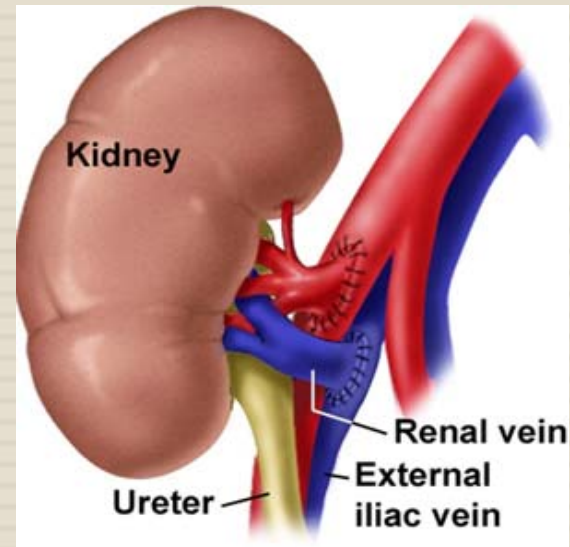


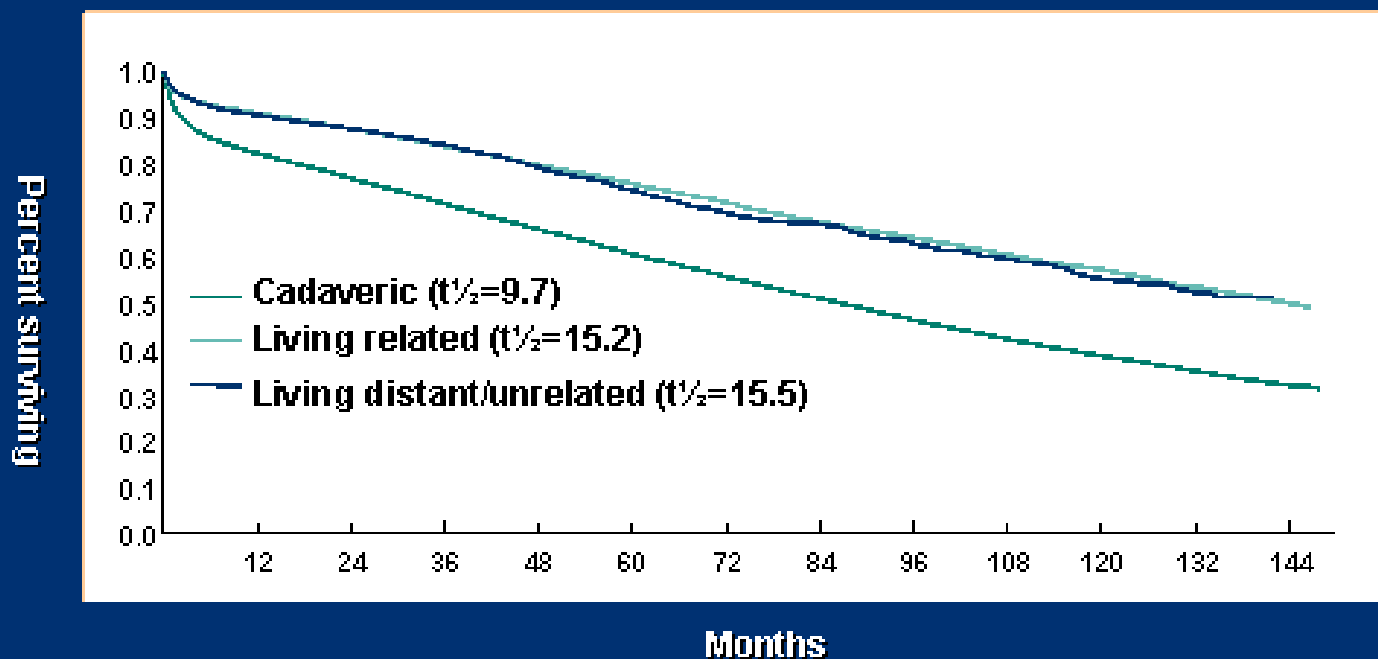
המהלך ארוך הטווח לאחר ההשתלה

ד"ר רותי רחמימוב

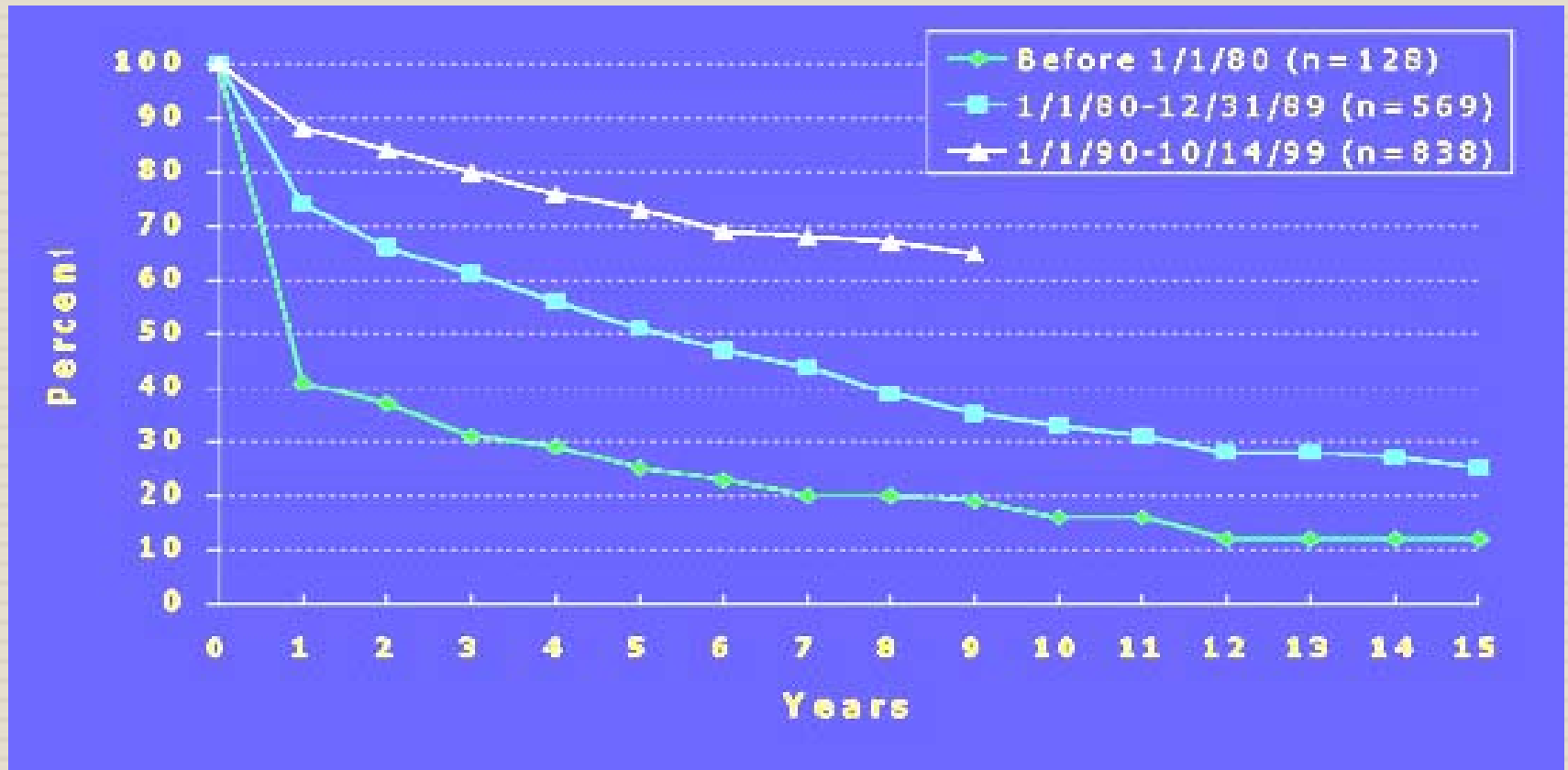


Graft Survival

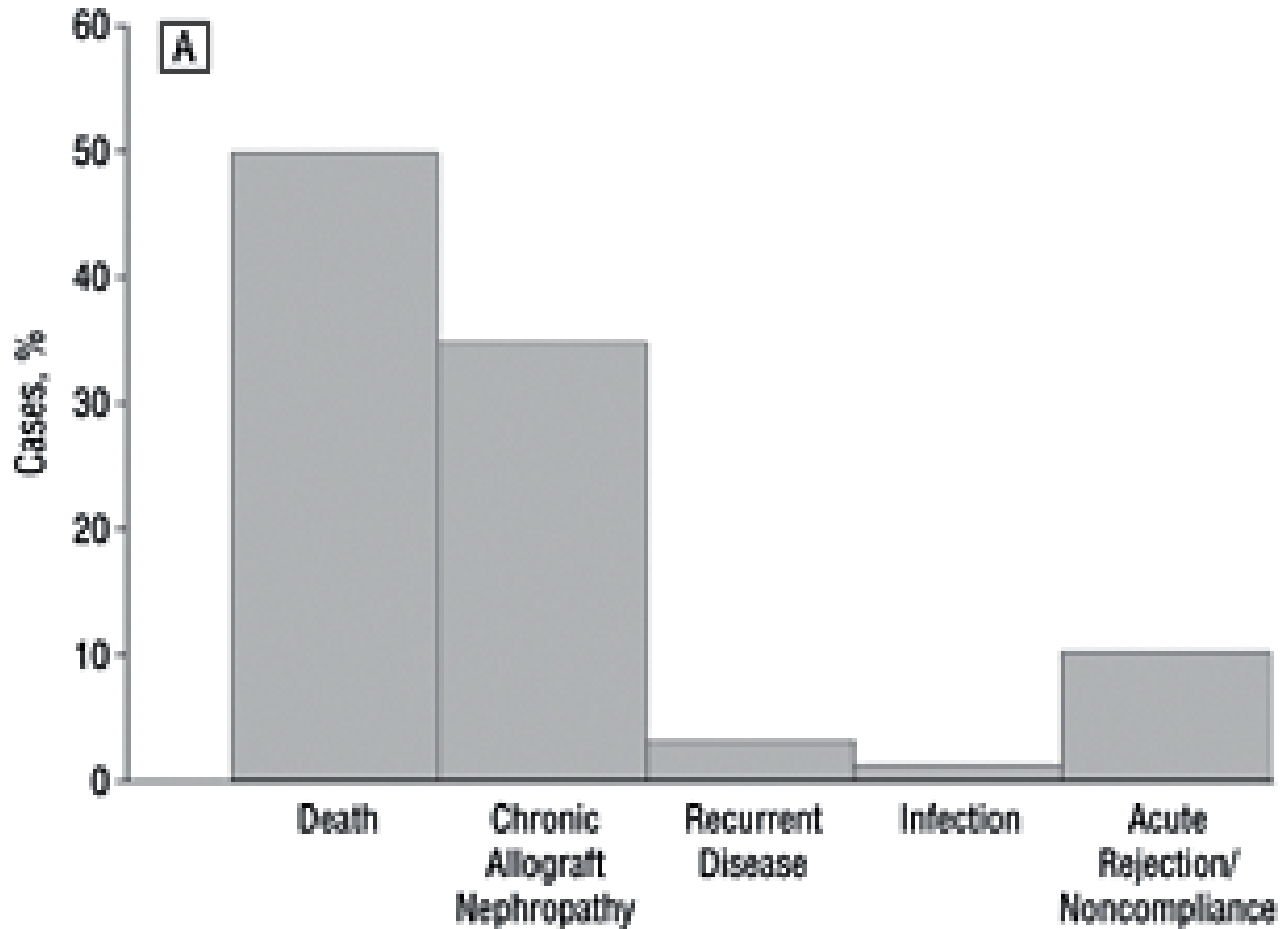
Graft Survival : Donor type (first transplant recipients, 1988–1998)



Graft survival cadaveric donor

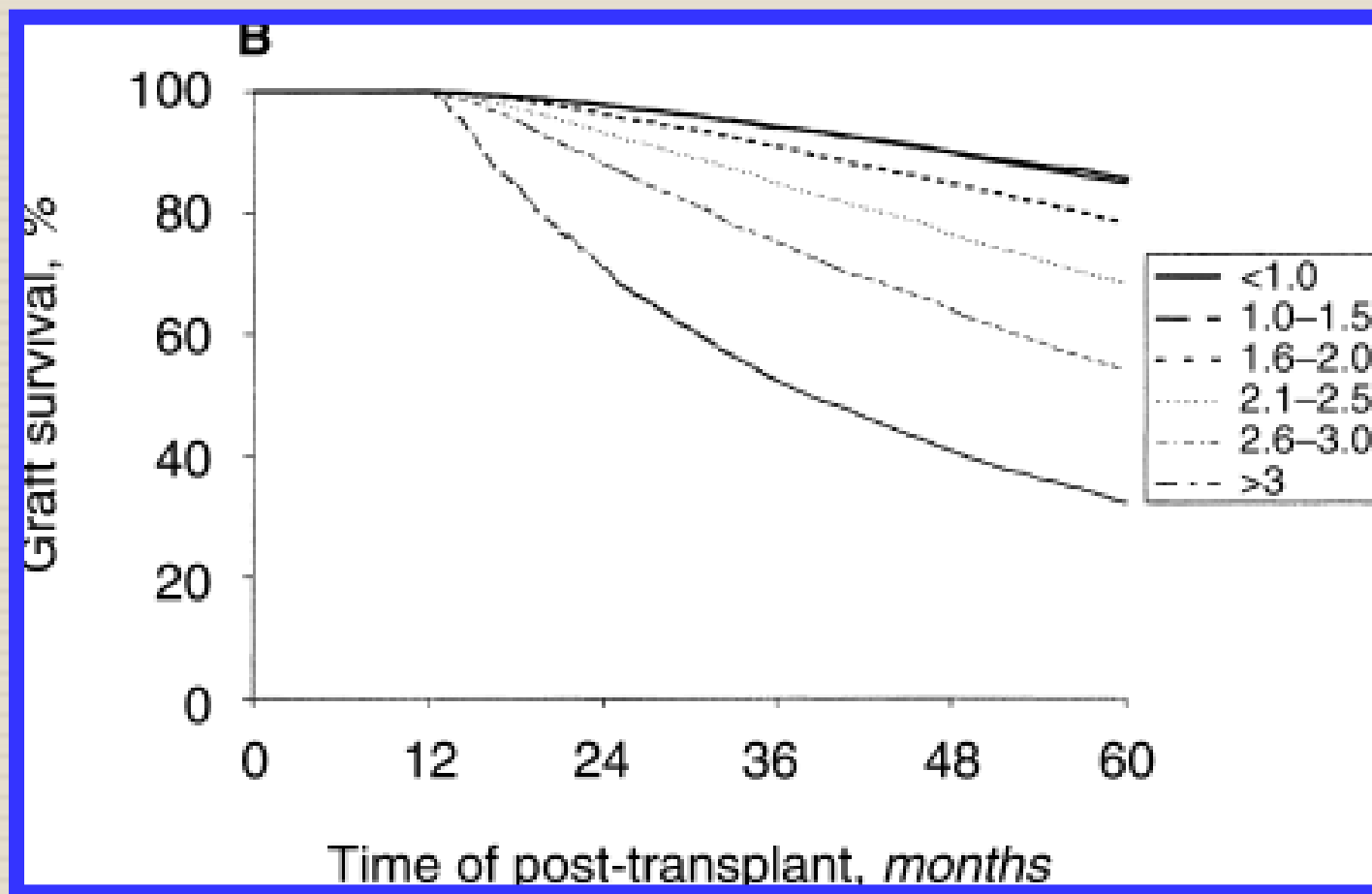


Causes of allograft loss



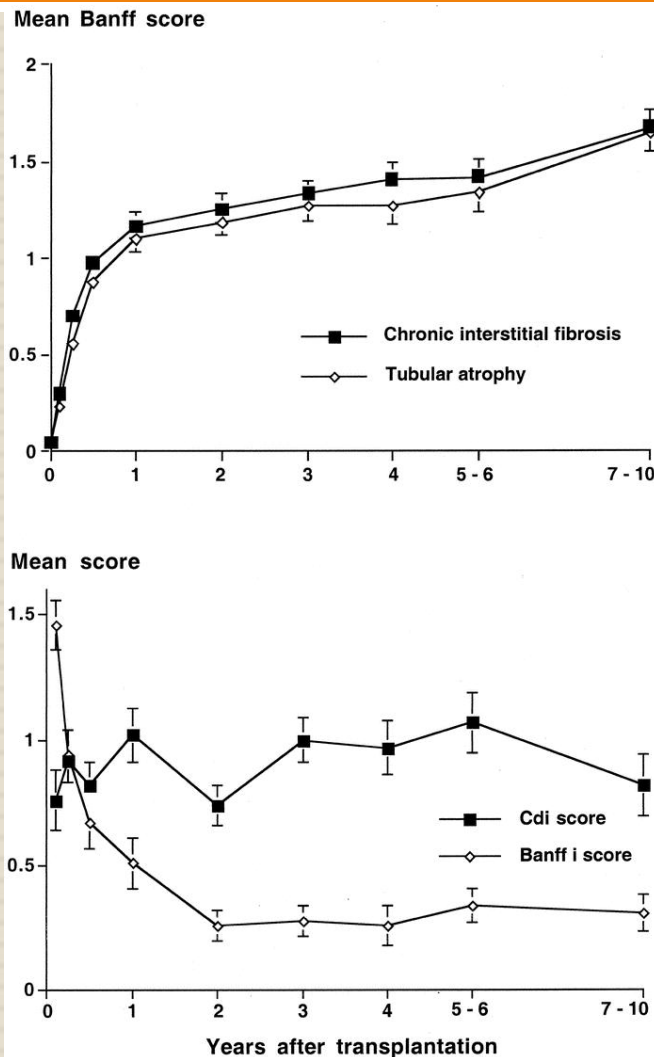
The UNOS Scientific Renal Transplant Registry--2000.

Post-transplant renal function in the first year predicts long-term kidney transplant survival



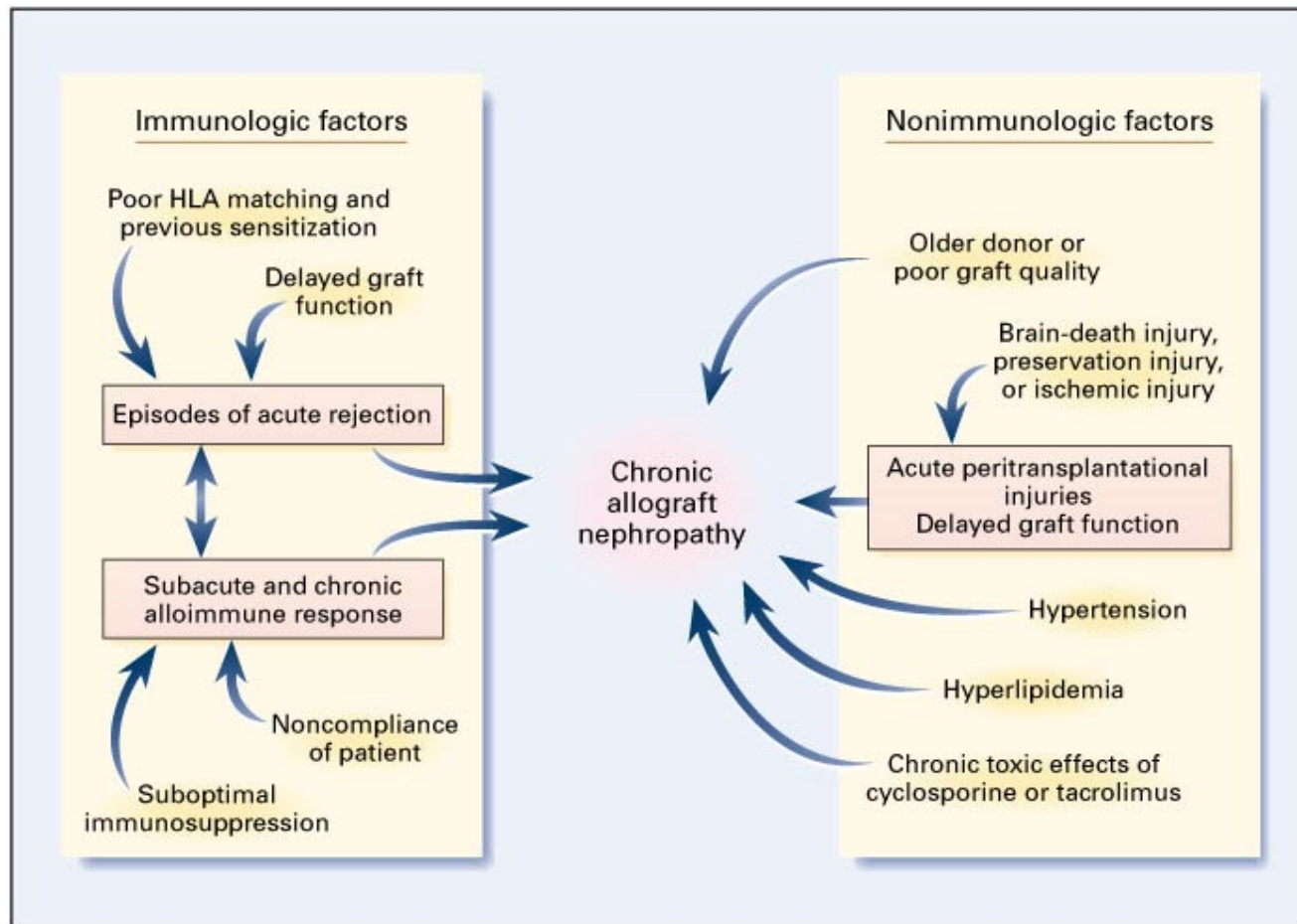
Hariharan S et al . KI 2002 Jul;62(1):311-8.

Time-course of renal tubulointerstitial damage



Nankivell: Transplantation,
Volume 78(3).August 15,
2004.434-441

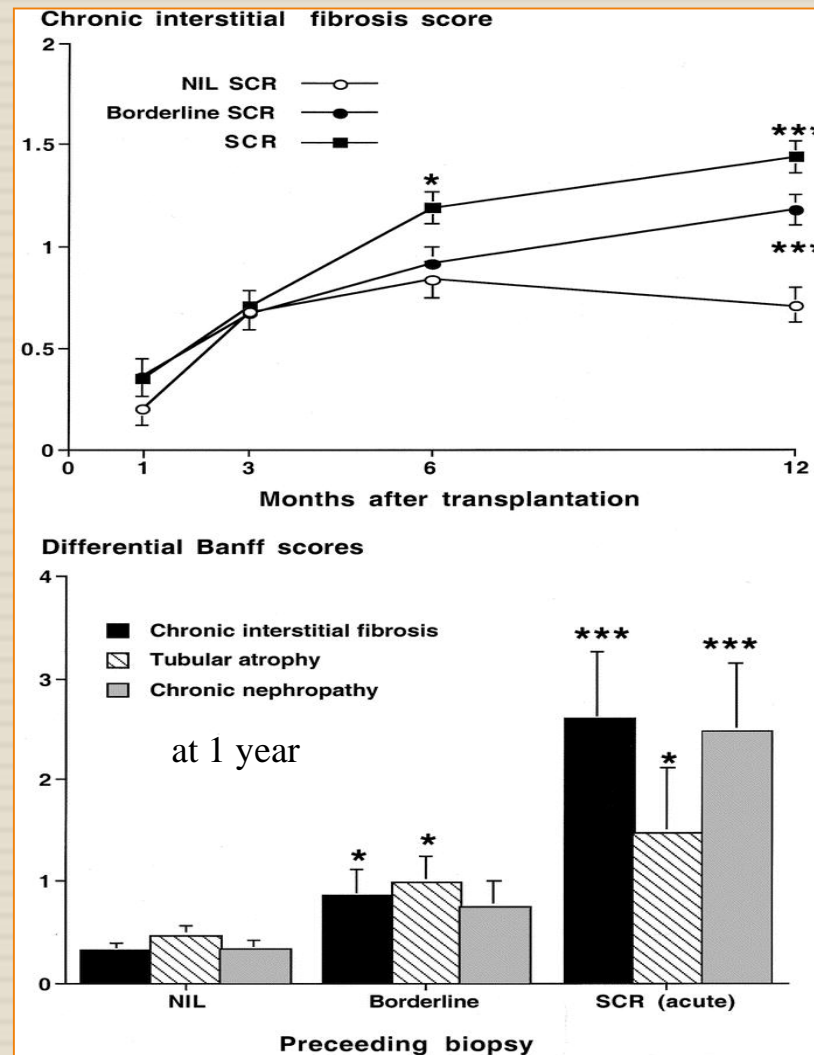
Pathogenesis of Chronic Allograft Nephropathy



Can we improve graft survival?

1. Diagnosis and treatment of subclinical rejection
2. Conversion from CNI to TOR inhibitors/PSI
3. Treatment of proteinuria
4. Treatment of chronic humoral rejection

Increased chronic interstitial fibrosis according to severity of sub clinical rejection



Nankivell, Brian J
et al
Transplantation
2004

Beneficial effects of treatment of early sub clinical rejection: a randomized study

Rush et al Manitoba, Canada . JASN 1998

72 patients on cyclosporine, aza, prednisone

were randomized to:

1. biopsies at 1, 2, 3, 6, and 12 mo (Biopsy group)–treated by pulse corticosteroids
- 2 . biopsies at 6- and 12-mo biopsies only (Control group)

Serum Creatinine

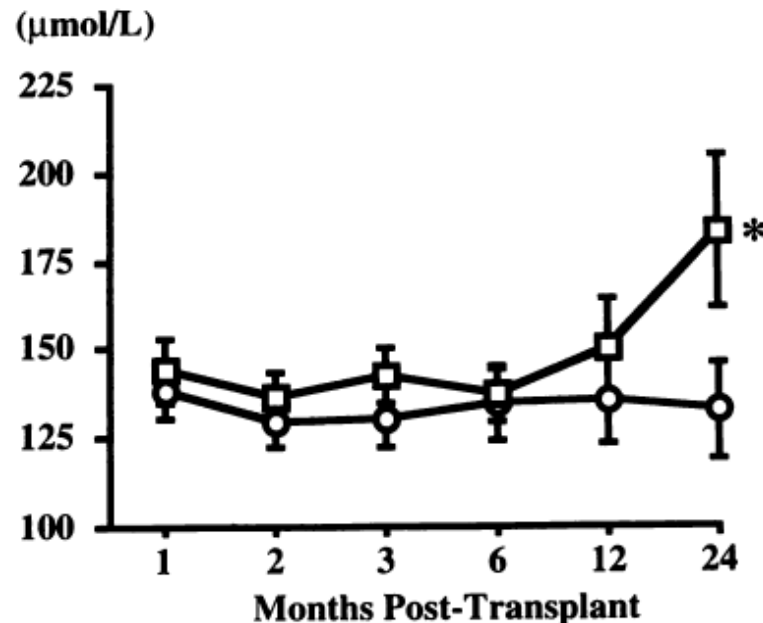


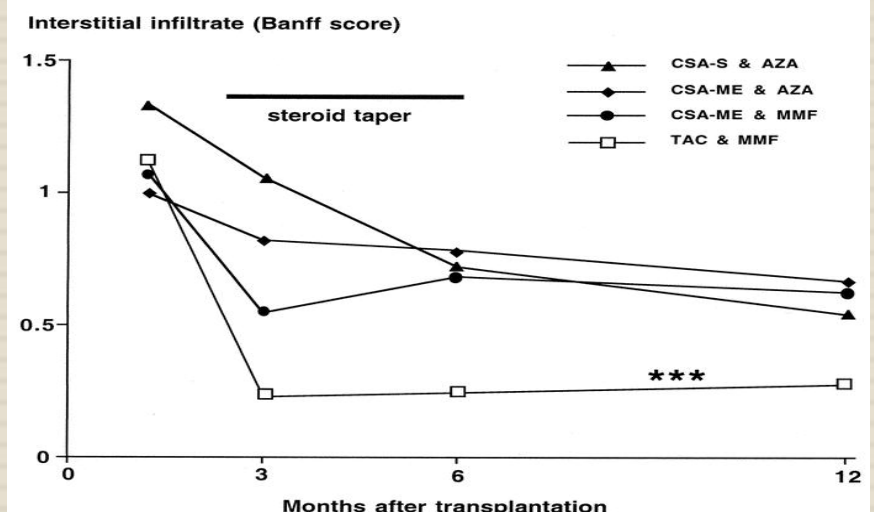
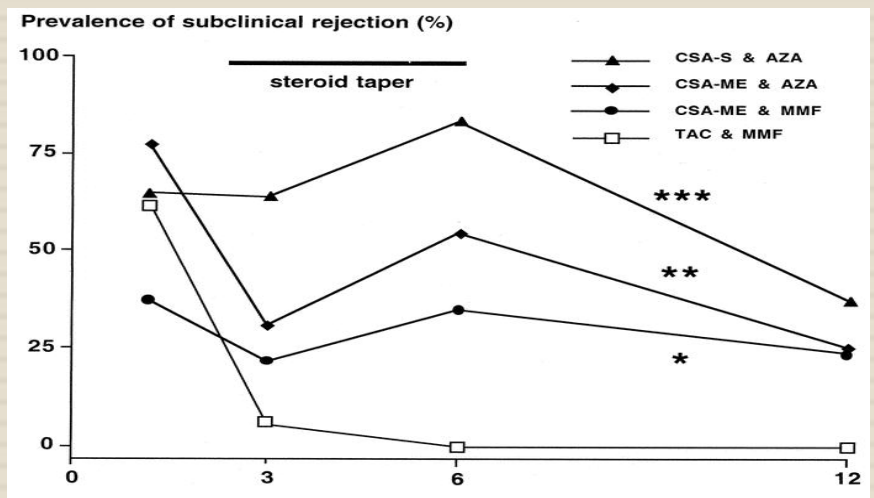
Figure 1. Mean serum creatinine over time for the Biopsy group (○) and the Control group (□). ANOVA. * $P < 0.05$ Biopsy versus Control.

graft survival at 2 years
97% -biopsy group
83% -control group

Effect of immunosuppression on the prevalence of subclinical rejection with time

961 protocol kidney biopsies from 119 kidney-pancreas transplant and 1 kidney transplant alone taken regularly up to 10 years after transplantation .

Nankivell, Brian J et al
Transplantation 2004



Lack of Benefit of Early Protocol Biopsies in Renal Transplant Patients Receiving TAC and MMF: A Randomized Study

D. Rush et al

American Journal of Transplantation

November 2007

Subclinical rejection in 4.6% of the biopsies overall

Table 5: Subclinical rejection (ITT biopsied)

Study period		No. (%) of subjects	
		Biopsy arm (n = 90)	Control arm (n = 102)
Implant	Subclinical acute/active rejection	0 (0.0)	0 (0.0)
	Subclinical borderline rejection with treatment	0 (0.0)	0 (0.0)
Month 1	Subclinical acute/active rejection	4 (5.7)	–
	Subclinical borderline rejection with treatment	1 (1.4)	–
Month 2	Subclinical acute/active rejection	0 (0.0)	–
	Subclinical borderline rejection with treatment	2 (3.0)	–
Month 3	Subclinical acute/active rejection	6 (8.1)	–
	Subclinical borderline rejection with treatment	1 (1.4)	–
Month 6	Subclinical acute/active rejection	7 (8.9)	5 (6.0)
	Subclinical borderline rejection with treatment	0 (0.0)	0 (0.0)

Creatinine clearance at 6 months

Biopsy arm=72.9 ± 21.7 mL/min

Control arm= 68.90 ± 18.35 mL/min(p = 0.18)

CALCINEURIN INHIBITORS TO
SIROLIMUS MAINTENANCE
THERAPY IN RENAL ALLOGRAFT
RECIPIENTS: 24-MONTH
EFFICACY AND SAFETY
RESULTS FROM **THE
CONVERT TRIAL**

January 27, 2009

Transplantation

Received 31 December
2007. Revision requested 14
January 2008

.Accepted 3 September 2008

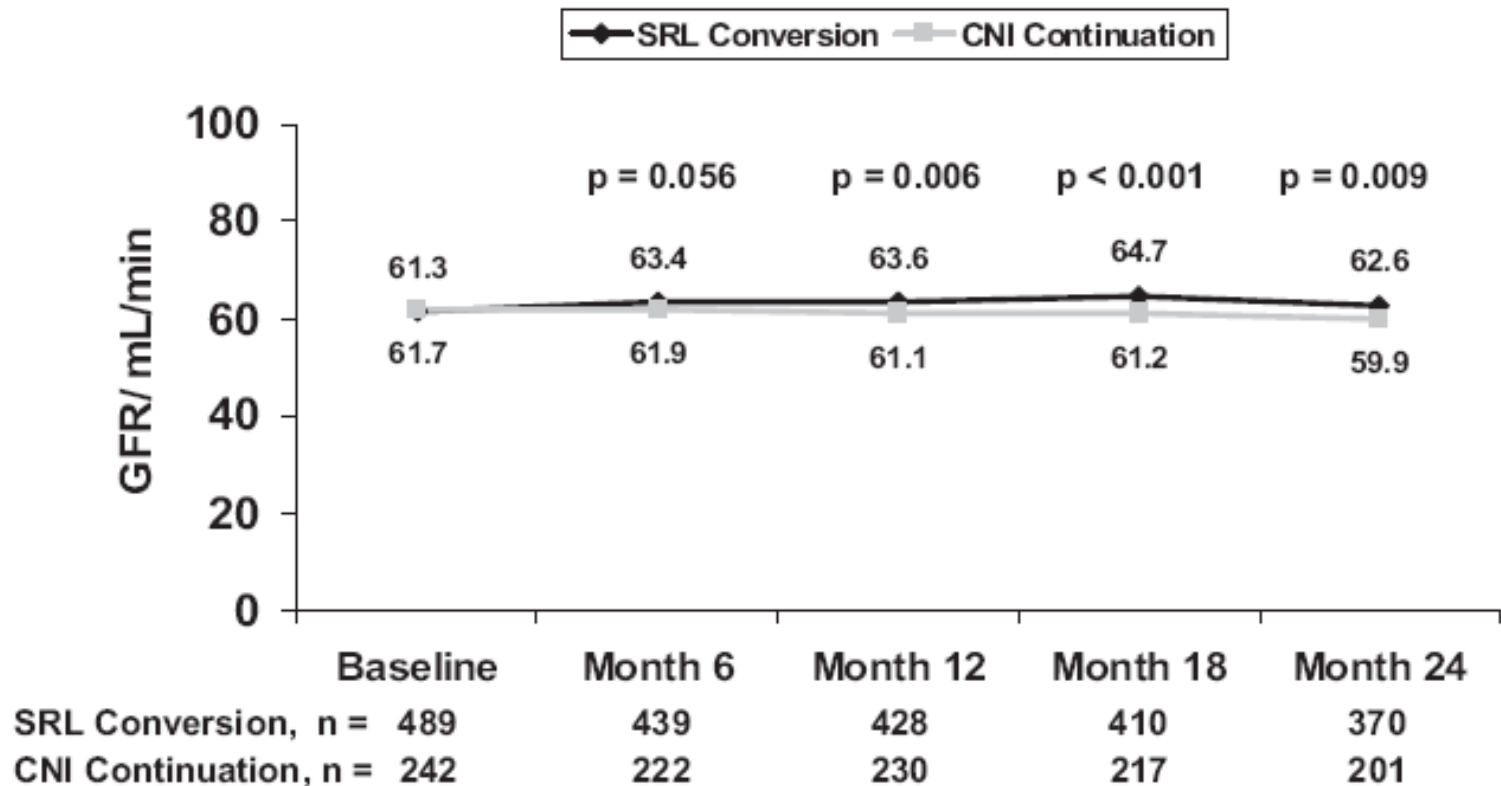
Eligibility Criteria

Patients were stratified into two groups GFR:

20 to 40 mL/min

or >40 mL/min

Mean Nankivell GFR (mL/min) in on-therapy patients with baseline **GFR more than 40** *.mL/min



*Values adjusted for baseline by ANCOVA.

But in -ITT analysis – no difference in GFR

GFR 20 -40 mL/min

- 87 of 830 patients (10.5%) had a GFR of 20 to 40 mL/min at randomization.
 - Enrollment in this stratum was halted by the Drug Safety Monitoring Board when, during a protocol-specified review of data,
 - the primary safety endpoint of AR, graft loss, or death was reached by :
 - 8 of 48 (16.7%) of SRL conversion patients
 - and 0 of 25 of CNI continuation patients
- P=0.045

Multiple linear regression analysis

- independent predictors of change from baseline GFR at 2 years.

 - specific for SRL conversion

 - Pr/Cr more than 0.11

 - black race

Urinary protein/creatinine ratios (UPr/Cr) (by treatment in patients with baseline GFR >40 mL/min

Time	Sirolimus conversion			Calcineurin inhibitor continuation		
	n	Mean±SD	Median	n	Mean±SD	Median
Baseline GFR >40 mL/min						
Baseline	413	0.35 ± 0.76	0.13	207	0.28 ± 0.61	0.11
Month 6	376	0.78 ± 1.79	0.25	189	0.31 ± 0.56	0.12 ^a
Month 12	383	0.83 ± 1.58	0.31	198	0.37 ± 0.88	0.13 ^a
Month 24	329	0.87 ± 1.48	0.33	176	0.48 ± 1.00	0.13 ^a
Baseline GFR >40 mL/min and U _{Pr/Cr} ≤0.11						
Baseline	195	0.04 ± 0.04	0.04	102	0.05 ± 0.04	0.05
Month 6	163	0.27 ± 0.95	0.12	81	0.13 ± 0.25	0.06 ^a
Month 12	165	0.36 ± 0.53	0.15	85	0.23 ± 0.70	0.07 ^a
Month 24	146	0.72 ± 1.50	0.21	72	0.22 ± 0.40	0.06 ^a

^a Sirolimus conversion vs. calcineurin inhibitor continuation, Wilcoxon Rank Sum test $P < 0.001$.

TABLE 3. Treatment-emergent adverse events^a in the safety population

	Sirolimus conversion (n=551)	Calcineurin inhibitor continuation (n=273)	<i>p</i> ^b
Infection, n (%)			
Pneumonia	70 (12.7)	14 (5.1)	<0.001
Herpes simplex	48 (8.7)	12 (4.4)	0.032
Fever	24 (4.4)	1 (0.4)	<0.001
Aphthous stomatitis	23 (4.2)	1 (0.4)	0.001
Stomatitis	21 (3.8)	1 (0.4)	0.002
Acne	10 (1.8)	0	0.036
Malignancies, n (%)			
Total	21 (3.8)	30 (11.0)	<0.001
Skin carcinoma	12 (2.2)	21 (7.7)	<0.001
Other, n (%)			
Hyperlipemia	295 (53.5)	72 (26.4)	<0.001
Hypercholesterolemia	231 (41.9)	33 (12.1)	<0.001
Diarrhea	216 (39.2)	63 (23.1)	<0.001
Anemia	200 (36.3)	45 (16.5)	<0.001
Peripheral edema	176 (31.9)	37 (13.6)	<0.001
Albuminuria	130 (23.6)	35 (12.8)	<0.001
Fever	113 (20.5)	25 (9.2)	<0.001
Acne	89 (16.2)	11 (4.0)	<0.001
Thrombocytopenia	77 (14.0)	9 (3.3)	<0.001
Leukopenia	74 (13.4)	12 (4.4)	<0.001
Skin rash	67 (12.2)	11 (4.0)	<0.001
Lactic dehydrogenase increased	64 (11.6)	3 (1.1)	<0.001
Hyperglycemia	62 (11.3)	18 (6.6)	0.034
Hyperuricemia	41 (7.4)	42 (15.4)	<0.001

^a Treatment-emergent adverse events were reported by the investigator.

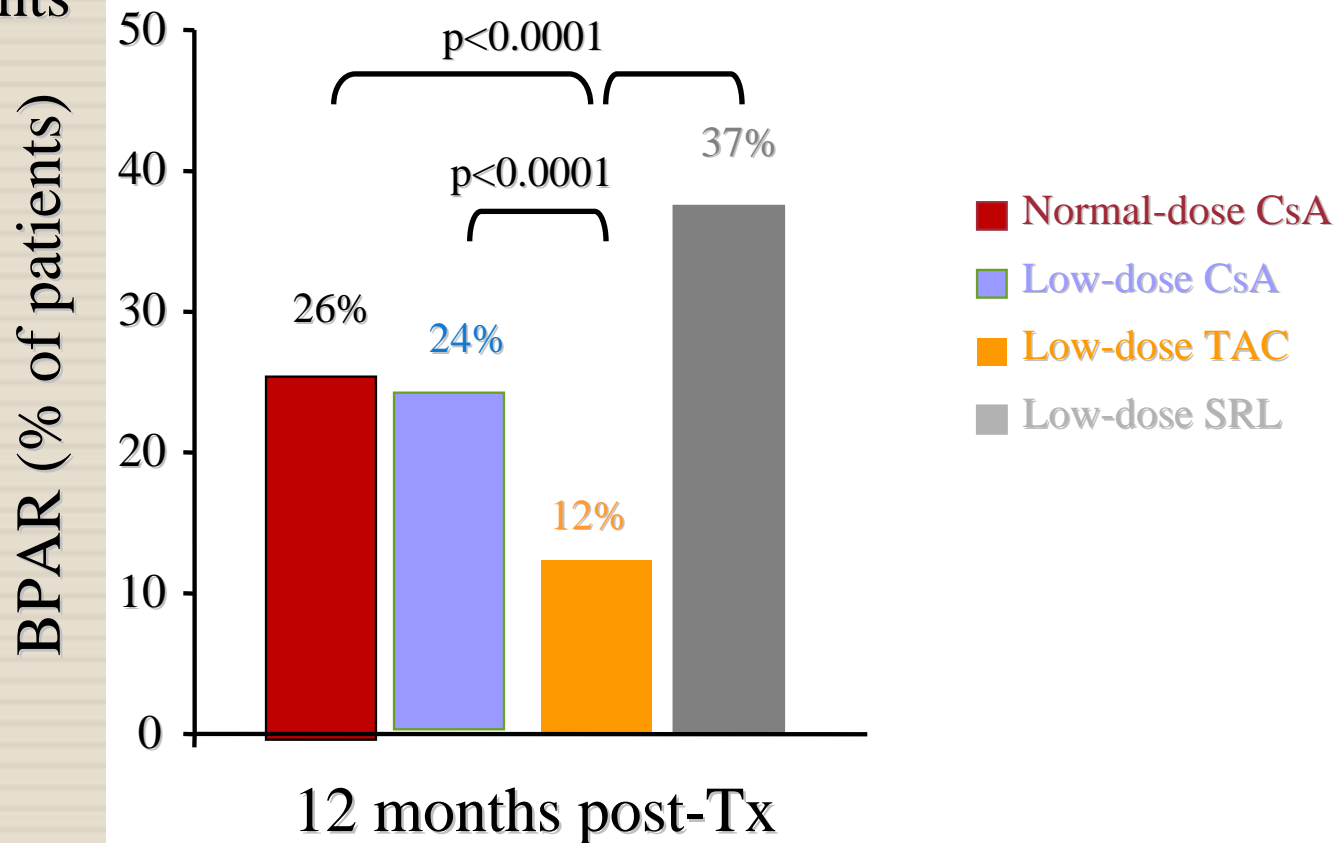
^b Fisher's exact test.

SYMPHONY:

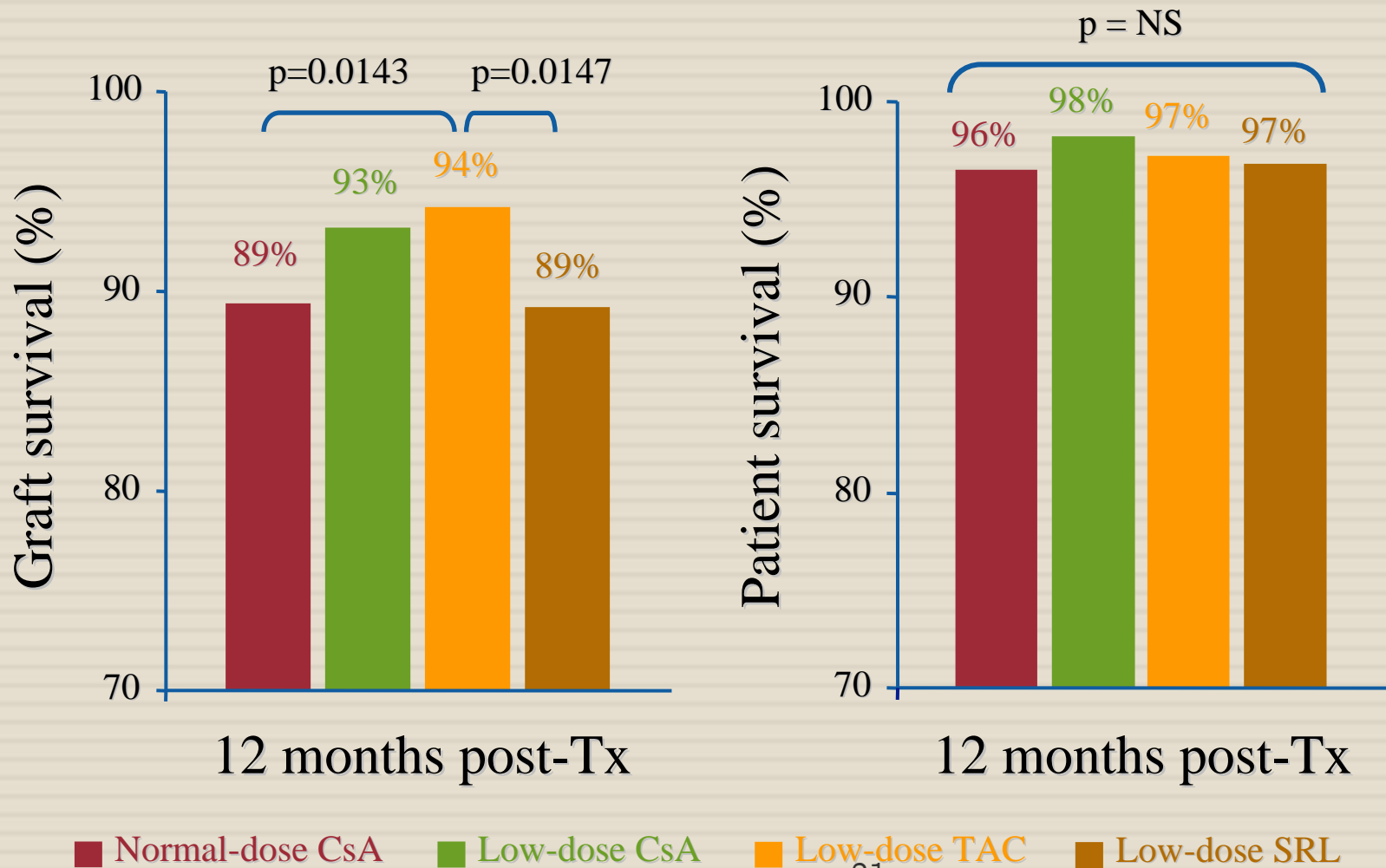
Comparison of 3 low-toxicity regimens with standard Immunosuppression

1645 patients

Biopsy
Proven
Acute
Rejection



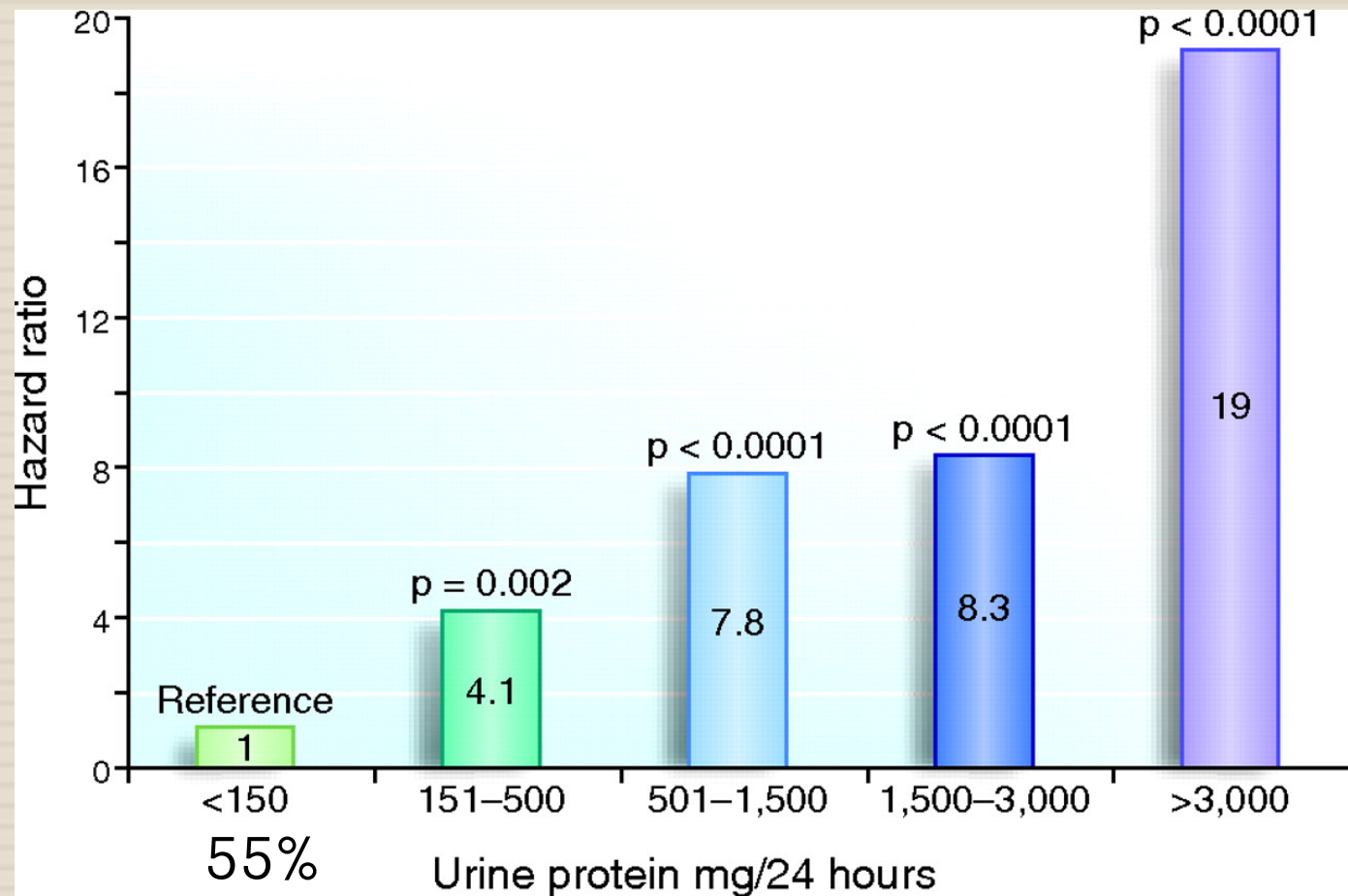
Graft and Patient Survival



Would conversion after 3-4 months be better???



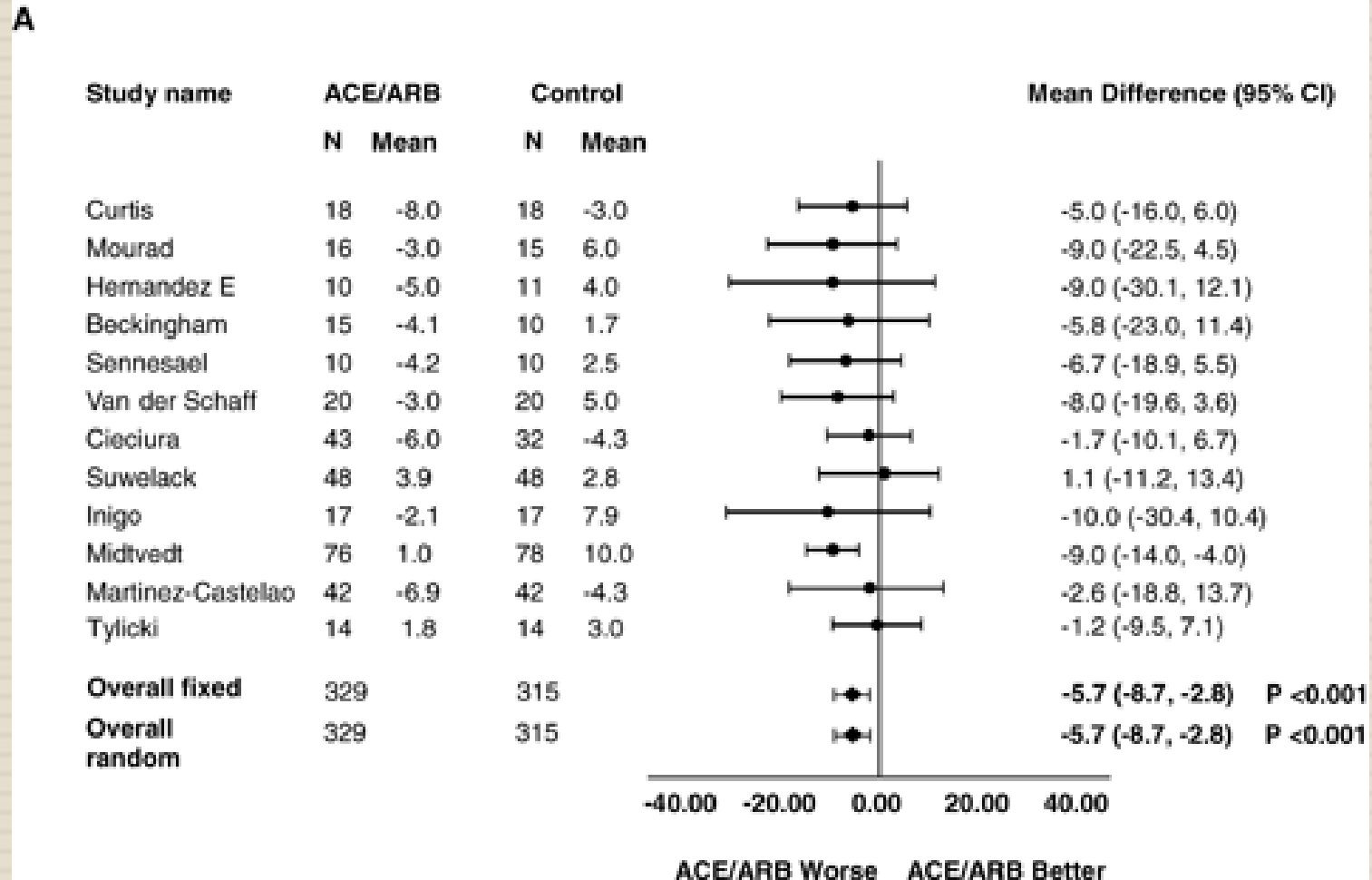
proteinuria at 1yr posttransplant and subsequent graft survival



Amer, H. et al. J Am Soc Nephrol 2009;20:2490-2492

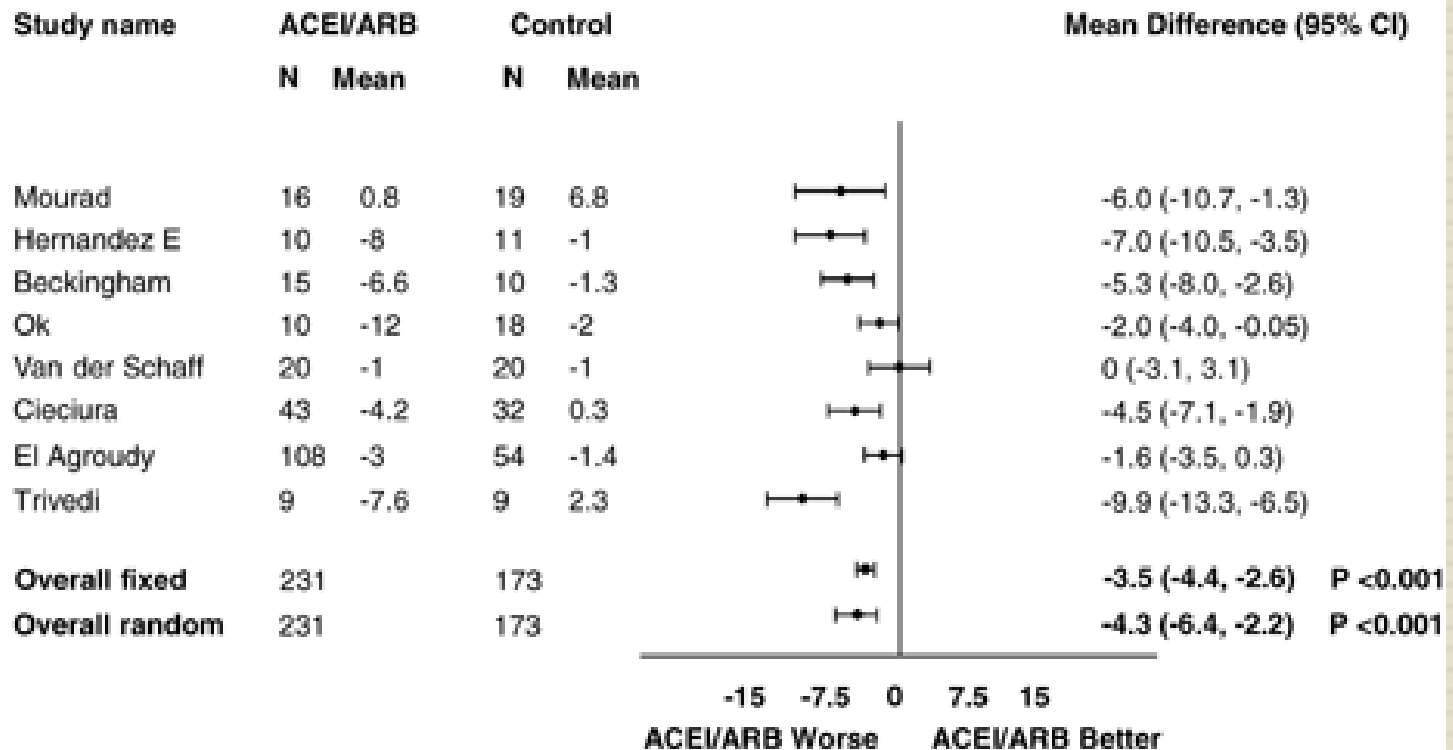
Renin Angiotensin System Blockade in Kidney Transplantation: A Systematic Review of the Evidence

Change in glomerular filtration rate



Change in hematocrit

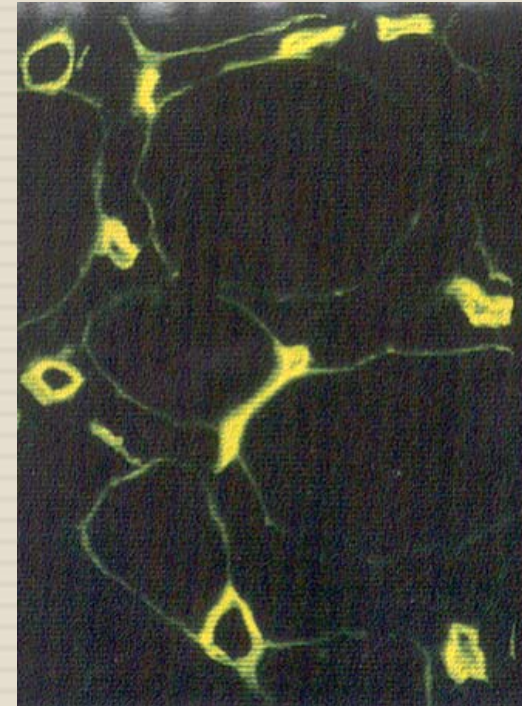
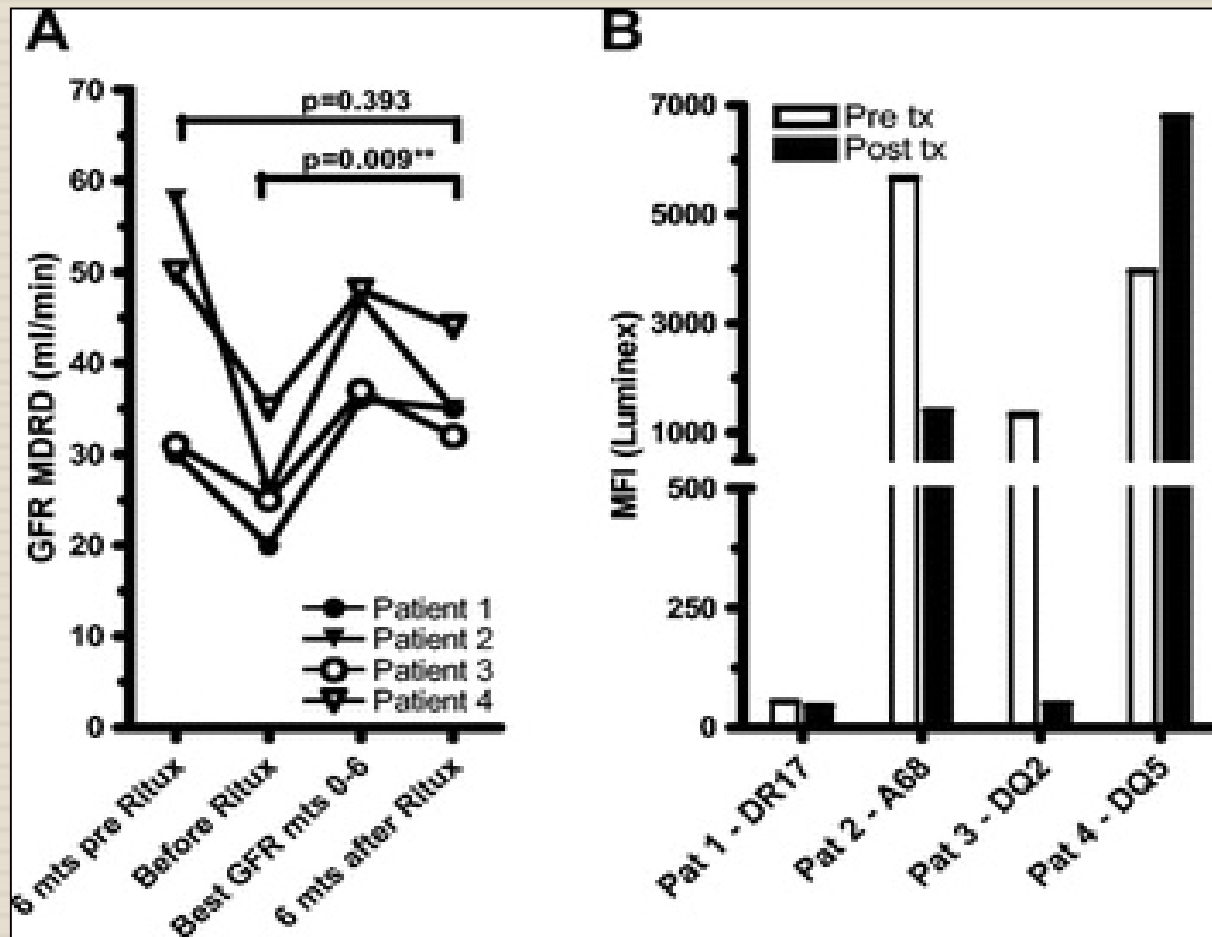
A



Waiting for:

- Nephrology Dialysis Transplantation 2008 23(1):354-358; doi:10.1093/ndt/gfm574
- **The Canadian ACE-inhibitor trial to improve renal outcomes and patient survival in kidney transplantation—study design**

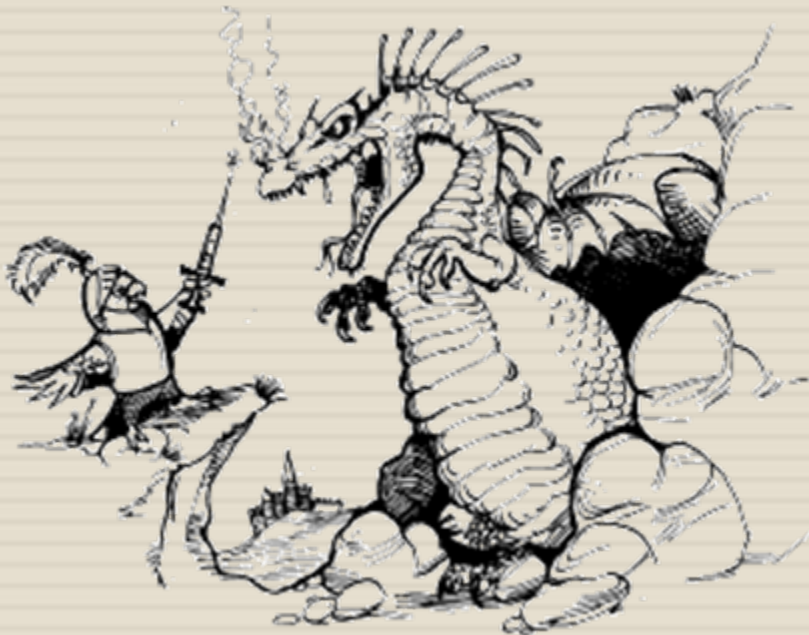
Rituximab and Intravenous Immunoglobulin Treatment of Chronic Antibody-Mediated Kidney Allograft Rejection



Transplantation. 87(12):1837-1841, June 27, 2009.

Infectious diseases

BK Polyoma nephropathy



Polyoma viruses

DNA genome □

שייכים ל papovavirus family □

כולל וירוסים של קופים, בקר, ארנבות, □

עכברים, חולדות ותוכים. בתוכם SV40

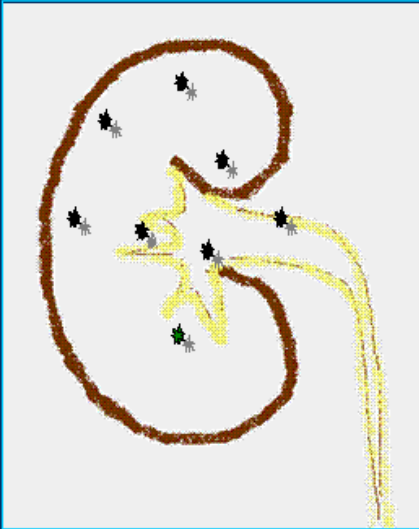
1971

BK virus - בשתן של מושגל כליה □

JC virus - במח חולה עם PML □

ההדבקה ב BKV - JCV נעשית בילדות כנראה דרך
דרכי הנשימה

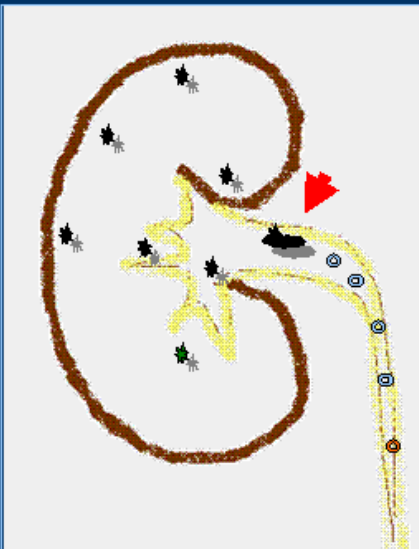
הוירוסים נשארים לטנטיים בכליות ובלימפוציטים



1) LATENT INFECTION

After primary infection BK and JC remain latent in the kidney and urothelium of ureters and urinary bladder.

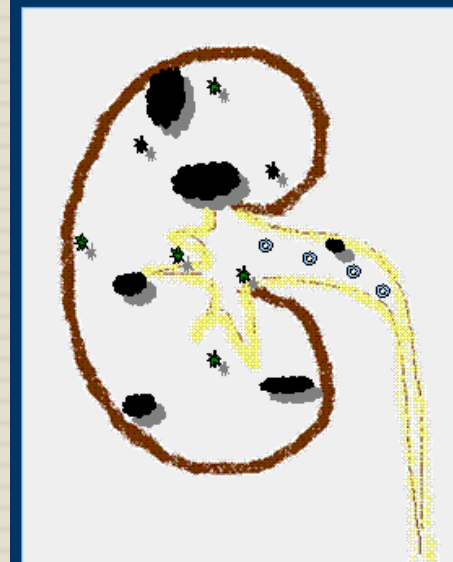
- Demonstration by tissue PCR
- No viruria (absence of decoy cell in urine, negative PCR studies in urine)
- No viremia
- No clinical significance (normal renal function)



2) LIMITED (low level) VIRAL REPLICATION

Mostly limited to the urothelium is common in immunosuppressed patients and may occur rarely in healthy individuals (i.e. pregnant women).

- 20-65% of renal transplant patients
- Transient or intermittent viruria
 - Decoy cells on urine cytology
 - Demonstration of viruria with PCR methods
- No viremia
- No clinical significance, normal renal function



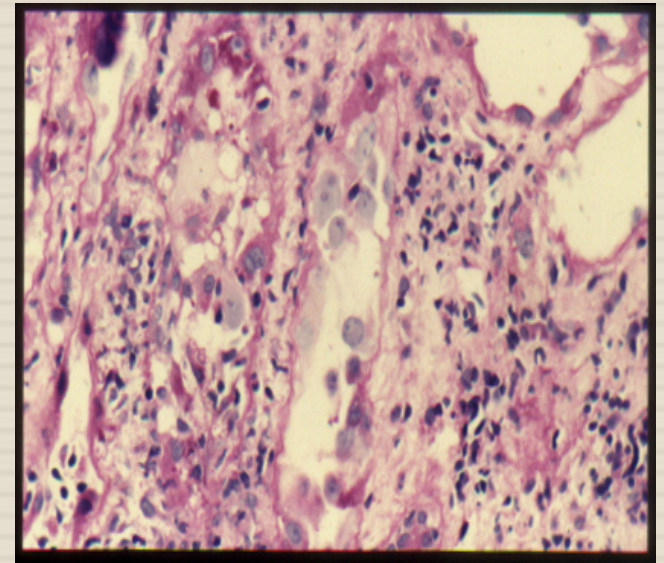
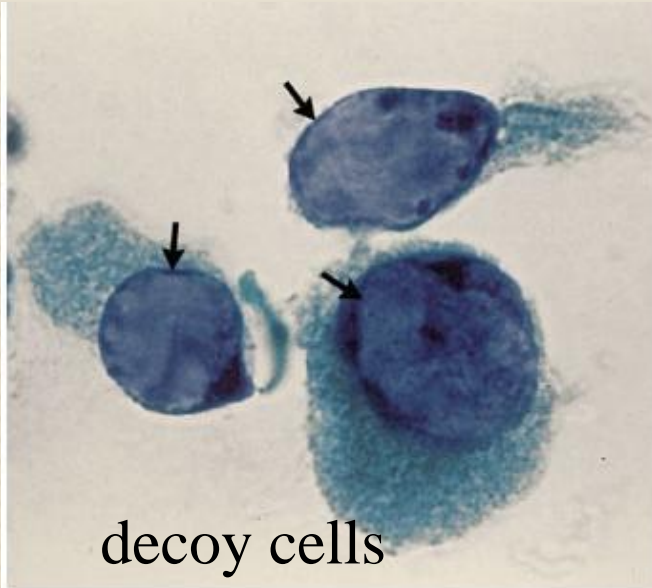
3) HIGH LEVEL VIRAL REPLICATION WITH TISSUE DESTRUCTION

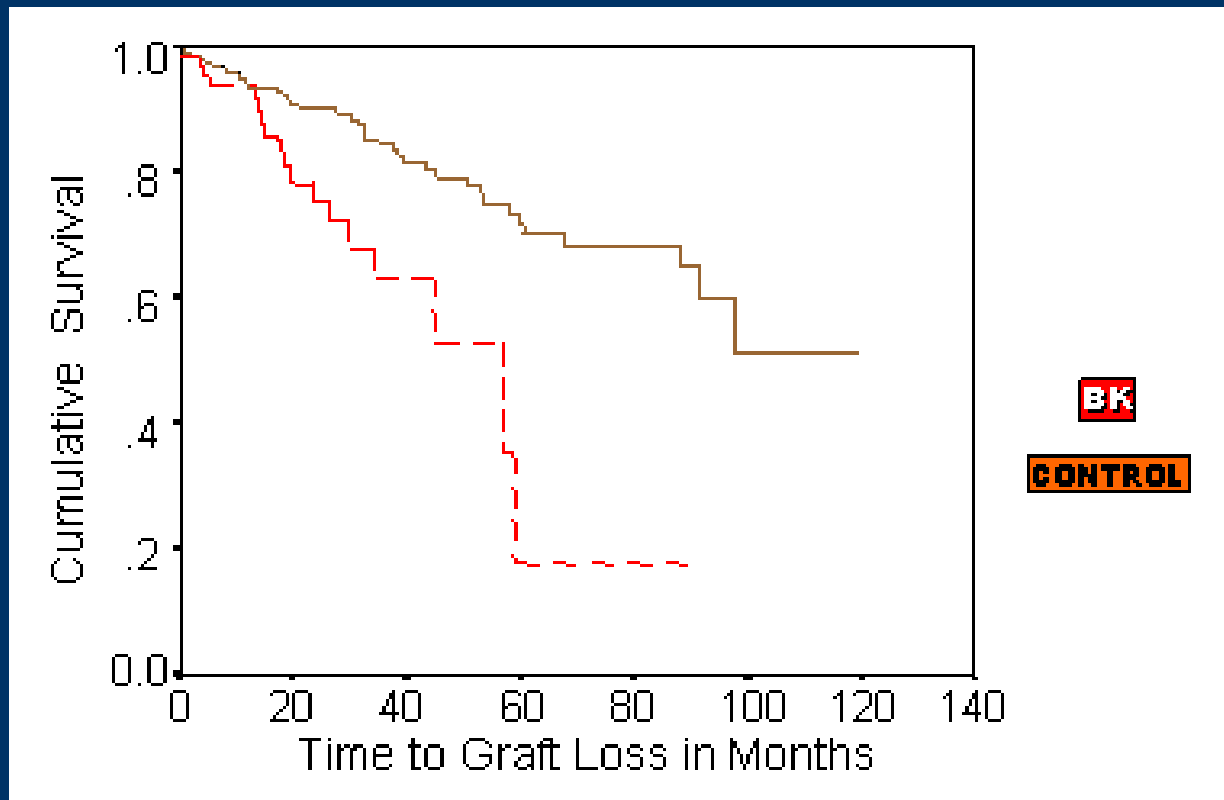
POLYOMA VIRUS ALLOGRAFT NEPHROPATHY

- Occurs only in a minority of renal transplant patients (5-10%).
- **Persistent viruria**
 - Decoy cells on urine cytology
 - Significant viruria by quant. PCR
- Viremia
- Abnormal renal function if parenchymal disease is extensive

BK Polyoma nephropathy

- נפרופטיה - עליית קראטינין זוחלת תוך ימים - שבועות
- הצרויות באורתר
- האתיולוגיה יותר מדי אימונוסופרסיה-בעיקר
MMF 1 tacrolimus





Graft survival analysis. Comparison between patients with polyoma virus nephropathy and controls ($p=0.004$).

BK: 67 patients with graft dysfunction and PV in biopsy and urine. Mean follow up 26 months.
Control: 162 patients with graft dysfunction and no evidence of PV in biopsy and urine. Mean follow up 25.3 months.

Diagnostic Testing for BK Virus Nephropathy

Test	Threshold Value	Correlation With PVAN on Biopsy
Decoy cells	>10 cells/cytospin	+
Urine BK virus DNA quantitative PCR	>1 × 10 ⁷ copies/mL	++
Blood/plasma BK virus DNA quantitative	>1 × 10 ⁴ copies/mL	+++

First step: reduction of immunosuppression

TABLE 5. Treatment of PVAN by modification of maintenance immunosuppression

Switching	Decreasing	Discontinuing
Tacrolimus→CsA (trough levels 100–150 ng/mL) (<i>B-III</i>)	Tacrolimus (trough levels <6 ng/mL) (<i>B-III</i>)	Tacrolimus or MMF (maintain or switch to dual drug therapy): CsA/prednisone (<i>B-III</i>)
MMF→azathioprine (dosing ≤100 mg/d) (<i>B-III</i>)	MMF dosing ≤1 g/day (<i>B-III</i>)	
Tacrolimus→sirolimus (trough levels <6 ng/mL) (<i>C-III</i>)	CsA (trough levels 100–150 ng/mL) (<i>B-III</i>)	Tacrolimus/prednisone (<i>B-III</i>)
MMF→sirolimus (trough levels <6 ng/mL) (<i>C-III</i>)		Sirolimus/prednisone (<i>C-III</i>)
MMF→leflunomide (<i>C-III</i>)		MMF/prednisone (<i>C-III</i>)

PVAN, polyomavirus-associated nephropathy; CsA, cyclosporine A; MMF, mycophenolate mofetil.

Hirsch HH, Brennan D
 .Drachenberg C, et al
Transplantation 2005

Ancillary Therapies

Intervention

Suggested Dose

Cidofovir

0.25-1.0 mg/kg IV biweekly for 8 wk without probenecid, prehydration recommended

Leflunomide

100 mg loading dose × 3 days, 20-60 mg/d, goal leflunomide trough 50-100 ng/mL (consider lower trough goals of 20-40 ng/mL given hemolysis risk)

IVIg

1-2 g/kg IV × 1-2 doses or 150 mg/kg IV biweekly for 8 wk

Fluoroquinolones

Ciproflaxacin, 500 mg/d, duration dependent on virological response

Screening protocol -Beilinson

BK PCR בדם

כל חודש בחודשים 1-6

בחודשים 9, 12

בעת עלית קראטינין

אם PCR חיובי בדם

הפחתת אימונוסופרסיה:

הפסקת MMF והפחתת CNI למינימום האפשרי

אופציונלי:

מעבר ל TOR/PSI

מעקב CYLEX

טיפול נוסף ב leflunomide

יועלה לדיון במקרה של חוסר תגובה

מעקב PCR חודשי עד העלמות הוירוס

ביופסיה : במקרה של עליית קראטינין לאחר הפחתת אימונוסופרסיה

במקרה של דחייה חריפה בנוסף לפוליומה נפרופטי-

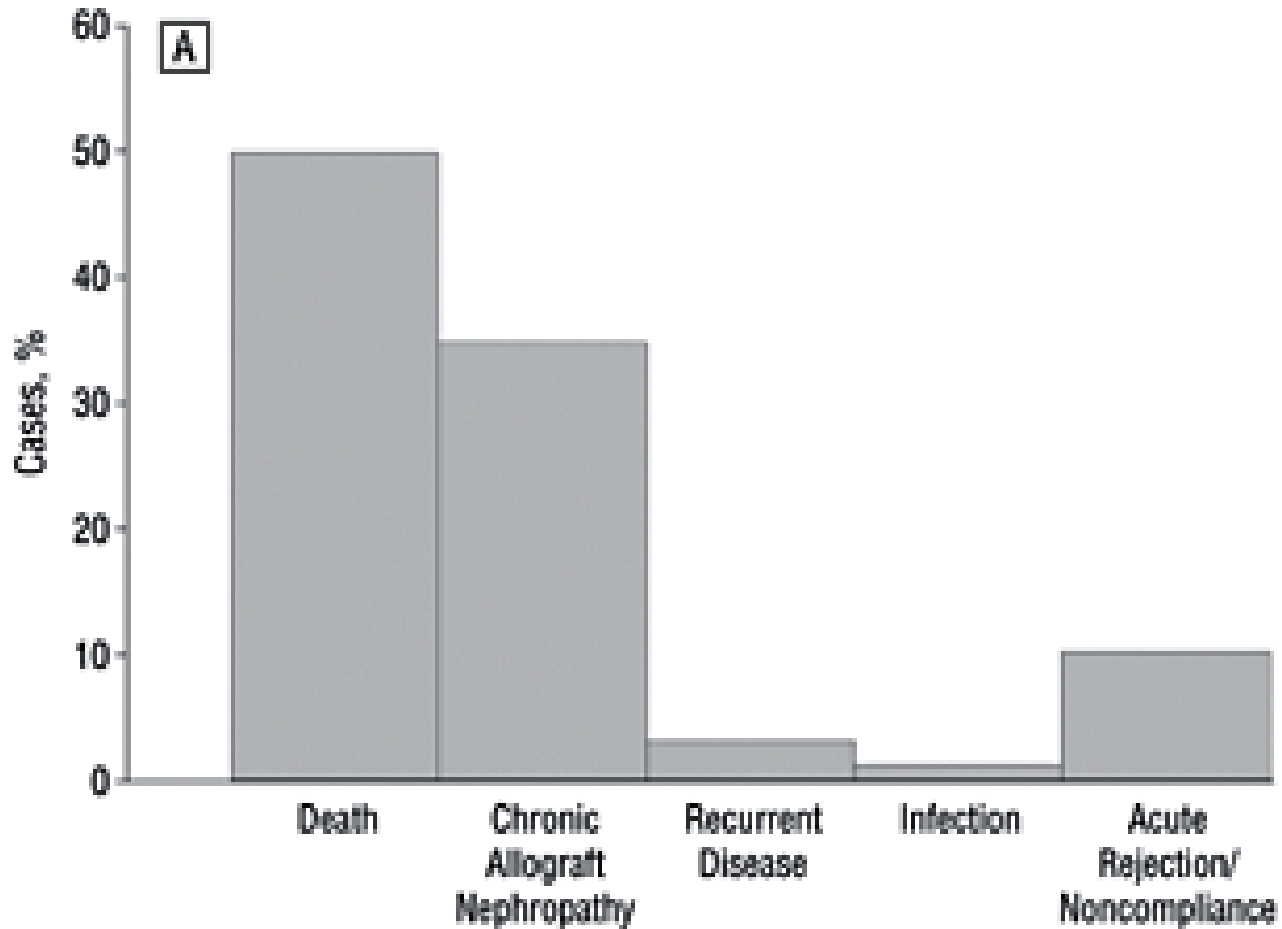
טיפול בדחייה על ידי סטרואידים או IVIG ואז מעבר לפרוטוקול עם

אימונוסופרסיה מינימלית כפי שצוין לפני כן

Current general consensus

- Retransplantation after allograft loss due to PAN can be considered
- PAN may recur despite transplant nephrectomy
 - graft nephrectomy is not a prerequisite
- Retransplantation should *not* be considered with on-going viral replication

Causes of allograft loss

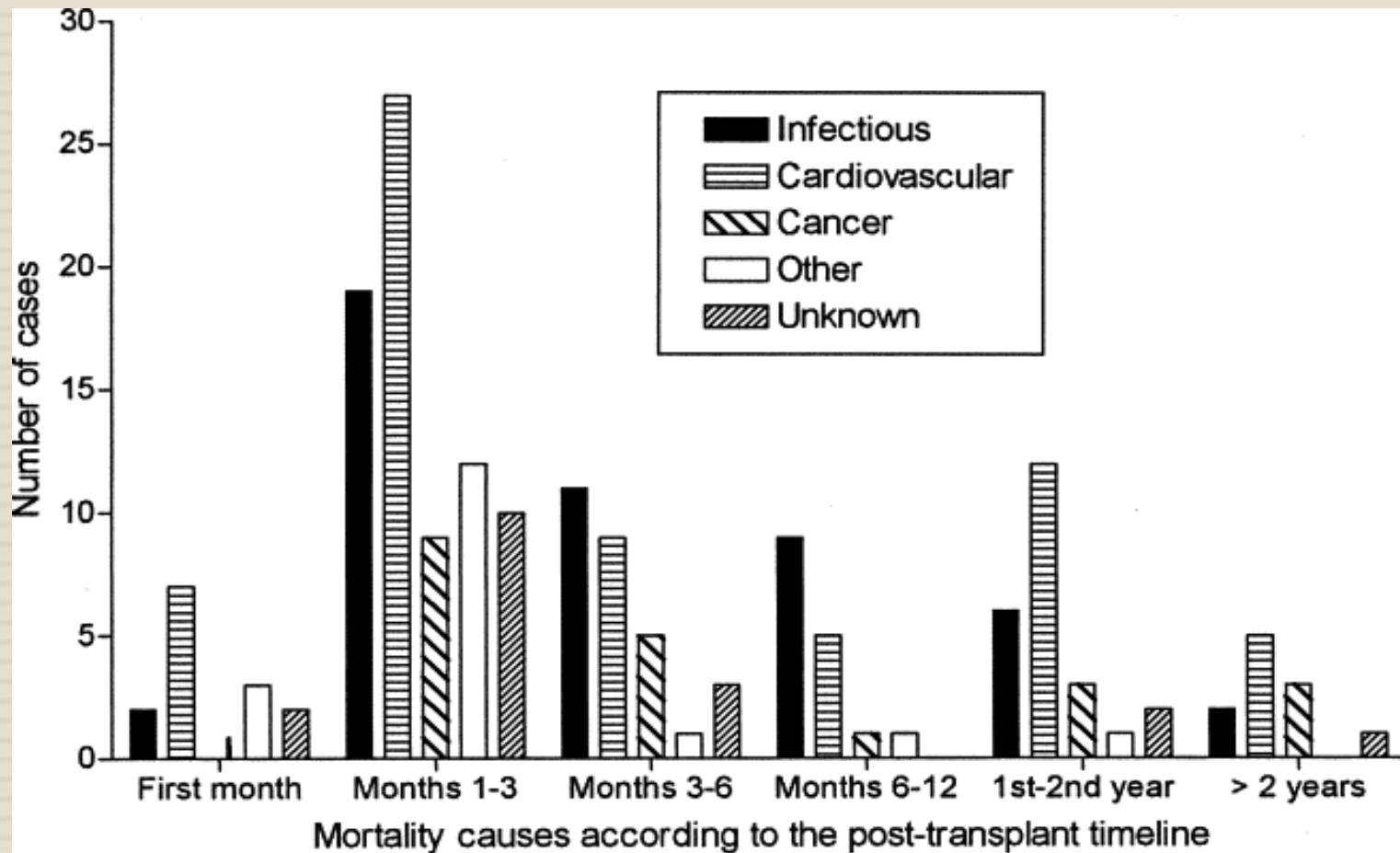


The UNOS Scientific Renal Transplant Registry--2000.

Disease Recurrence

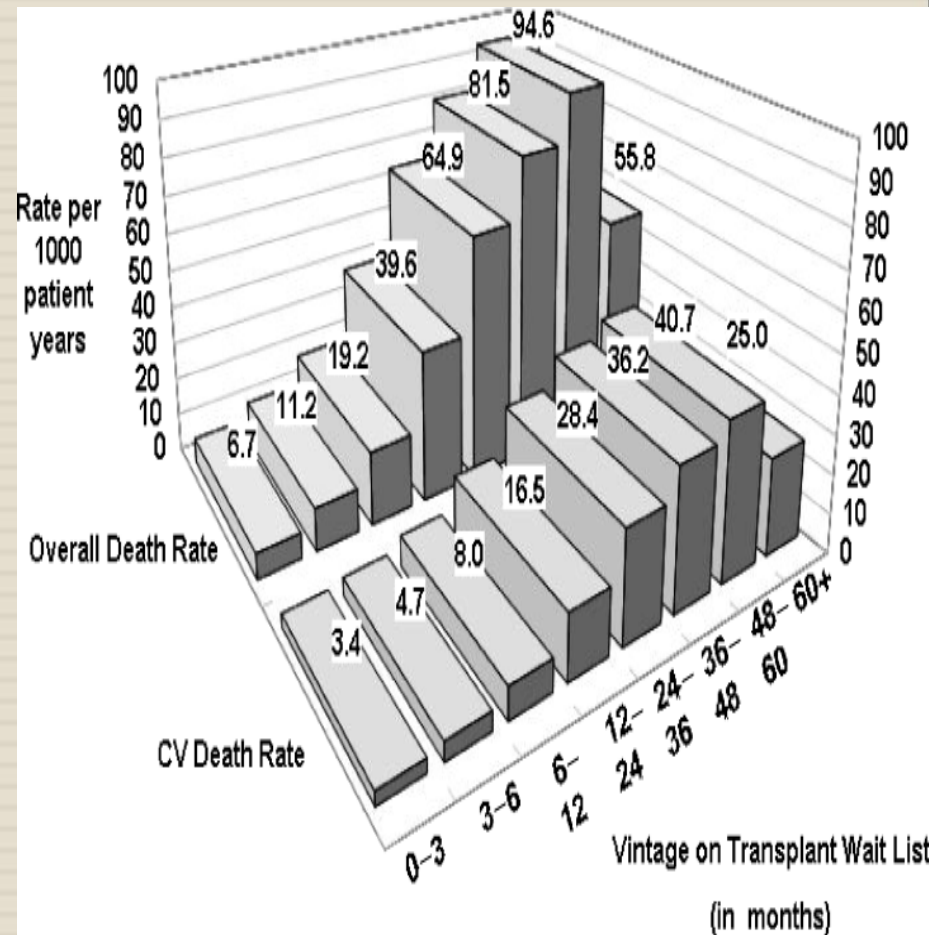
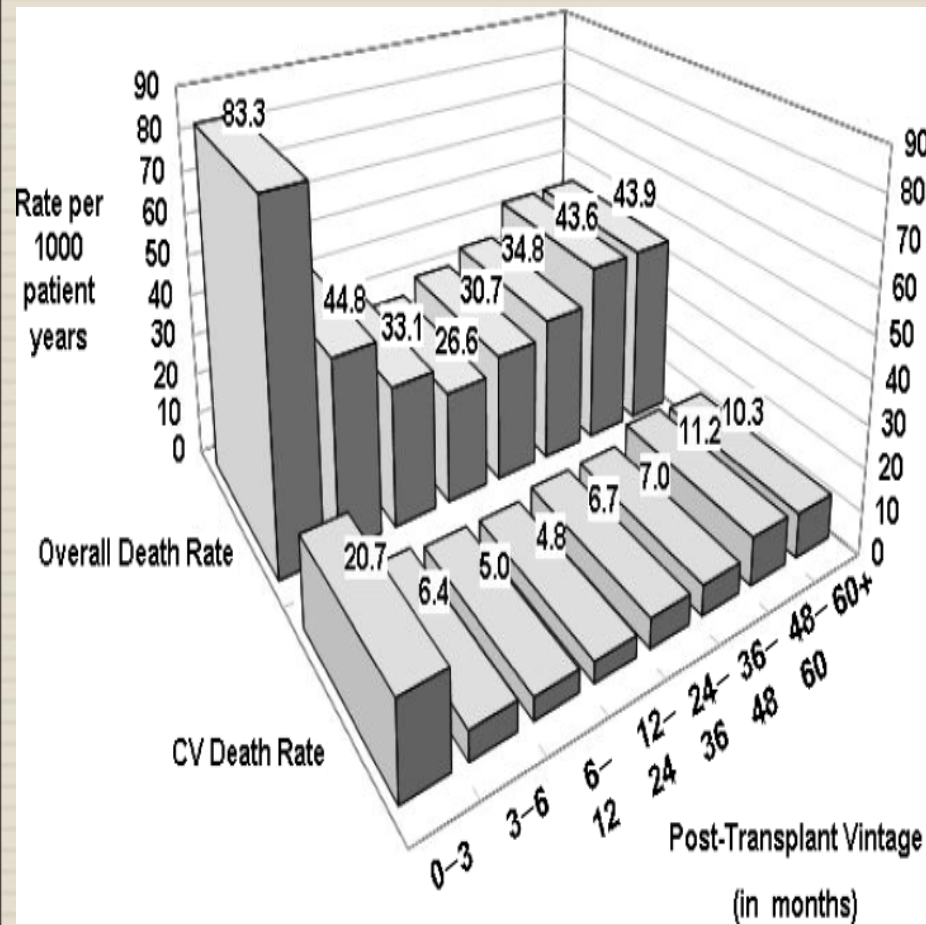
Disease	Recurrence	Graft failure	Recommendations
FSGS	20-30%	40-50%	PF
IgA nephry	40-50%	6-33%	
HSP	10-20%	11% by 5 years	
MPGN I	20-30%	40%	
MPGN II	80-90%	10-20%	
Mem.	10-20%	50% by 10y	
HUS/TTP	10-25%	50%	
Anti GBM	10-25%	<10%	Anti GBM-
SLE	<10%	rare	Serology- ,pred10mg
Wegener's	15-50%	<10%	ANCA+ (OK)

Mortality in a Large Cohort of Renal Transplant Recipients



Transplantation Proceedings sep.
2007

CV death rate on dialysis and after cad. Tx.



Risk factors for CV disease after kidney Tx.

- Older age
- Male
- Smoking
- Hyperlipidemia
- Obesity
- Hyperhomocystinemia
- DM
- Hypertention
- hyperparathyroidism



Table 39. Relative Effect of Different Immunosuppressive Agents on Cardiovascular Disease Risk Factors after Kidney Transplantation.

	AZA or MMF	Prednisone	Cyclosporine	Tacrolimus	Sirolimus
Hypertension	—	↑↑	↑↑	↑	—
Dyslipidemia	—	↑↑	↑↑	—	↑↑↑
Diabetes	—	↑	↑	↑↑	↑

Arrows offer a crude, semiquantitative comparison of the relative effect of each agent on cardiovascular disease risk factors. Abbreviations: AZA, azathioprine; MMF, mycophenolate mofetil.

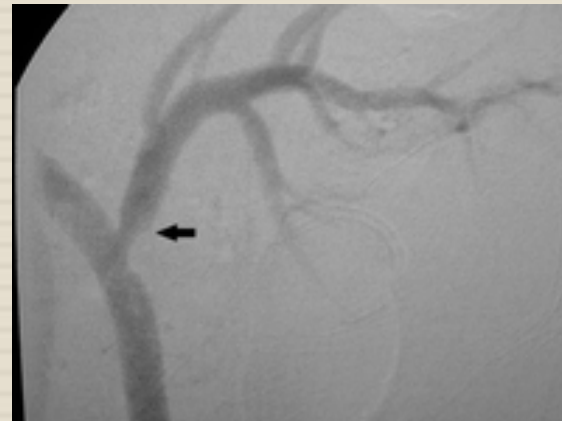
Renal artery stenosis

- occurs 3 mo to 2 yr after Tx.
- prevalence 1- 23% in different series
- 1 to 5% of cases of posttransplant hypertension
- frequently presents with worsening or refractory hypertension and/or graft dysfunction after adding diuretic or ACE /ATA II
- can cause edema,CHF , or flash pulmonary edema

- anastomotic stenosis is most likely related to trauma to the donor or recipient vessels during harvesting, clamping, or suturing and usually arises early after transplantation
- Stenoses occurring later, sometimes several years posttransplant, usually reflect atherosclerotic disease either of the transplant renal artery or of the adjacent proximal iliac artery

Diagnosis

- Doppler us-
 - peak systolic velocity (PSV) at the stenotic site vessel, resistive index (RI) in poststenotic intrarenal arteries
- MR angiography
- sensitivity 67% to 100%, specificity 75% to 100%



Treatment

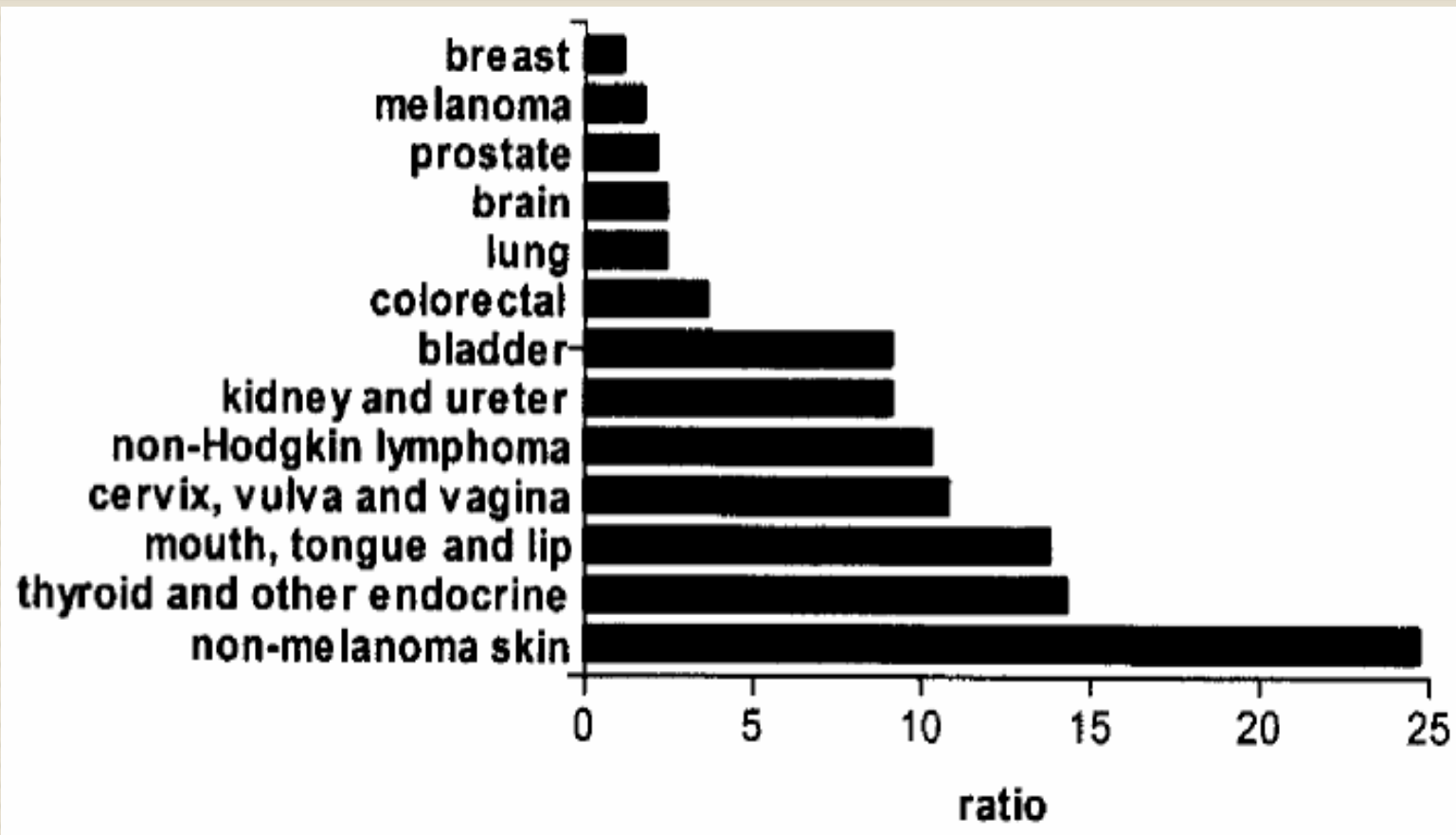
Indications

- When BP can no longer be controlled
- Renal function progressively deteriorates
- Progression of the stenosis by non-invasive procedures

a diagnostic arteriography should be performed combined with angioplasty and stenting

- Surgery is indicated for stenoses that cannot be treated by PTA or that recur after it

Malignancy after renal transplantation.



J Am Soc Nephrol. 2004 Jun;15(6):1582-8.

Risk factors for malignancy

Immunosuppression

Conventional risk factors, *i.e.*, age, smoking

Chronic viral infection

Genetic risk factors

History of treatment with cytotoxic agents, *i.e.*,
cyclophosphamide

Viruses associated with malignancy

EBV	Lymphoma
HHV 8	Kaposi sarcoma Lymphoma
Human papillomaviruses (HPV)	Cervix cancer Penis carcinoma Vulvar carcinoma
HPV 58	Bowen disease
HPV 8, 19	Nonmelanoma skin cancer
HPV 16, 20	Skin and tonsillar carcinoma
HCV, HBV	Hepatocellular carcinoma

^a EBV, Epstein-Barr virus; HHV 8, human herpesvirus type 8; HCV, hepatitis-C virus; HBV, hepatitis-B virus.

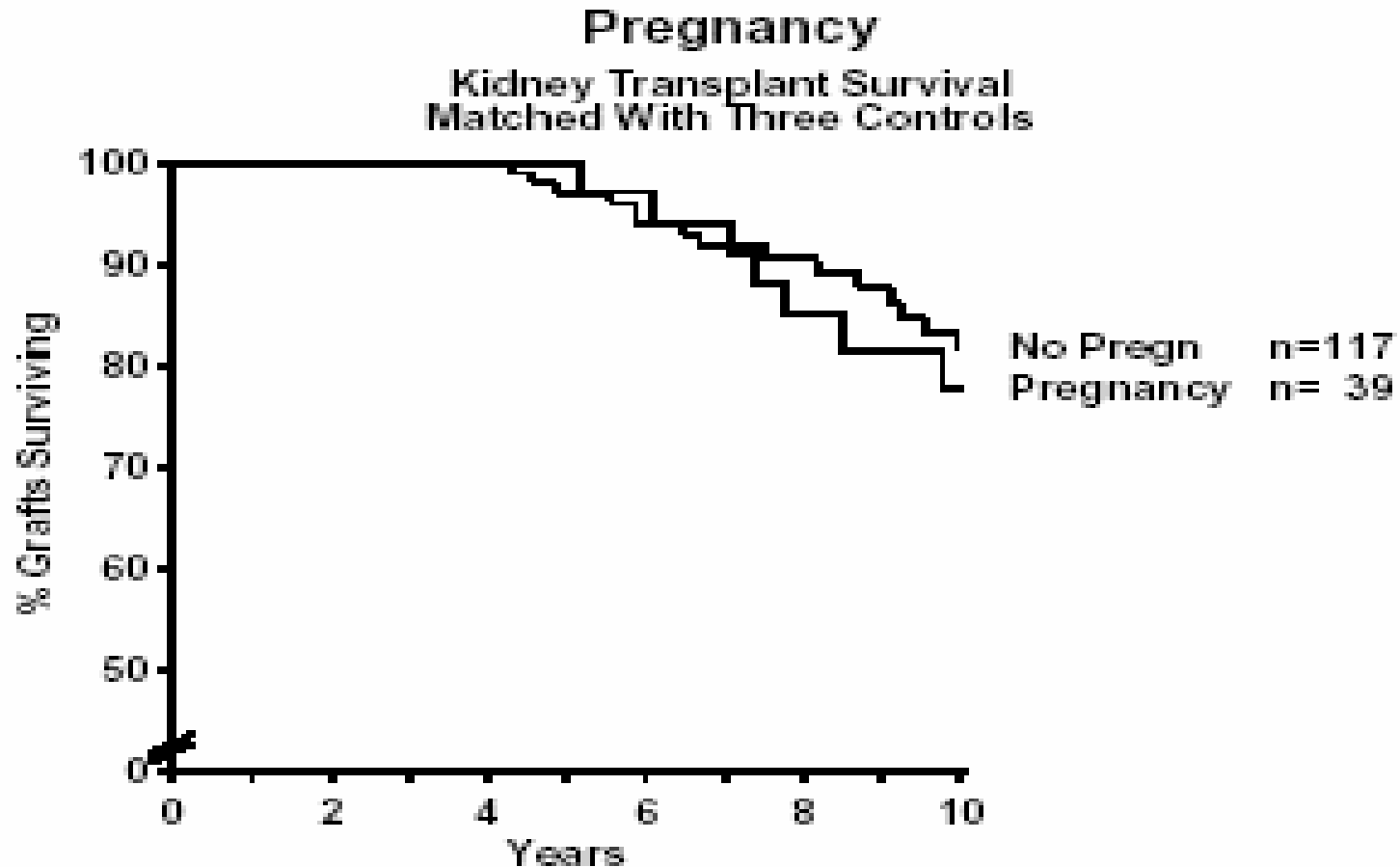
Treatment of malignancy

- Reducing immunosuppression
- Convert to TOR inhibitors/PSI (CAPOCI, SCC)
- Specific therapy

הריון לאחר השתלה

- מומלץ- לפחות שנה לאחר ההשתלה
- קראטיני-1.4-2.0 מג% עדיף פחות מ-1.4 מג%
- לחץ דם מאוזן ופרוטאינוריה מינימלית
- MMF, MFA, TOR inhibitors, PSI-אסור בהריון
- אין שכיחות יתר של הפלות, הריון אקטופי או מומים
- 50% לידות מוקדמות
- 20% SGA
- לאורך זמן אין פגיעה בתפקוד השתל

Long term effect of pregnancy on graft survival



תודה

