HLA – Part II: My Patient Has DSA, Now What?

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THE UNIVERSITY OF BRITISH COLUMBIA

HLA Part II – My Patient Has DSA, Now What?

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CST Fellows Symposium
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Case 1

- 57 F ESRD due to IgA
- History of multiple pregnancies
- Deceased donor transplant April 2017
- Negative FCXM, no DSA pretransplant

Case AJ

Pre-transplant	Post-transplant (6 months)
DR13	DR13, **8, 11, 14, 17, 18**
DQ6	DQ6
DP1, 5, 11	DP1, 5, 11
cPRA = 58%	cPRA = 85%

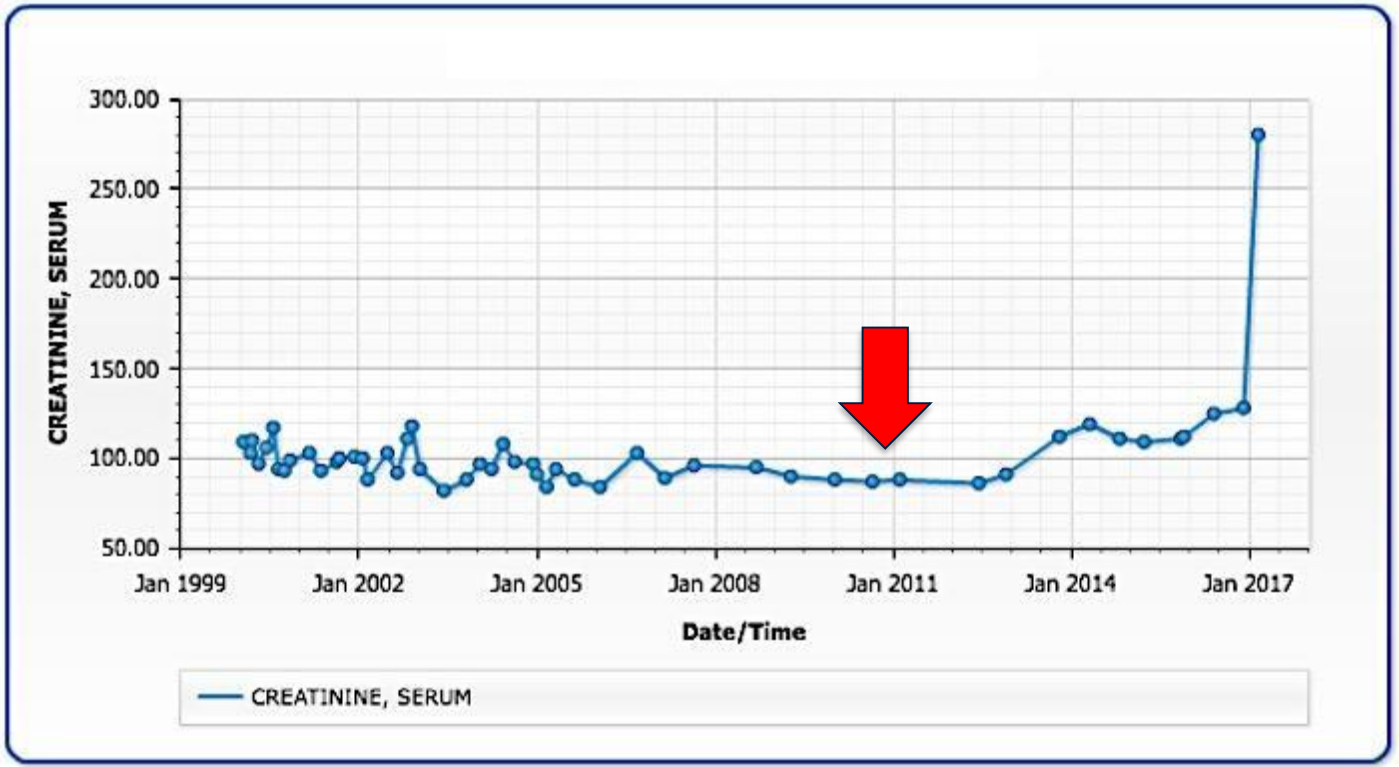
Moderately reactive (MFI=3039) donor specific antibody to DR8 was detected
Moderately reactive (MFI=3162) donor specific antibody to DR11 was detected

- Clinically asymptomatic, Cr 60 umol/L
- Mechanical mitral valve on warfarin

Case 2

- 51 M unknown native kidney disease
- Living donor transplant 1997 from sister (1 haplotype match)
- Excellent graft function Cr 90-100 for 20 years
- March 2017: Cr 100 → 120 → 250

Case 2


300.00
250.00
200.00
150.00
100.00
50.00
CREATININE, SERUM
Jan 1999
Jan 2002
Jan 2005
Jan 2008
Jan 2011
Jan 2014
Jan 2017
Date/Time
CREATININE, SERUM

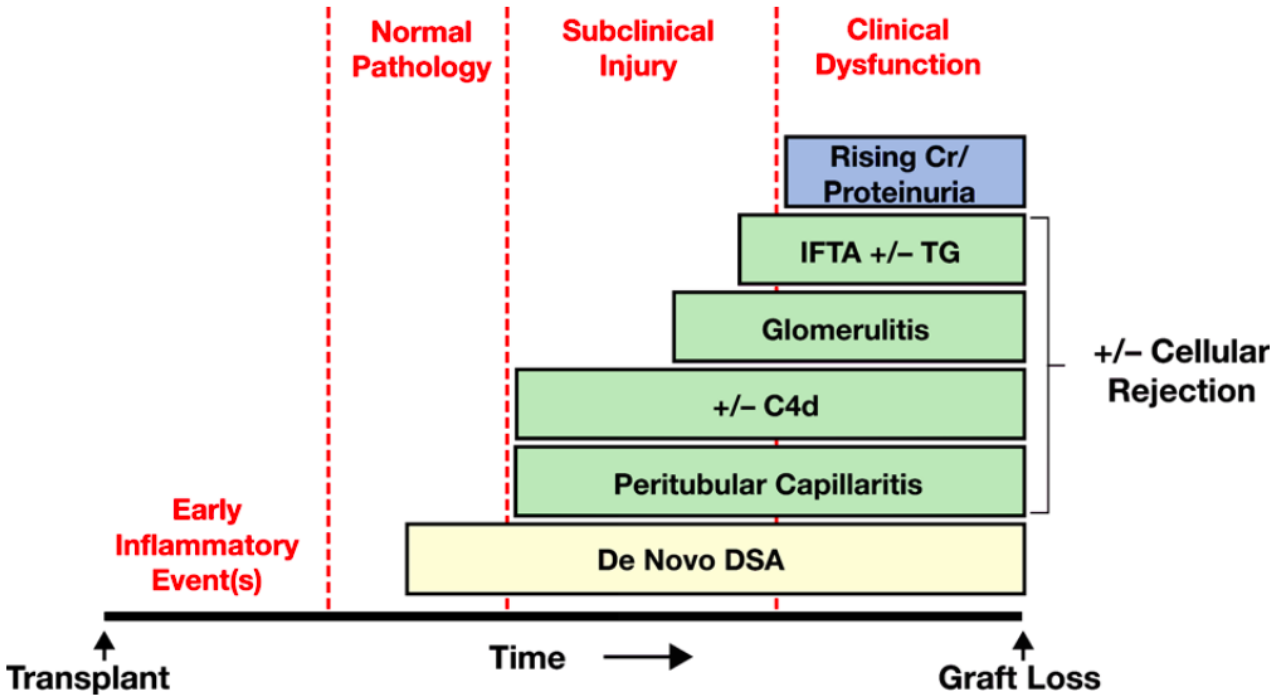
Case 2

Final Diagnosis :

- Features suspicious for chronic, active antibody-mediated rejection (g-1, i-0, t-0, ptc-1, C4d-3, v-0, ah-3, cg-1, ci-2, ct-2, cv-3, mm-3)

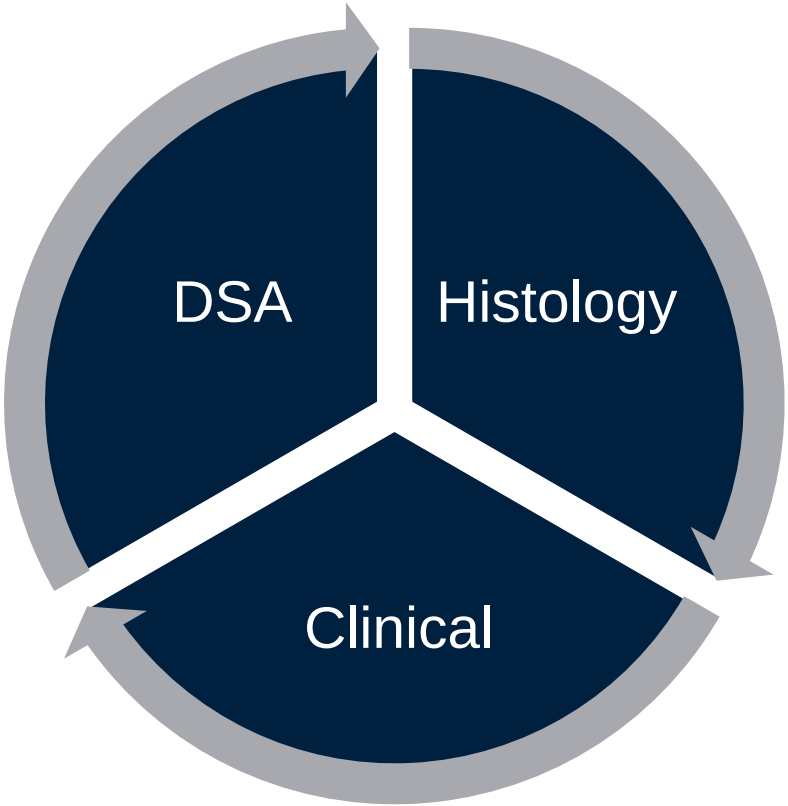
- Strongly reactive DSA to HLA-A1 (MFI 25223)

AMR is a heterogeneous disease

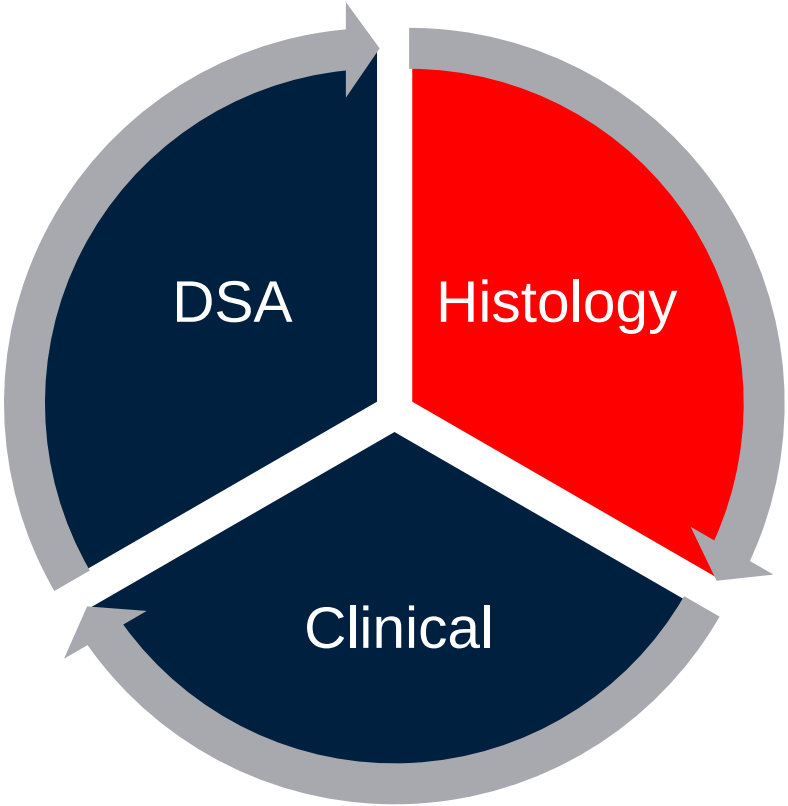


Wiebe et al, AJT, 2012

Who should be treated?



Who should be treated?

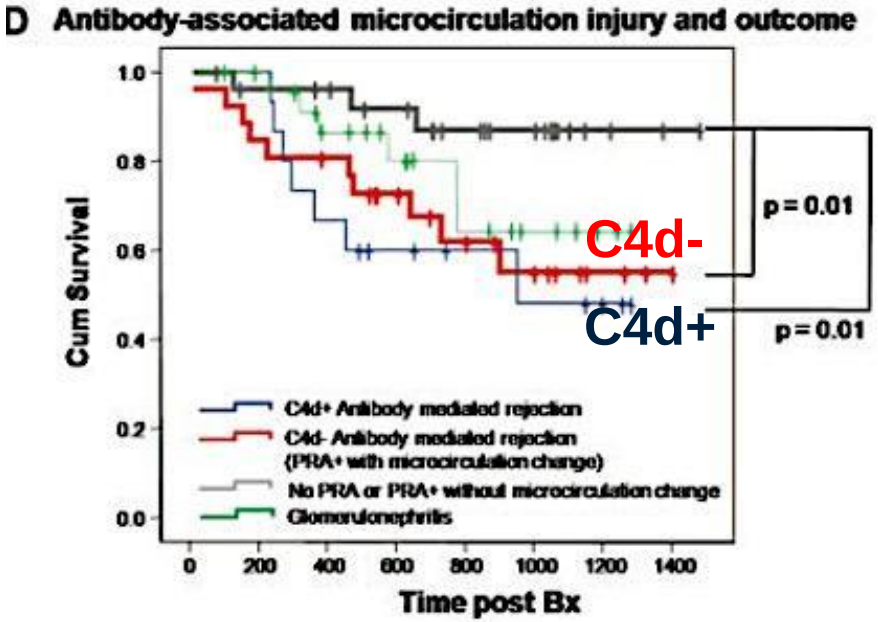


Revised Banff 2013 diagnosis of AMR

	Acute/Active AMR	Chronic/Active AMR
Histology:	1. Microvascular injury: (g or ptc) 2. Arteritis 3. Thrombotic microangiopathy 4. ATN-unknown cause	1. Transplant glomerulopathy (cg) 2. Peritubular basement membrane duplication 3. Arterial intimal fibrosis
Serology:	Donor-specific antibodies (HLA, AT1R-Ab, MICA)	
Interaction:	C4d Moderate microvascular inflammation (g+ptc >= 2) Endothelial cell gene transcripts	

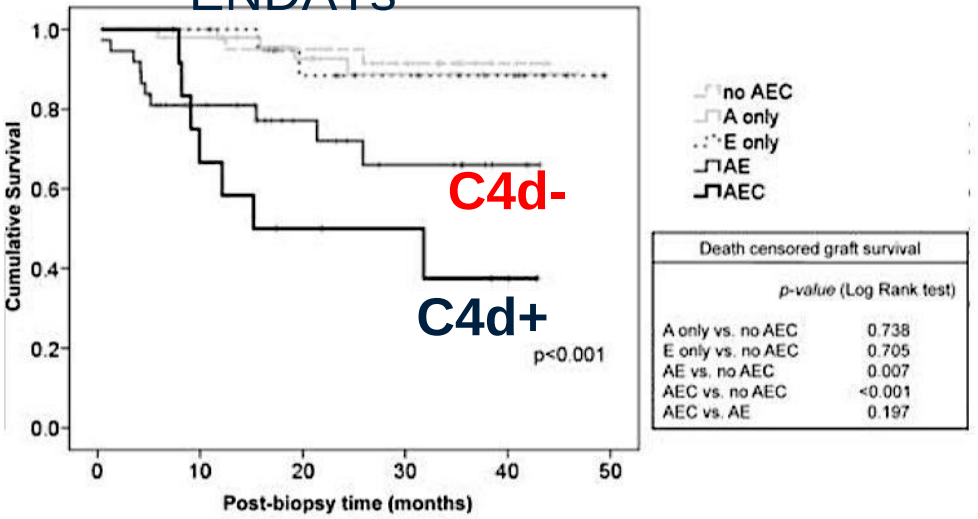
Recognition of C4d- AMR

DSA + Microcirculatory injury



Einecke, AJT, 2009

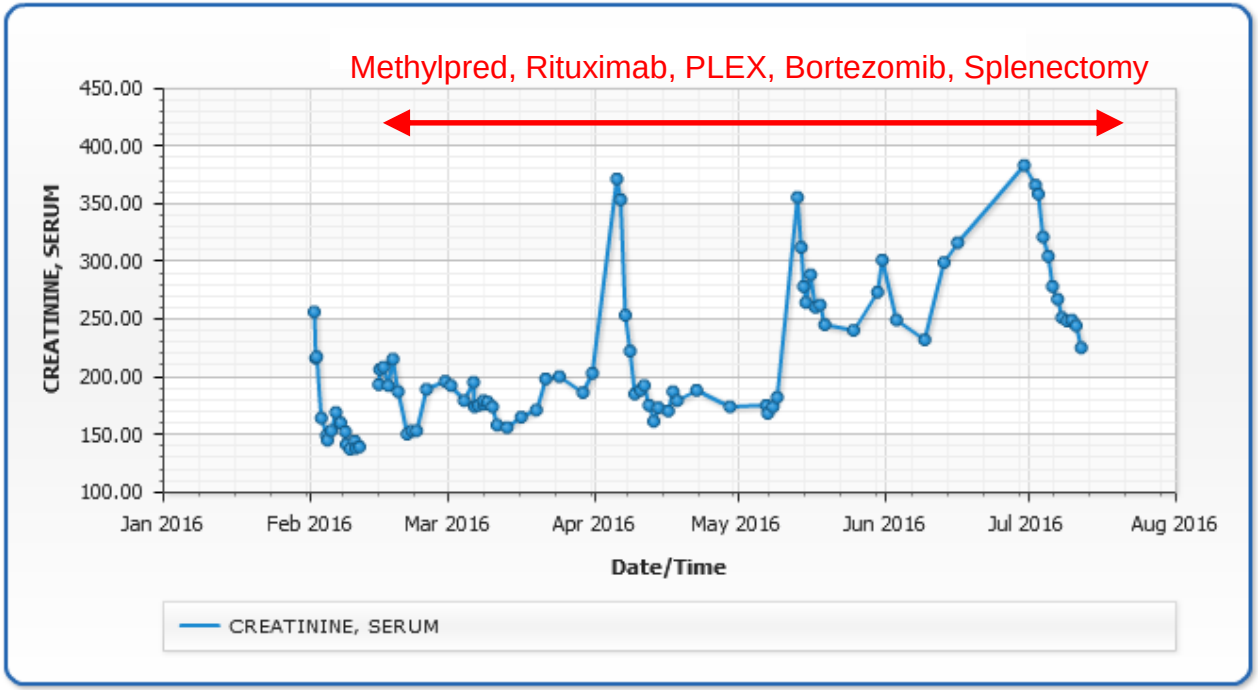
DSA + increased ENDATs



Sis et al, AJT, 2009

Why the need for molecular diagnostics

- 2nd kidney transplant 2016 (LD)
- Donor and recipient completely matched across all HLA loci

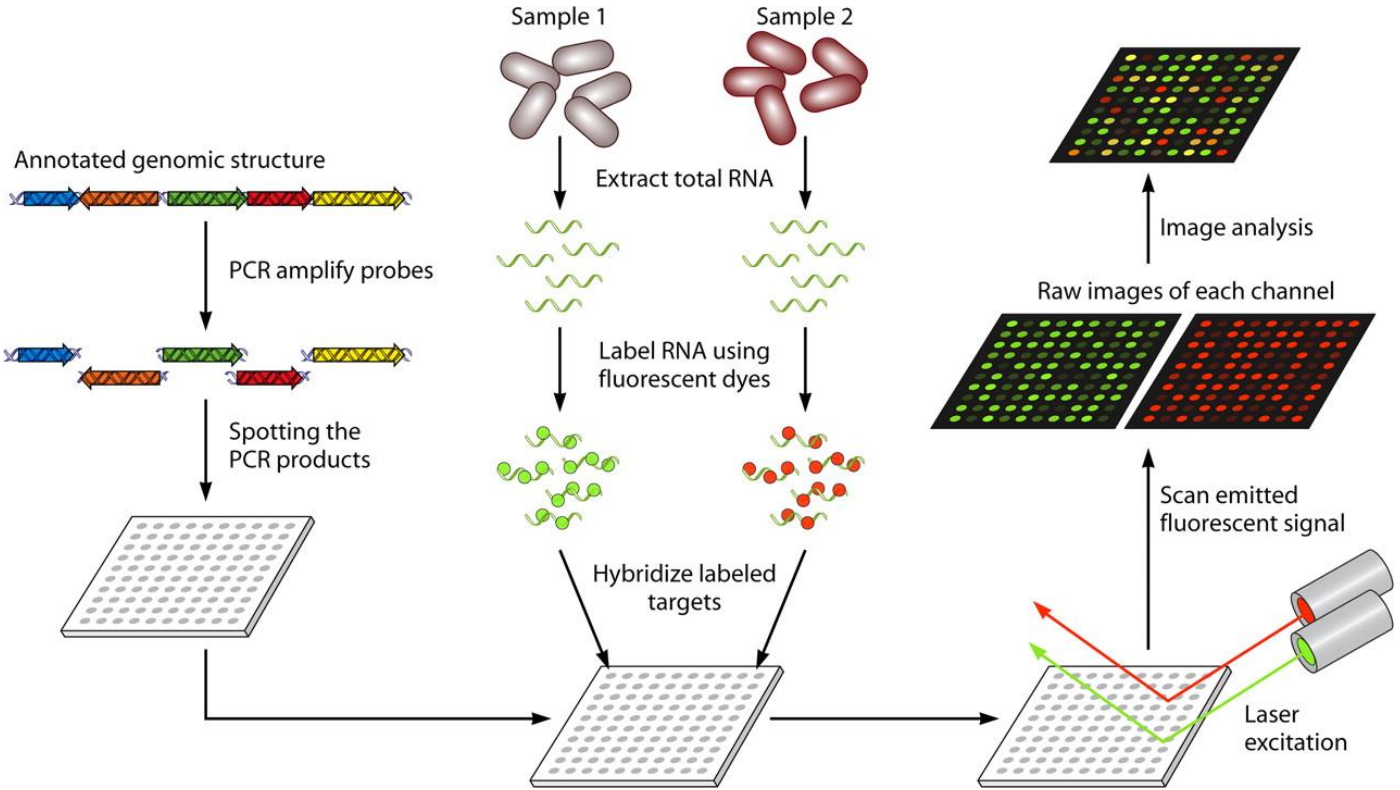


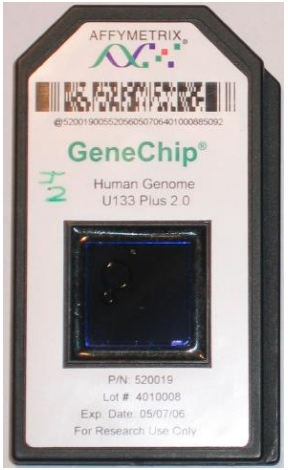
	Pathology	DSA
Feb 2, 2016	Suspected AMR	Negative
Feb 11, 2016	Suspected AMR	Negative
Feb 18, 2016	Suspected AMR	Negative
April 11, 2016	Suspected AMR	Negative
June 2, 2016	Suspected AMR	Negative

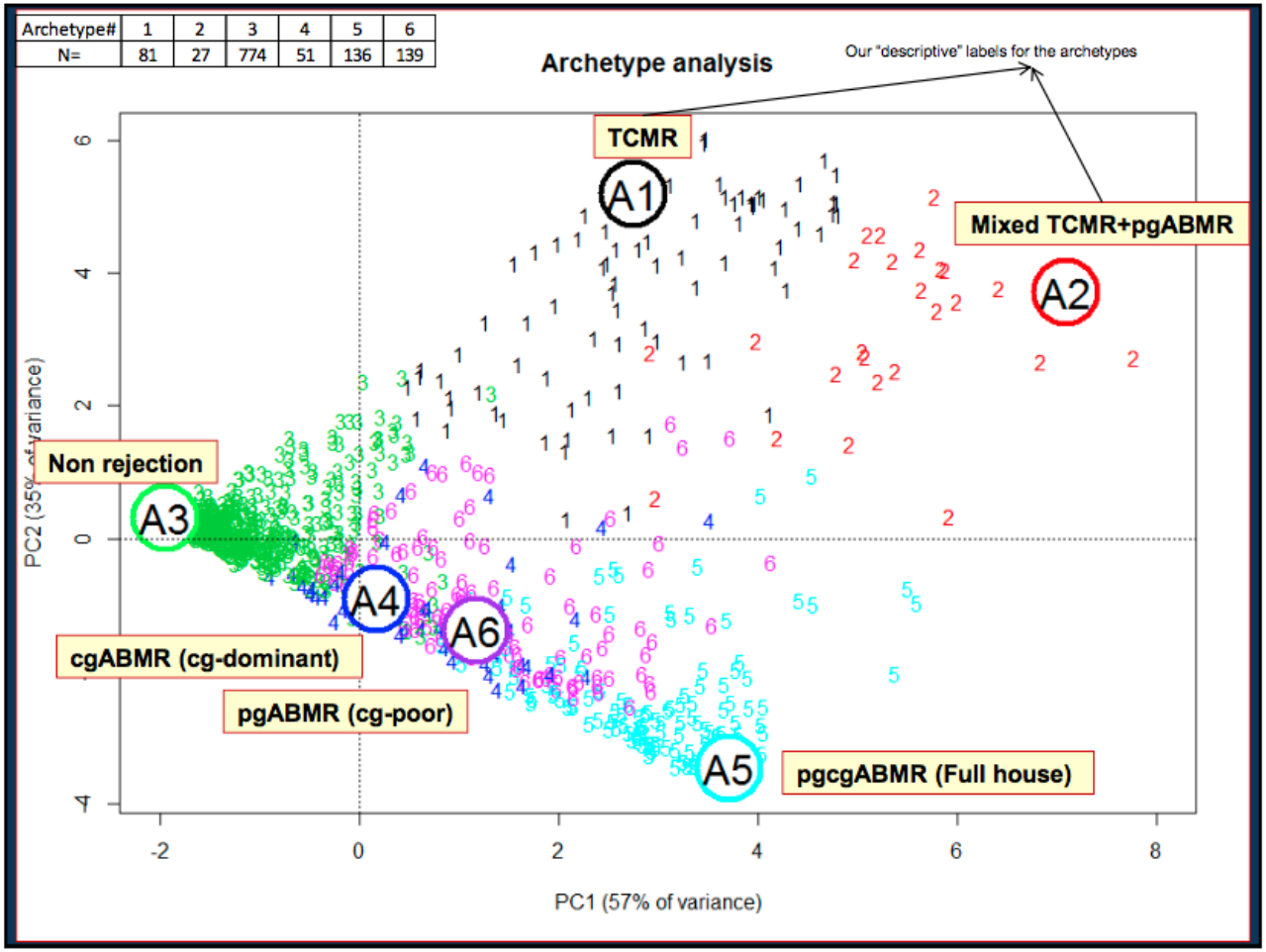
Non-HLA antibodies

	DSA	MICA Screen	AT1R Ab
Oct 19, 2016	Neg		
June 30, 2016	Neg		
April 13, 2016	Neg		
Feb 15, 2016	Neg	Neg	Neg
Feb 4, 2016	Neg	Neg	Neg

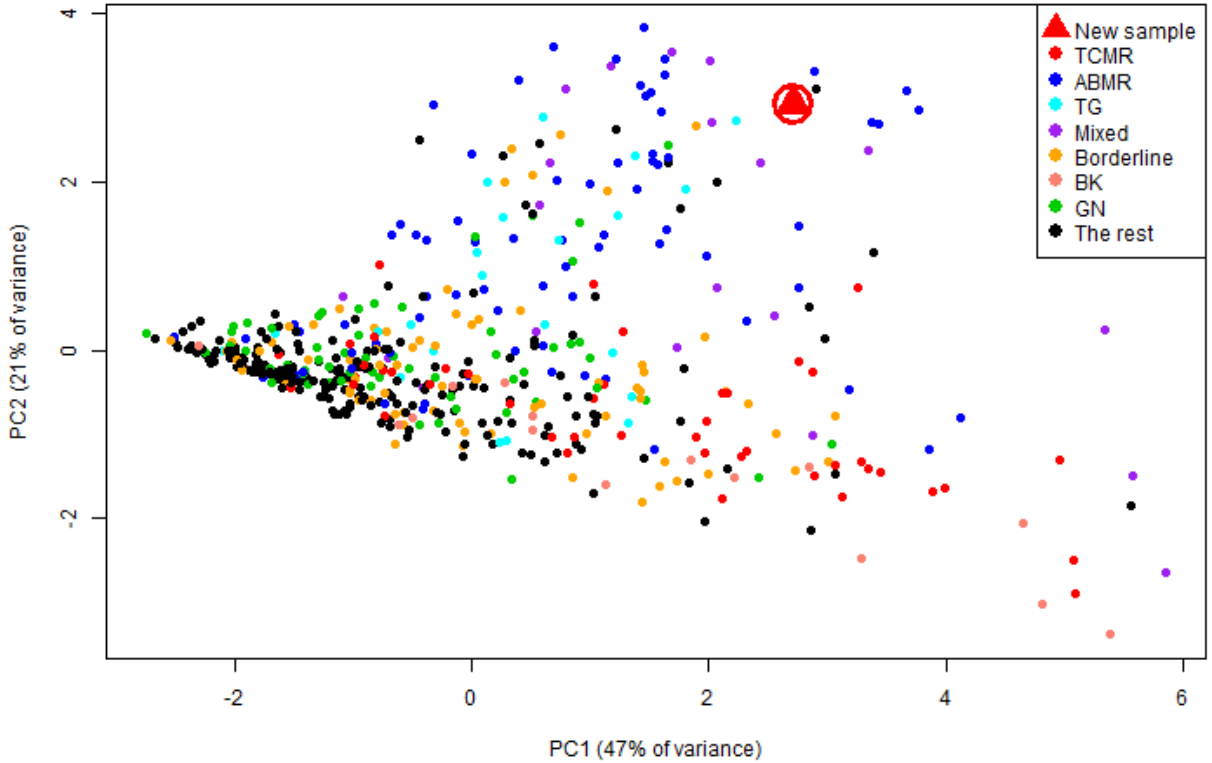
Molecular microscope to diagnose AMR





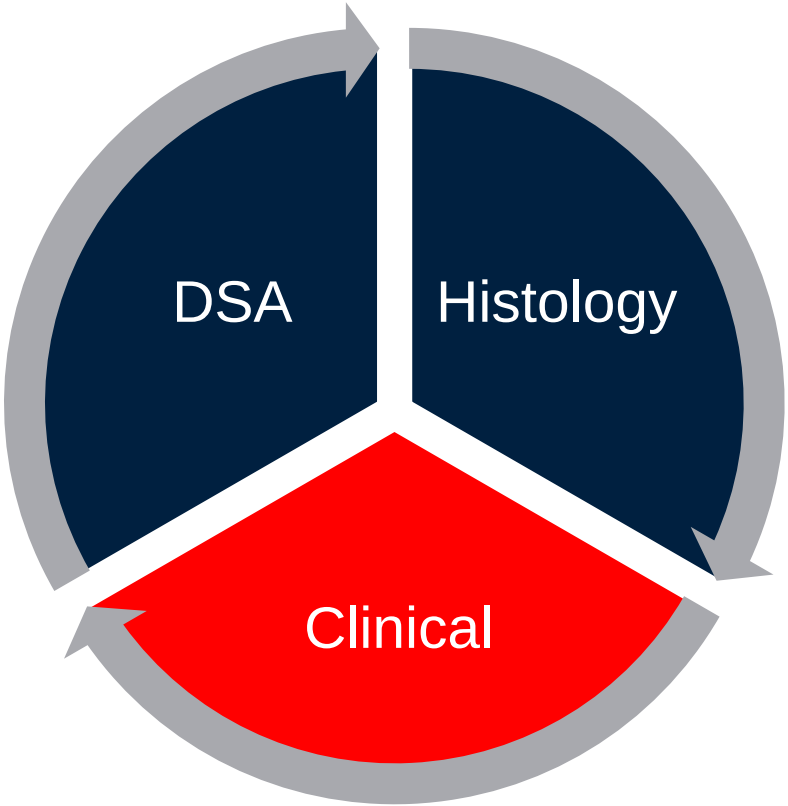

Archetype# 1 2 3 4 5 6
N= 81 27 774 51 136 139
Archetype analysis
Our "descriptive" labels for the archetypes
TCMR
A1
Mixed TCMR+pgABMR
A2
Non rejection
A3
A4
A6
cgABMR (cg-dominant)
pgABMR (cg-poor)
A5
pgcgABMR (Full house)
PC2 (35% of variance)
PC1 (57% of variance)
6
4
2
0
-2
-4
-2
0
2
4
6
8

Patient J.M.: molecular diagnosis of AMR



Molecular Phenotype: the Edmonton Molecular Microscope System		
Classifier/PBT	Biopsy Score	Interpretation
Global Disturbance Score	4.14	**High**
Acute kidney injury Score	1.02	**High**
Atrophy-Fibrosis Score	0.61	Not applicable
Rejection Score	0.84	**High**
TCMR Score	0.04	Low
ABMR Score	0.91	**Very High**

Who should be treated?



Clinical predictors of allograft loss

Multivariate Model (n=70, 27 events)*		Hazard Ratio	p value
A)	C1q positive	1.06 (0.5-2.4)	0.88
	Non-Adherence	4.22 (1.4-14.4)	<0.01
	Clinical vs. Subclinical Phenotype	2.38 (1.0-6.9)	0.05
B)	*dn*DSA Titer ≥1:64	1.41 (0.4-9.4)	0.65
	Non-Adherence	3.97 (1.2-14.0)	<0.01
	Clinical vs. Subclinical Phenotype	2.51 (1.0-6.9)	0.04
C)	*dn*DSA Titer ≥1:1024	0.57 (0.2-1.4)	0.23
	Non-Adherence	5.17 (1.6-18.0)	<0.01
	Clinical vs. Subclinical Phenotype	3.04 (1.2-8.6)	0.02

*A multivariate model identified non-adherence and clinical phenotype as the only two significant predictors. The effect of C1q and dnDSA titer after adjustment for non-adherence and clinical phenotype are shown above.

Wiebe et al, AJT 2017

Challenges in AMR Treatment

6.4: We suggest treating antibody-mediated acute rejection with one or more of the following alternatives, with or without corticosteroids *(2C)*:

- **plasma exchange;**
- **intravenous immunoglobulin;**
- **anti-CD20 antibody;**
- **lymphocyte-depleting antibody.**

KDIGO, AJT, 2009

Standard of Care:

1. PLEX + IVIG
2. High dose IVIG

FDA AMR Workshop, Archdeacon, AJT, 2011

Building provincial consensus in AMR treatment

Recognition of clinical need to standardize treatment

Review evidence for acute AMR treatment

Finalize acute AMR treatment protocol

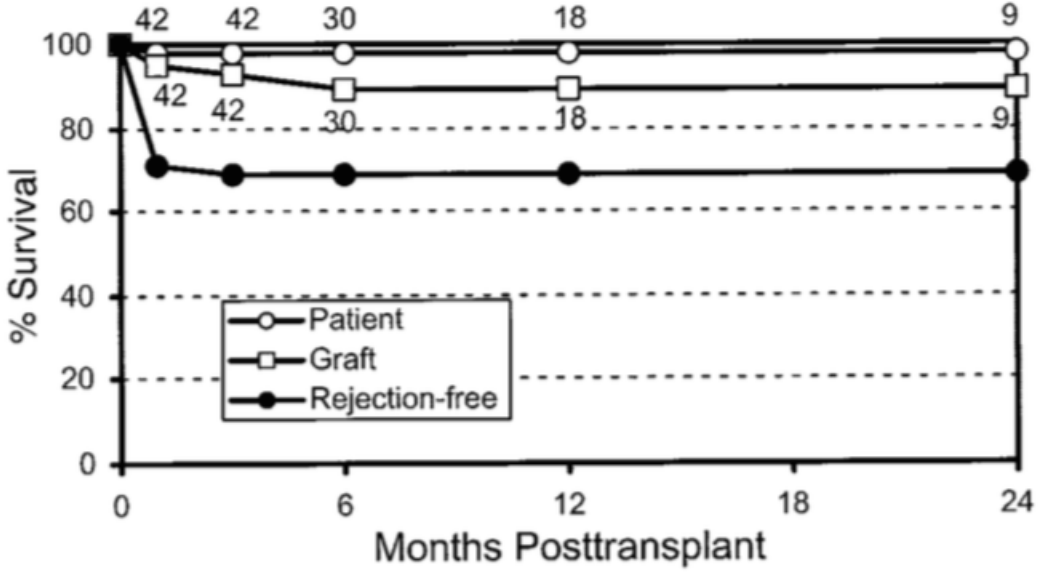
Treatment endpoints and failure

High Dose IVIG [1]

- N=42 CDC+ transplants
- 30% rejection rate
- 7% graft loss due to AMR

INTRAVENOUS IMMUNE GLOBULIN TREATMENT INHIBITS CROSSMATCH POSITIVITY AND ALLOWS FOR SUCCESSFUL TRANSPLANTATION OF INCOMPATIBLE ORGANS IN LIVING-DONOR AND CADAVER RECIPIENTS[1]

S. C. JORDAN,[2,3,5] A. VO,[2] S. BUNNAPRADIST,[2] M. TOYODA,[3] A. PENG,[2] D. PULIYANDA,[2] E. KAMIL,[2] AND D. TYAN[4]



Jordan et al, Transplantation, 2003

High Dose IVIG [2]

- N=12 preformed DSA+ living donor transplants
- Received IVIG 2 g/kg pre-Tx

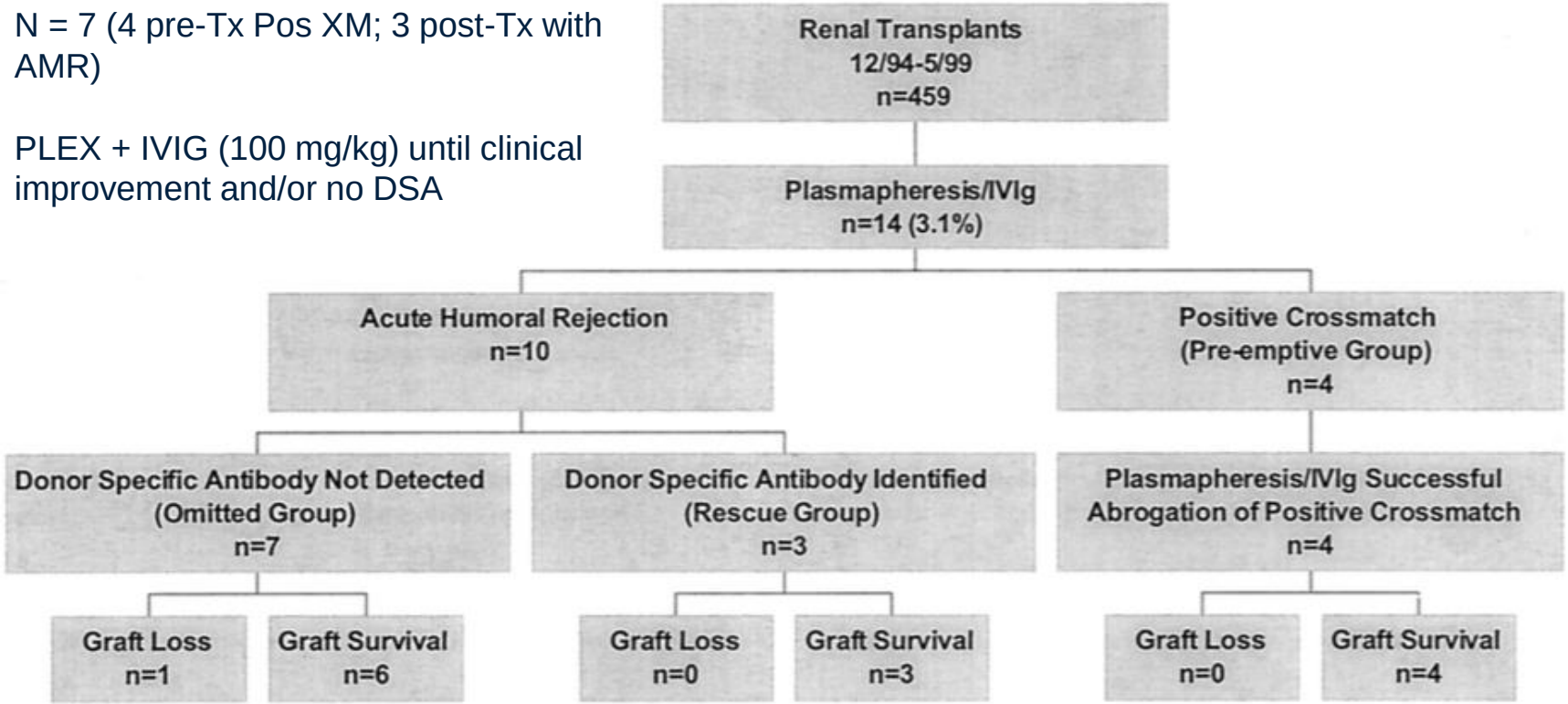
Table 3 | Transplant immunological data for patients who underwent DSA(+)KPD

Patient no.	Crossmatch and DSA to intended donor[a]	Crossmatch and DSA to matched DSA(+)KPD donor[b]	Benefit from DSA(+)KPD match[c]	Immunosuppression	Follow-up DSA to matched DSA (+)KPD Donor	Rejection type, time from transplant and DSA present
1	T-FXM (17) B-FXM (341) DR7 (12557) , DQ2 (11667)	T-FXM (8) B-FXM (123) DQ2 (11667)	B-FXM <200 ↓DSA	IVIG/alemtuzumab FK/MMF/prednisone	12 Months: DQ2 (11421) A1 (2075) A11 (1739) B35 (5693)	AMR 17 Days 6 Days DQ2 (5982) 17 Days no serum 40 Days DQ2 (7628)
2	ABO-I T-FXM (419) B-FXM (379) A3 (4512), A33 (7188), DR11 (11993), DR13 (11331), DR52 (13732)	T-FXM (42) B-FXM (60) B71 (2613)	ABO-C T-FXM <50 B-FXM <100 ↓DSA	IVIG/ ATG FK/MMF/prednisone	No DSA at 6, 12, and 24 months	No rejection
3	T-FXM (44) B-FXM (247) DR51 (8587)	T-FXM (15) B-FXM (159) DQA 0501 (3578)	B-FXM <200 ↓DSA	IVIG/ ATG Sirolimus/prednisone	6 Months: no DSA 12 Months: DQA 0501 (2200)	No rejection
4	ABO-I T-FXM (136) B-FXM (412) DR14 (11796), DQ5 (9955) DR52 (2279)	ABO-I T-FXM (85) B-FXM (142) A1 (6123), DR52 (2279)	B-FXM <200 ↓DSA	ABO-I protocol/ ATG FK/MMF/prednisone	No DSA at 1 and 2 months	No rejection
5	T-FXM (201) B-FXM (381) A24 (14575), DR11 (4528) DR 13 (7746), DQ6 (7422)	T-FXM (161)[d] B-FXM (172) DQ5 (5452)	B-FXM <200 ↓DSA	IVIG/ ATG FK/MMF/prednisone	No DSA at 6,12, and 24 months	No rejection
6	ABO-I T-FXM (45) B-FXM (36) A2 (6328)	ABO-C T-FXM (20) B-FXM (77) A3 (2605)	ABO-C ↓↓DSA	IVIG/ daclizumab FK/MMF/prednisone	No DSA at 24 months	No rejection
7	CDC(+) T-FXM (226) B-FXM (340) B58 (7793) DR16 (14341), DQ5 (2688)	CDC(−) T-FXM (69) B-FXM (222) B44 (3139), DP17 (2658).DQ5 (2688)	(−)CDC B-FXM < 300 ↓DSA	IVIG/ alemtuzumab FK/MMF/prednisone	12 Months: DR9 (1308), DR10 (2428), DQ5 (3745) 18 Months: DR10 (2005), DQ5 (2362)	AMR + ACR 6 Months DR9 (8000), DR10 (15000), DQ5 (13000)
8	T-FXM (33) B-FXM (363) DR4 (15741), DQ7 (3716)	T-FXM (6) B-FXM (27) DQ7 (3716), DR9 (3489)	B-FXM <100 ↓DSA	IVIG/ ATG FK/MMF/prednisone	No DSA at 6 and 12 months	No rejection

Blumberg et al, KI, 2013

PLEX + Low Dose IVIG

- N = 7 (4 pre-Tx Pos XM; 3 post-Tx with AMR)
- PLEX + IVIG (100 mg/kg) until clinical improvement and/or no DSA



Montgomery et al, Transplantation 2000

Rituximab and IVIG in Acute AMR [1]

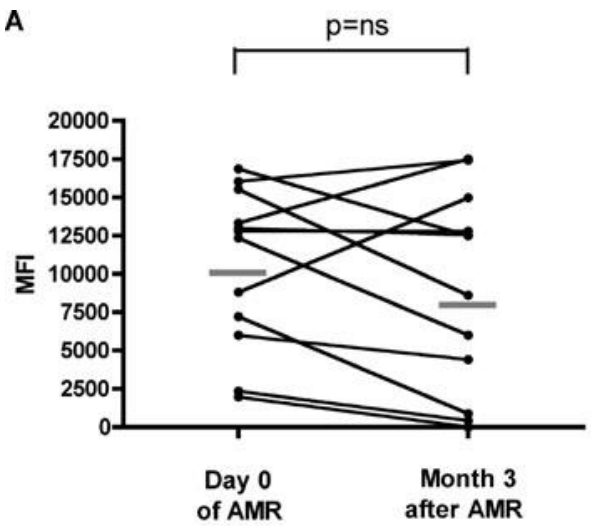
Group A (n=12): 2000-2003

- 2 g/kg IVIG, given over 2 days q 3 weeks, × 4 doses

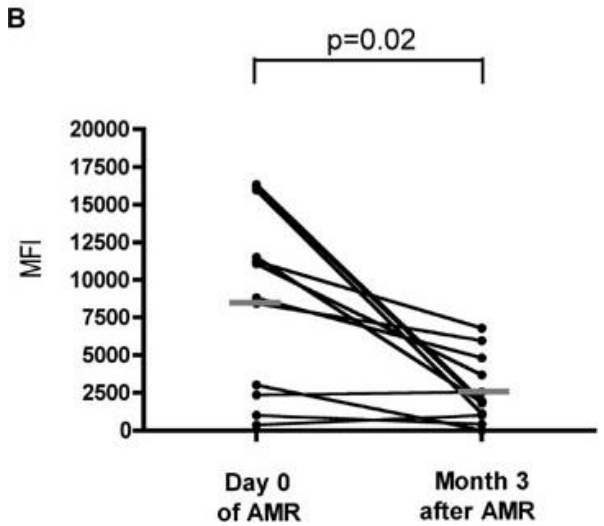
Group B (n=12): 2004-2005

- Daily PLEX + low dose IVIG(100 mg/kg) for 4 sessions
- High dose IVIG as above
- Two weekly doses of rituximab (375 mg/m2)

High Dose IVIG

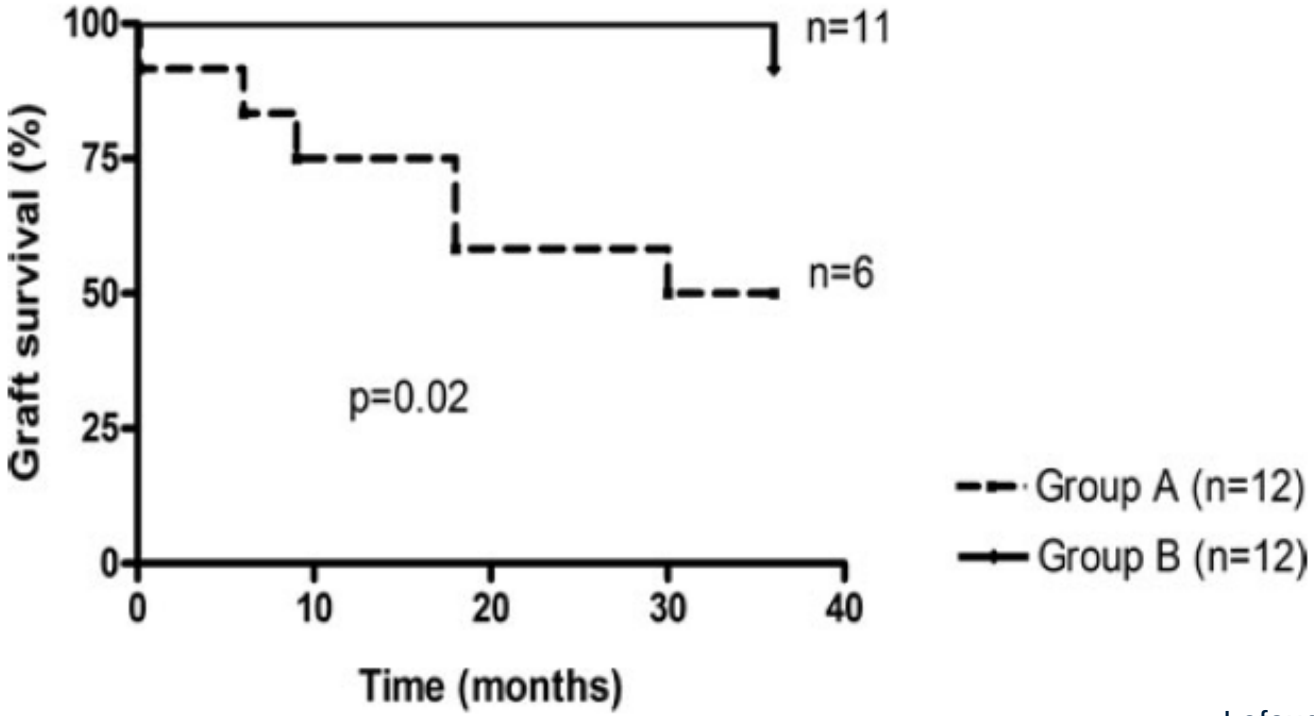


High Dose IVIG + PLEX + Rituximab x 2



Lefaucher et al, AJT 2009

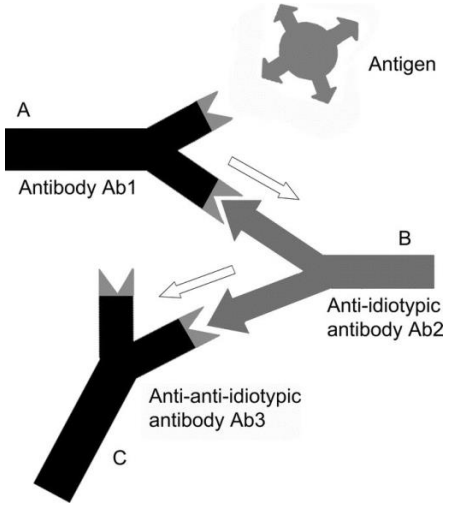
Rituximab and IVIG in Acute AMR [2]

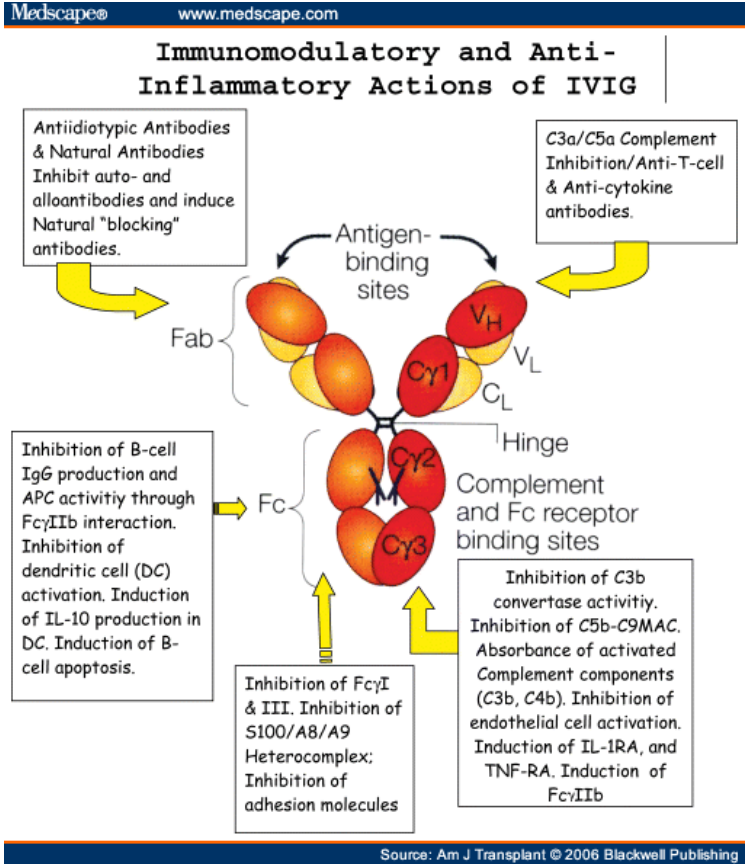


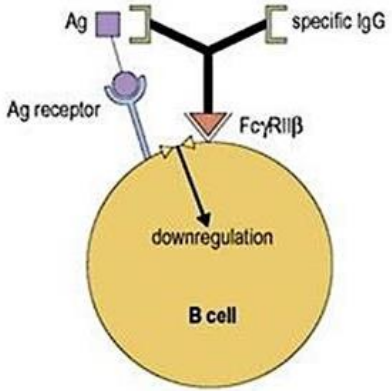
Lefaucher et al, AJT 2009

IVIG

Mechanisms of IVIG







IVIG side effects

Adverse Events:

1. Acute kidney injury

1. Infusion-related: headache, N, V, back pain, fever, tachycardia

1. Aseptic meningitis (1-10%)

1. Thrombosis

1. RBC hemolysis

1. Anaphylaxis (IgA deficiency)

AKI with IVIG

Table 1
Demographic and Clinical Data on Reported Cases of Renal Failure Following IVIg Therapy

	Published case reports ($N = 87$)	FDA report ($N = 88$)	FRPC report ($N = 49$)
Age—median (range)	64.2 (20–90)	62.5 (3–91)	67 (22–92)
Male/female ratio	49/38 (56%)	48/40 (55%)	30/19 (61%)
Indications for use			
Hematological	46 (53%)	39 (44%)	29 (59%)
Immunological	20 (23%)	20 (23%)	6 (12%)
Neurological	14 (16%)	17 (19%)	13 (27%)
Infectious diseases	7 (8%)	9 (11%)	0
Not reported		3 (3%)	1 (2%)
Preexisting renal disease	40/87 (46%)	14/54 (26%)	21/45 (47%)
Sucrose-containing products	64/87 (74%)	79/88 (90%)	44 (90%)
Maltose/glucose products	14/86 (16%)	7/88 (8%)	1/49 (2%)
Undetermined stabilizer	7/86 (8%)	2/88 (2%)	4/49 (8%)
Acute hemodialysis	28/87 (32%)	35/88 (40%)	17/49 (34%)
Deaths	8/87 (9%)	13/88 (15%)	4/49 (8%)

FRPC, French Regional Pharmacovigilance Center.

Orbach, Clinical Reviews in Allergy and Immunology, 2005

Different preparations of IVIG

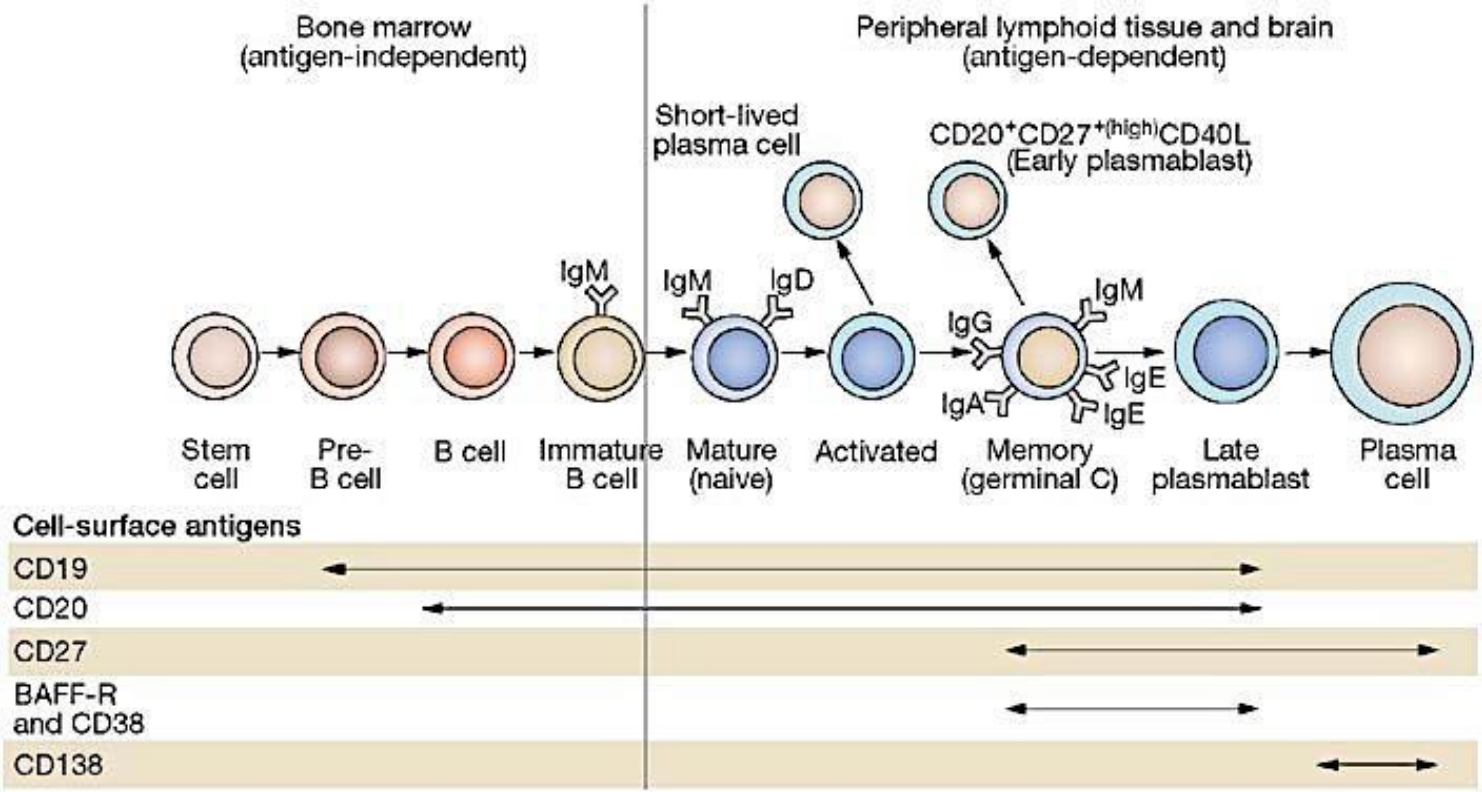
Product[a]	Sodium Content (at 5% Concentration)	Sugar Content	Osmolality	Shelf Life[k]	Reconstitution Time	Administration[l]
Cytomegalovirus Intravenous Immune Globulin						
CytoGam	1-1.5 mEq/ 50 mL	5% sucrose	>206-222 mOsm/kg	24 mo	Not applicable (liquid solution)	0.2- to 15-mcm filter required; compatible with NaCl, D5W; 60 mg/kg/h or 75 mL/h maximum rate
Intravenous Immune Globulin						
Carimune NF	0% water; 0.9% saline	5% sucrose	In sterile water: 3%, 192 mOsm/kg; 6%, 384 mOsm/kg; 12%, 768 mOsm/kg In NS: 3%, 498 mOsm/kg; 6%, 690 mOsm/kg; 12%, 1,074 mOsm/kg	24 mo	Several minutes	No filter required; compatible with NaCl, D5W, sterile water
Flebogamma 5% DIF	<3.2 mmol/L	5% sorbitol (polyol)	240-370 mOsm/L	24 mo RT	Not applicable (liquid solution)	15- to 20-mcm filter recommended; IV, first 30 min: 0.01 mL/kg/min; if tolerated, gradually increase rate up to 0.1 mL/kg/min
Gammagard Liquid 10%	Not detectable	No sugar	240-300 mOsm/kg	36 mo refrigerated; 9 mo RT	Not applicable (liquid solution)	No filter required; compatible with D5W; not compatible with NaCl
Gammagard S/D	0.85%	2% glucose	5%, 636 mOsm/L; 10%, 1,250 mOsm/L[m]	24 mo	<5 min at RT; >20 min if cold	Filter required; compatible with sterile water
Gamunex	Trace	No sugar	258 mOsm/kg	36 mo refrigerated; 6 mo RT	Not applicable (liquid solution)	No filter required; avoid NaCl even in evacuated containers; 0.08 mL/kg/min maximum rate
Octagam 5%	0	10% maltose[n]	310-380 mOsm/kg	24 mo	Not applicable (liquid solution)	No filter required; compatible with D5W, NS, sterile water; latex-free
Privigen 10%	≤0.05 mmol/L (≤1 mmol/L at 10% IgG)	No sugar	240-440 mOsm/kg	24 mo RT	NA	No filter required; compatible with D5W, 0.9% NaCl

How to avoid IVIG associated adverse events

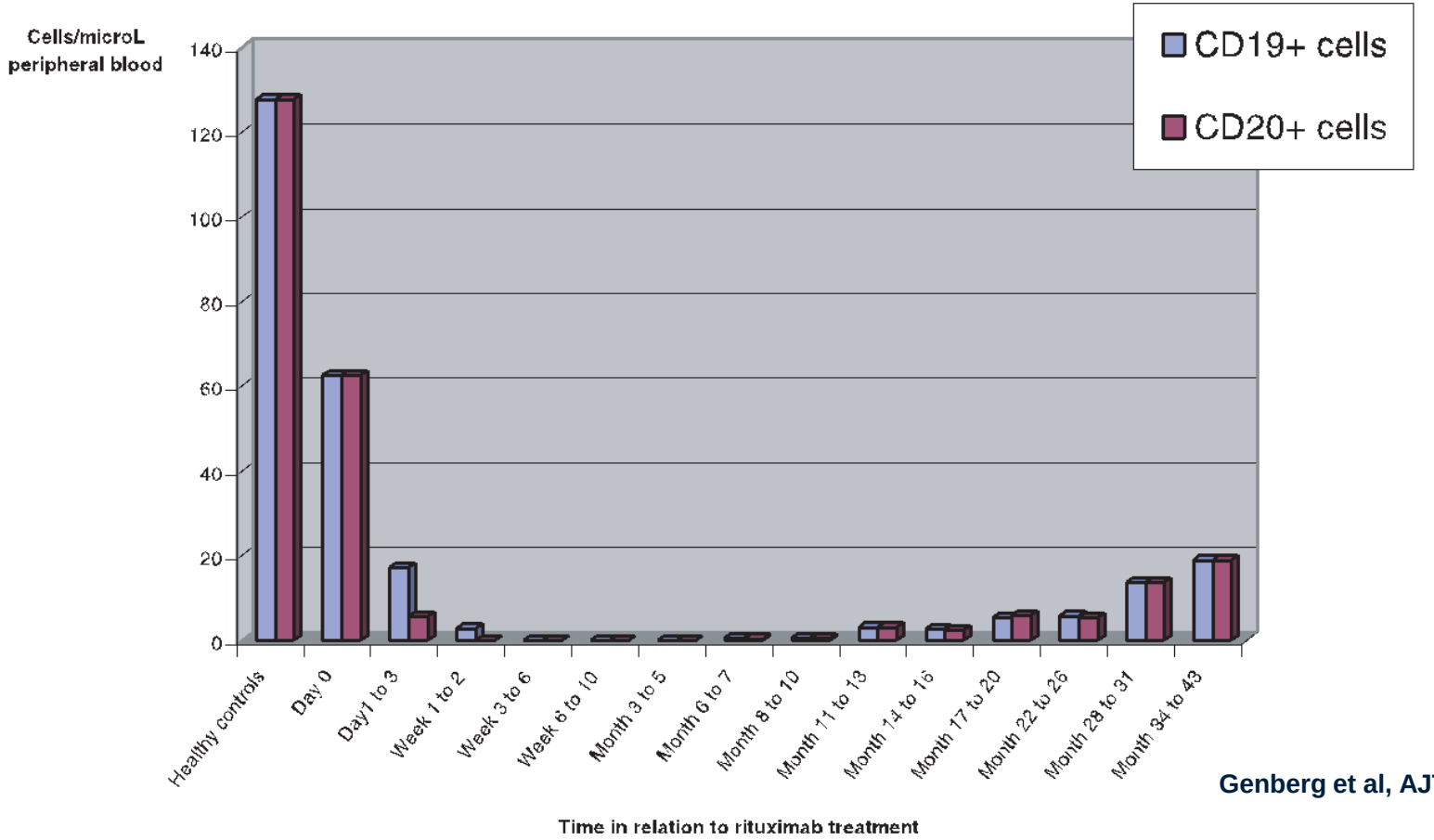
1. Slow infusion: 2-3 mg/kg/min
2. Premedicate: benadry (loratidine), acetaminophen
3. Adequate hydration
4. Avoid high osmolarity products
5. Avoid sucrose-based products
6. Avoid large doses (< 1 g/kg/day)

Rituximab

B Cell Maturation

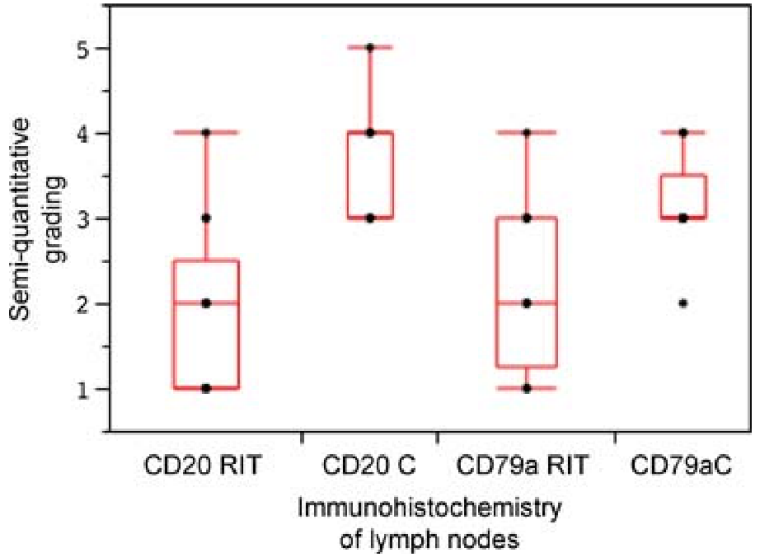


Peripheral B cell depletion



Genberg et al, AJT, 2006

Lymph node B cell depletion

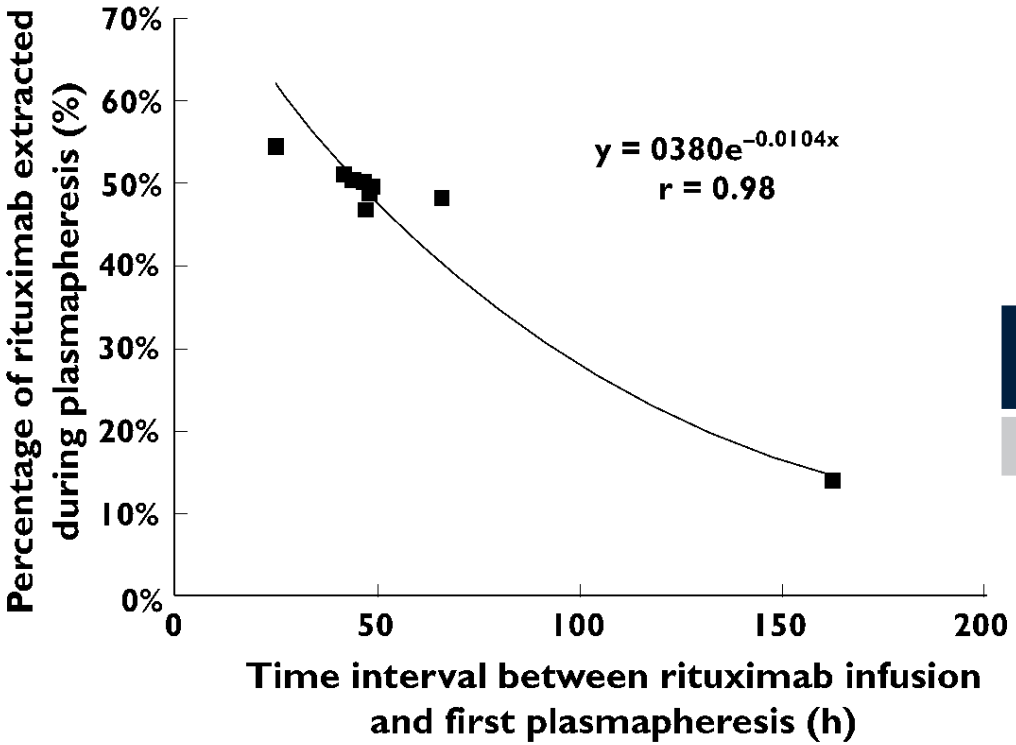


0 = 0% positive cells
1 = 1–10% positive cells
2 = >10–25% positive cells
3 = >25–50% positive cells
4 = >50–75% positive cells
5 = >75% positive cells

Figure 5: Immunohistochemical stainings of lymph nodes, using CD20 and CD79α as B-cell markers. CD20 = immunohistochemstry using anti-CD20 MAb L26 (BD Bioscience) and CD79a = immunohistochemstry using anti-CD79α MAb JCB117(Dako). RIT = induction therapy with rituximab, in combination with triple immunosuppression. C = conventional immunosuppression only.

Genberg et al, AJT, 2006

Dosing of Rituximab with PLEX



PLEX Timing	24 hr	48 hr	72 hr
↓ in AUC	26%	20%	16%

Puisset, Br J Clin Pharmacol, 2013

One-Year Results of the Effects of Rituximab on Acute Antibody-Mediated Rejection in Renal Transplantation

RITUX ERAH, a Multicenter Double-Blind Randomized Placebo-Controlled Trial

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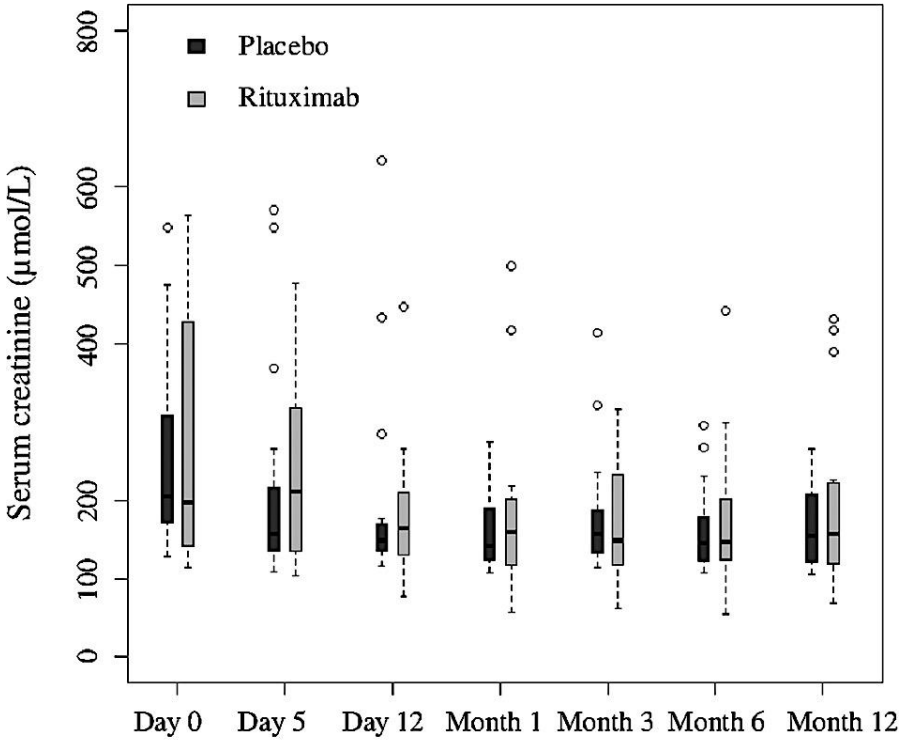
- Acute C4d+ AMR with HLA-DSA within 1st year
- N = 19 (Placebo)
- N = 19 (Rituximab)

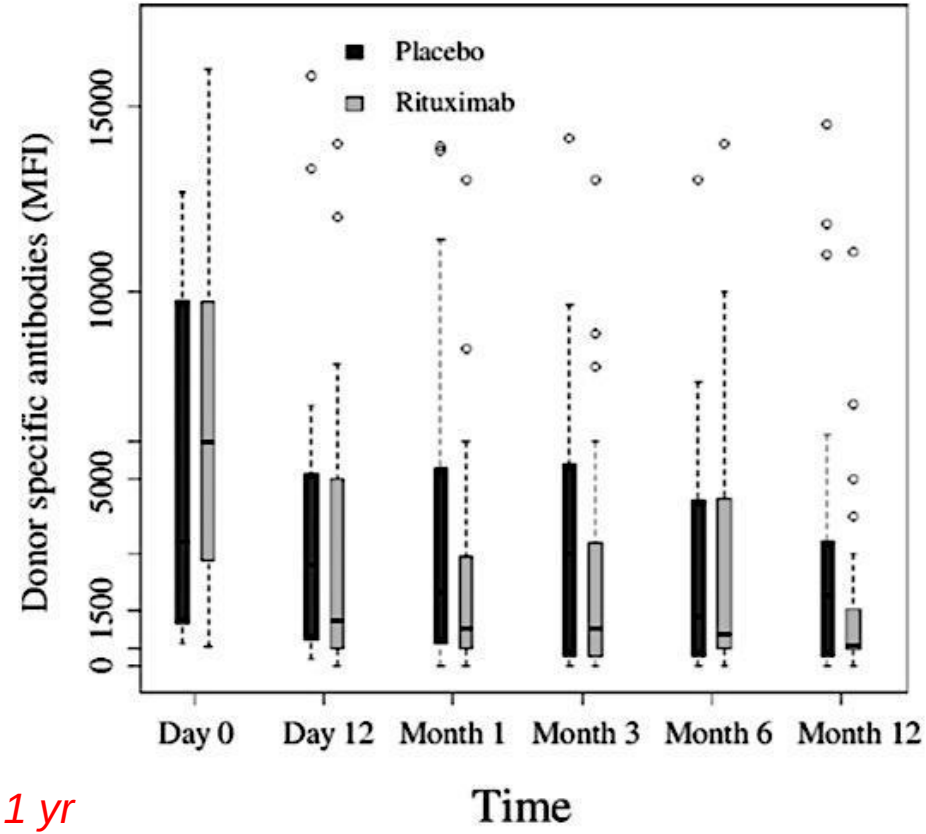
- Primary endpoint: treatment failure = composite graft loss or no improvement in Cr (<30% decrease of peak Cr) at Day 12

- Usual Care: Methylpred pulse x 3 days
  PLEX x 6 + low dose IVIG over 12 days

- Rituximab (375 mg/m2) at Day 5 (option for 2 additional doses)

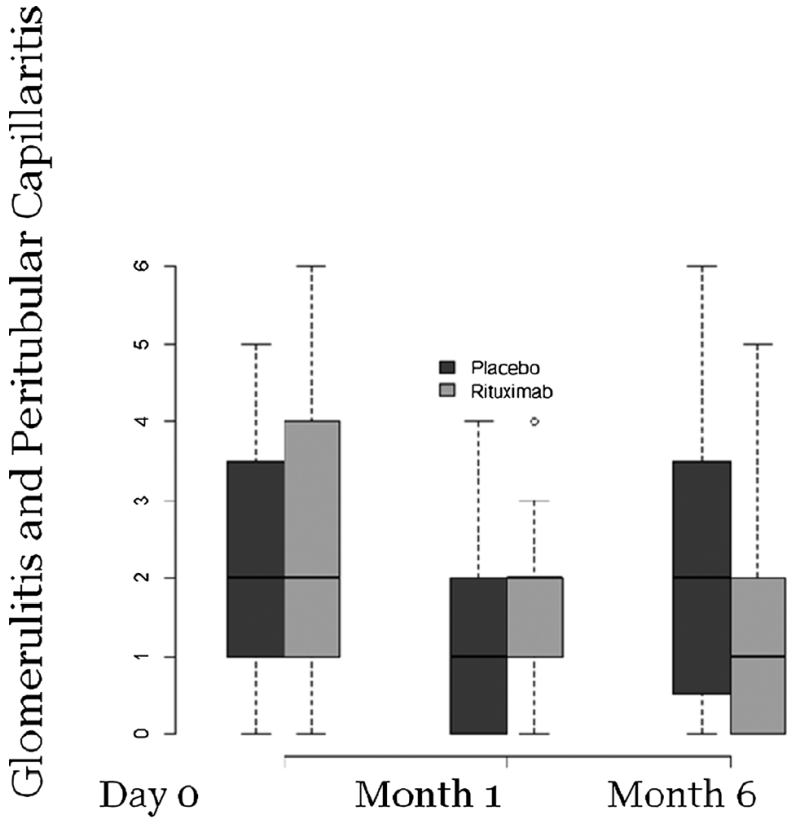
Sautenet et al, Transplantation, 2015

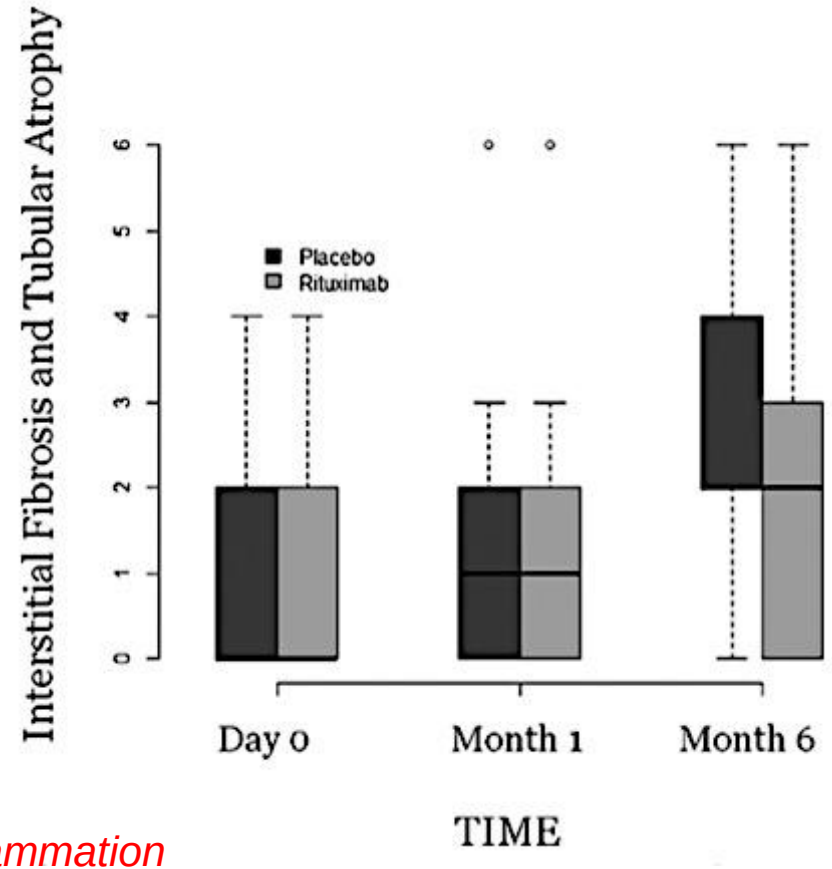




- *No difference in SCr improvement at 1 yr*
- *Trend towards greater DSA reduction at 1 yr with Ritux*

Sautenet et al, Transplantation, 2015

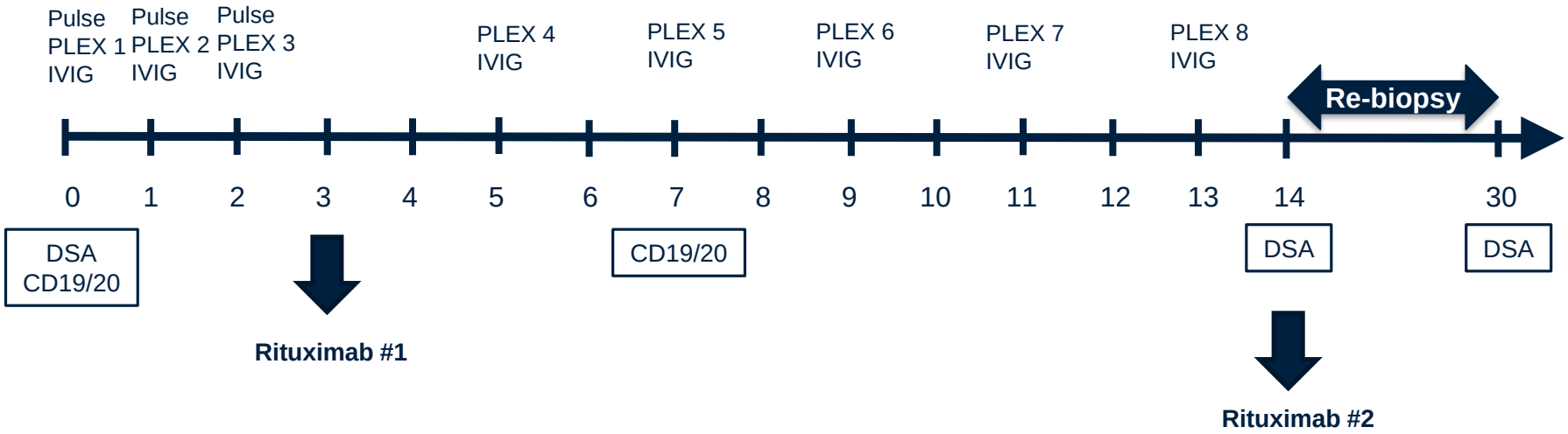




- *Trend towards reduced microvascular inflammation and reduced chronicity with Rituximab*

Sautenet et al, Transplantation, 2015

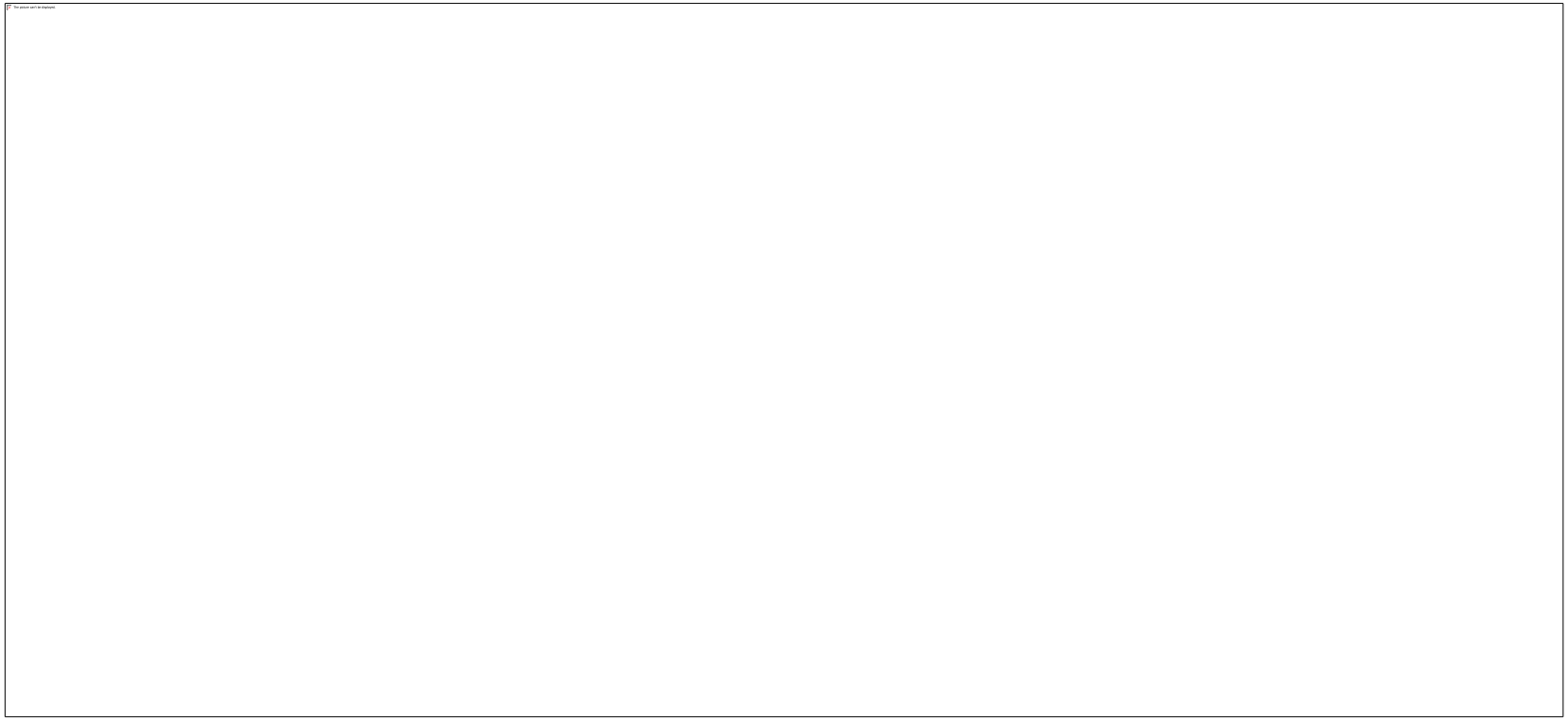
Acute AMR Treatment Protocol



[1]IVIG = 100 mg/kg
Pulse = methylpred 500 mg IV
Optimize MMF and Tacrolimus

[2]Rituximab dose #2 based on clinical indication and if CD19/20 ≥ 5 cells/mm^2

AMR is a heterogeneous disease



Novel Therapeutics for AMR

Bortezomib

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

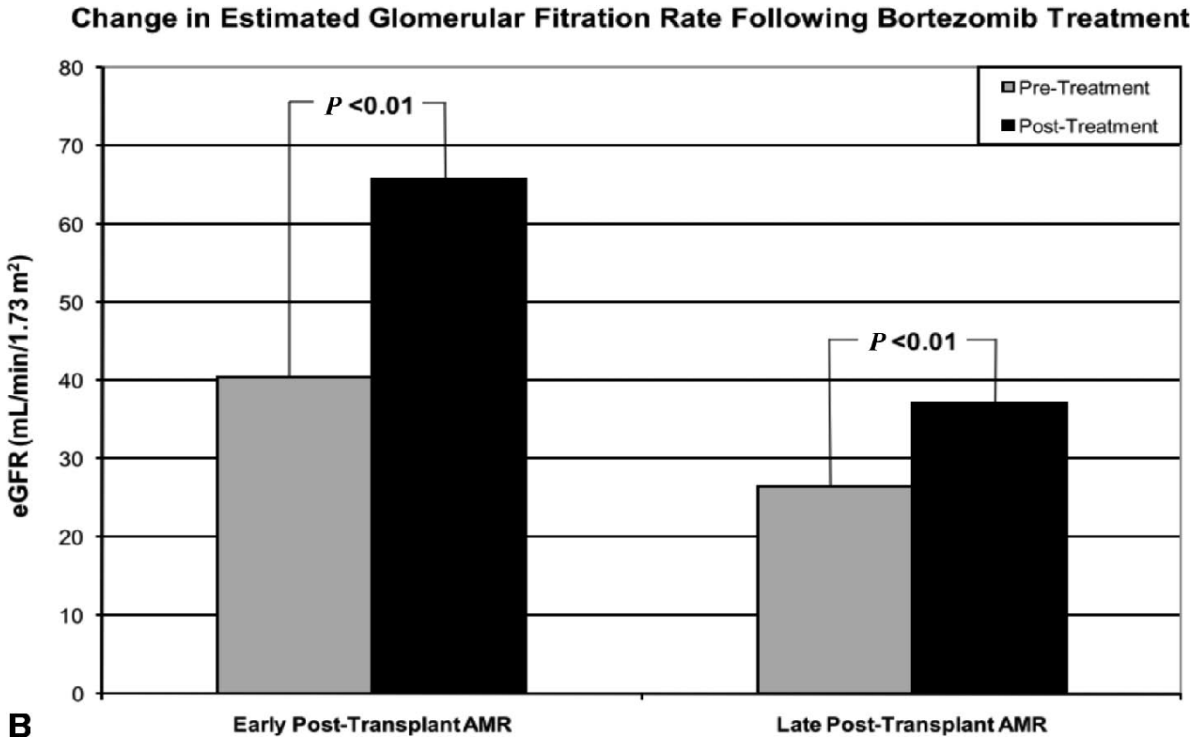
R. Carlin Walsh,[1] Paul Brailey,[2] Alin Girnita,[2] Rita R. Alloway,[3] Adele Rike Shields,[1] Garth E. Wall, Basma H. Sadaka, Michael Cardi,[4] Amit Tevar,[1] Amit Govil,[3] Gautham Mogilishetty,[3] Prabir Roy-Chaudhury,[3] and E. Steve Woodle[1,5]

- Early AMR (< 6 months post-Tx): N=13
- Late AMR (> 6 months post-Tx): N=16

Protocol:

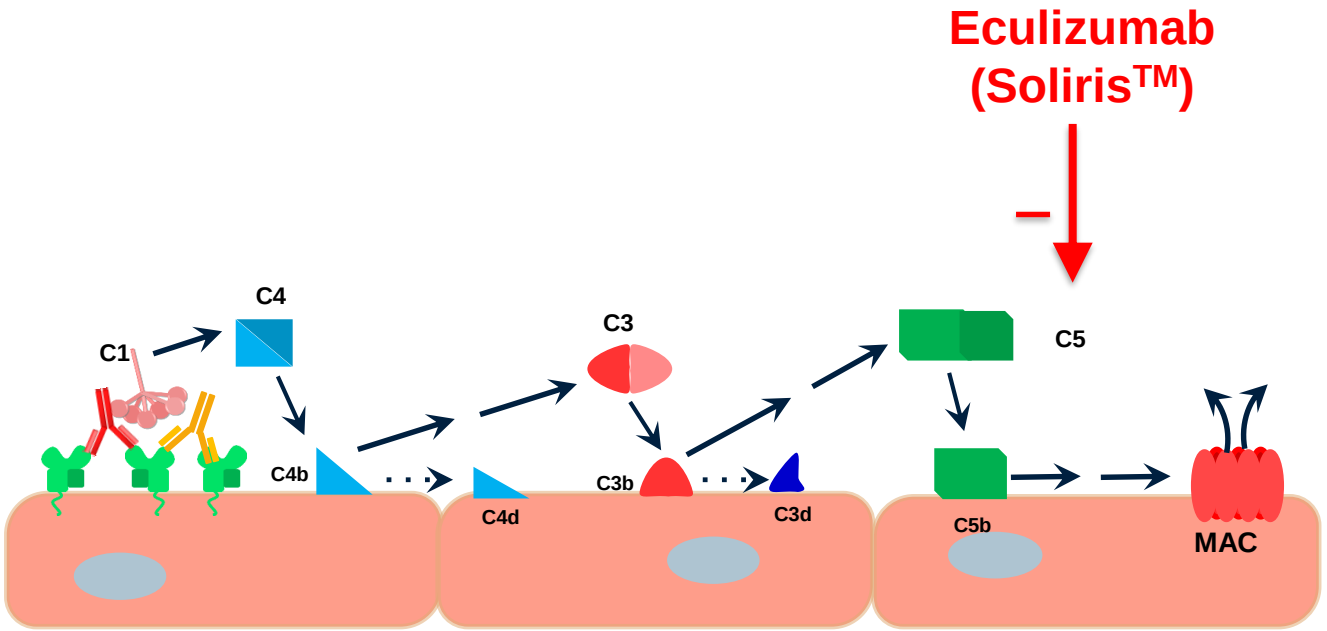
- Rituximab 375 mg/m2 x 1 dose before Bortezomib
- Bortezomib 1.3 mg/m2 x 4 doses over 11 days
- PLEX performed before each bortezomib dose + 3 daily PLEX 72 hr after last bortezomib dose

Late AMR is difficult to treat



Walsh et al, Transplantation, 2011

Complement inhibitors (extinguishing the fire)



Courtesy of Nicole Venezuela

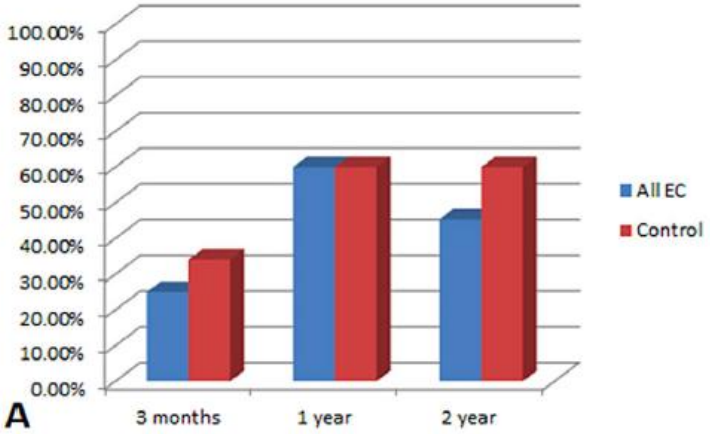
World's most expensive drug — which costs up to $700,000 per year — too expensive, Canada says

TOM BLACKWELL | February 3, 2015 | Last Updated: Feb 3 1:47 AM ET
More from Tom Blackwell | @tomblackwellNP

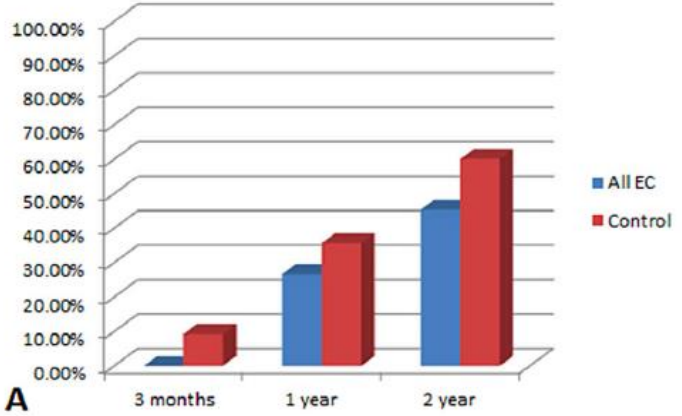
Positive Crossmatch Kidney Transplant Recipients Treated With Eculizumab: Outcomes Beyond 1 Year

L. D. Cornell[1], C. A. Schinstock[2], M. J. Gandhi[3], W. K. Kremers[2] and M. D. Stegall[2,*]

AJT, 2015



Moderate-to-Severe Peritubular capillaritis in Controls vs. Eculizumab			
	3-4 months	1 year	2 year
All EC	25.0% (7/28)	60.0% (18/30)	45.4% (10/22)
Control	34.1% (14/41)	60.0% (21/35)	60.0% (15/25)
p-value (control vs. EC)	P= 0.59	P=1.00	P=0.39



Transplant Glomerulopathy in Controls vs. Eculizumab			
	3-4 months	1 year	2 year
All EC	0% (0/28)	26.7% (8/30)	45.4% (10/22)
Control	9.3% (4/43)	39.5% (15/38)	63.6% (21/33)
p-value (EC vs. control)	P=0.15	P=0.31	P=0.27

C1 esterase inhibitor

Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study

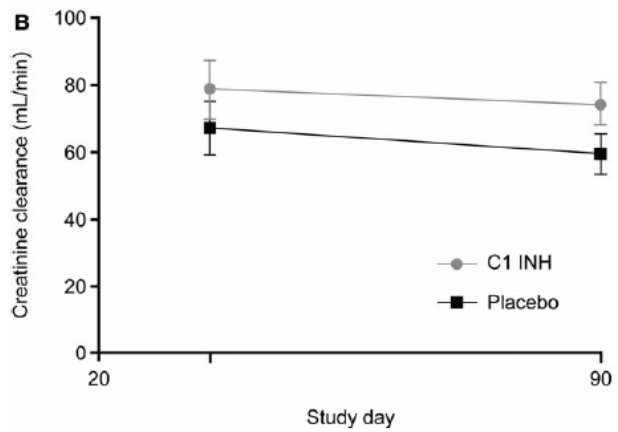


Table 4: Change in histopathology scores from qualifying biopsy to day-20 biopsy

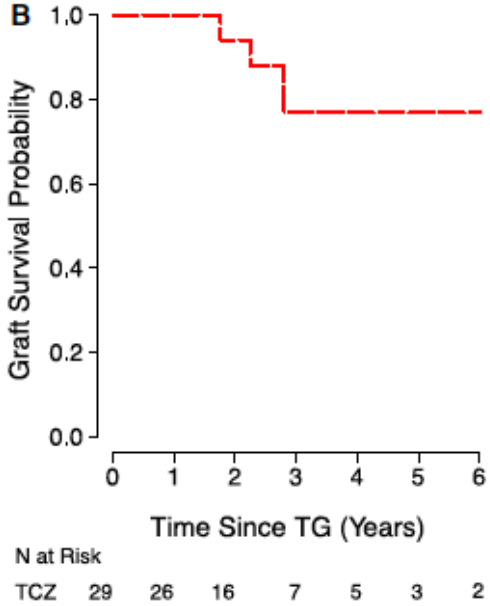
Histopathology end point	Placebo (n = 9)			C1 INH (n = 9)			p-value for treatment difference[1]
	Qualifying biopsy	Day-20 biopsy	Change	Qualifying biopsy	Day-20 biopsy	Change	
C4d score							
Mean ± SD	60.8 ± 41.2	15.8 ± 32.9	−45.0 ± 46.9	68.7 ± 41.8	32.6 ± 39.1	−36.1 ± 33.4	0.6498
Margination score							
Mean ± SD	23.0 ± 24.8	17.0 ± 25.8	−6.0 ± 14.0	9.2 ± 15.2	21.8 ± 29.3	12.6 ± 25.9	0.0768
Glomerulitis score							
Mean ± SD	17.0 ± 24.9	23.7 ± 30.9	6.7 ± 26.6	16.3 ± 23.4	19.0 ± 28.8	2.7 ± 13.6	0.6928
Vasculitis score							
Mean ± SD	3.9 ± 7.8	0 ± 0.0	−3.9 ± 7.8	0 ± 0.0	3.2 ± 6.4	3.2 ± 6.4	0.0508
Glomerulosclerosis score							
Mean ± SD	4.2 ± 6.8	2.8 ± 3.6	−1.4 ± 7.8	8.9 ± 9.6	2.6 ± 4.3	−6.3 ± 7.9	0.2042
Chronic glomerulopathy score							
Mean ± SD	0.3 ± 1.0	0.6 ± 1.7	0.2 ± 0.7	0 ± 0.0	0 ± 0.0	0 ± 0.0	0.3322
Interstitial fibrosis score							
Mean ± SD	3.2 ± 6.6	9.1 ± 14.1	5.9 ± 9.8	0.7 ± 1.3	12.2 ± 20.4	11.6 ± 20.9	0.4723
Chronic vasculitis score							
Mean ± SD	8.3 ± 12.8	6.7 ± 11.7	−1.7 ± 18.2	2.6 ± 4.5	5.4 ± 7.7	2.9 ± 9.0	0.5103

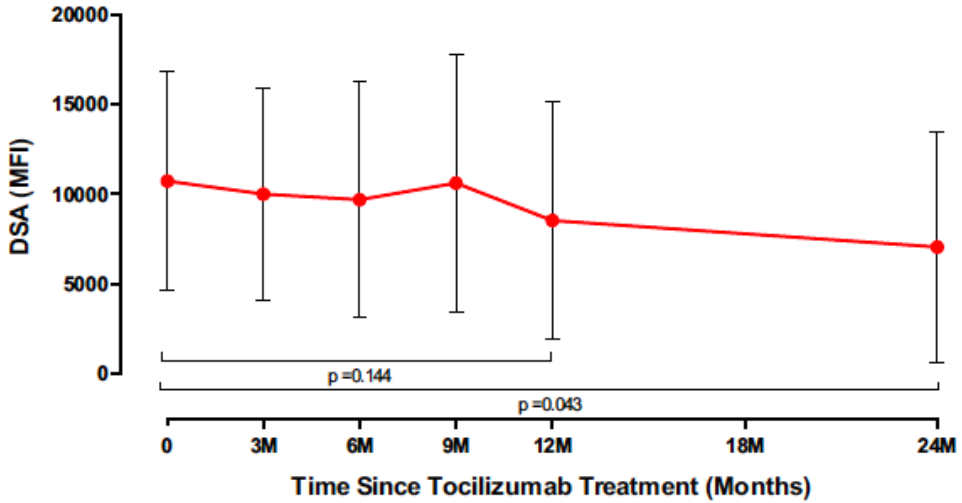
C1 INH, C1 esterase inhibitor.
[1]p-value is from ANOVA model with treatment as the factor.

Tocilizumab

Assessment of Tocilizumab (Anti–Interleukin-6 Receptor Monoclonal) as a Potential Treatment for Chronic Antibody-Mediated Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Allograft Recipients

J. Choi[1,*], O. Aubert[2], A. Vo[1], A. Loupy[2], M. Haas[3], D. Puliyanda[1], I. Kim[1], S. Louie[1], A. Kang[1], A. Peng[1], J. Kahwaji[1], N. Reinsmoen[3], M. Toyoda[4] and S. C. Jordan[1]



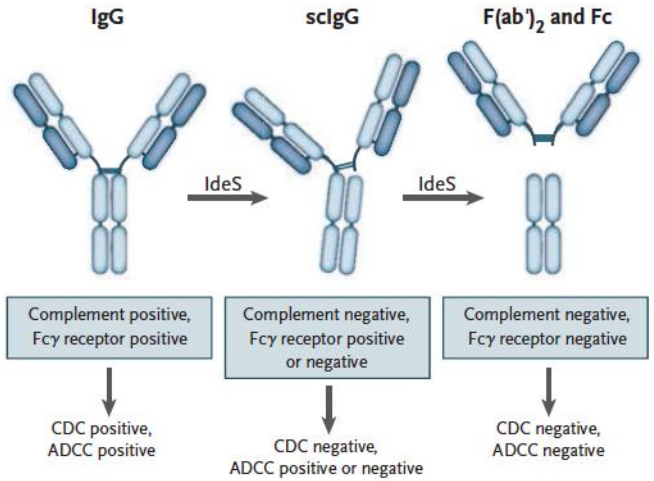


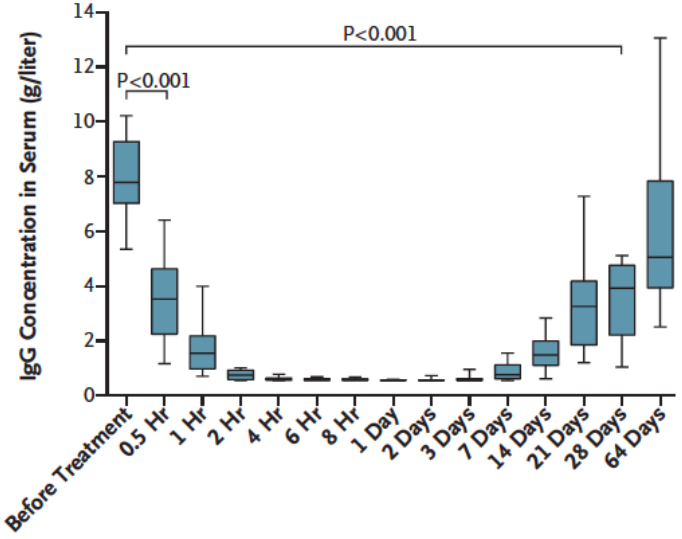
IdeS

IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation

S.C. Jordan, T. Lorant, J. Choi, C. Kjellman, L. Winstedt, M. Bengtsson, X. Zhang, T. Eich, M. Toyoda, B.-M. Eriksson, S. Ge, A. Peng, S. Järnum, K.J. Wood, T. Lundgren, L. Wennberg, L. Bäckman, E. Larsson, R. Villicana, J. Kahwaji, S. Louie, A. Kang, M. Haas, C. Nast, A. Vo, and G. Tufveson

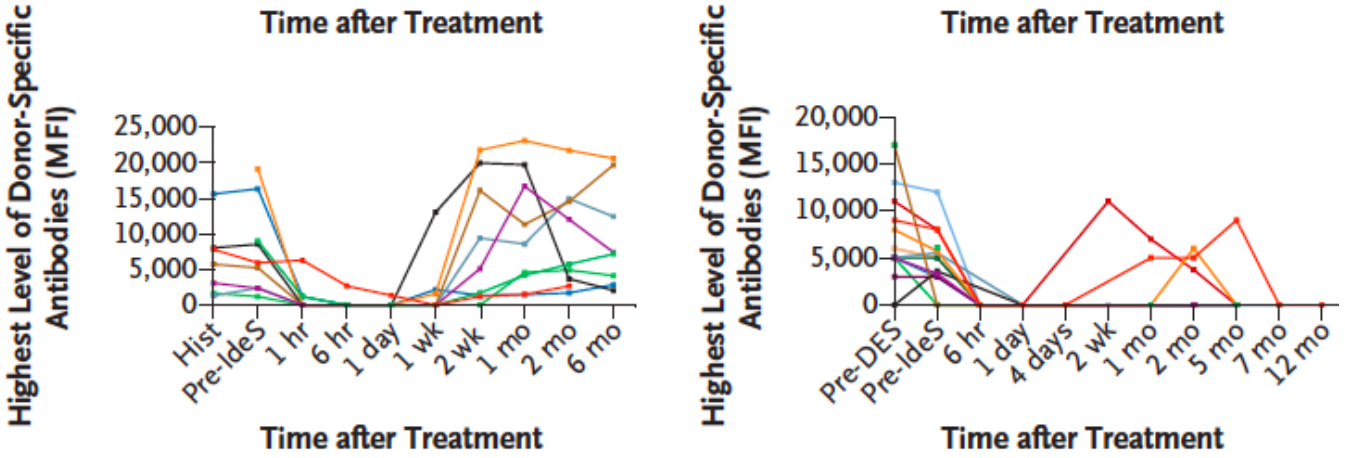
NEJM, 2017





Ides (IgG-degrading enzyme derived from Streptococcus pyrogenes)

- Open-label, phase 1-2, desensitization trial (US, Sweden)
- N=25 highly sensitized patients, cPRA ≥ 95%
- All IgG-DSA eliminated at time of transplantation
- N=10/25 with AMR, 1 patient with hyperacute rejection (non-HLA) – ***rebound phenomenon***



Challenges with AMR treatment

1. Rituximab: *does not target plasma cells, incomplete penetration of B cells in lymphoid organs*

1. Bortezomib: *humoral compensation in germinal center*

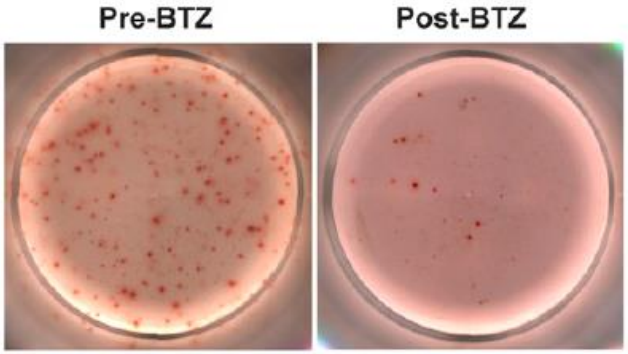
1. Complement inhibitors: *non-complement-mediated pathways*

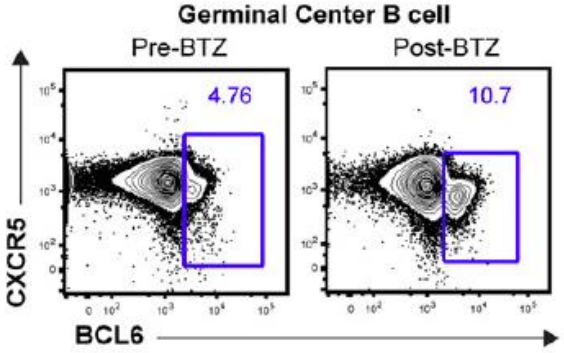
1. IdeS: *rebound antibody production*

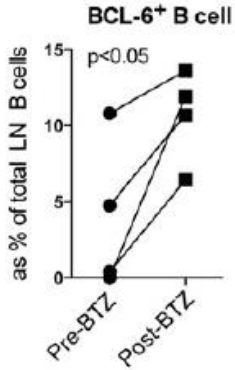
Humoral Compensation after Bortezomib Treatment of Allosensitized Recipients

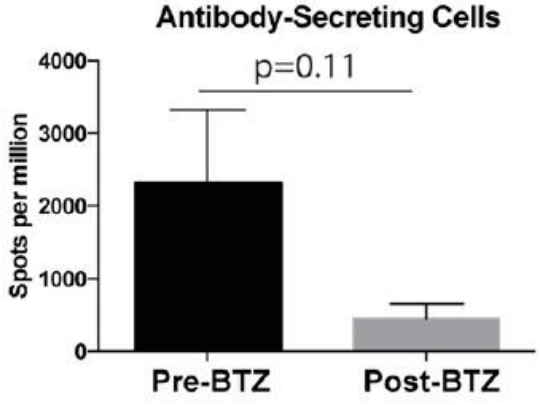
JASN 2017

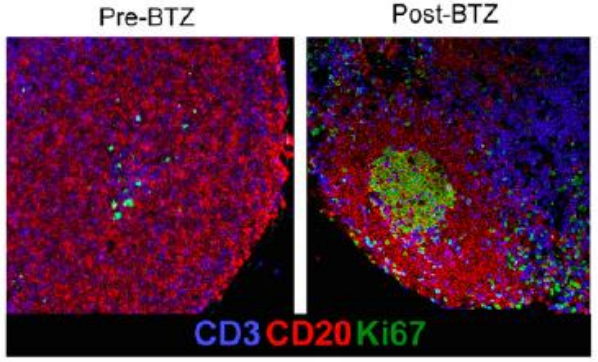
Jean Kwun,*† Christopher Burghuber,†‡ Miriam Manook,* Neal Iwakoshi,† Adriana Gibby,†
Jung Joo Hong,§ and Stuart Knechtle*†

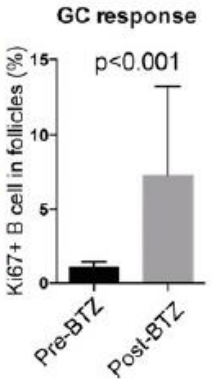












When B cells are out of the gate all is lost

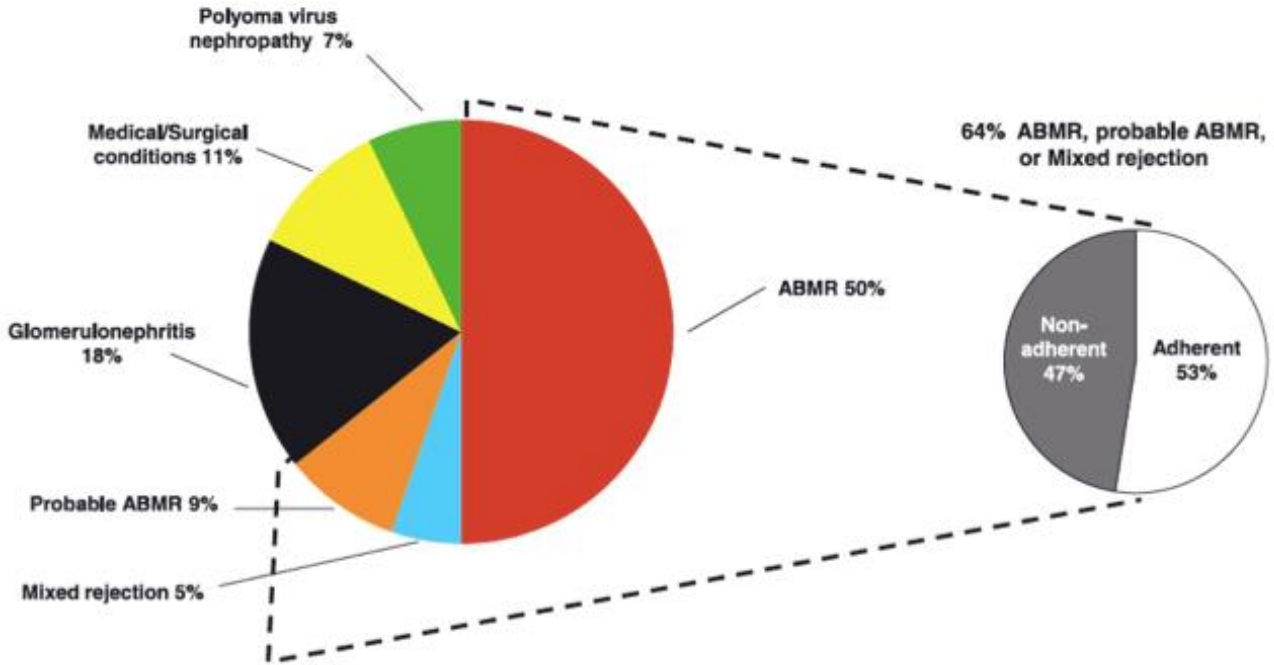
An ounce of prevention is worth a pound of cure

1. Multidisciplinary approach to target non-adherence

1. Optimize immunosuppression

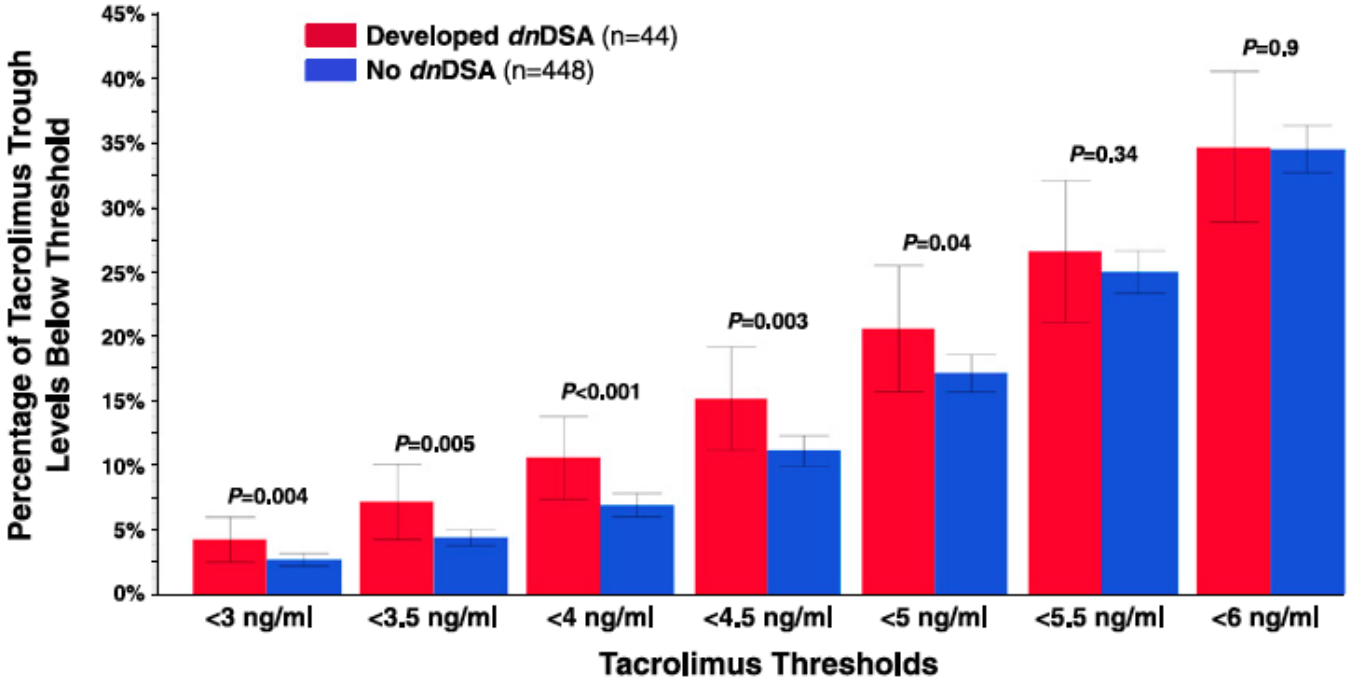
1. A better way of matching using epitope?

Non-adherence in AMR



Sellares, AJT 2012

Optimizing CNI Level

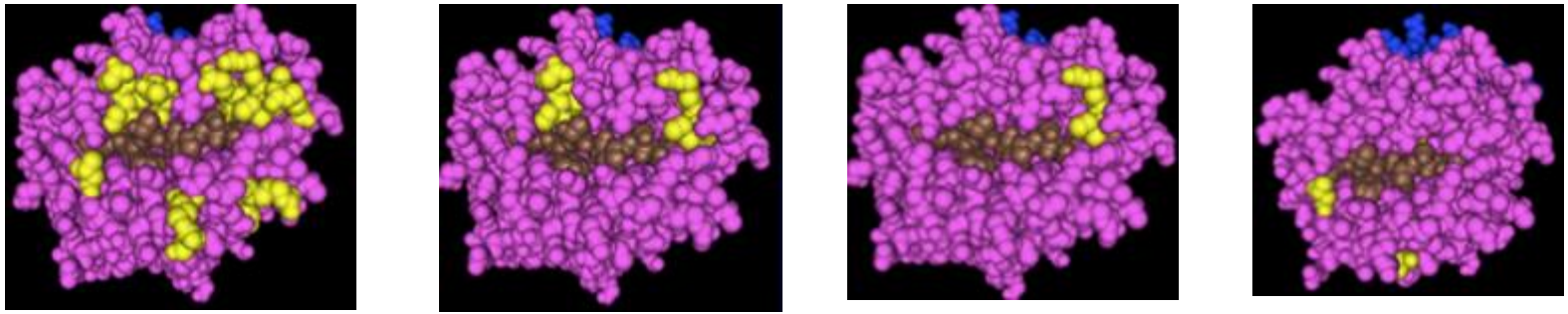


Wiebe, JASN 2017

Epitope analysis: not all mismatches are created equal

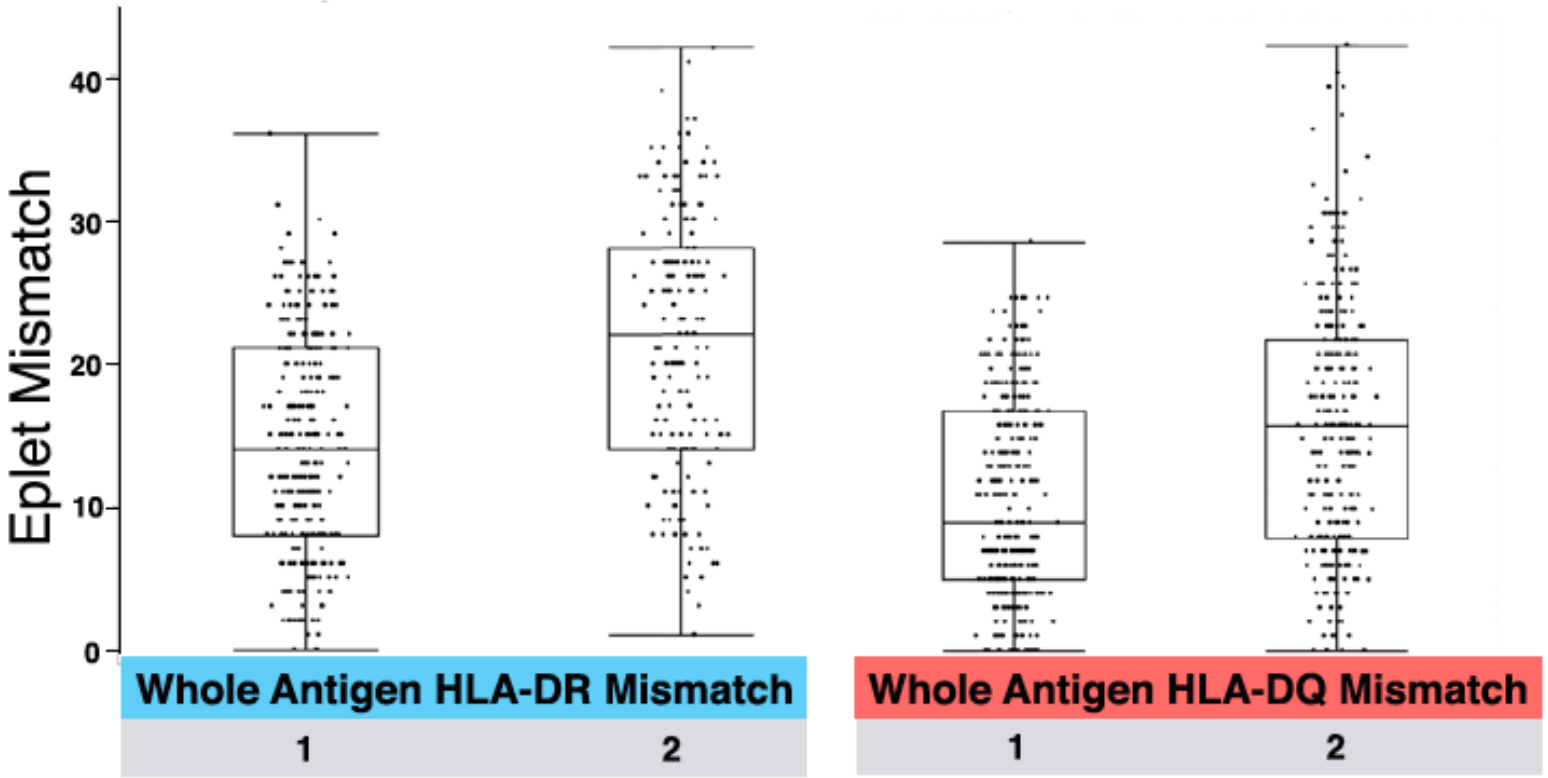
Recipient:
B7

Donor 1 | Donor 2 | Donor 3 | Donor 4

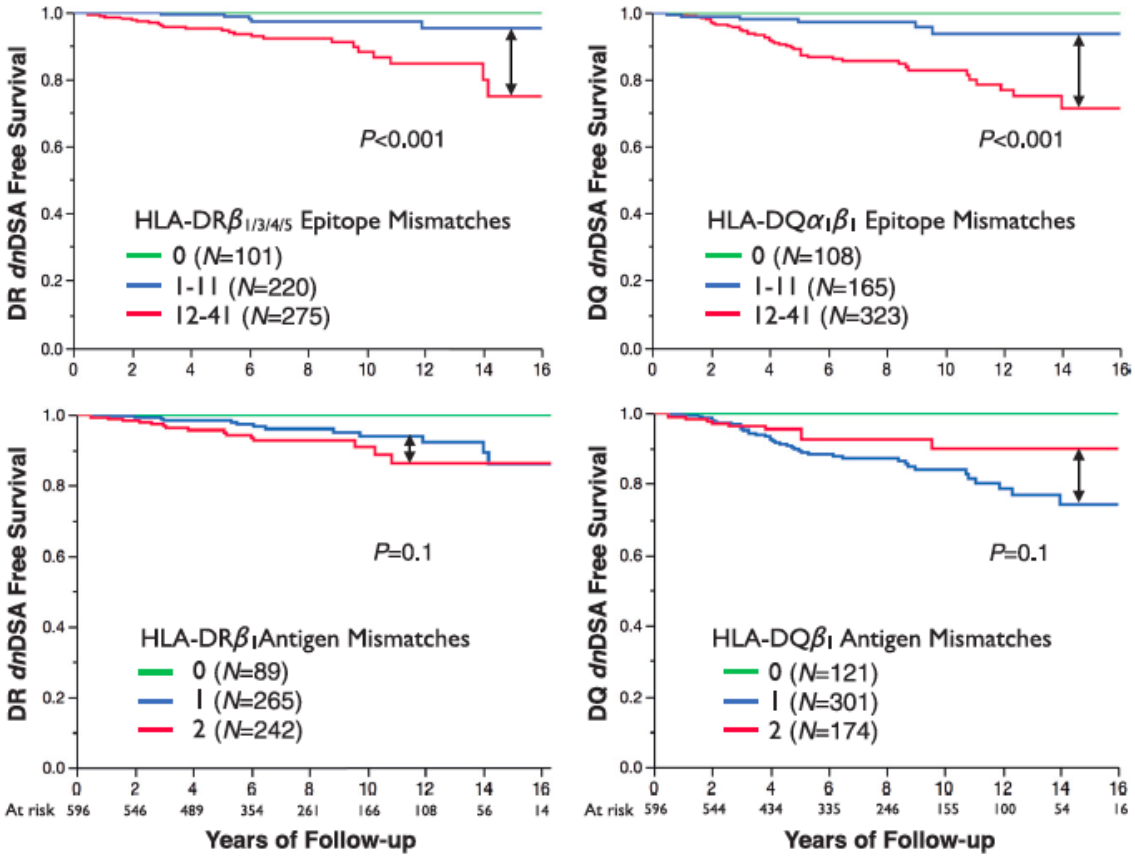


B51 | B44 | B35 | B8

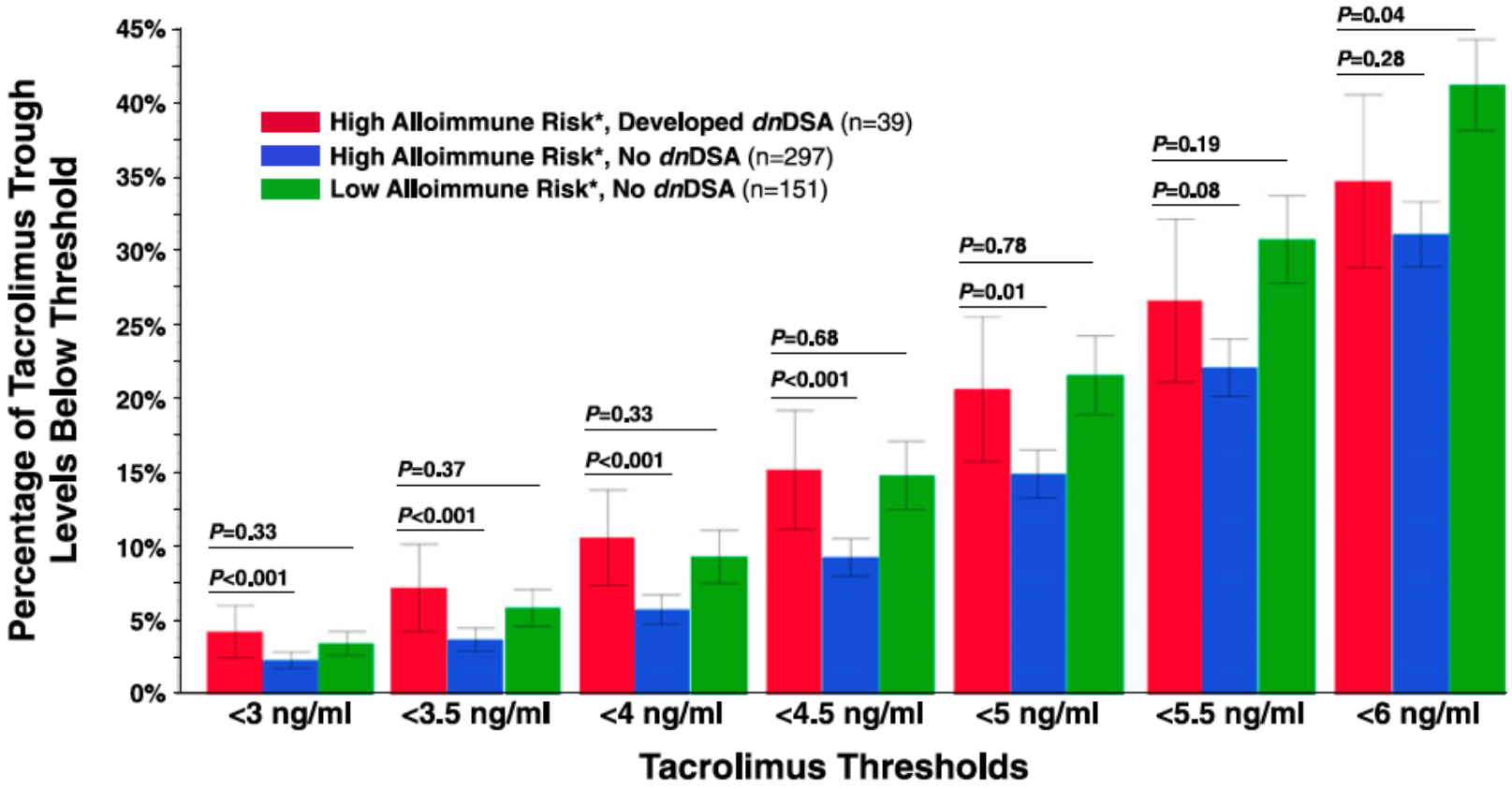
Major differences between antigen vs. epitope mismatches



A novel strategy of matching using epitope analysis



Interaction of Immunosuppression and epitope mm



Summary

- Current AMR treatment options are only moderately effective and carry significant treatment-related toxicities
- Consider clinical, antibody, and histologic characteristics to identify the appropriate patients to undergo treatment
- Early AMR, preformed DSA, class I DSA are most susceptible to immunomodulation
- Prevention remains the best strategy to overcome AMR:
  - Identify and address non-adherence
  - Consider donor-recipient matching at the epitope level
  - Optimize immunosuppression

THANK YOU

Questions?

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