Prevention of sensitization: transfusions, nonadherence, and management of a failed allograft

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Disclosures

I have the following financial relationships to disclose:

Consultant during the past 12 months for: CTI Clinical Trials, Immucor, Novartis, Veloxis

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Prevention of sensitization

- DSA's are the consequence of appropriate immunologic response to foreign antigen
  - Heterologous immunity (broadly)
  - Pregnancy
  - Blood transfusion
  - Previous transplant

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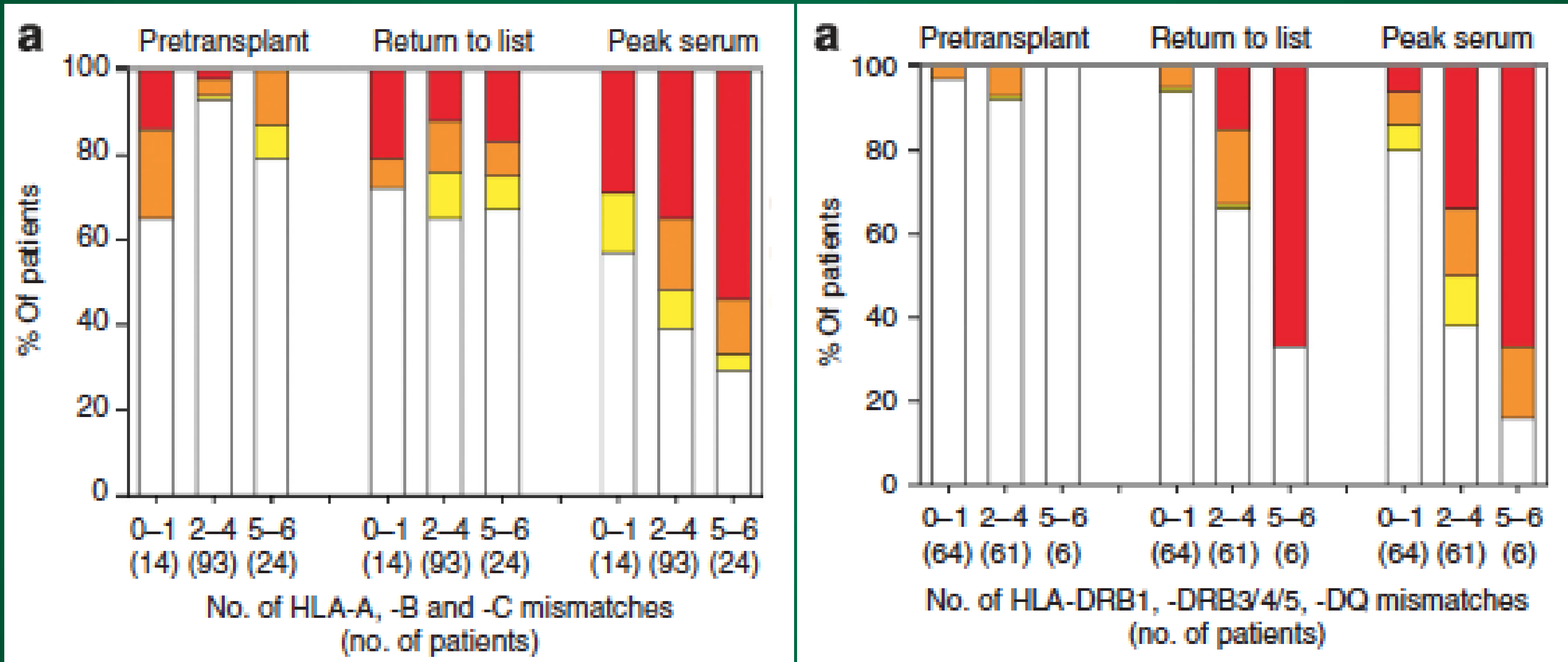
Serologic MM and presensitization

MFI>2000 131 patients with failed grafts



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Kosmoliaptsis V et al. *Kidney Int* 86: 1039, 2014

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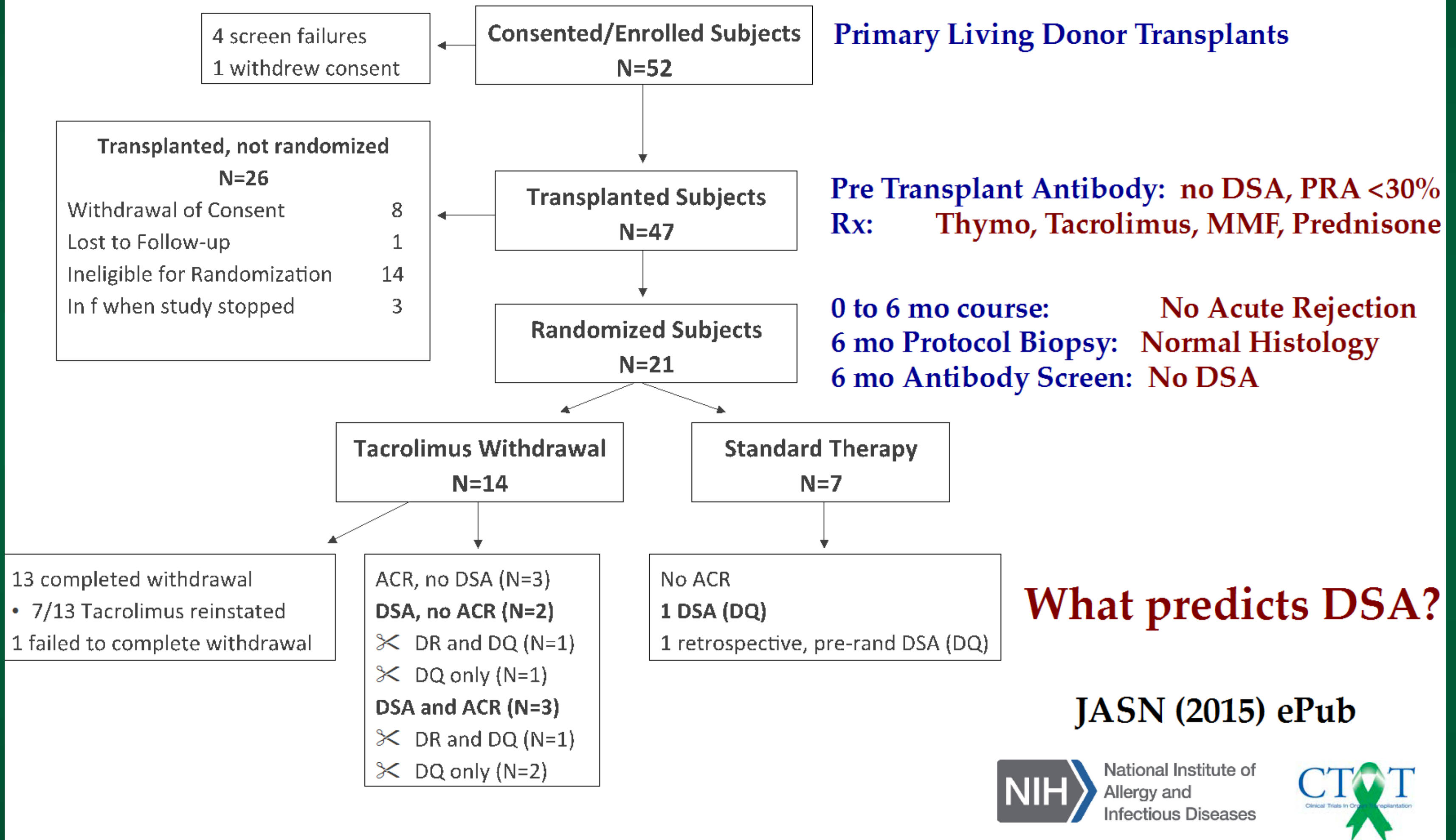
CTOT$09:((Tacrolimus(Withdrawal(in(Immune(Quiescent,(Low$risk,((Kidney(Transplant(Recipients((



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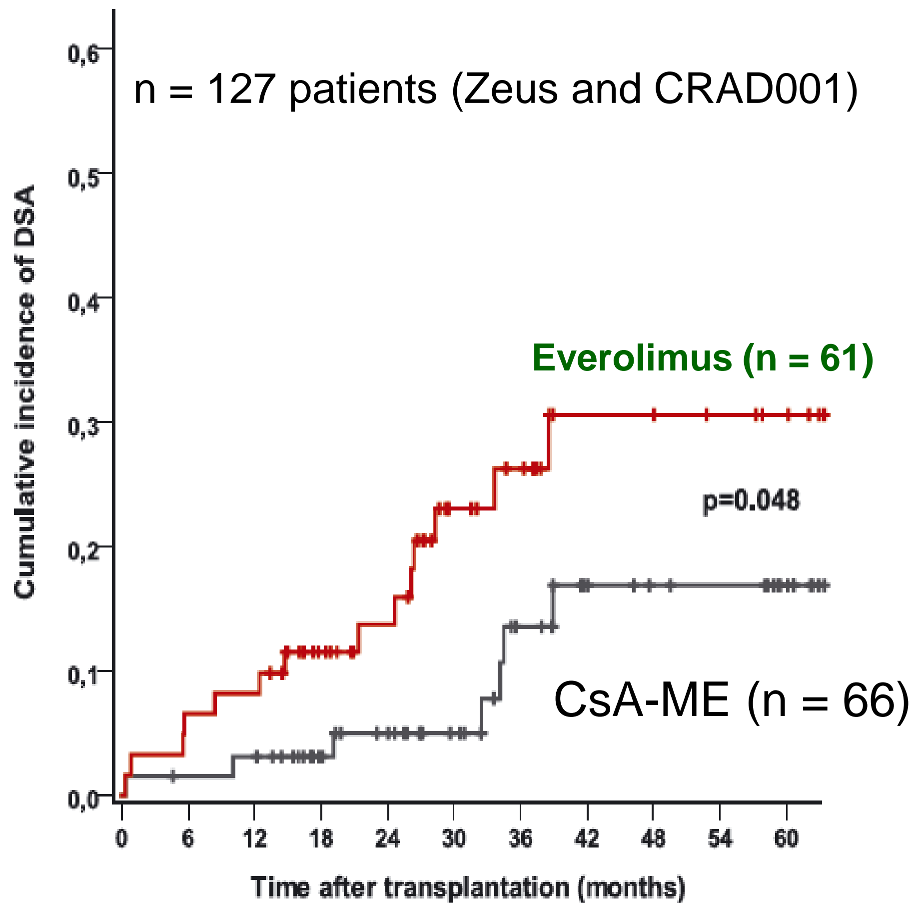
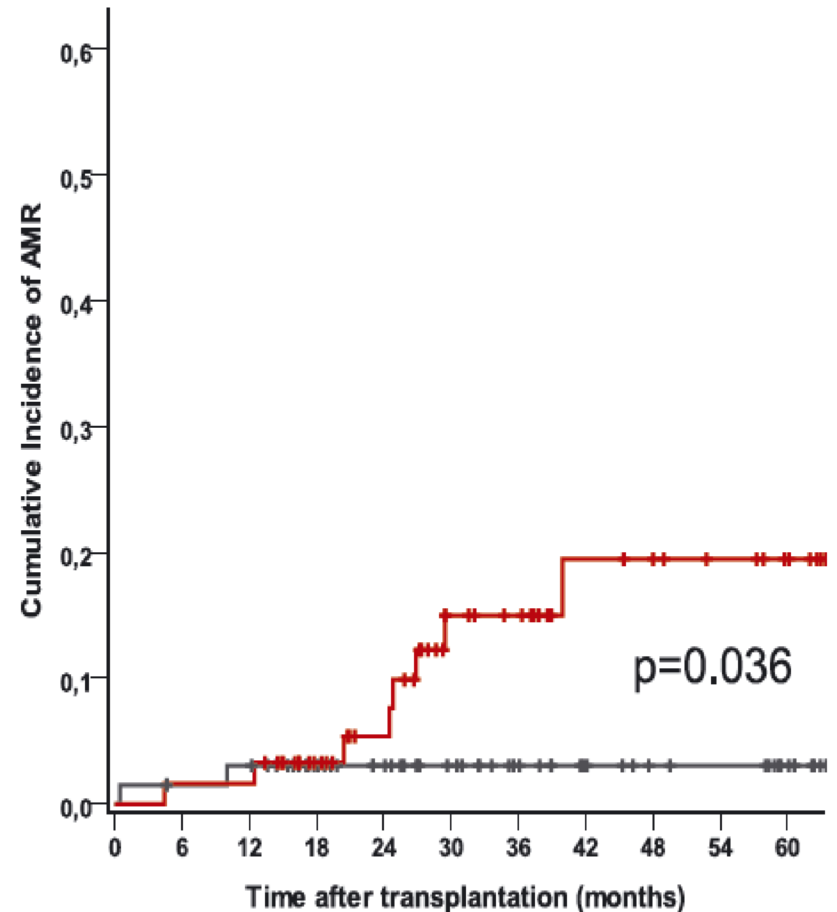
Hricik DE et al,
J Am Soc Nephrol 26: 3114, 2015

Immunosuppessant minimization is associated with DSA





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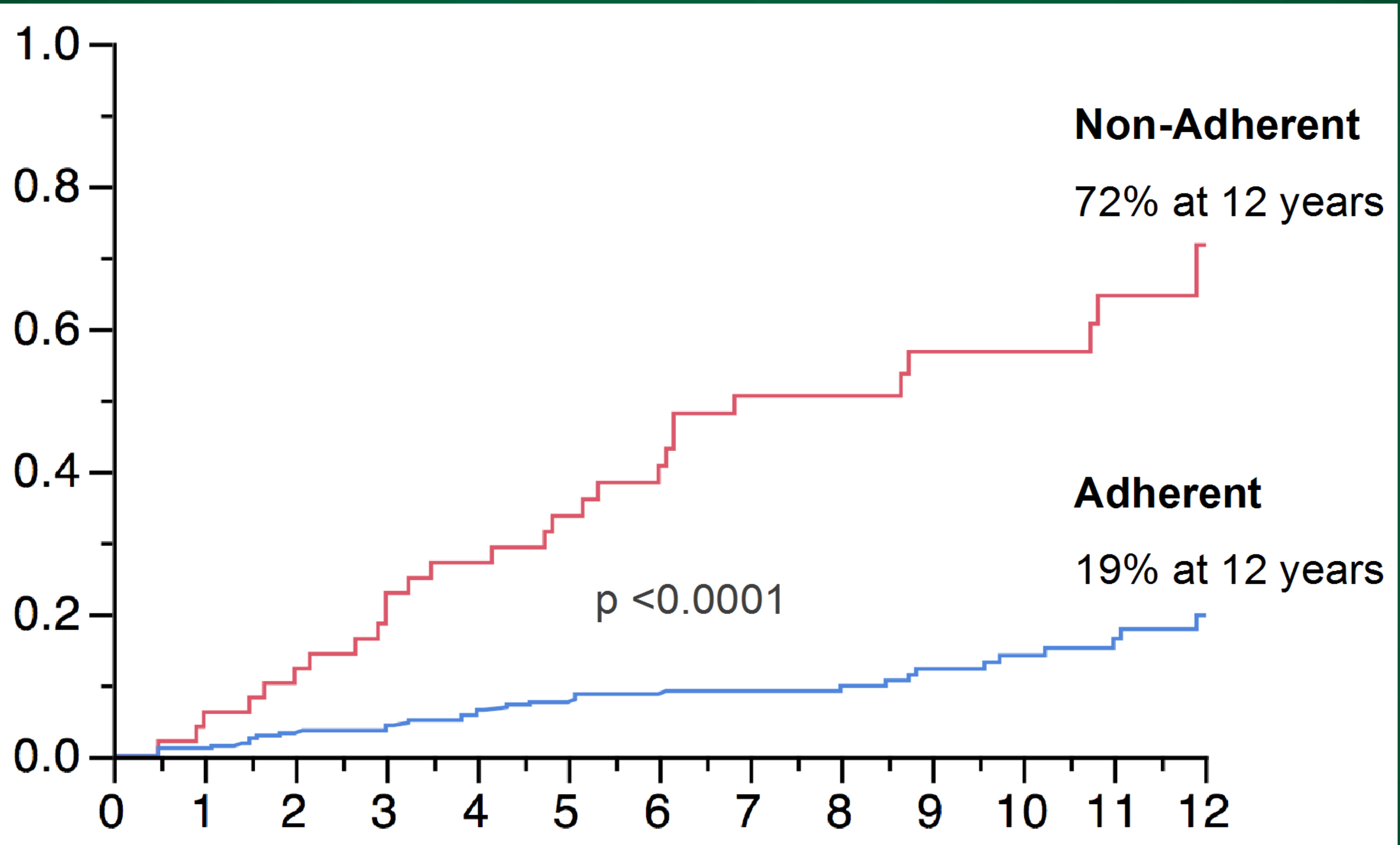
Liefeldt et al. *Am J Transplant* 2012;12:1192

Nonadherence and DSA



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Wiebe et al.
Am J Transplant 15: 2921, 2015

Nonadherence, DSA, and graft failure

Post-dnDSA Graft Survival
1.0
0.8
0.6
0.4
0.2
0.0
0 1 2 3 4 5 6 7 8 9 10
Follow-up (years)

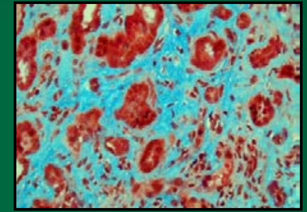
24% Nonadherent

90% Nonadherent

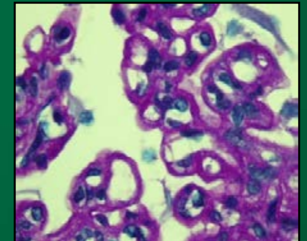
p<0.0001

Subclinical dnDSA
Clinical dnDSA

IFTA
ci3,ct3



TG
cg3



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Wiebe et al.
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- DSA's are the consequence of appropriate immunologic response to foreign antigen
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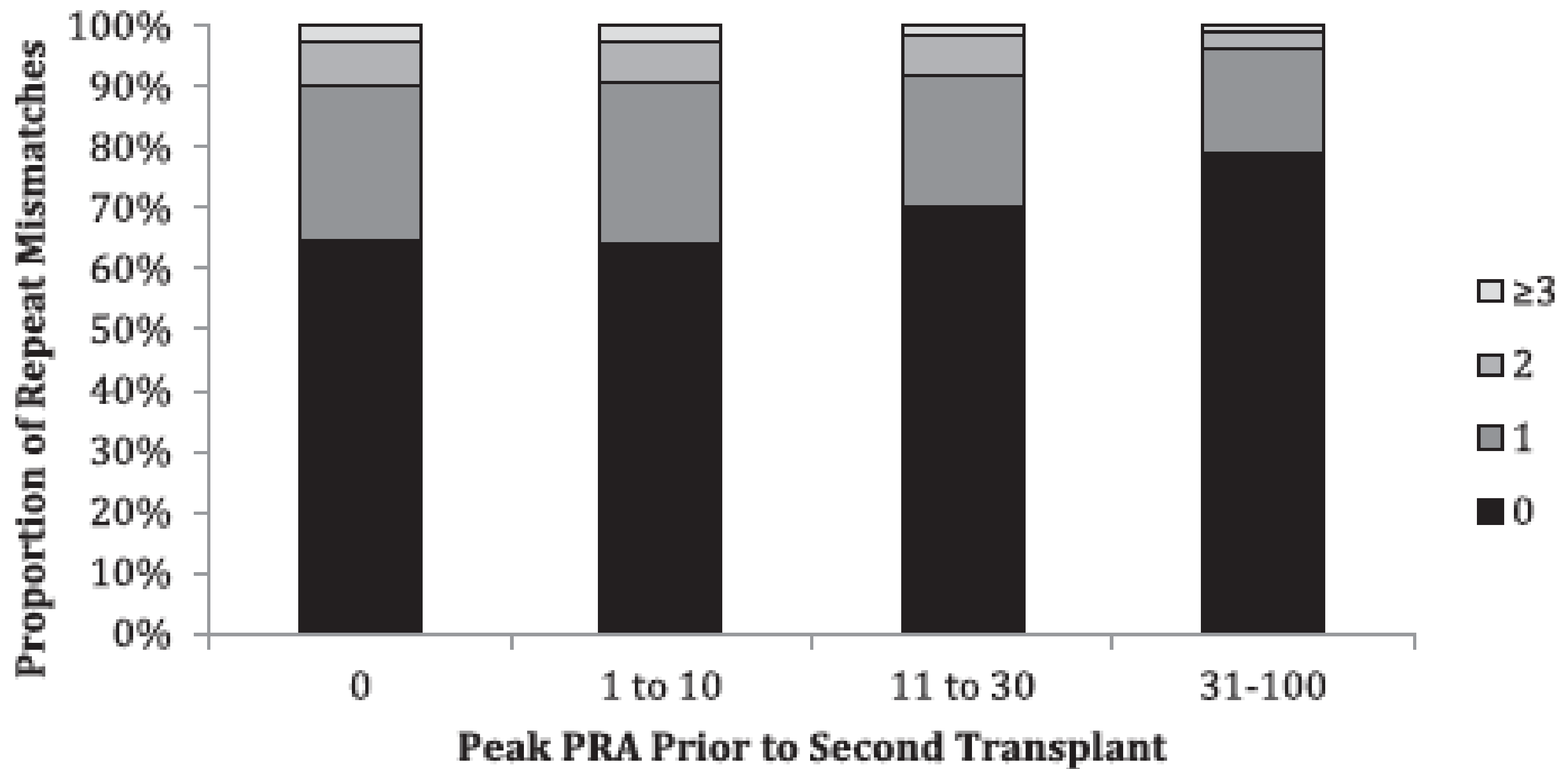
- Not all DSA exerts adverse impact in retransplantation
  - Characteristics of DSA

Impact of DSA on RMM



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Tinckam et al. *J Am Soc Nephrol* 2016;27:2833

Impact of Class 2 RMM on outcome

Table 5. Class 2 RMM increase risk for DCGL only in sensitized recipients before second transplant

Covariate	HR (95% CI)	
	ACGL	DCGL
No RMM	1.00	1.00
Class 1 only	0.98 (0.91 to 1.06)	0.97 (0.88 to 1.06)
Any class 2	1.08 (1.00 to 1.17)	1.11 (1.00 to 1.22)
Peak PRA at second transplant		
PRA=0		
No RMM	1.00	1.00
Class 1 only	0.91 (0.76 to 1.09)	0.98 (0.78 to 1.23)
Any class 2	0.99 (0.82 to 1.20)	1.07 (0.84 to 1.35)
PRA>0		
No RMM	1.00	1.00
Class 1 only	0.97 (0.88 to 1.07)	0.91 (0.81 to 1.03)
Any class 2	1.11 (1.00 to 1.22)	1.15 (1.02 to 1.29)

Models are adjusted for age, sex, race, cause of ESRD, donor age, donor type, duration of first graft survival, HLA match for second graft, PRA for second graft, induction, immunosuppression, and year of transplant.

Tinckam et al. *J Am Soc Nephrol* 2016;27:2833

Some preformed DSA disappears

N=34 (%)	Persistent	Transient
Sensitizing event (%)		
Transfusion	58	59
Pregnancy	67	100
Previous transplant	92	50
More than one	67	50
DSA (%)		
Class I	42	77
Class II	25	23
Class I and II	33	0
iDSA MFI	7241±4407	1757±1317
sDSA MFI	10605±6388	1912±1442
Number of specificities	2.1±1.2	1.1±0.3

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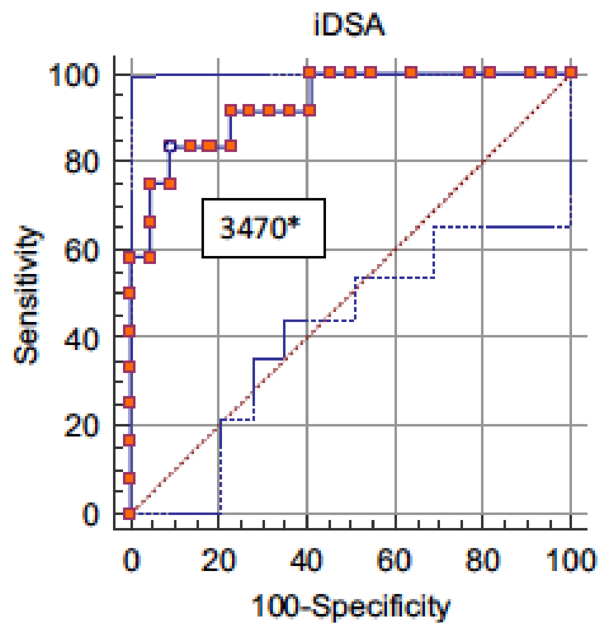
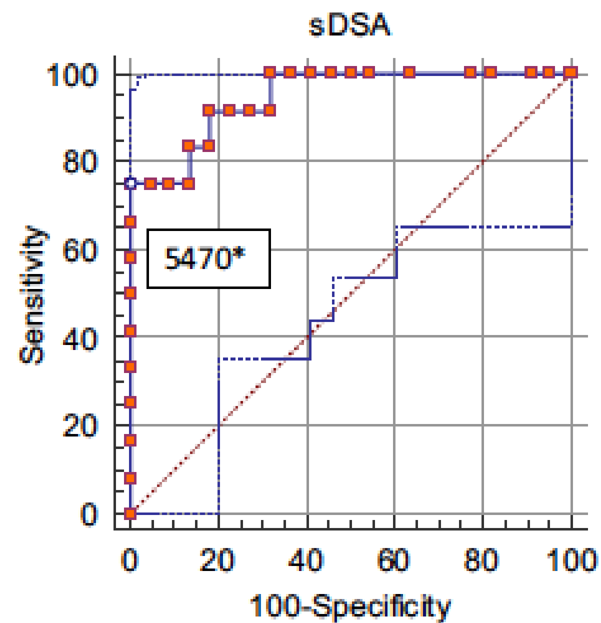
Caillard S et al. *Transplant Int* 30: 29, 2017

Predicting DSA persistence in retransplantation

	Area under the curve	*P*	Sensitivity for a MFI of 1500 (%)	Specificity for a MFI of 1500 (%)	Specificity for a MFI of 3500 (%)	Specificity for a MFI of 3500 (%)	Specificity for a MFI of 5500 (%)	Specificity for a MFI of 5500 (%)
iDSA	0.932	<0.001	92	60	83	91	58	100
sDSA	0.947	<0.001	100	68	83	86	75	100





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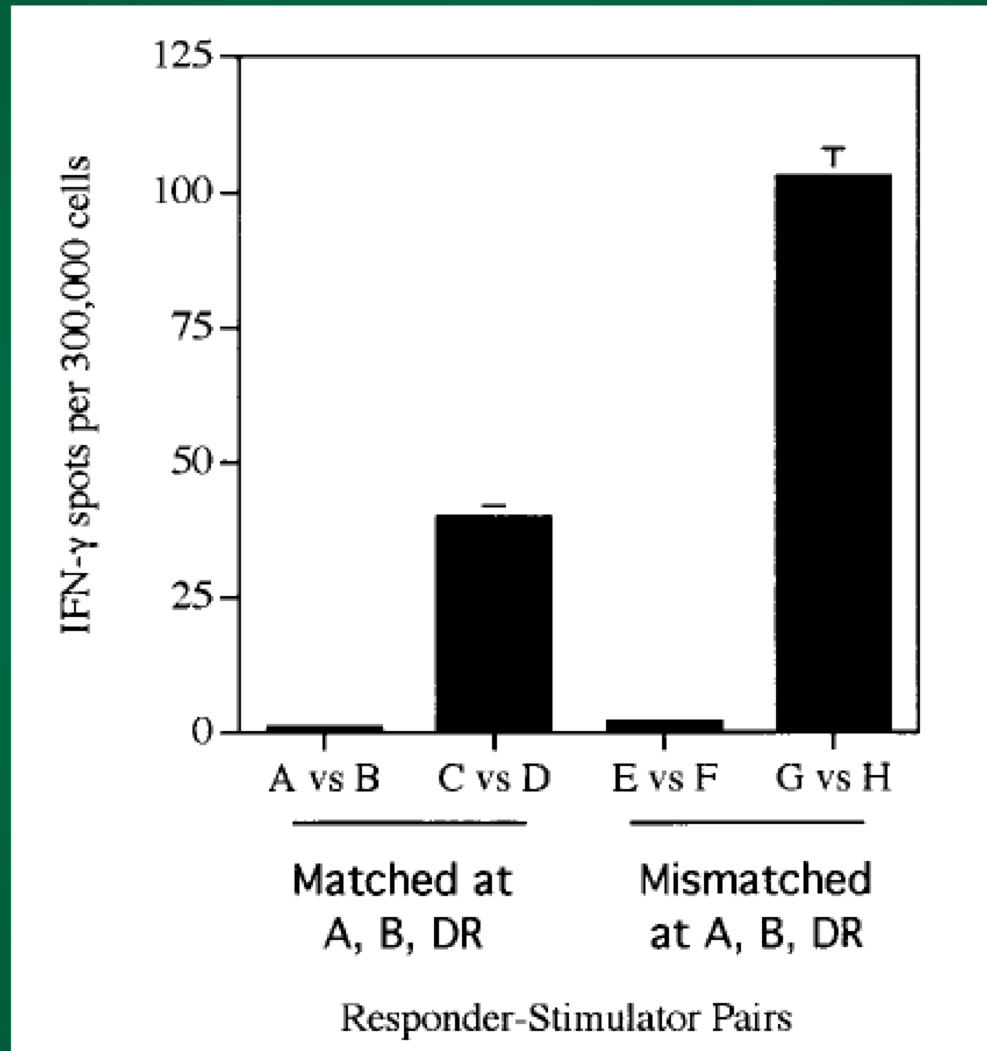
- Not all DSA exerts adverse impact in retransplantation
  - Characteristics of DSA
  - Memory/inflammatory milieu in recipient

Elispot assay of pretransplant T cell reactivity



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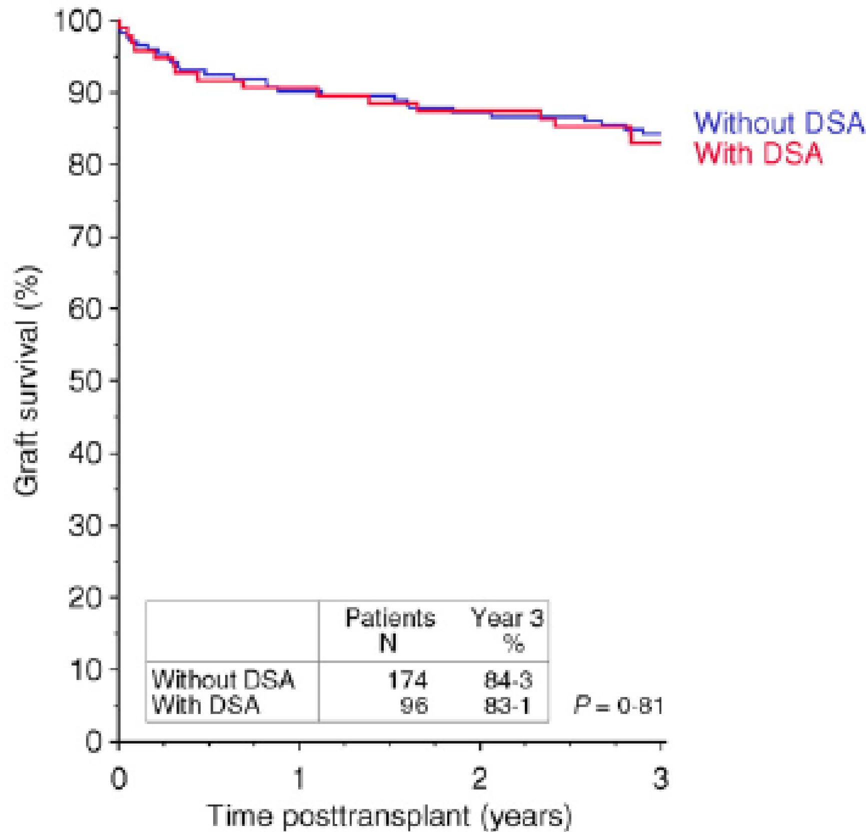
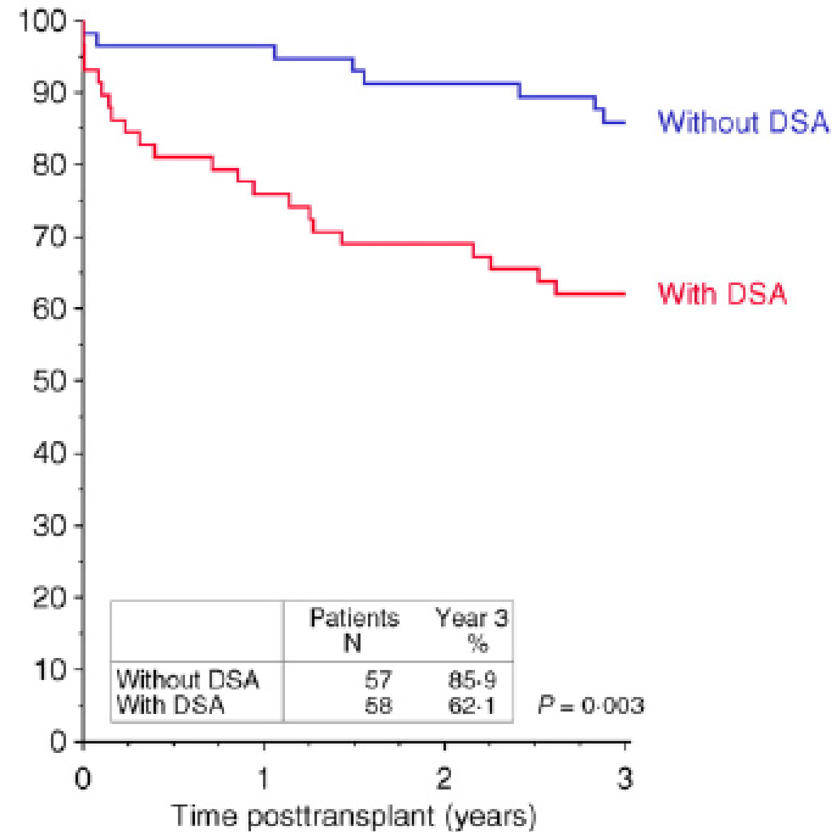
Heeger PS et al. *J Immunol* 163: 2267, 1999

Inflammatory milieu



At risk	0	1	2	3
Without DSA	174	156	149	141
With DSA	96	87	82	76



At risk	0	1	2	3
Without DSA	57	55	52	48
With DSA	58	44	40	36

Susal C et al. *EBioMedicine* 9: 366, 2016

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- DSA's are the consequence of appropriate immunologic response to foreign antigen
- Can be directed at MHC and non-MHC antigens
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- Not all DSA exerts adverse impact in retransplantation
- Management of the patient with a failed allograft
  - Immunosuppression?
  - Transplant nephrectomy?

Immunosuppressant targeting

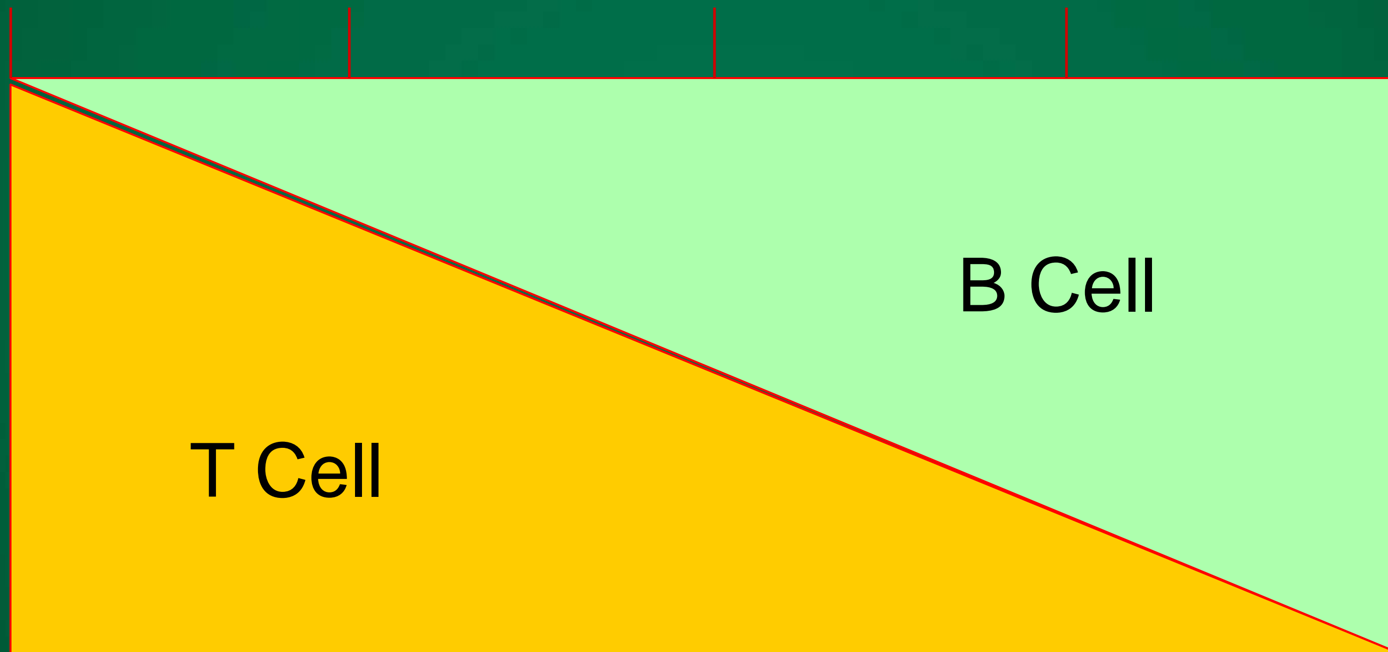
CNI
Basiliximab
Belatacept
mTORi

Mycophenolate
Azathioprine

ATG
Alemtuzumab
Steroids
Cyclophosphamide

Tocilizumab

Belimumab
Rituximab
Obinutuzumab
Eculizumab



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Anti-humoral therapy

is not essential

for successful long-term outcomes

providing T cells *are* under complete control

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Courtesy of Kathryn Wood

Serologic MM and presensitization

MFI>2000 131 patients with failed grafts

	Adjusted OR	P
Immunosuppression None (n=56) Single (n=36) Dual (n=30)	 0.90 (0.33, 3.31) 0.15 (0.05 ,0.4)	 0.84 <0.001
> 1 year since relisting > 5 years since relisting	3.53 (1.4, 9.4) 8.36 (2.6, 31.2)	0.01 <0.001
Nephrectomy (n=56)	3.42 (1.5, 8.3)	0.004
Blood transfusion	2.01 (0.61, 6.64)	0.253
Pregnancy	1.44 (0.88, 2.74)	0.185

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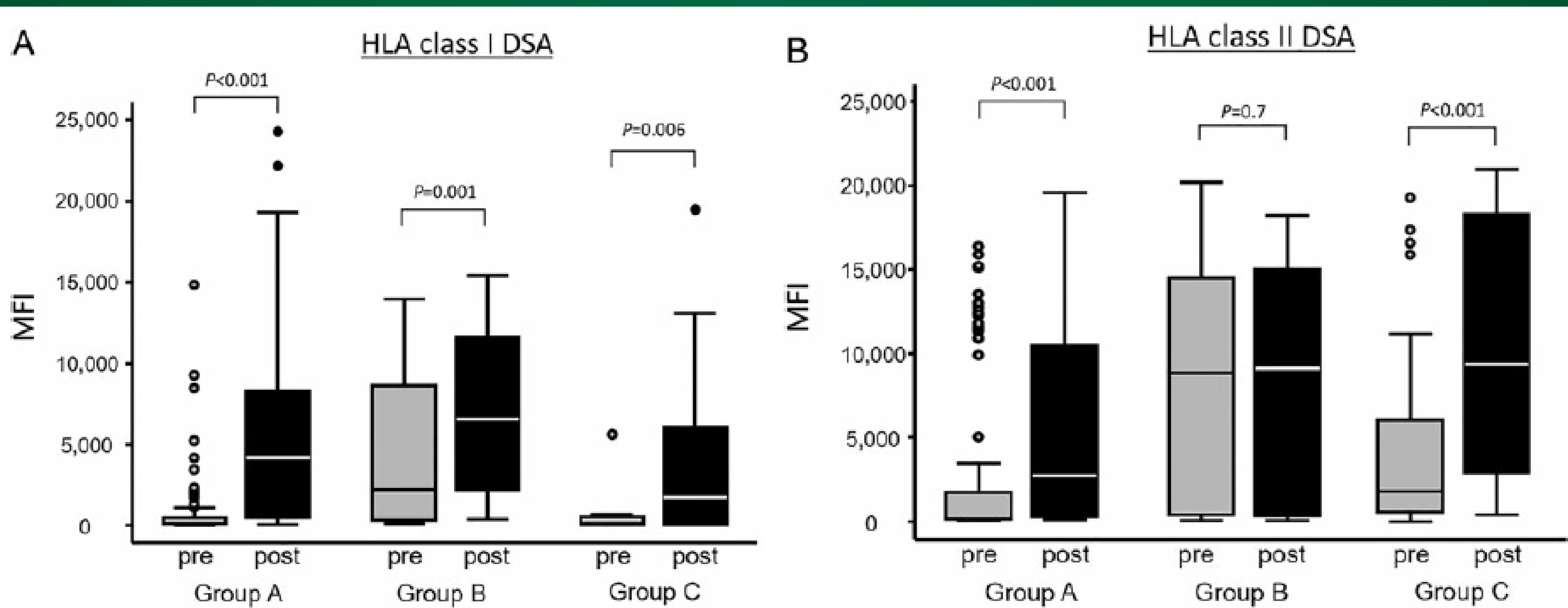
Kosmoliaptsis V et al. *Kidney Int* 86: 1039, 2014

Impact of nephrectomy on DSA

With and without immunosuppression



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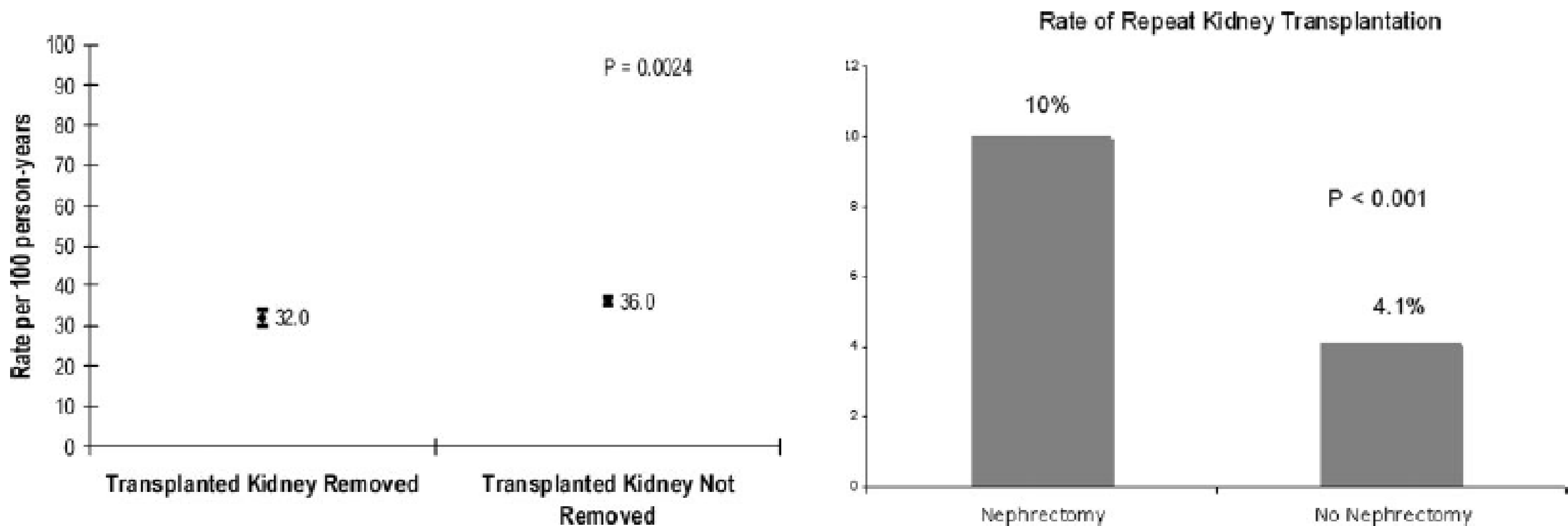
Lachmann N et al.
Nephrol Dial Transplant 31: 1351, 2016

Nephrectomy associated with lower mortality and increased rate of retransplantation



Ayus JC et al. *J Am Soc Nephrol* 21: 374, 2010

Interaction of nephrectomy and RMM

Table 6. RMM increased risk of ACGL and DCGL in those recipients with nephrectomy that occurred before second transplant, and class 2 RMM increased risk of ACGL and DCGL only in recipients with nephrectomy of first allograft

Covariate	HR (95% CI)	
	ACGL	DCGL
Any RMM		
Nephrectomy of first allograft before second transplant, *n*=1719	1.13 (1.01 to 1.26)	1.13 (1.00 to 1.29)
No nephrectomy, *n*=4454	0.94 (0.83 to 1.06)	0.97 (0.82 to 1.15)
Nephrectomy		
No RMM, *n*=1369	1.00	1.00
Class 1 RMM alone, *n*=175	1.13 (0.92 to 1.38)	1.20 (0.94 to 1.54)
Any class 2 RMM, *n*=175	1.30 (1.07 to 1.58)	1.41 (1.12 to 1.78)
No nephrectomy		
No RMM, *n*=3198	1.00	1.00
Class 1 RMM alone, *n*=701	0.91 (0.81 to 1.03)	0.90 (0.76 to 1.05)
Any class 2 RMM, *n*=555	1.04 (0.92 to 1.18)	1.06 (0.90 to 1.25)

Any RMM restricted to Medicare only and first graft failure before 2010

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- Can be directed at MHC and non-MHC antigens
- Development of DSA is attenuated by immunosuppression
- Not all DSA exerts adverse impact in retransplantation
- Management of the patient with a failed allograft
  - Immunosuppression: YES, if graft in place and candidate for retransplantation
  - Transplant nephrectomy: Only if clinically indicated