Acute and Chronic ABMR Outcomes in the Context of Memory or Naïve Alloimmunity

FDA Workshop, ABMR in Kidney Transplantation

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Peter Nickerson, MD, FRCPC, FCAHS

Flynn Family Chair in Renal Transplantation

Professor of Internal Medicine and Immunology

University of Manitoba

Health Sciences Centre Winnipeg

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Relevant Financial Relationship Disclosure Statement

Peter Nickerson, University of Manitoba, Winnipeg, Canada

Consultant for Astellas, GSK, Novartis and Vitaeris

AND

My presentation does include discussion of off-label or investigational use of drugs

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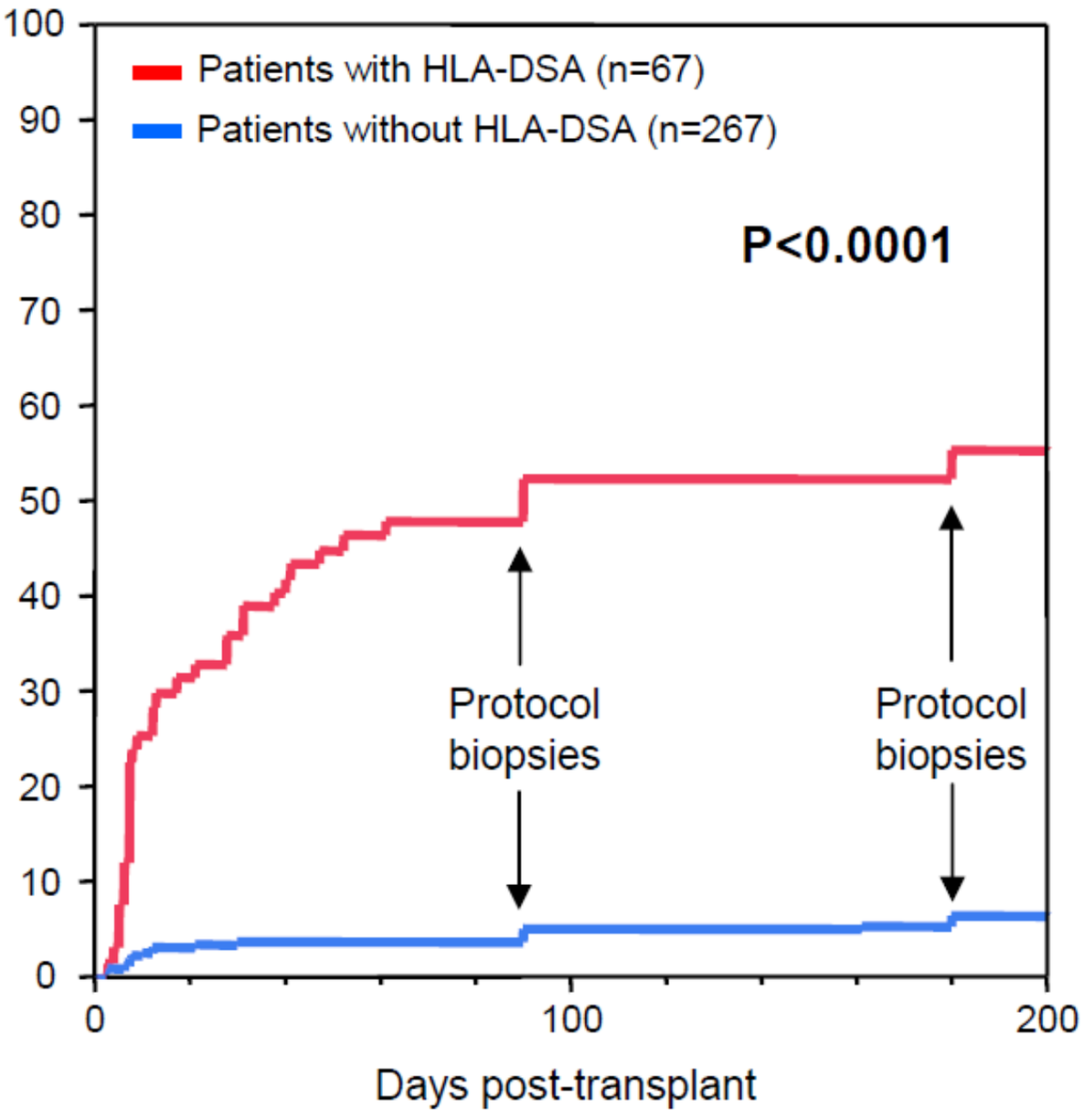
Preformed DSA and Kidney Graft Outcomes

NATURAL HISTORY

Unrecognized Immunologic Memory

Clinical & Subclinical ABMR prevalent with Pre-transplant DSA



CDC CXM negative
pre-transplant

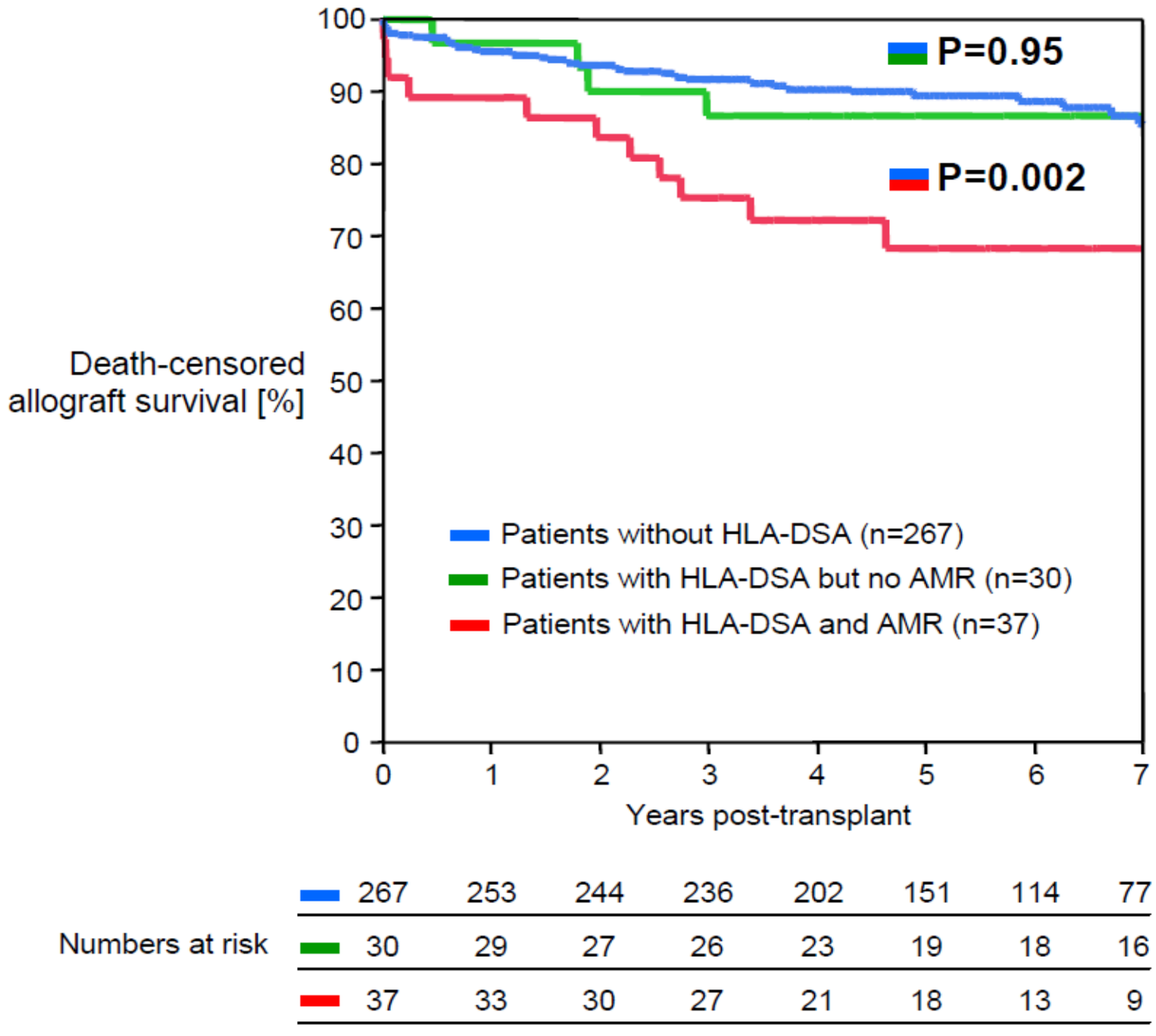
Pre-Tx SAB DSA +ve
(MFI >500)

Pre-Tx SAB DSA -ve

55% of patients with HLA-DSA developed clinical/subclinical AMR if not desensitized pre-transplant

Amico P. **Transplantation (2009) 87:1681-1688**

Death-censored graft survival



Numbers at risk								
267	253	244	236	202	151	114	77
30	29	27	26	23	19	18	16
37	33	30	27	21	18	13	9

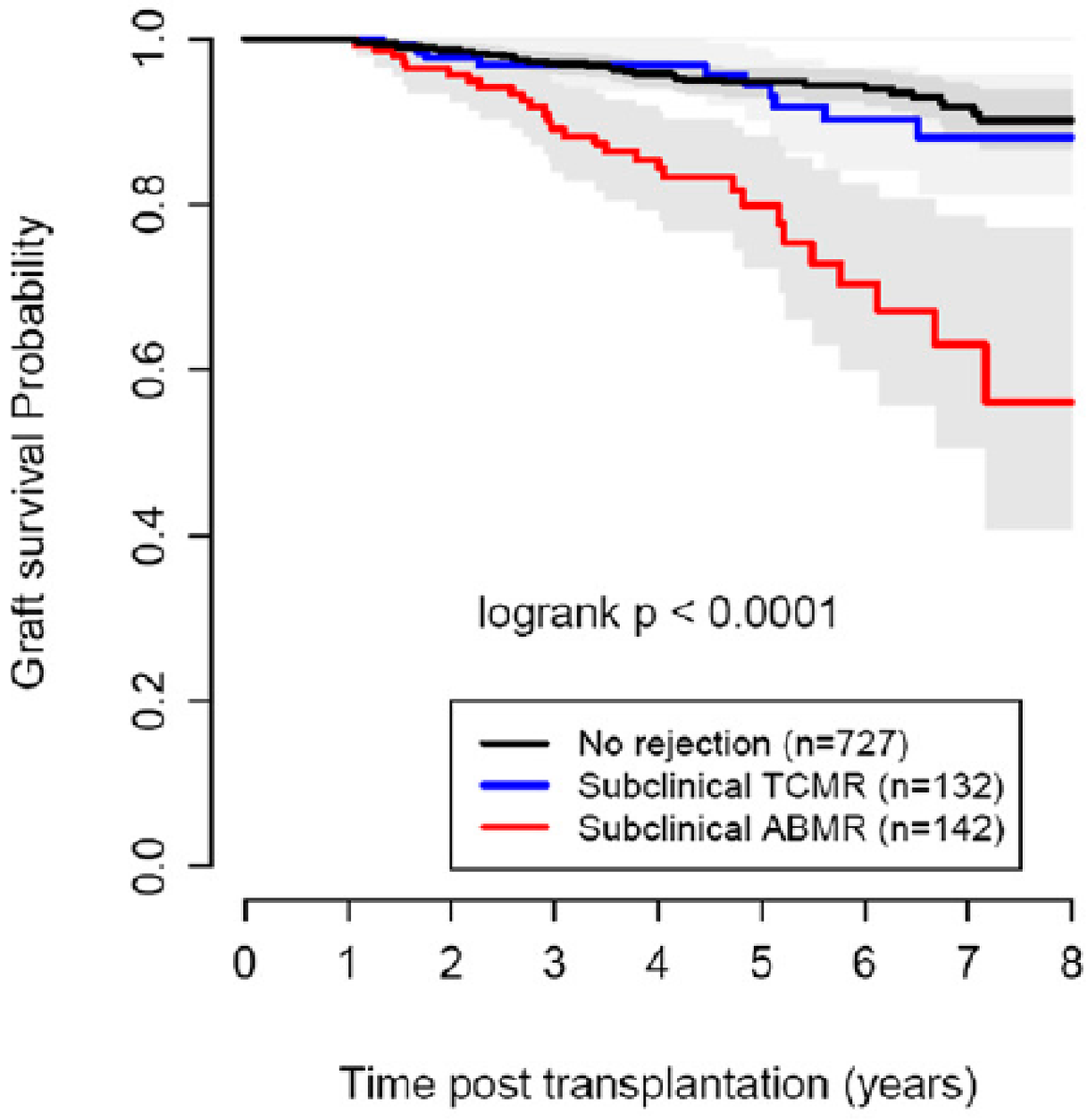
Patients with HLA-DSA and clinical/subclinical AMR had a 20% lower death-censored graft survival at 5 years

Amico P. **Transplantation (2009) 87:1681-1688**

Subclinical Rejection Phenotypes at 1 Year Post-Transplant and Outcome of Kidney Allografts

Alexandre Loupy,*† Dewi Vernerey,*‡ Claire Tinel,† Olivier Aubert,* Jean-Paul Duong van Huyen,*§ Marion Rabant,§ Jérôme Verine,‖ Dominique Nochy,¶ Jean-Philippe Empana,* Frank Martinez,† Denis Glotz,** Xavier Jouven,* Christophe Legendre,*† and Carmen Lefaucheur**

JASN (2015) 26:1721-1731



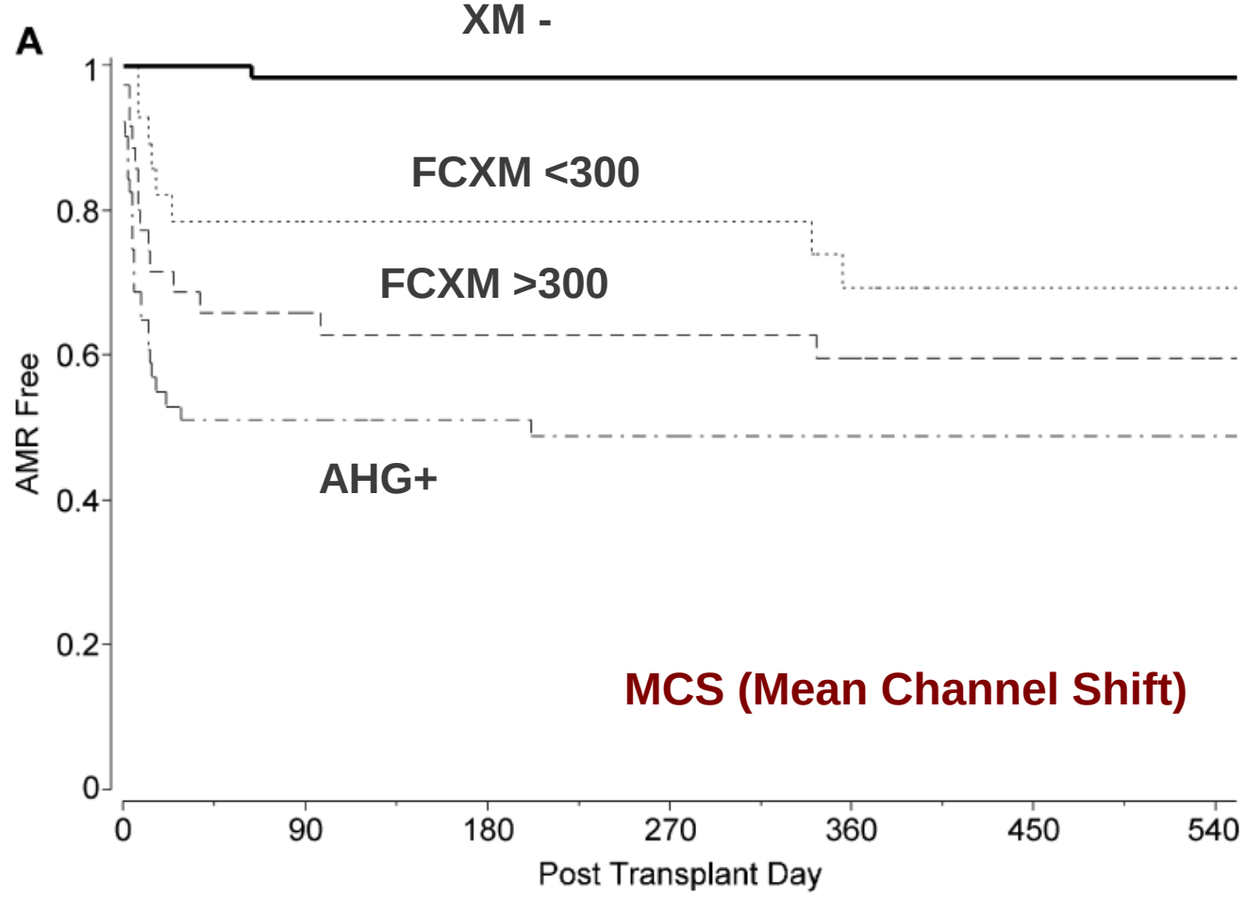
78% subclinical ABMR had pre-transplant DSA

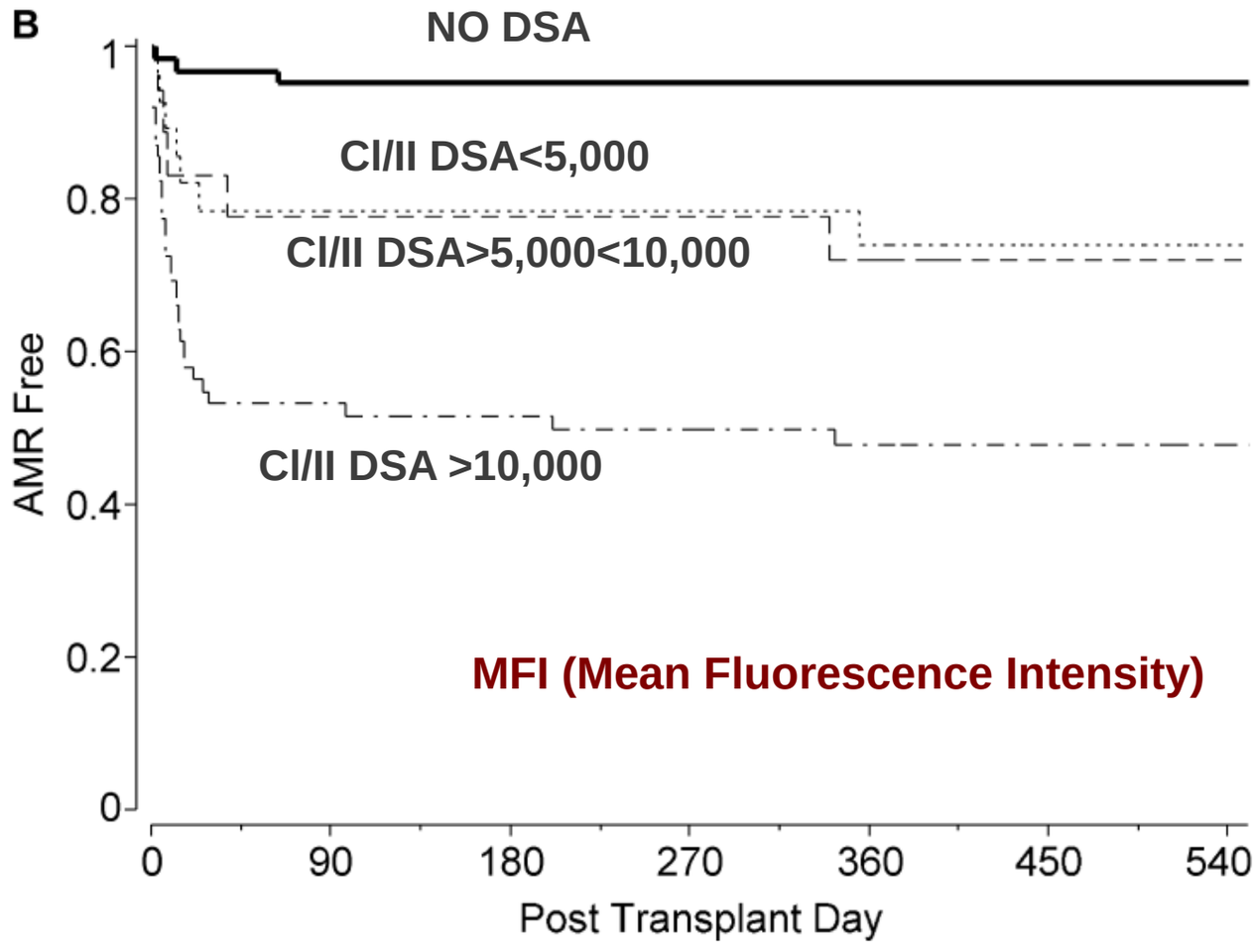
At 1 year all subclinical ABMR had DSA detectable SAB MFI = 2550 ± 580

Baseline Donor-Specific Antibody Levels and Outcomes in Positive Crossmatch Kidney Transplantation

J. M. Gloor[a,*], J. L. Winters[b], L. D. Cornell[b]
L. A. Fix[c], S. R. DeGoey[b], R. M. Knauer[b],
F. G. Cosio[a], M. J. Gandhi[b], W. Kremers[d]
and M. D. Stegall[c]

AJT (2010) 10: 582-589





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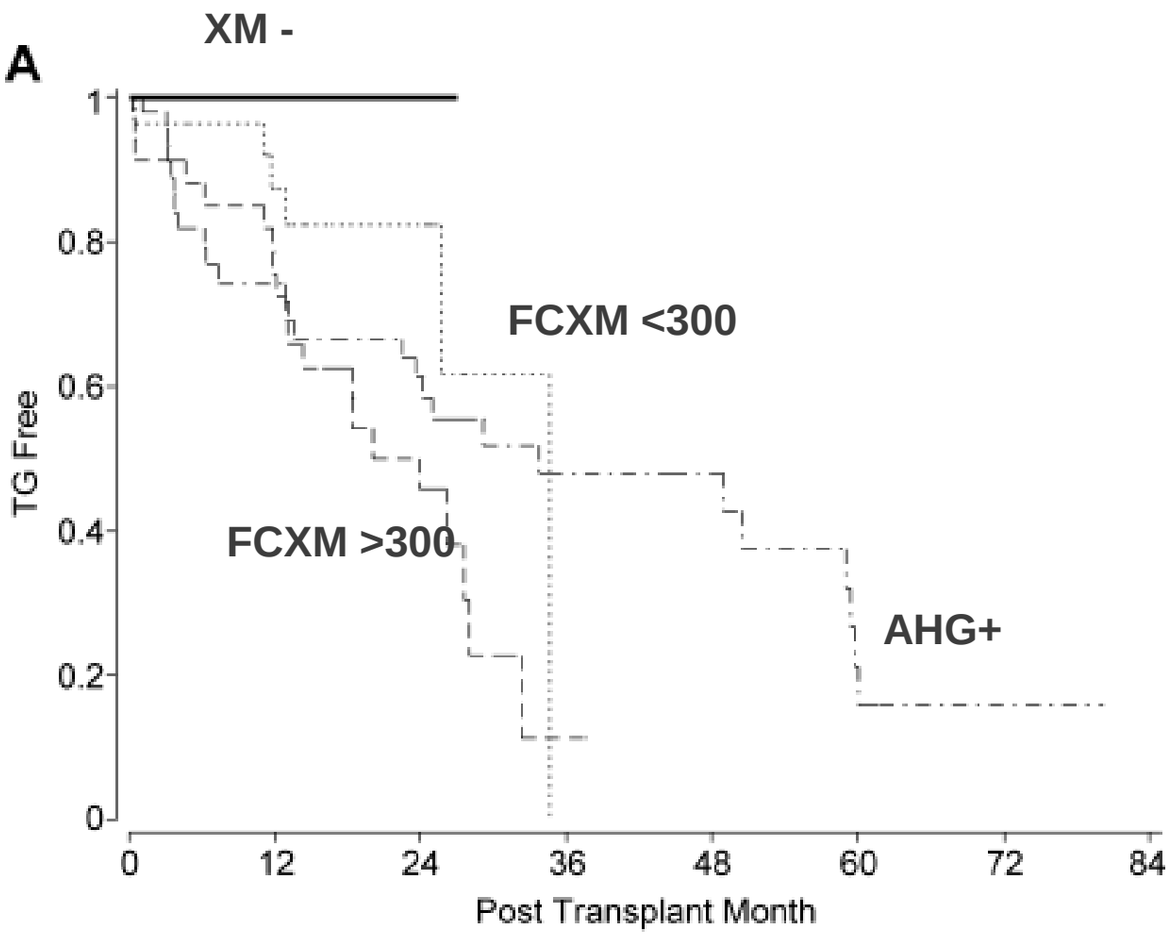

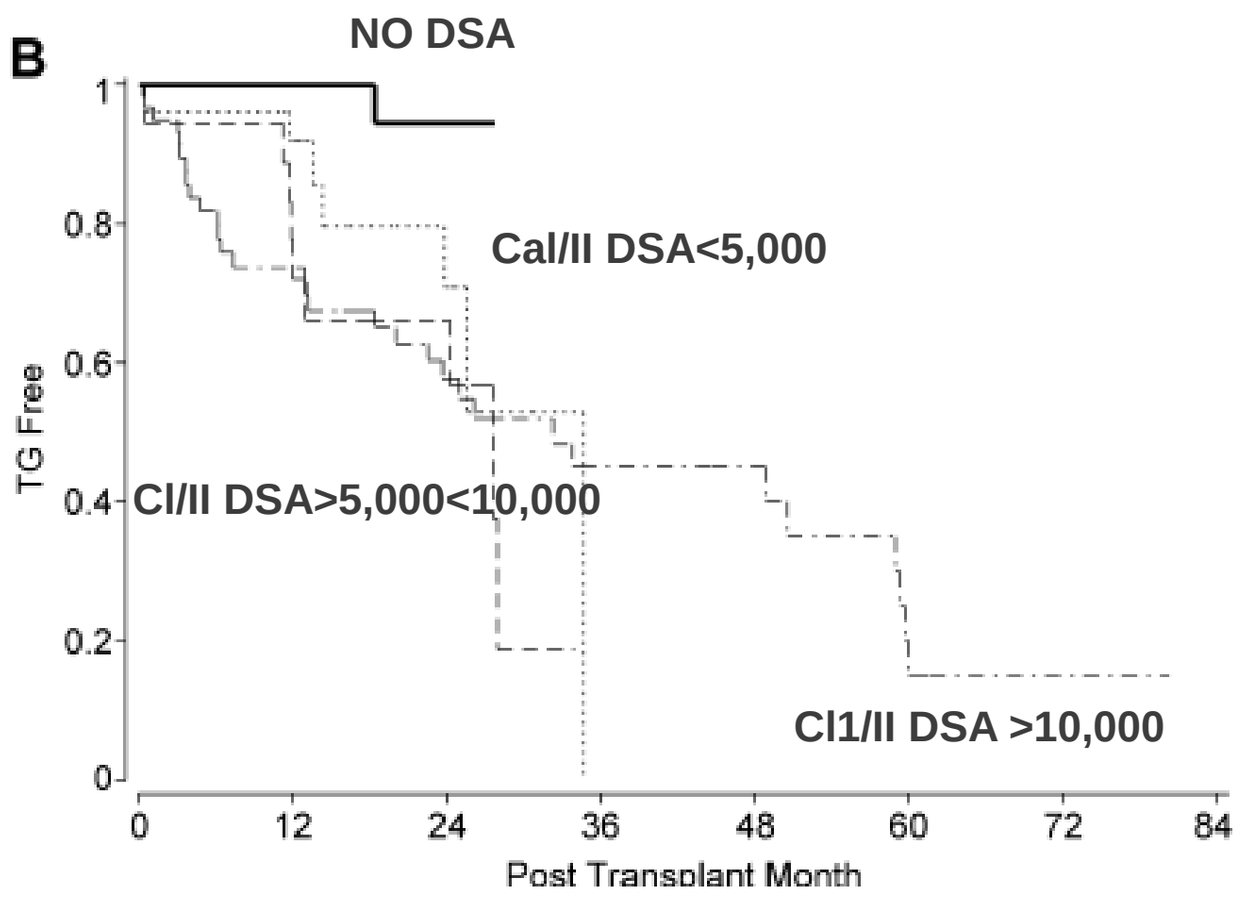

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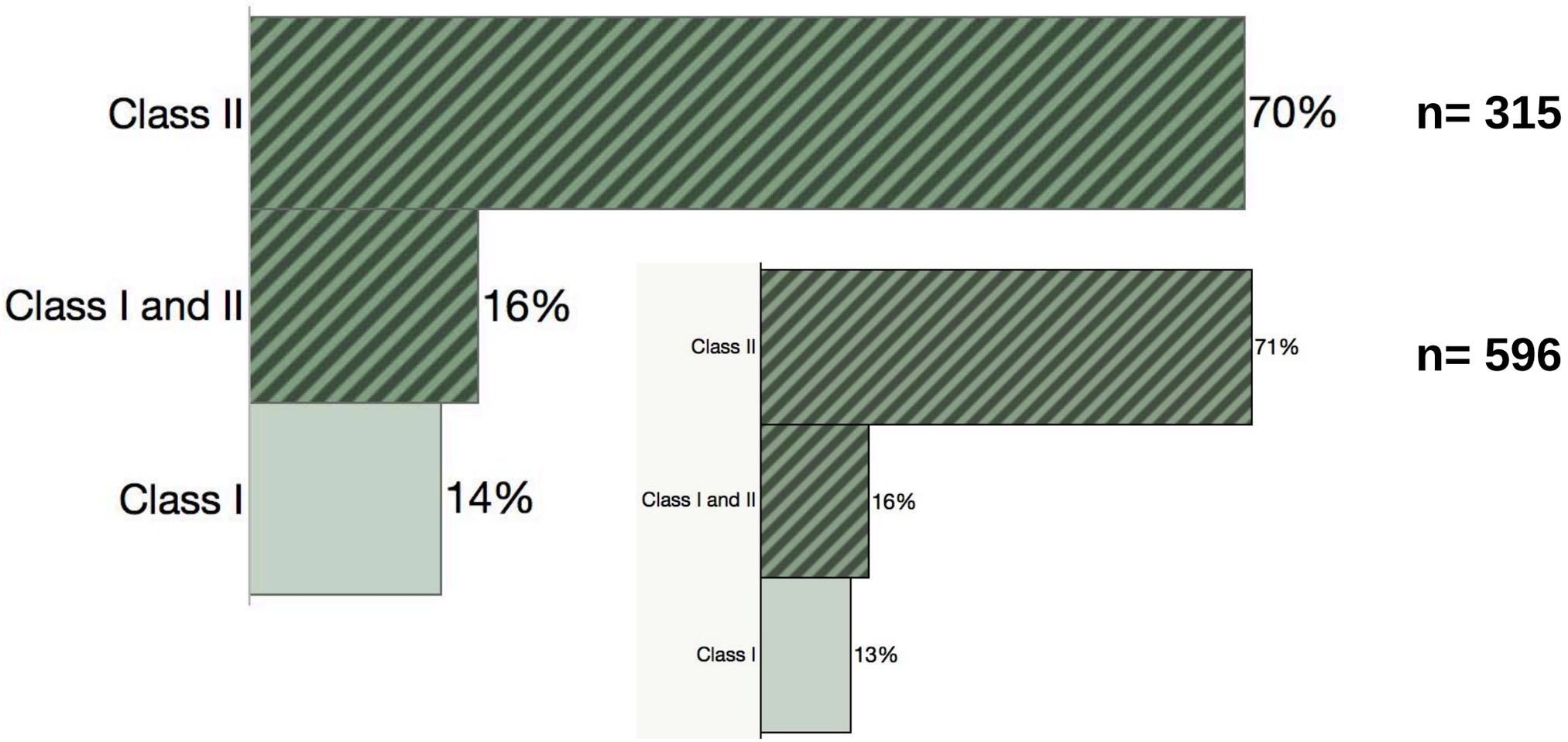
De novo DSA and Outcomes

ETIOLOGY AND NATURAL HISTORY

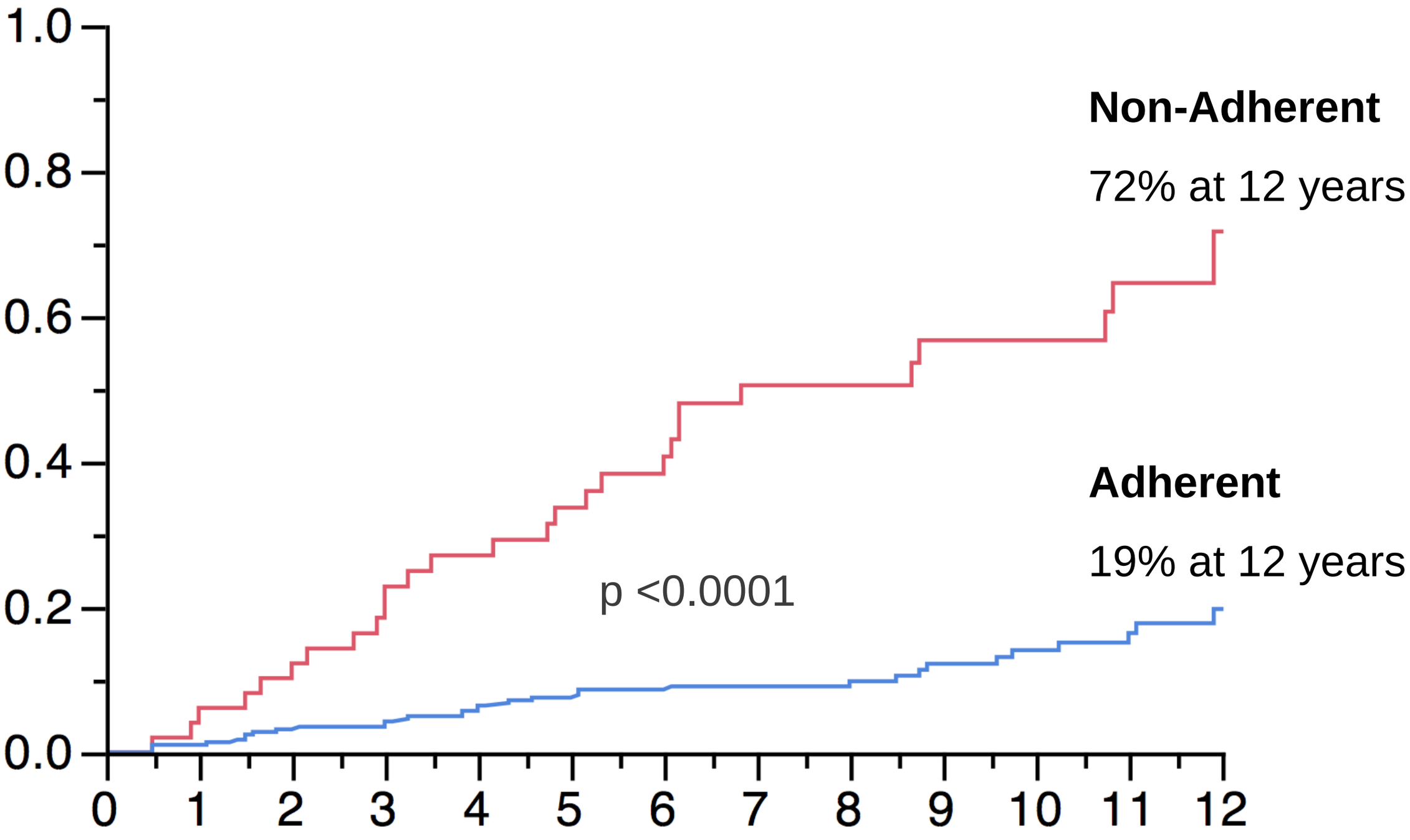
Class II is the dominant de novo DSA



Only 1 patient with an isolated Class I dnDSA has resulted in graft failure, out of 596 transplants

Wiebe et al., Am Journal Transplant (2012) 12: 1157

Non-Adherence is a major risk factor for *de novo* DSA



Wiebe et al., AJT (2015) 15: 2921-2930

At onset of de novo DSA, 76% meet ABMR criteria (Banff 2013)

Banff Grade	0	1	2	3
g	(55%,	32%,	13%,	0%)
i	(28%,	24%,	24%,	24%)
t	(39%,	32%,	11%,	18%)
v	(94%,	3%,	0%,	3%)
ptc	(24%,	10%,	45%,	21%)
C4d	(52% C4d positive)			
cg	(87%,	8%,	5%,	0%)
ci	(29%,	37%,	19%,	5%)
ct	(11%,	53%,	26%,	10%)
cv	(40%,	47%,	13%,	0%)

TCMR (Banff 2007) common (91% with ABMR)

- 32% Borderline
- 29% ≥ Grade 1

Only 18% have no TCMR or ABMR

Transplant glomerulopathy uncommon

IFTA common

Wiebe et al., AJT (2015) 15: 2921-2930

Biopsy Predictors for Graft Loss at DSA onset

Consecutive Adult and Pediatric Kidney Transplants (n=508, 1999 to 2012)

76% ABMR$_{(Banff\ 2013)}$ at biopsy for *de novo* DSA

			Univariate		Multivariate	
B. Banff Histologic Predictors‡ (n=38)						
g	(55%, 32%, 13%, 0%)		1.53 (0.8-2.9)	0.2015	-	
i	(28%, 24%, 24%, 24%)		1.77 (1.2-2.9)	0.0083	-	
t	(39%, 32%, 11%, 18%)	**Tubulitis**	2.73 (1.6-5.0)	0.0002	3.01 (1.7-5.6)*	<0.0001
v	(94%, 3%, 0%, 3%)		0.95 (0.1-2.1)	0.9240	-	
ptc	(24%, 10%, 45%, 21%)		1.11 (0.7-0.9)	0.6663	-	
C4d	(52% C4d positive)		1.33 (0.4-4.4)	0.6203	-	
cg	(87%, 8%, 5%, 0%)	**CG**	2.14 (1.0-4.1)	0.0575	3.01 (1.2-7.1)*	0.0221
ci	(29%, 37%, 19%, 5%)		1.38 (0.8-2.5)	0.2735	-	
ct	(11%, 53%, 26%, 10%)		1.36 (0.8-2.4)	0.2840	-	
cv	(40%, 47%, 13%, 0%)		1.11 (0.6-2.1)	0.7434	-	

Banff cg score increases 1 grade per 3 years of post *de novo* DSA follow-up

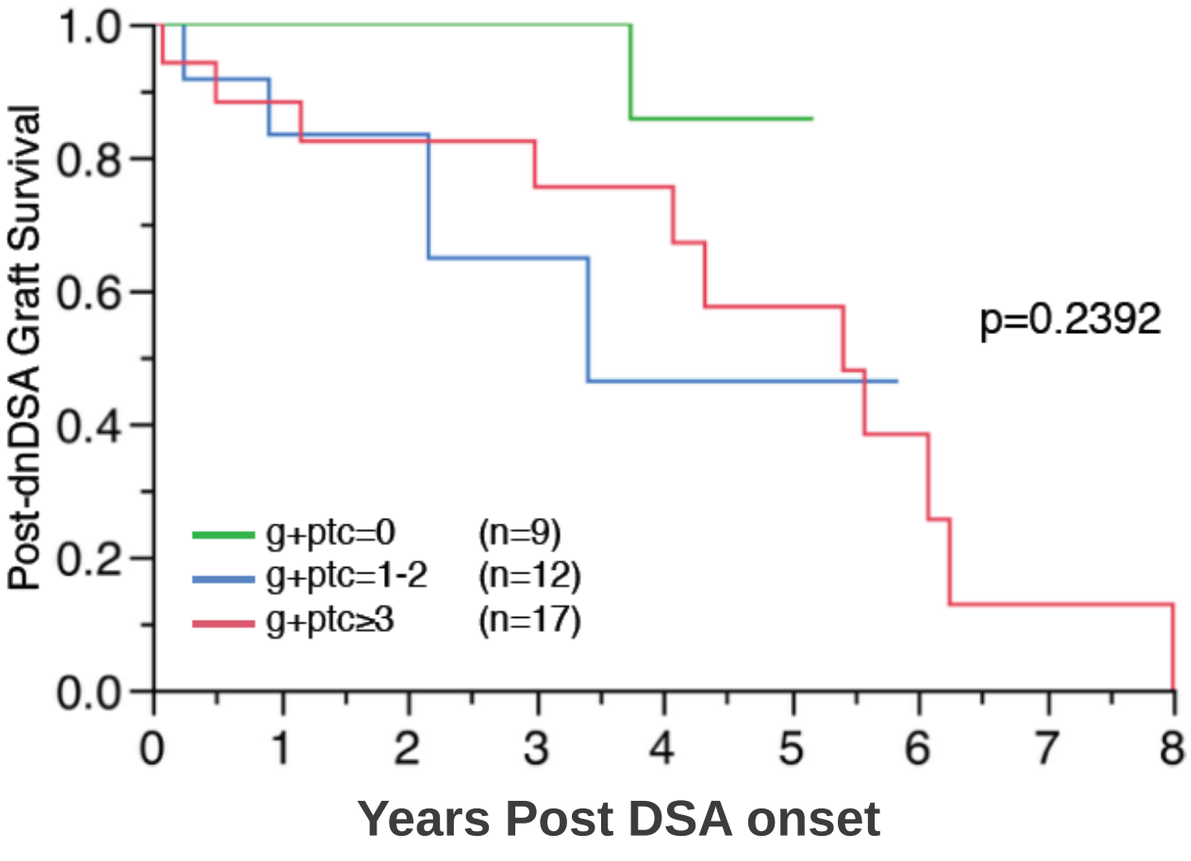
(R^2 = 0.36, p=0.0018)

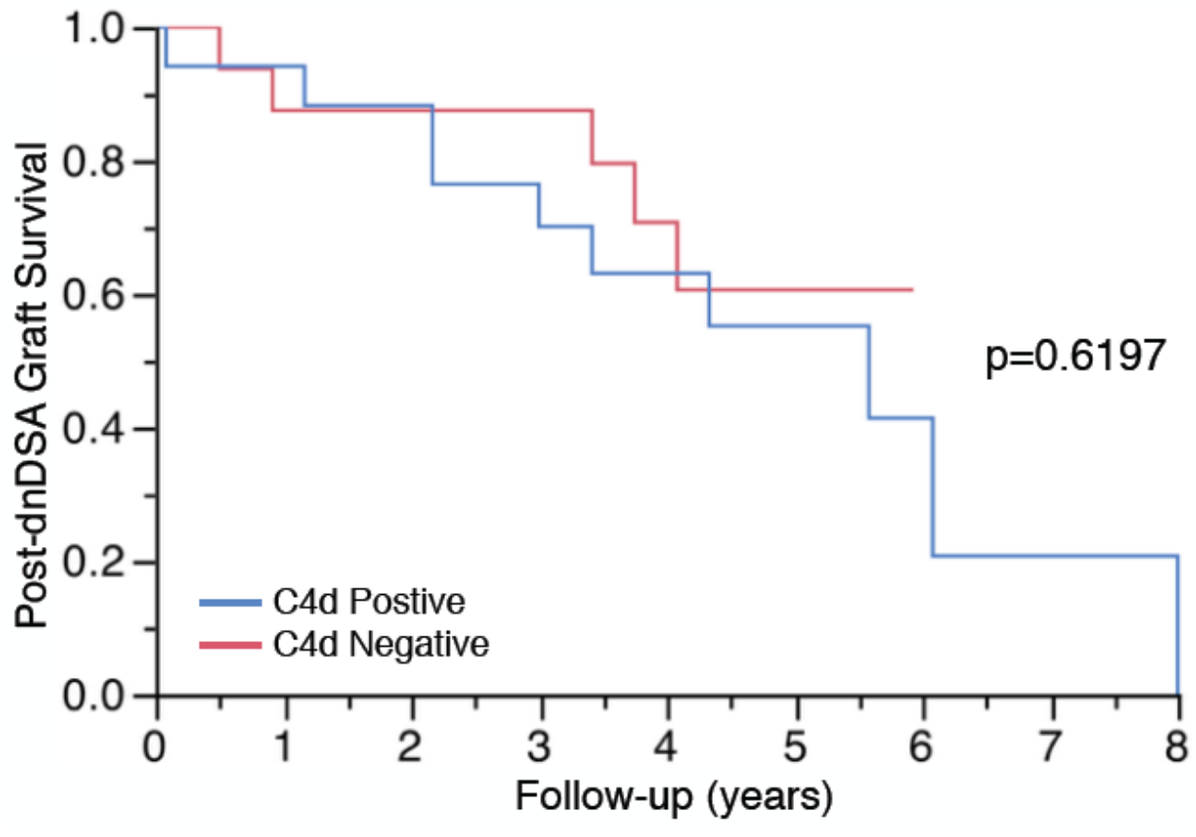
Wiebe et al., AJT (2015) 15: 2921-2930

Biopsy Predictors for Graft Loss at DSA onset

Consecutive Adult and Pediatric Kidney Transplants (n=508, 1999 to 2012)

Microvascular inflammation grade & C4d⁺ does not correlate with graft loss

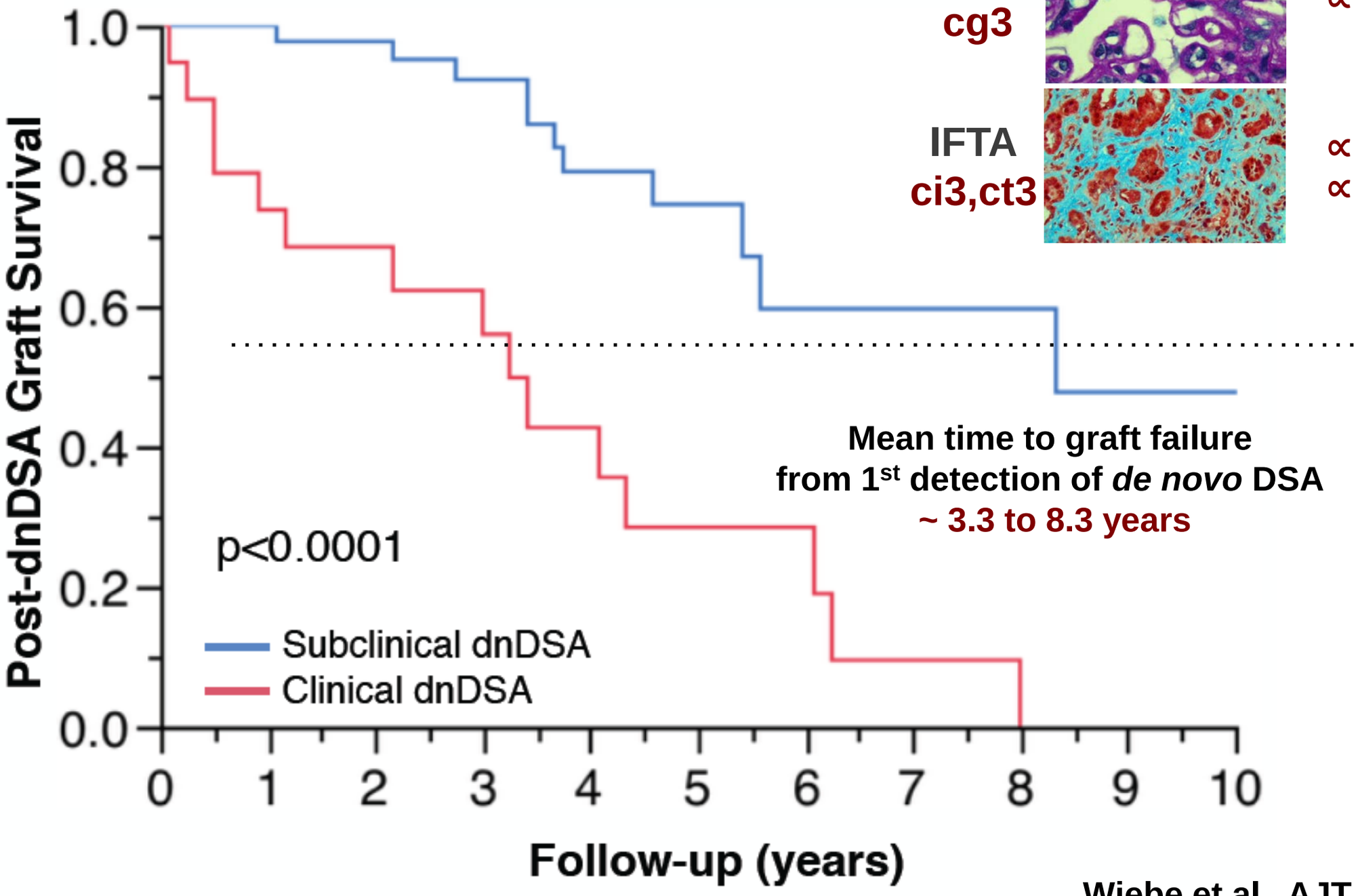




Wiebe et al., AJT 2015; 15: 2921-2930

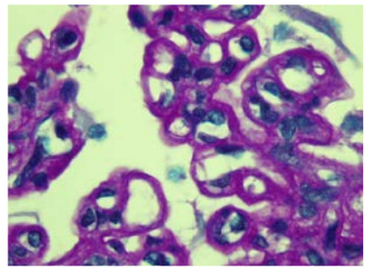
Time to Graft Loss from de novo DSA Onset

Consecutive Adult and Pediatric Kidney Transplants (n=508, 1999 to 2012)



Mean time to graft failure from 1st detection of *de novo* DSA
~ 3.3 to 8.3 years

TG
cg3



IFTA
ci3,ct3

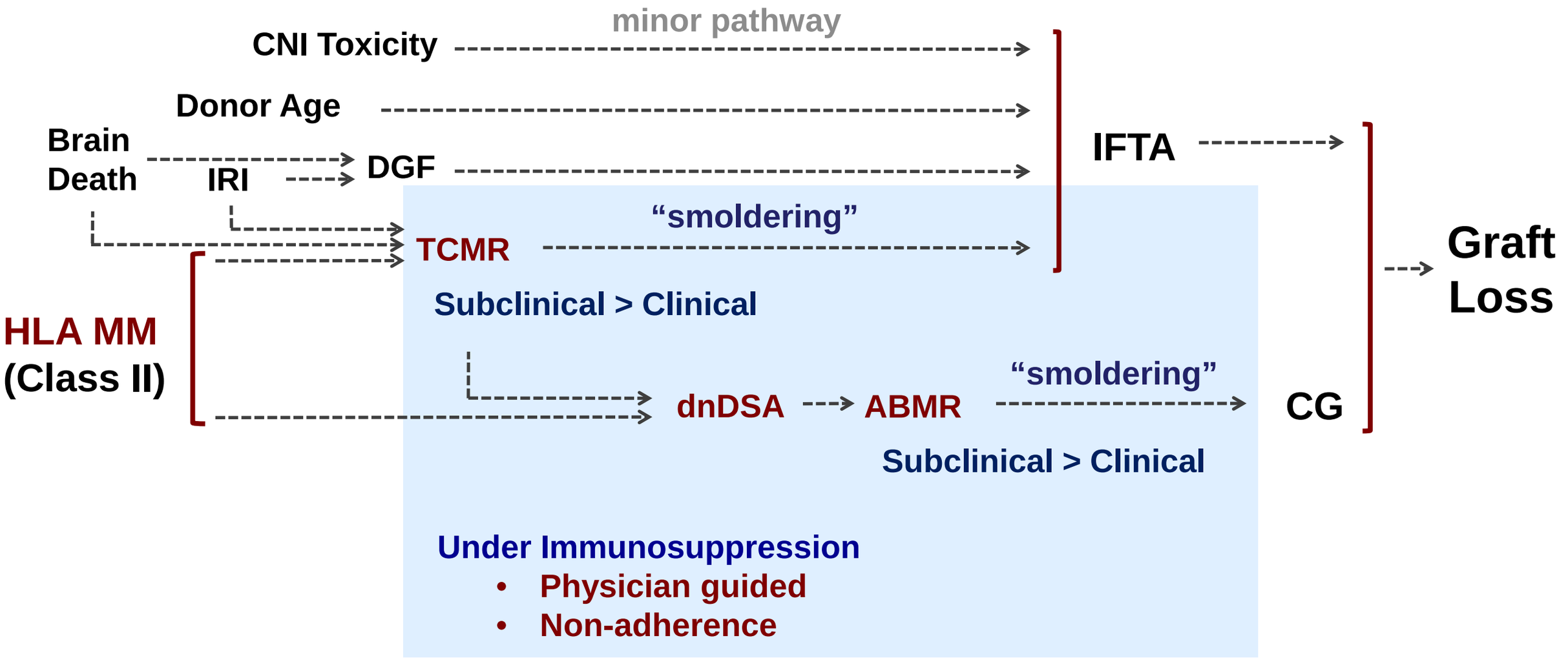
Multivariate

∝ de novo DSA

∝ early $TCMR_{0\text{-}12\ mo}$
∝ non-adherence

Wiebe et al., AJT (2015) 15: 2921-2930

Model of Alloimmune Mediated Graft Loss



Wiebe et al., Transplantation (2016) 100:2048-2052

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DSA

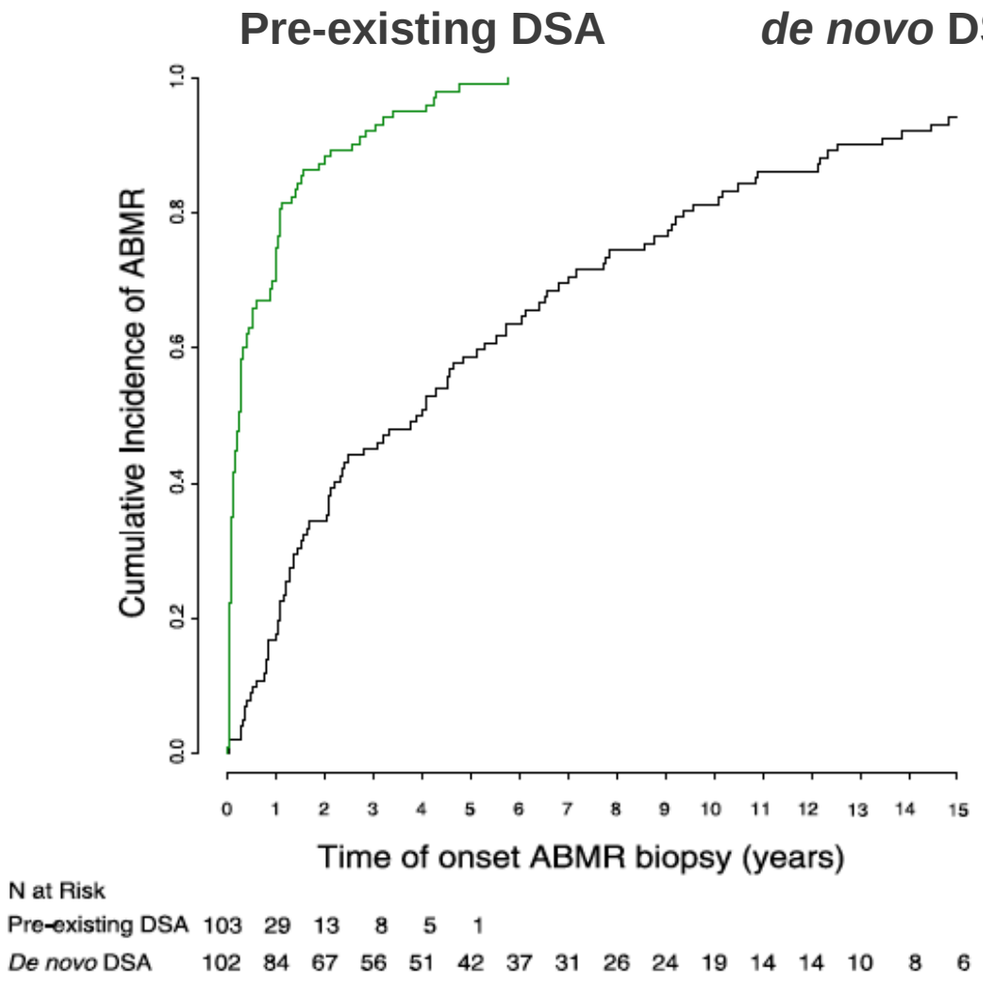
MEMORY VS. DE NOVO

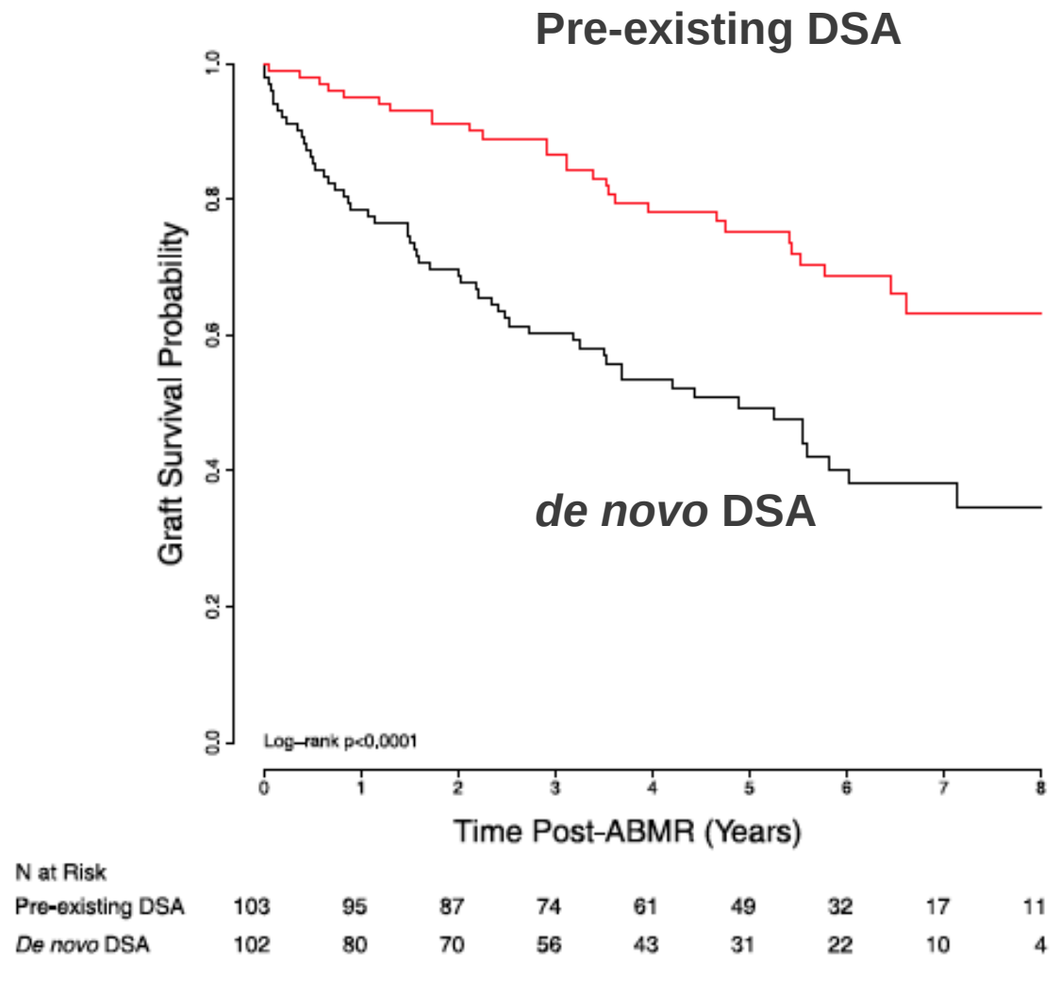
Antibody-Mediated Rejection Due to Preexisting versus *De Novo* Donor-Specific Antibodies in Kidney Allograft Recipients

Olivier Aubert,* Alexandre Loupy,*†‡ Luis Hidalgo,§‖ Jean-Paul Duong van Huyen,¶ Sarah Higgins,** Denis Viglietti,*†† Xavier Jouven,* Denis Glotz,*†† Christophe Legendre,*†‡ Carmen Lefaucheur,*†† and Philip F. Halloran‖‡‡

JASN (2017) ePub

Preexisting, compared to *de novo,* DSA ABMR occurs sooner and has a lower rate of graft failure





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JASN (2017) ePub

de novo DSA ABMR has more TG, TCMR, IFTA and proteinuria at diagnosis

- likely delayed recognition of the process with _de novo_ DSA

→ Subclinical ABMR 22.3% pre-existing vs. 8.8% _de novo_ DSA

Parameters	Preexisting Anti-HLA DSA ABMR (*n*=103)	*De Novo* Anti-HLA DSA ABMR (*n*=102)	*P* Value
Histology			
g (0–3), mean (SD)	1.71 (1.02)	1.06 (0.91)	<0.001
ptc (0–3), mean (SD)	1.76 (0.98)	1.66 (1.00)	0.47
C4d positive, *n* (%)	53 (51.46)	39 (42.39)	0.13
cg (0–3), mean (SD)	0.48 (0.94)	1.28 (1.15)	<0.001
i (0–3), mean (SD)	0.61 (0.92)	1.23 (1.01)	<0.001
t (0–3), mean (SD)	0.59 (0.90)	1.01 (1.11)	0.003
v (0–3), mean (SD)	0.32 (0.65)	0.22 (0.60)	0.29
ci (0–3), mean (SD)	0.96 (1.04)	1.60 (0.92)	<0.001
ct (0–3), mean (SD)	0.99 (0.99)	1.60 (0.91)	<0.001
cv (0–3), mean (SD)	1.26 (1.00)	1.44 (0.98)	0.2
ah (0–3), mean (SD)	0.97 (0.92)	1.53 (1.05)	<0.001
Immunology at the time of the ABMR biopsy			
Anti-HLA DSA class 1, *n* (%)	40 (38.83)	26 (25.49)	
Anti-HLA DSA class 2, *n* (%)	63 (61.17)	76 (74.51)	0.02
Anti-HLA DSA MFI, median [IQR]	2561 [1252–6937]	7295 [1948–11,814]	<0.001
Renal function			
eGFR, ml/min per 1.73 m^2, mean (SD)	39.00±18.26	41.65±21.19	0.34
Proteinuria, g/g creatinine, mean (SD)	0.51±1.05	1.51±2.51	<0.001

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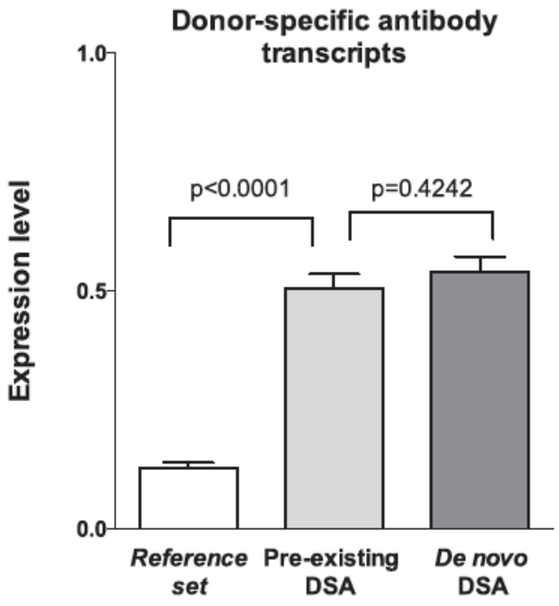
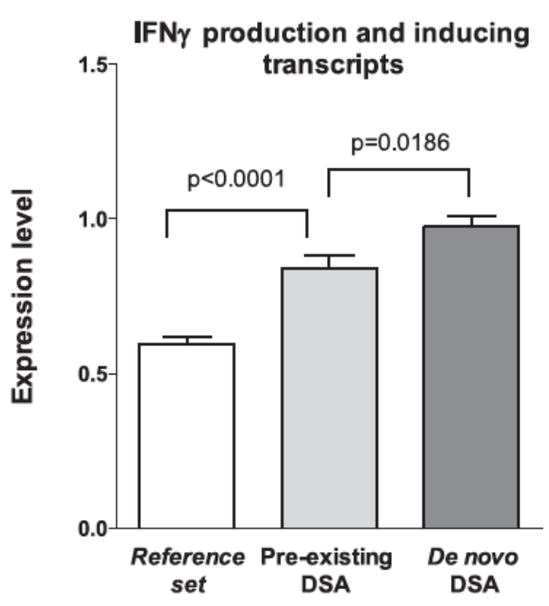
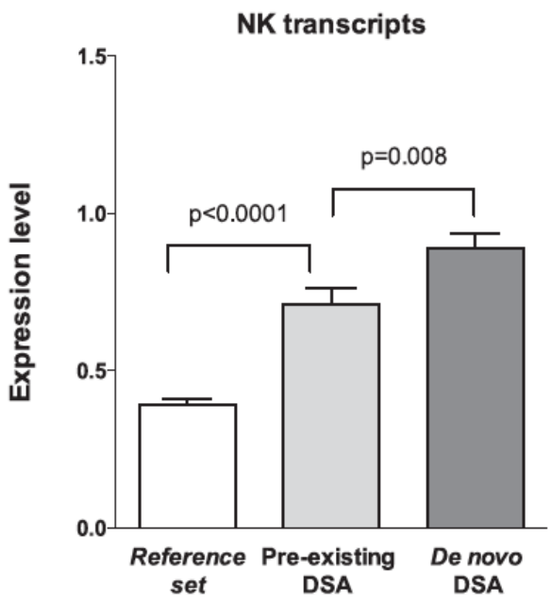
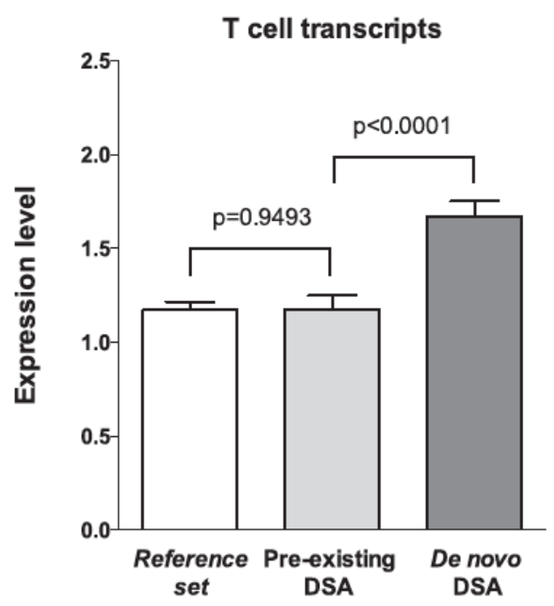
JASN (2017) ePub

de novo DSA ABMR has more IFNγ, NK and T-cell transcripts









Differences in pathologic features and graft outcomes in antibody-mediated rejection of renal allografts due to persistent/recurrent versus *de novo* donor-specific antibodies

Kidney International (2017) **91,** 729–737;

Mark Haas[1], James Mirocha[2], Nancy L. Reinsmoen[3], Ashley A. Vo[4], Jua Choi[4], Joseph M. Kahwaji[4], Alice Peng[4], Rafael Villicana[4,5] and Stanley C. Jordan[4]

Table 1 | Comparison of pathologic and clinical features of types 1 and 2 ABMR

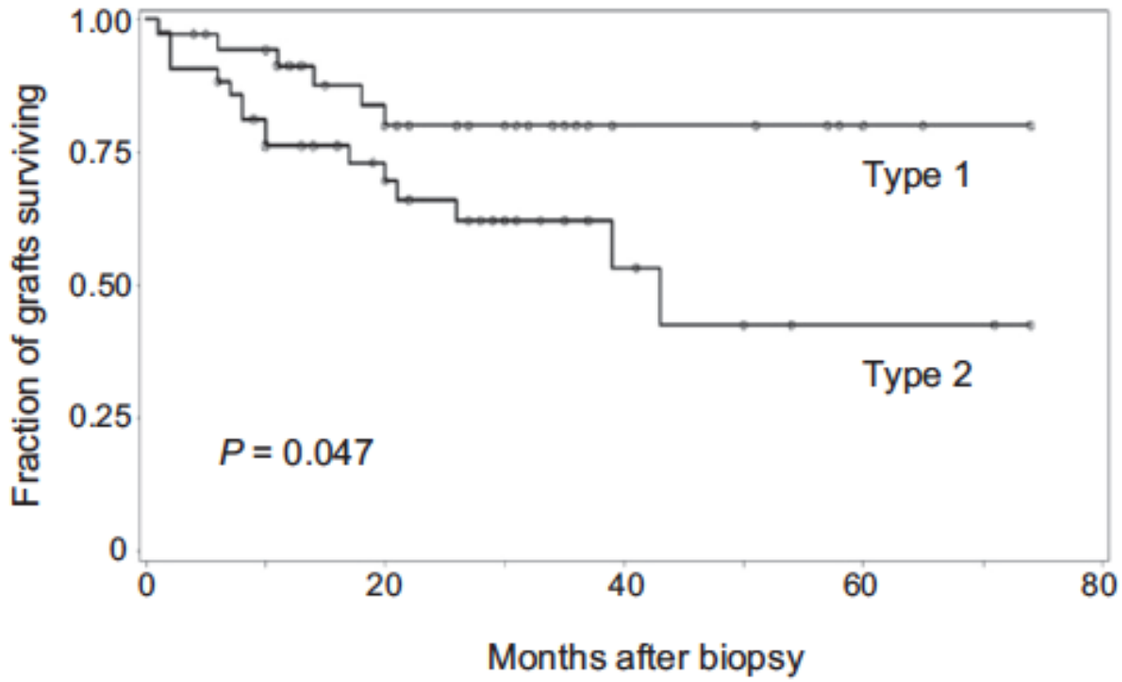
	Type 1 (n = 37)	Type 2 (n = 43)	P value
Mo post-tx of biopsy (median, IQR)	3 [1–7]	72 [30–108]	<0.0001[b]
Biopsy indication			0.005[a]
Acute graft dysfunction	25 (68%)	14 (33%)	
Progressive graft dysfunction	8 (22%)	23 (53%)	
Proteinuria	4 (11%)	6 (14%)	
No CMR	27 (73%)	15 (28%)	0.0008[a]
CMR ≥ Banff 1a + borderline	10 (27%)	28 (72%)	
No CMR + borderline	29 (78%)	26 (60%)	0.097[a]
CMR ≥ Banff 1a	8 (22%)	17 (40%)	
No CMR + borderline + isolated v	33 (89%)	27 (63%)	0.009[a]
CMR ≥ Banff 1a (excluding isolated v)	4 (11%)	16 (37%)	
Banff scores			
g (median [IQR])	1 [1–2]	1 [1–2]	0.84[b]
ptc (median [IQR])	2 [1–2]	2 [1–2]	0.83[b]
cg (median [IQR])	0 [0–1]	1 [1–2]	0.010[b]
max. ptcbm layers (median [IQR])	3 [2–5] (36)[c]	5 [4–7] (39)[c]	0.0004[b]
(ci + ct) (median [IQR])	0 [0–2]	2 [2–4]	<0.0001[b]
C4d score (median [IQR])	3 [0–3]	3 [1–3]	0.30[b]
cg score 0	27 (73%)	20 (47%)	0.023[a]
cg score ≥1	10 (27%)	23 (53%)	
(ci + ct) <3	33 (89%)	27 (63%)	0.009[a]
(ci + ct) ≥3	4 (11%)	16 (37%)	
C4d score 0–1	11 (30%)	11 (26%)	0.80[a]
C4d score 2–3	26 (70%)	32 (74%)	
ABMR activity			0.005[a]
Acute/active	26 (70%)	16 (37%)	
Chronic, active	11 (30%)	26 (60%)	
Chronic	0	1 (2%)	

***de novo* DSA associated ABMR**

- **More Class II DSA**
- **More TCMR (borderline / Ia+)**
- **Worse graft survival**

Table 2 | Comparison of donor-specific antibodies in types 1 and 2 ABMR

	Type 1 (n = 37)	Type 2 (n = 43)	P value
Anti–class I DSA only	15 (41%)	5 (12%)	0.0004[a]
Anti–class II DSA only	10 (27%)	30 (70%)	
Anti–classes I + II DSA	12 (32%)	8 (19%)	



Early and Late Acute Antibody-Mediated Rejection Differ Immunologically and in Response to Proteasome Inhibition

R. Carlin Walsh,[1] Paul Brailey,[2] Alin Girnita,[2] Rita R. Alloway,[3] Adele Rike Shields,[1] Garth E. Wall, Basma H. Sadaka, Michael Cardi,[4] Amit Tevar,[1] Amit Govil,[3] Gautham Mogilishetty,[3] Prabir Roy-Chaudhury,[3] and E. Steve Woodle[1,5]

	< 6mo	> 6mo
Immunologic Response		
% of patients with >50% decline in DSA MFI D14 post-treat	**77%**	**35%**
Histologic Response		
% patients resolved or resolving with repeat bx	**88%**	**54%**
Allograft Function Response		
Mean pre-treatment eGFR (ml/min/1.73m2)	**40±17**	**27±12**
Mean post-treatment eGFR (ml/min/1.73m2)	**66±31**	**37±25**

Walsh et al, Transplantation (2011) 91:1218

Summary

	Pre-existing DSA	De novo DSA
HLA DSA	Class II ≥ Class I	Class II >> I
Level of Immunosuppression	⇑⇑⇑	⇔
Non-adherence	⇔	⇑⇑⇑
ABMR	⇑⇑⇑	⇑⇑
TCMR	⇑	⇑⇑
Response to Therapy	⇑⇑⇑	⇑

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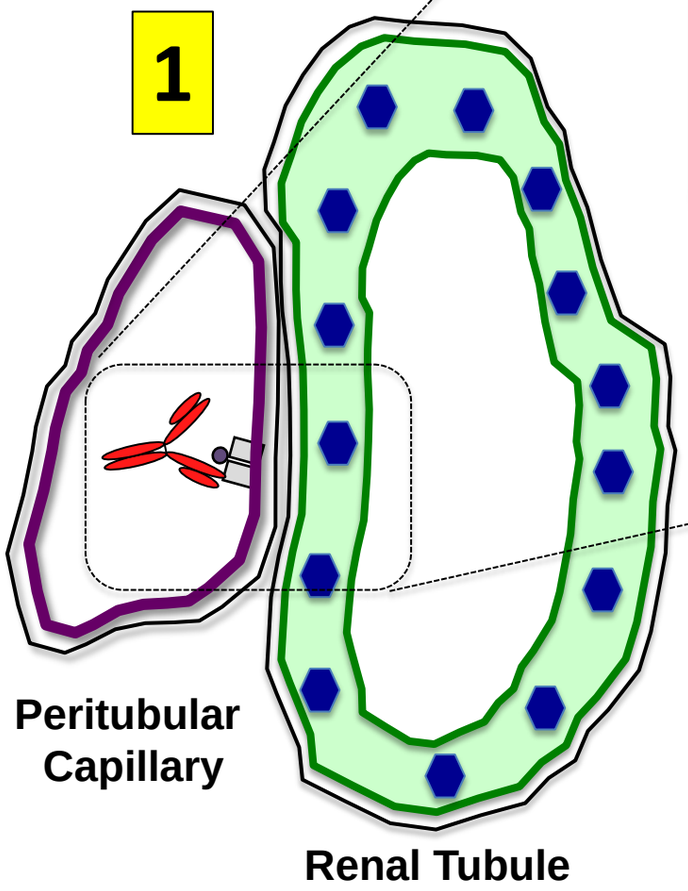
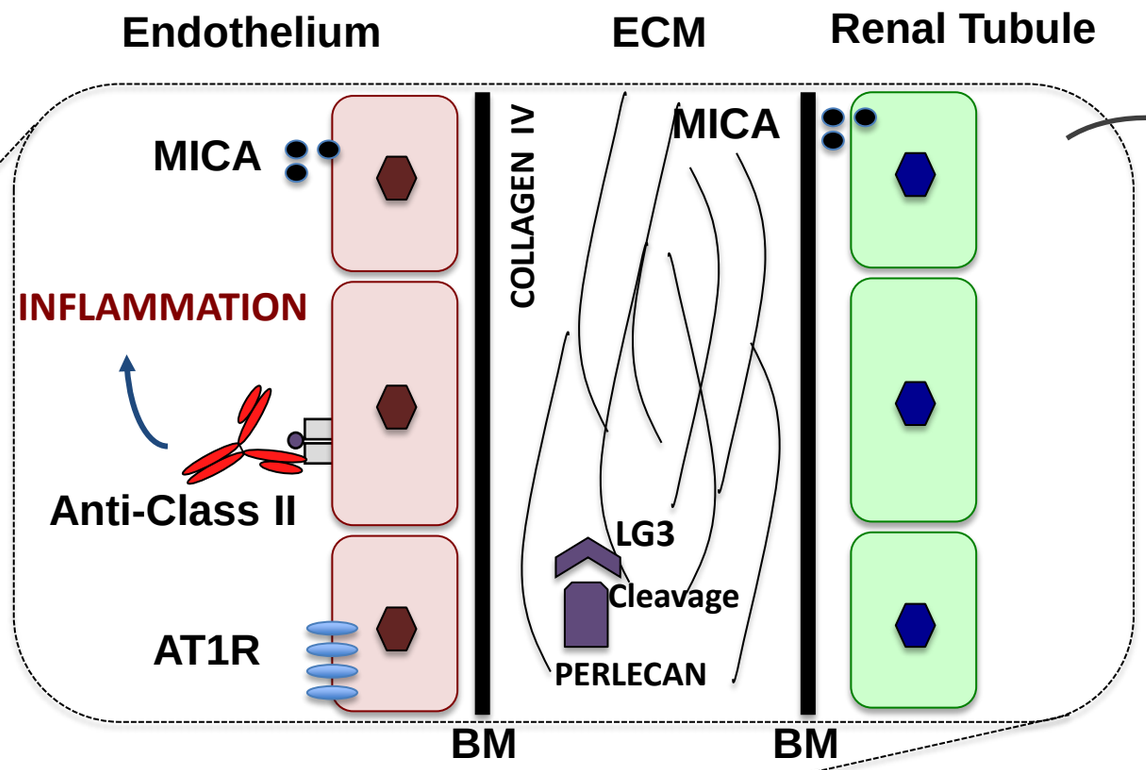
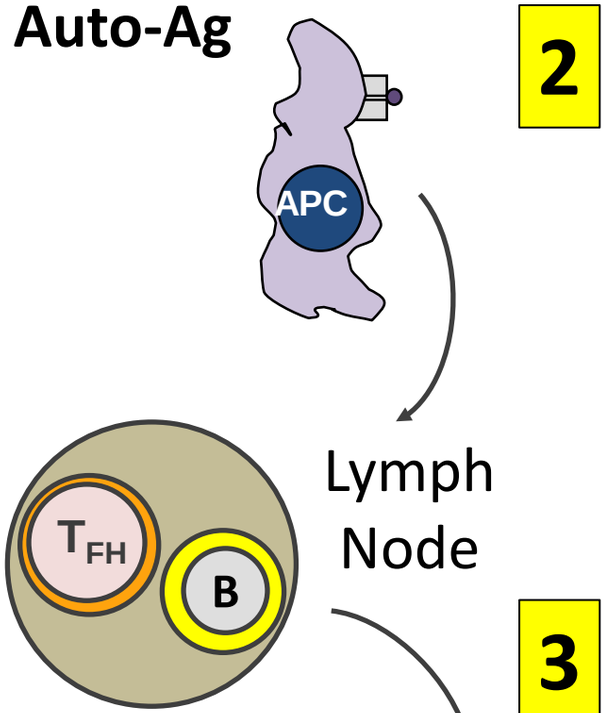
DSA

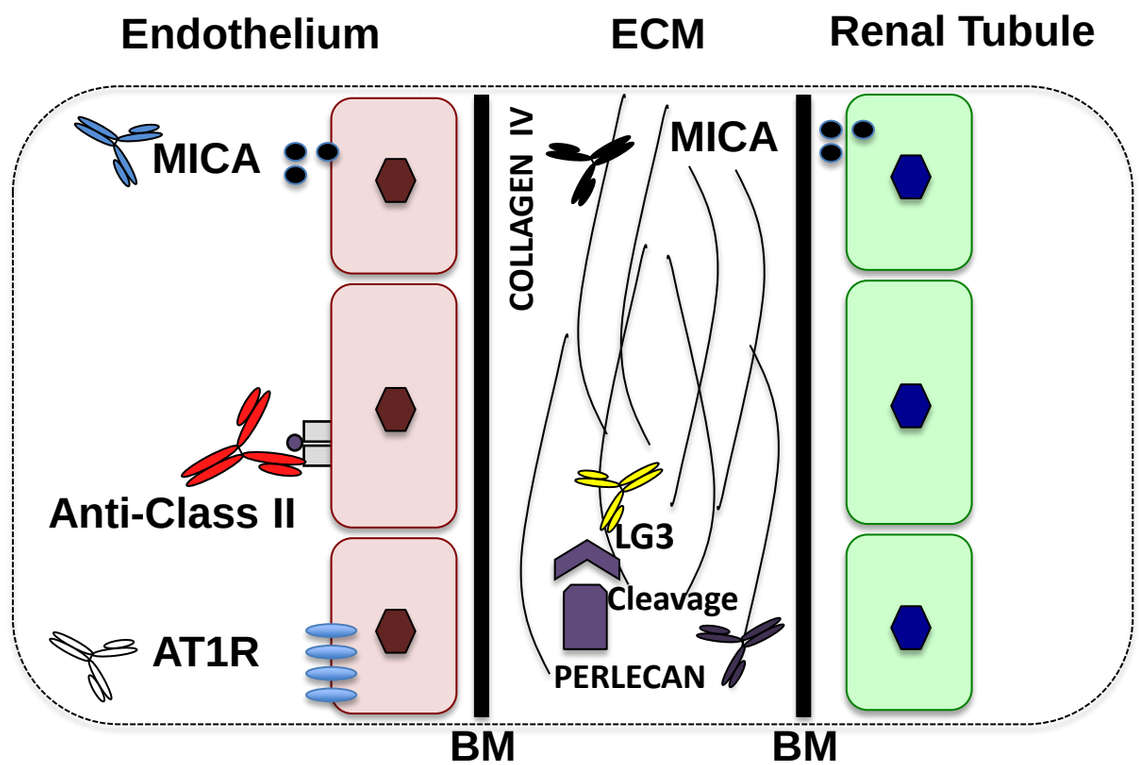
ROLE FOR NON-HLA?

Epitope Spread to Auto-antigens









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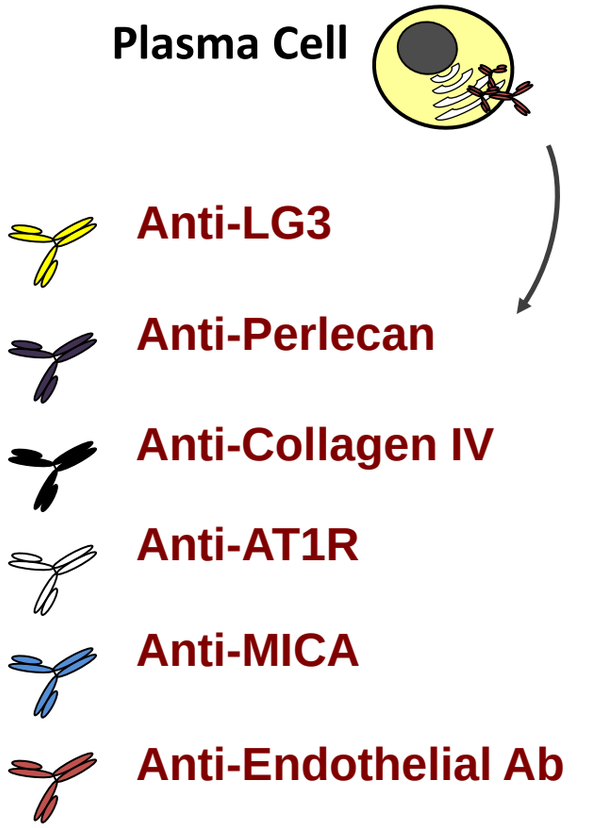

Non-HLA Antibodies in Kidney Transplantation

University of Manitoba

AT_1R Ab

- **Pre-existing → acute rejection and/or graft loss**
  - Giral et al, AJT (2013) 13:2567-76
  - Taniguchi et al AJT (2013) 13:2577-89

Anti-Perlecan Ab

- **Associated with vascular rejection**
  - Cardinal et al, AJT (2013) 13:861-74
- **Associated with chronic allograft rejection**
  - Joosten et al, Am J Path (2002) 160:1301-10

Anti-Collagen IV and Fibronectin

- **Associated with transplant glomerulopathy**
  - Angaswamy et al, AJT (2014) 14:685-93
- **Associated with chronic allograft rejection**
  - Joosten et al, Am J Path (2002) 160:1301-10

Issues:

- **Frequently confounded by pre-existing HLA DSA**
- **Inadequate assessment for HLA DSA using solid phase technology**

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