumatoid factor, hematuria or proteinuria
- Treatment: Aspirin, steroids, cyclophosphamide, plasmapheresis is not useful

Rates of Graft Failure by Cause in the First 5 Years Post-Tx (per 100 patient-years)

Cause of Kidney Disease	TX in 1988-1994			TX in 1995-2003		
	Recurrence	Death	Other	Recurrence	Death	Other
→ MPGN	0.82	1.59	5.79	1.73	1.40	3.79
Other GN	0.43	1.78	4.99	0.47	1.64	3.43
Cystic Disease	0.05	2.33	2.64	0.09	1.68	1.72
Diabetes	0.14	4.85	3.90	0.14	4.73	2.77
Hypertension	0.28	3.41	6.35	0.29	2.99	4.65
Other	0.16	2.40	3.60	0.19	1.93	2.70

- USRDS database, total n=140,109, MPGN=1,574
- the rate of graft failure due to recurrent MPGN was more than 2-fold greater after TX in 1995-03 compared to TX in 1988-94

Kasiske, B, et al, WTC 2006, abstract#1765

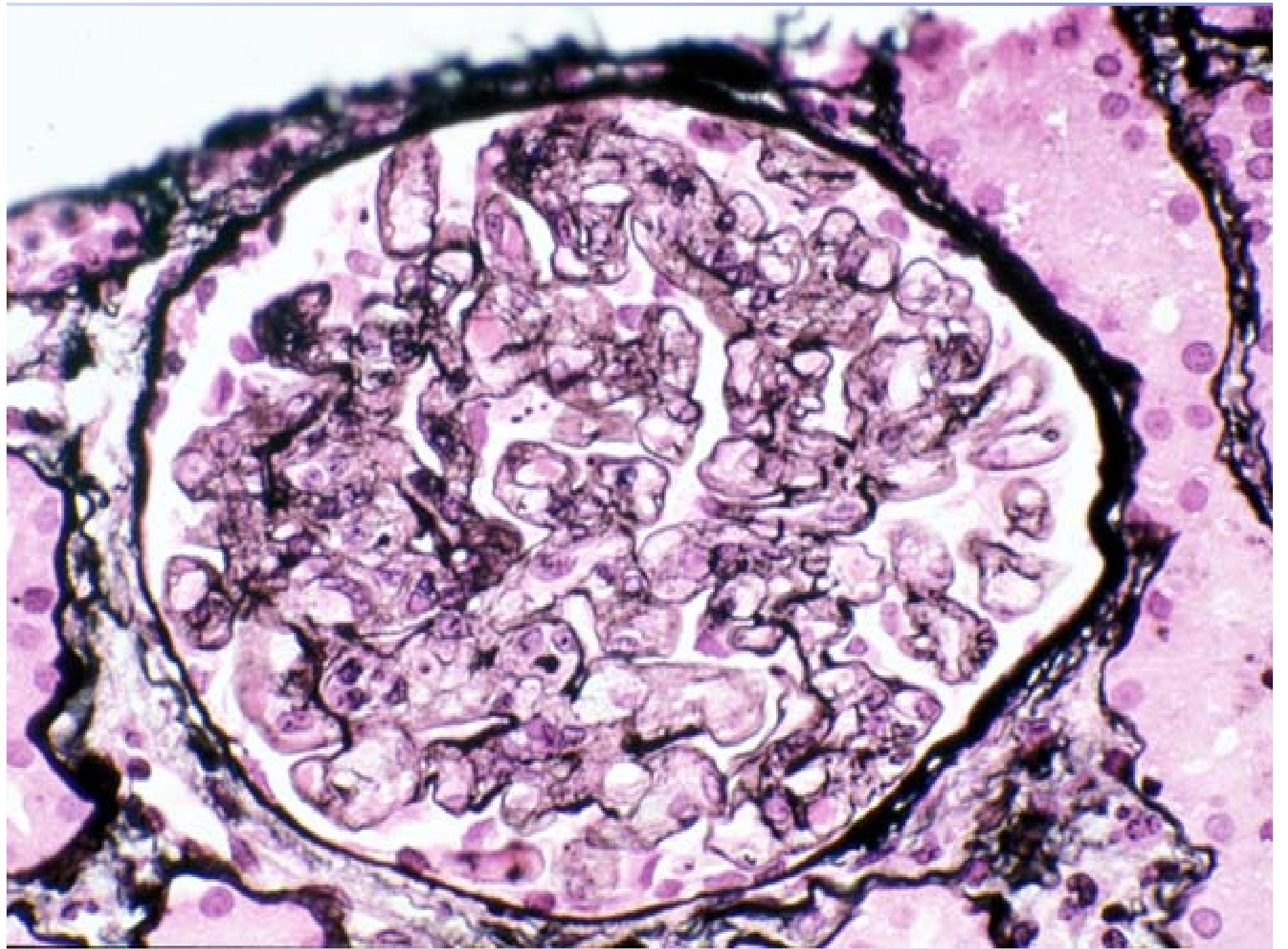
Recurrent (MPGN): Assessment with Protocol Biopsies

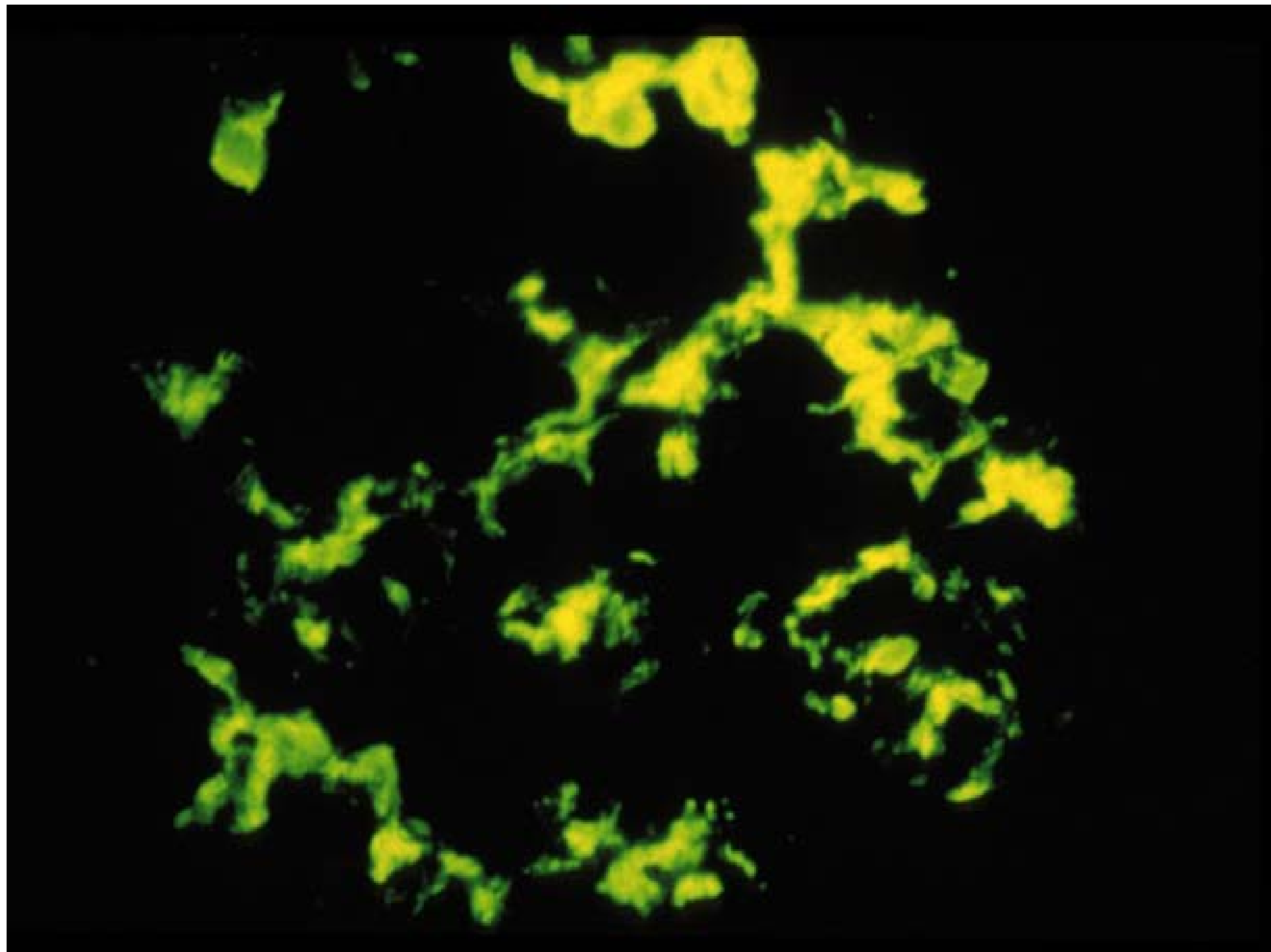
- In 1321 patients (transplanted 1996-2006), 36 (3%) had MPGN-biopsy-proven
- Recurrent MPGN was diagnosed in 11/29 patients (38%)
- The diagnosis time varied from 1 week to 10 months post-transplant (median 3 months)
- During follow up, 4/29 grafts (13.8%) were lost
- Recurrent disease is a common cause of allograft failure

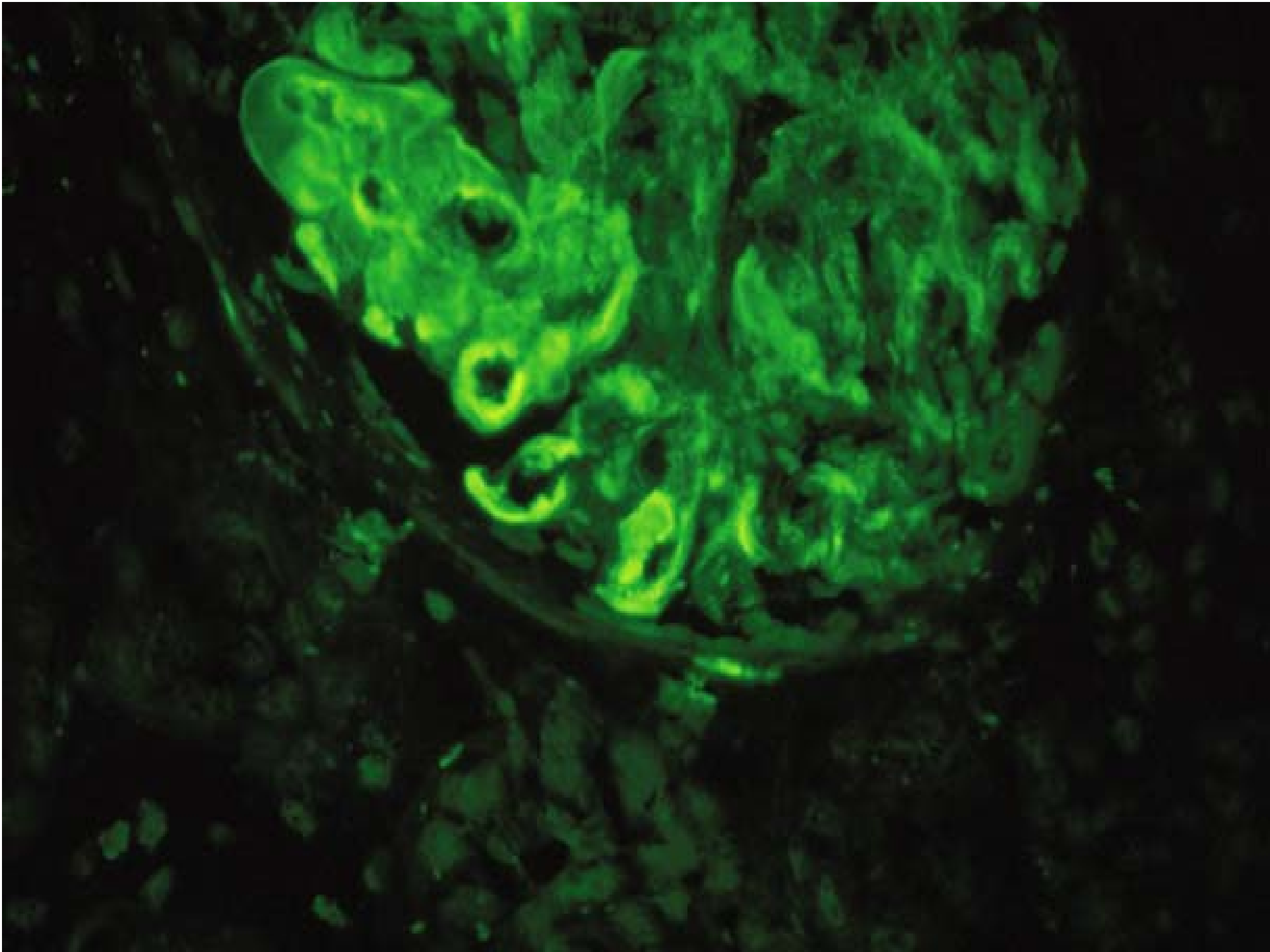
Lorenz E, et al. ATC Boston 2009, abstract #632

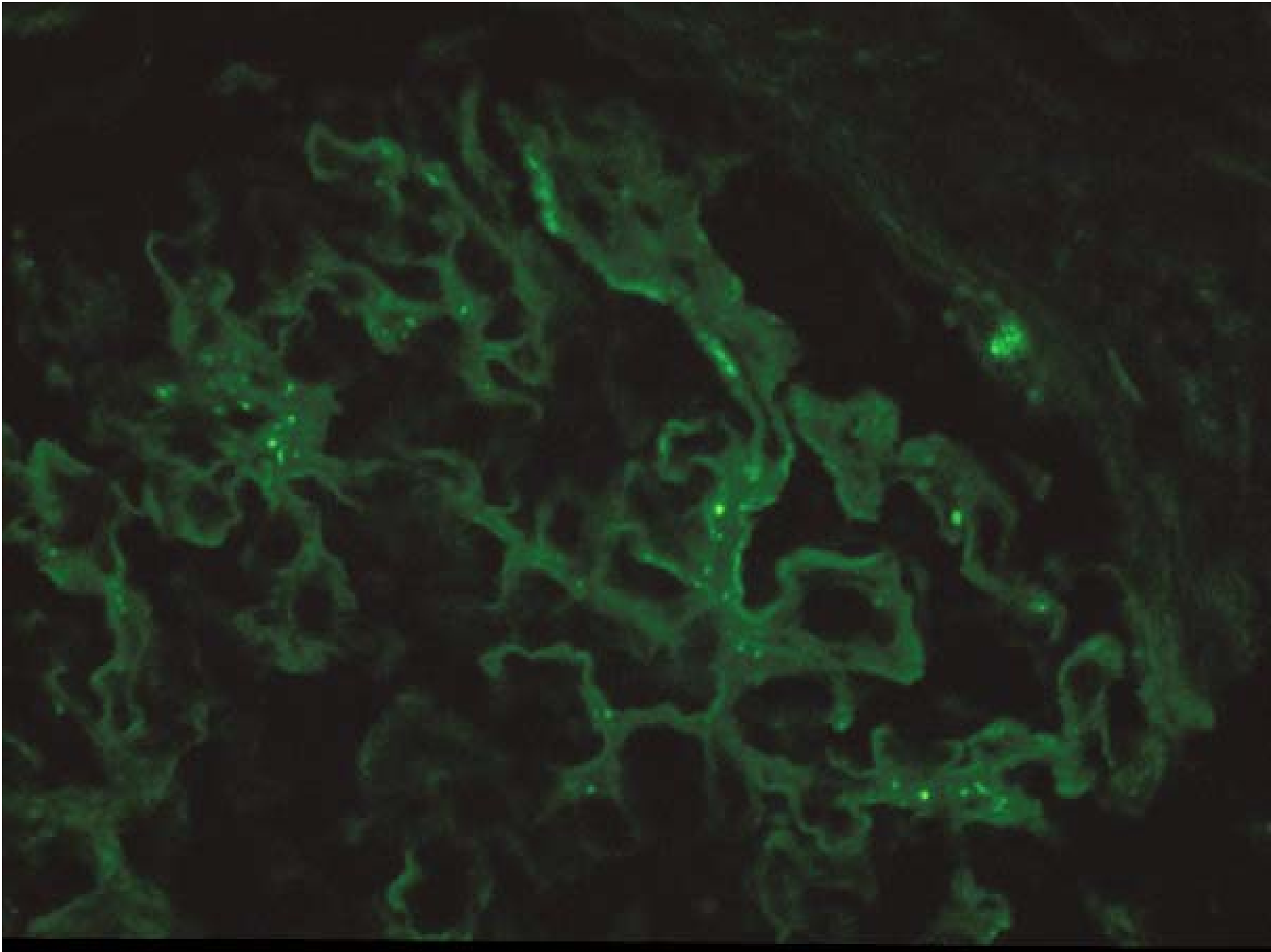
Recurrent Lupus Nephritis (RLN)

- Recurrence rate: <10% in the literature
- Graft loss: reported rare
- Risk factors: active disease at the time of transplant (controversial), longer duration on dialysis before transplant (>25 weeks)
- Clinical: proteinuria, hematuria, and/or elevated serum creatinine, rarely extrarenal manifestations such as arthralgia, fever, skin rash and leukopenia









RLN-Vanderbilt Experience

- 50 SLE patients with at least 3 months of follow-up
- Induction with antithymocyte ab: 39 patients
- Immuno: AZA+pred (n=11), CsA (n=39), only 9 patients on CsA+MMF+pred
- Mean follow-up: 6.8±4.9 years; biopsy in 31 patients (62%)
- Recurrence rate: 52% of the patients biopsied, 30% of total patients
- One graft loss due to recurrent SLE

Goral S et al, Transplantation 2003

RLN-Vanderbilt Experience

- Patient survival: 96% at 1 year, 82% at 5 years
- Graft survival: 87% at 1 year, 60% at 5 years
- No difference in graft survival between group 1 (RLN) and group 2 (no RLN)
- Graft survival was worse in patients who were biopsied compared to patients who never had any biopsies
- Worse outcome: one or more acute rejection and presence of chronic rejection

Goral S et al, Transplantation 2003

Graft Failure Rates by Cause in the First 5 Years Post-Tx (per 100 patient-years)

Cause of Kidney Disease	TX in 1988-1994			TX in 1995-2003		
	Recurrence	Death	Other	Recurrence	Death	Other
→ SLE	0.39	1.59	6.27	0.39	1.59	3.93
Other GN	0.45	1.79	4.89	0.54	1.63	3.38
Cystic Disease	0.05	2.33	2.64	0.09	1.68	1.72
Diabetes	0.14	4.85	3.90	0.14	4.73	2.77
Hypertension	0.28	3.41	6.35	0.29	2.99	4.65
Other	0.16	2.40	3.60	0.19	1.93	2.70

(USRDS database, total n=140,109,
SLE=4,832)

Kasiske, B et al, WTC 2006, abstract#1764

Recurrence of Lupus Nephritis Assessed by Surveillance Biopsies

- Cross-sectional study from Norway; 36 surveillance biopsies in 43 recipients with SLE
- Of the 36 patients biopsied, 18 had a histological recurrence of LN
- There was a preponderance of living donors in patients with recurrent LN
- “Surveillance biopsies are necessary for the diagnosis of recurrence of lupus nephritis”

Norby, G, et al. ATC Boston 2009, abstract #634

Spectrum of Glomerular Pathology in Recurrent Glomerulonephritis (GN)

- 43 recipients with lupus nephritis; biopsies were examined by light microscopy, and by IF and EM in selected cases
- A role for nonimmune complex-mediated glomerular injury in recurrent lupus GN
- Categories of glomerulopathies:
 - Immune complex glomerulopathies, including mesangial GN (28%) and membranous GN (4%);
 - Atypical glomerulopathies, including acute proliferative GN (32%) and focal segmental glomerulosclerosis (12%), with scant immune deposits in glomerular capillaries, frequent endothelial tubuloreticular inclusions, and thrombotic microangiopathy
 - Transplant-associated glomerulopathies (24%)

Recurrent Lupus Nephritis

- It is difficult to predict when RLN will occur after transplantation
- RLN can occur as early as 6 days after transplantation
- Surveillance biopsies might be helpful
- RLN may or may not have the same pattern as the original disease

Recurrent Lupus Nephritis

- Treatment: No definite treatment options (MMF), the impact of new immunosuppressive agents?
- **Transplant kidney biopsy specimens from patients with history of ESRD due to SLE should be evaluated by both IF and EM in addition to LM (8 of 15 patients with RLN had mesangial LN)**

Recurrent Diabetic Nephropathy

- Recurrence rate: up to 100%
*Recurrence of GBM thickening and mesangial expansion 2 years beyond transplantation
- Reported as early as 2.5 years after transplant in the literature
- Graft loss: <5% in short-term, ?predictor of graft loss
- Risk factors: suboptimal glycemic control (histological lesions are not observed in kidney-pancreas recipients)
- Treatment: No studies

Recurrent Diabetic Nephropathy: An Unexpected Finding on a Kidney Transplant Biopsy

Kapitsinou P, Warburton K, Tomaszewski J, Goral S

ISN Nexus Symposium on Diabetes and Kidney, Dublin, Ireland June 26 - 29, 2008

- 60 year-old woman with a long-standing history of hypertension and type 2 diabetes
- The primary renal disease of the patient was unknown but diabetic nephropathy was presumed to be the most likely diagnosis in the presence of proteinuria, diabetic retinopathy and neuropathy
- DD kidney transplant (ECD kidney)
- Basiliximab induction; cyclosporine, mycophenolate mofetil and prednisone

Recurrent Diabetic Nephropathy: An Unexpected Finding on a Kidney Transplant Biopsy

Kapitsinou P, Warburton K, Tomaszewski J, Goral S

ISN Nexus Symposium on Diabetes and Kidney, Dublin, Ireland June 26 - 29, 2008

- Kidney biopsy 14 months after transplantation for worsening proteinuria
- Scr was 1.3 mg/dl at the time of the biopsy
- Results: diffuse and nodular glomerulosclerosis consistent with diabetic nephropathy
- Biopsy of the graft at the time of transplant (“time-zero” biopsy) did not show any signs of diabetic nephropathy
- **The earliest recurrence of DN reported in the literature**

Potential Problems for Identifying Recurrent GN in the Transplant

- Primary disease-native kidney disease-is unknown for many patients
 - Late presentation
 - Primary vs secondary FSGS: difficult to differentiate
- No unified approach for patients with urinary abnormalities and increased serum creatinine after transplantation (histological vs clinical diagnosis)
- Transplant biopsy is not routinely submitted for IF and EM examination

Potential Problems for Identifying Recurrent GN in the Transplant

- Interpretation of the biopsy: DIFFICULT, *de novo* vs recurrent-MPGN vs chronic rejection vs changes already present in the grafted kidney
- Most of the studies are small and retrospective with variable follow-up periods (mostly short-term, inconsistent f/u)
- *No randomized, prospective studies for different treatment regimens (only case reports: MMF promising)

Recommendations

- The selection of recipients and donors should be no different for patients with GN from other candidates for kidney transplantation
- Potential recipients and donors should, however, be informed of the risk of recurrence

Post-Transplant GN- Recurrent or *De Novo*

- The best predictor factors that correlated with graft survival were:
- Proteinuria <3.5 g [relative risk (RR) = 0.24, p = 0.017]
- Serum creatinine below 2.0 mg/dl (RR = 0.06, p = 0.016) at the time of biopsy
- The use of angiotensin-converting enzyme inhibitors (ACEI) (RR = 0.12, p = 0.005). The use of ACEI markedly improved one-year graft survival rates (92% vs. 47%, p < 0.001)

Requiao-Moura LR, et al. Clin Transplant 2007

Challenges/Recommendations

- Awareness of recurrence
- Why do certain primary diseases affecting the native kidney recur?
- Obtain an exact diagnosis of primary disease
- Clarify the causes of prior graft loss
- Careful urinalysis in renal transplant recipients
- Early histological evaluation-low threshold for biopsy
- Prospective studies for specific treatments in individual diseases

Future Studies

- Prospective trials/registries:
 - Recurrence rate
 - Living donor vs. cadaver transplantation
 - Various immunosuppressive protocols
 - History of prior dialysis
 - The recurrence rate for degree of HLA mismatch
 - Identify risk factors for recurrence

Future Studies

- Selective prospective, interventional studies to prevent, delay recurrence and modify progression for individual diseases
 - Prevention and treatment of FSGS with plasmapheresis
 - Prevention of SLE and IgA nephritis with mycophenolate mofetil in renal transplant recipients
 - Role of sirolimus in *de novo* HUS/TTP
 - Management of HUS/TTP with plasmapheresis



Recurrent Diabetic Nephropathy

- 58 patients; 74% had pretx-DM and 26% had posttx DM
- Biopsy proven diabetic nephropathy (done for clinical indications): 70% recurrent DN and 30% de novo DN
- De novo diabetic nephropathy at least as frequent as recurrent DN

Bhalla V, Transplantation 2003

Recurrence of ANCA-Associated Vasculitis

- 35 patients with ANCA-associated vasculitis: microscopic polyangiitis (20 patients) and Wegener's granulomatosis (15 patients)
- The median time from diagnosis to transplantation: 25 months
- All patients in clinical remission
- 15 patients ANCA-positive at time of the transplant with 13 preemptive transplants
- Mean follow-up: 4.4 ± 2.5 years

Recurrence of ANCA-Associated Vasculitis

- Antibody induction, steroids, mycophenolate mofetil, and tacrolimus
- Biopsy-proven AR in 6 recipients (23%) and BK nephropathy in 3 recipients (6%)
- Overall and death-censored graft survivals were 94 and 100%, respectively, 5 years post-transplantation
- Relapse of vasculitis in three of 35 patients (8.6% all nonrenal, reported up to 20% relapse rate in the literature-50% renal involvement)

Recurrent Hemolytic Uremic Syndrome

- Recurrence rate: 13-50%
- Graft loss: 10-50%
- Risk factors: older age at onset of HUS, shorter interval between HUS onset and transplantation, LRDs, the use of calcineurin inhibitors *(a meta-analysis, Ducloux D et al, Transplantation 1998)*
- Clinical: microangiopathic hemolytic anemia, thrombocytopenia, worsening renal function
- *Sporadic HUS generally does not recur

Oxalosis

- Recurrence rate: early experience very high recurrence with allograft loss, now better results with:
 1. Early transplantation (GFR 20 ml/min)
 2. Aggressive preoperative dialysis
 3. High urine flow after surgery
 4. Simultaneous/sequential liver and kidney transplants
- Liver transplant followed by a kidney transplant (56): superior death-censored graft survival compared with patients who received a cadaveric or living-donor kidney transplant alone (134) (*Cibrik DM et al, Transplantation 2002*)

Amyloidosis

- Living-related kidney transplantation in 23 patients with ESRD due to amyloidosis, 47 controls
- Familial Mediterranean fever (FMF) in 16 patients and primary (idiopathic) in 7 transplant recipients
- Five- and 10-year actuarial graft survival rates were similar in both groups (79.35% vs 84.04% and 65.92% vs 56.61%, respectively)
- Five- and 10-year actuarial patient survival rates also were similar (80% vs 94% and 68% vs 87%, respectively)

Sherif AM et al, Am J Kidney Dis 2003

Amyloidosis

- Only one recurrence 10 years after transplantation (4.3%)
- Maintenance colchicine
- More GI problems and low blood pressure

Sherif AM et al, Am J Kidney Dis 2003

- Twenty of 30 patients (67%), biopsy confirmed recurrence after transplant (mostly well-matched LRDs)

Ozdemir B et al, Tissue Antigens 2002

Vasculitis or Anti-GBM Disease

- 43 patients: Wegener's granulomatosis (n = 8), microscopic polyangiitis (n = 7), renal limited vasculitis (n = 18) and anti-GBM disease (n = 10)
- Average follow-up: 62+/-57 months
- No graft was lost due to recurrence of the underlying disease
- Patient and graft survival at 5 years after transplantation were 77% and 60%
- More malignancies

Deegens JK et al, Clin Nephrol 2003

Recurrent Fibrillary GN

- Recurrence rate: up to 50 %
- 14 patients reported in the literature
- Clinical: benign course, prolonged graft survival is possible
- No evidence of systemic disease
- No definite treatment modality

Risk of Recurrent Disease

1. Should a kidney from a live donor be used if the recipient has an increased risk of recurrent disease?
2. Is there a greater chance that the recipient will lose the allograft from recurrent disease if a relative donor is used?
3. Will the same disease recipient has some day cause renal failure in the donor?

Kidney Transplantation In Patients With Lupus Nephritis Utilizing Modern Immunosuppression

- 29 patients with lupus nephritis (26 females and 3 males; 13 AA, 13 W, 2 Asians and 1 Hispanic)
- Transplanted between 1/2000 and 6/2005
- Treated uniformly with antibody induction and the combination of tacrolimus, MMF and prednisone
- Three patients (11%) were treated for acute rejection

Goral S, et al. WTC 2006, abstract.

Kidney Transplantation In Patients With Lupus Nephritis Utilizing Modern Immunosuppression

- Of 13 patients biopsied, only 2 had LM, IF and EM done, only one had recurrent lupus nephritis (5 years after the transplant)
- One-year graft and patient survival rates were 96% and 96%, respectively
- Three-year graft and patient survival rates were 88% and 88%, respectively
- Could this be due to uniform use of MMF in combination with tacrolimus in this population?
- The impact of this immunosuppressive combination on long-term survival and recurrence remains to be seen

A Prospective Study from RADR

- Recipients transplanted from 1998-2002
- 90/3216 (2.7%) with recurrent or de novo disease
- 853/3216 (26%) with prior native kidney biopsy, 36/853 (4.2) developed recurrence
- FSGS (7.4%), SLE (7.2%), MPGN (6.8%), and IgA (4.2%)

Hussain SA et al, abstract #323, AST 2003

RECURRENT DISEASE AFTER KIDNEY TX: LITTLE PROGRESS IN 2 DECADES

Table 1 - Primary transplants

	1984 - 1994	1995-2005	p	1984 - 1994	1995 - 2005	p
	n - % 10-yr recurrence	n - % 10-yr recurrence		n - % 10-yr GL to recurrence	n - % 10-yr GL to recurrence	
FSGS - adult	39 - 15%	74 - 18%	.7	39 - 4%	74 - 17%	.08
FSGS - peds	16 - 14%	12 - 25%	.3	16 - 14%	12 - 19%	.6
MPGN	46 - 8%	38 - 31%	.02	46 - 5%	38 - 13%	.3
HUS	12 - 47%	11 - 0%	.08	12 - 47%	11 - 0%	.07
IgA	45 - 0%	96 - 8%	.07	45 - 0%	96 - 2%	.35
GN	10 - 15%	17 - 6%	.9	10 - 0%	17 - 0%	1
Lupus	30 - 8%	36 - 0%	.2	30 - 5%	36 - 0%	.4
Wegener's	5 - 0%	7 - 33%	.1	5 - 0%	7 - 33%	.1

GL = graft loss

Sturdevant, M et al. WTC 2006, abstract#298

Recurrence After Transplantation

	Recurrence Rate	Graft Loss due to Recurrence
FSGS	20-50%	40-50%
Anti-GBM disease	10-25%	unusual
Membranous GN	10-20%	50%
IgA nephropathy	40-50%	6-33%
Type I MPGN	20-30%	20-40%
Type II MPGN	80-90%	10-20%

Recurrence After Transplantation

	Recurrence Rate	Graft Loss due to Recurrence
Henoch-Schönlein	15-35%	10-20%
Lupus nephritis	1-25%	Rare
HUS	10-25%	50%
Diabetic nephropathy	100%	5%
Amyloidosis	2-33%	20%
Wegener's	15-50%	10%

Treatment for Recurrent FSGS

- 100 consecutive pediatric renal transplants
- 20 patients with FSGS, 8/20 (40%) with recurrence within 1 month of transplantation
- Plasmapheresis (mean: 24 ± 17 , range: 8-51 treatments to achieve a remission) in 5/6 pts
- One plasma volume was replaced with 5% albumin, 4 times per week then tapered when proteinuria decreased

Greenstein SM et al, Pediatr Nephrol 2000