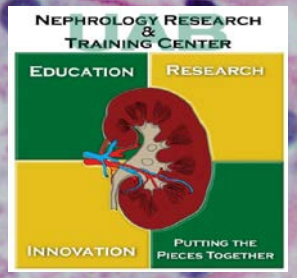


UAB MEDICINE
NEPHROLOGY

New Developments in Kidney Transplantation In the Current Decade

Roslyn B. Mannon, M.D.

Professor of Medicine, Division of Nephrology
Professor of Surgery, Division of Transplantation
Director of Research, Comprehensive Transplant Institute

UAB COMPREHENSIVE

Relevant Financial Relationship Disclosure Statement

Roslyn Bernstein Mannon, MD
University of Alabama at Birmingham

I have financial relationship(s) within the last 12 months relevant to my presentation with:

1. Grant Support relationship with Alexion
2. Grant Support relationship with Astellas
3. Grant Support relationship Quark Pharmaceuticals
4. Grant support relationship with Care Dx
5. Honorarium with CareDx

AND

My presentation may include discussion of off-label or investigational use

Outline of Topics

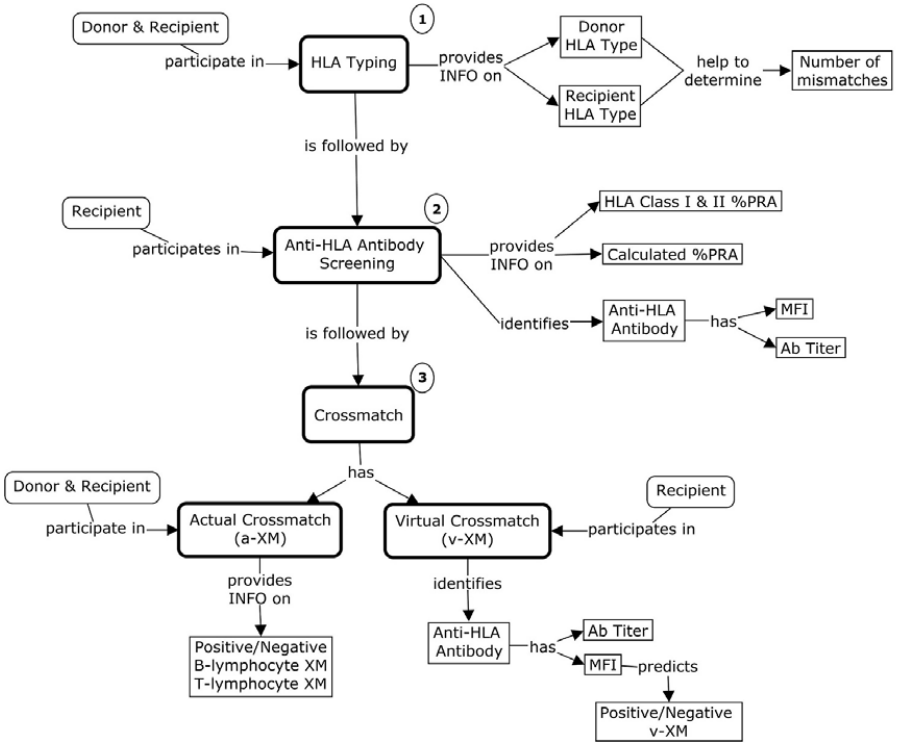
- FDA meetings and successes
- Banff Pathology updates in AMR, CAMR
- Scientific updates in brief in kidney Tx
  - DSA and outcomes
  - IFTA + I, i-IFTA, cTCMR
  - New Immunosuppressants
  - Genomics/Biomarkers
- Nonadherence
- The new importance of HLA mismatches
- Kidney Allocation

FDA Public Workshops

- 2010: Antibody Mediated Rejection
- 2011: Ischemia Reperfusion Injury
- 2012: Clinical Endpoints in Kidney Transplantation
- 2012: Meeting with Generics Group
- 2015: Surrogate Endpoints in Clinical Kidney Transplantation
- 2016: Patient-Focused Drug Development Who Have Received an Organ Transplant (PDUFA)

Kidney Transplant v1.0 Standard: TAUG-KT

- Therapeutic Area Data Standards User Guide for Kidney Transplant (TAUG-KT) [aka Kidney Transplant v1.0 standard]
  - a compilation of terms and processes focused on studies of therapeutic interventions to prevent rejection of transplanted kidneys in adult recipients. Published October 2016.
- With funding from FDA, the standard was developed through the Coalition for Accelerating Standards and Therapies (CFAST) , a joint initiative of CDISC (Clinical Data Interchange Standards) and C-Path (Critical Path), ASN KHI, AST
- Goal: to accelerate clinical research and medical product development by creating and maintaining data standards, tools, and methods for conducting research in transplantation.



Banff and Cultural Changes: Multiple Phenotypes

- Acute cellular rejection
  - Acute T cell mediated rejection
  - Acute antibody mediated rejection
- Chronic rejection
  - Chronic antibody mediated rejection
  - Chronic T cell mediated rejection
- Mixed cellular and antibody mediated rejection
- Mixed acute and chronic rejections (antibody / cellular)

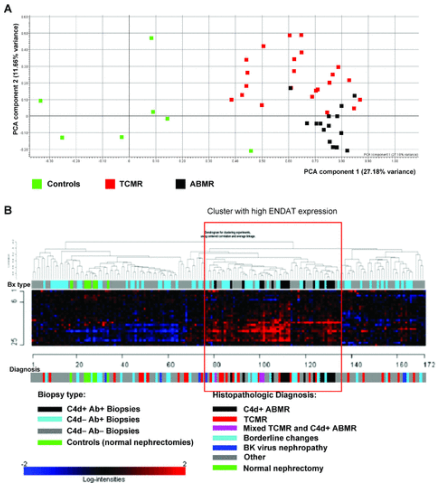
Revised AMR Criteria: Banff 2013 Revisions

Table 2: Revised (Banff 2013) classification of antibody-mediated rejection (ABMR) in renal allografts

Acute/active ABMR; all three features must be present for diagnosis[1,2]

1. Histologic evidence of acute tissue injury, including one or more of the following:
   - Microvascular inflammation ($g > 0$[3] and/or $ptc > 0$)
   - Intimal or transmural arteritis ($v > 0$)[4]
   - Acute thrombotic microangiopathy, in the absence of any other cause
   - Acute tubular injury, in the absence of any other apparent cause
2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
   - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or $C4d > 0$ by IHC on paraffin sections)
   - At least moderate microvascular inflammation ($[g + ptc] \geq 2$)[5]
   - Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated[6]
3. Serologic evidence of donor-specific antibodies (DSAs) (HLA or other antigens)

Hence C4d is NOT required but there must be evidence of endothelial interaction



Sis et al. Am Jnl Transplant 2009; 9:2312— endothelial gene expression in kidney allograft with alloantibody indicates antibody mediated injury regardless of C4d status

Changes in Morphologic Criteria of CAMR (Banff 2013)

- Banff 2007: 1 or more of the following
  - Transplant glomerulopathy (cg≥1)
  - Peritubular capillary basement membrane multilayering
  - Fibrosis intimal thickening of arteries
    - IFTA now deleted

- Banff 2013 : 1 or more of the following
  - Transplant glomerulopathy (cg>0)
  - Severe peritubular capillary basement membrane layering by EM
  - Arterial intimal fibrosis of new onset

Impact of New Banff Criteria

- De Serres et al. AM Jnl Transplant 2016: 123 biopsies
  - Looked at impact of diagnosis of AbMR on death-censored graft survival or doubling of serum creatinine
  - **By 2007 criteria, 18% had AbMR**
  - **By 2013 criteria, 36% had AbMR**
  - 2013 criteria were associated with worse outcomes
  - When looking at individual components, the key change was the C4d staining requirement.

- Gimeno et al. Nephrol Dial Transplant 2016
  - 73 biopsies for chronic allograft dysfunction , proteinuria, or presence of de novo DSA
  - **With 2007 criteria, 40% with AbMR**
  - **With 2013 criteria, 74% with AbMR (P=0.006)**
  - Main differences were inclusion of microvascular inflammation (g+ptc>2) and EM diagnosis

Literature Review of dnDSA

Sensitization in Transplantation: Assessment of Risk (STAR)- North American 2017 Working Group

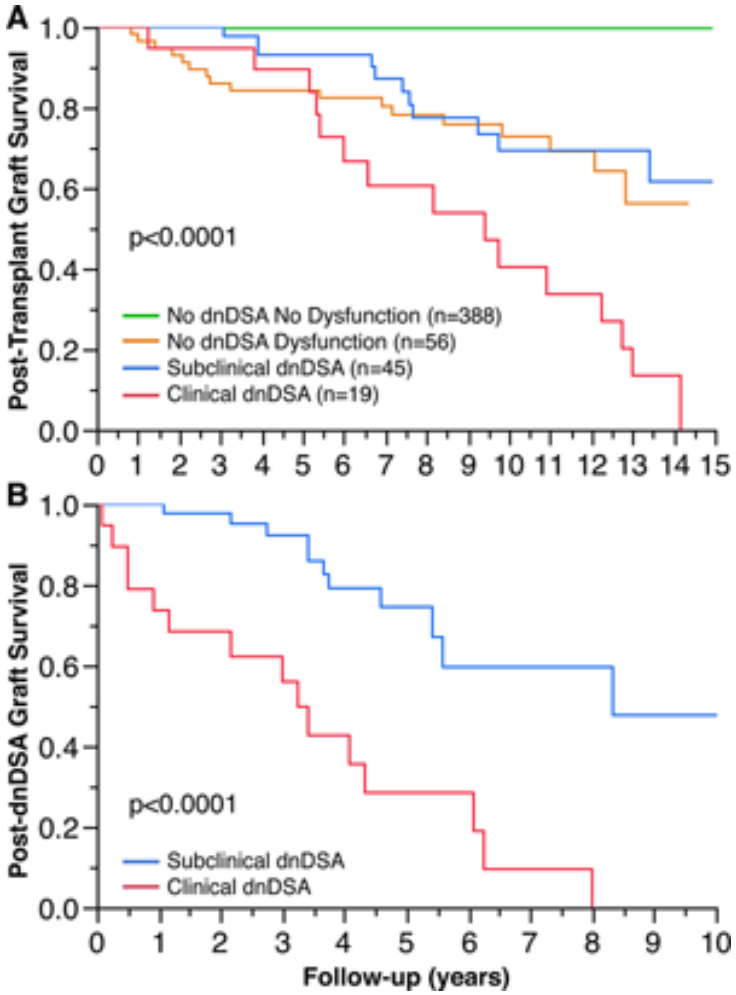
Post-Tx DSA Method	Post-Tx DSA kit configuration	Post-Tx DSA Serum inhibition	Post-Tx DSA Serum dilution	Post-Tx DSA testing	Post-Tx C1q	Post-Tx C3d	Post-Tx IGG subclasses	Pathology	Induction therapy	Maintenance therapy	Surveillance Biopsy (y/N)	DSA detected	Rejection (Y/N)	TCMR (Y/N)	AMR (Y/N)	eGFR	Patient Survival	Graft Survival	Main conclusion / Recommendation
Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Banff 1997	Rabbit ATG or basiliximab	Tac	N	Not reported	Y	Not reported	16 patients with bk and AMR	Not reported	Not reported	Not reported	BK infection is not associated with
Luminex	LabScreen Mixed beads - One	Not reported	Not mentioned: positive >500 MFI	@ 1m, 6m, 12m, 24m	Not reported	Not reported	Not reported	Banff 2007	Rabbit ATG / Basiliximab (only	Tac/MMF/CS	N	65/244 = 26.6% with 52/65 found by	36/244 = 15% Overall / 14/31 in	31/244 = 13% /	5/244 = 2% with all 5 in DSA + only	12m eGFR : 66.2 in DSA neg; 59.8 in	97.7 / 100 for neg versus pos	98.9 DSA Neg / 93.9 DSA Pos /	De novo DSA has worse graft
Luminex	Not reported	Not reported	Not reported	For cause (I think)	Not reported	Not reported	Not reported	Banff 2007	All 3 agents (79% campath)	steroid free, CNI only with campath	N looks like for cause and not every	79 (12.4%) dn DSA at a median of 3.8m	Y	Y but not indicated %	Y but not indicated by %	Not reported	Not reported	22% loss with dn DSA	Microcirculation changes had worse
Luminex	LabScreen Mixed beads - One	Not reported	Not mentioned: positive >1000 MFI	@1y, 2y, 3y, 4y, 5y	Not reported	Not reported	Not reported	Not reported	Rabbit ATG only	Tac/MMF +/- CS in trial	N	Yes, 1/16 (6%) CCS and 0/21 CSWD	Not Reported	Not reported	Not reported	Not reported	1 ccs death	1 CCS graft loss	Renal transplant recips withdrawn
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Advocates for high resolution typing
Luminex	Single antigen flow bead assay (One	Not reported	ND	Protocol: POD 3, 7, 10, 14, 28, 60, 90,	ND	ND	ND												
Luminex	LabScreen Mixed beads - One	Not reported	Not reported	Not Reported; only 52/94 (55%)	Not reported	Not reported	Not reported	Banff 1997 and 2003	Not reported (2003-2007)	No reported	N	only 52 of 94 were assayed and	Y (ACMR, AMR, MIXED)	Y 30/52 (58%)	10/52 (19%) MIXED = 12/52 (23%)	SCR 3.6 mg/dL in nonreduced DSA;	Not Reported	ACR with 100% survival; AMR with	1. DSA is an independent
Luminex	LabScreen Mixed beads - One Lambda / positives reassayed on SAB /	Not reported	Not reported	pre, 1m, 3m, 6m, 9m, 12m annually and clinically indicated	Not reported	Not reported	Only IgM or IgG	Banff 1997 and 2005	13% Rabbit ATG (PRA>20%) ; 86% anti-IL2R	69% CSA; 30% tacrolimus	N	30 total developed anti HLA antibody (15/group); 17 dn DSA; 9 DSA pos in @1y: 9%	23% in dnDSA neg; 33% in dnDSA pos	34/189 (18%) ; 14 (7%) mixed	0 episodes	1.8 mg /dL at time of initial detection;	Not Reported	@2years: 128/142 (88.7%) in dnDSA neg; 32/47 (68%) in dnDSA POS	11% of recips with no detectable DSA at time of transplant
Luminex	LabScreen Mixed beads; SAB if positive (LABScan	Not reported	Not reported	Annually and with for cause biopsy	Not reported	Not reported	Not reported	AMR=microcirculation injury, pos C4D and with/without	9.2% Rabbit ATG; 68% anti-IL-2R	15% CNI conversion to mTORi	N	@1y: 9% developed HLA Ab with 94% in Tf	17 AMRs (14%) and 43 (12%) ACMR in all	43 TCMR ; 32 in Tf versus 10 in non Tf	17 AMRs : 15 in TF versus 2 in non Tf	Not reported	5 / 390 = 98.7%; all in Tf group	98% GS with 1 Graft lost in Tf group	Post transplant blood Tf has signficant risks; HR
Solid Phase ELISA screen; Luminex if positive	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported (maybe in original report)	sirolimus-mmf-pred versus CSA-mmf-pred	N	anti HLA antibody (15/group); 17 dn DSA; 9 DSA pos in	Not Reported	Not reported	Not reported	eGFR 54.4 in sirolimus vs 49.7 in CSA	14 deaths; GS 86.3% sirolimus versus 90.6% in CSA	21 grafts lost; 85.5% and 85.8% respectively	time of transplant as maintenance was NOT
Labscreen SAB (one Lamda), MFI >	SAB	Not mentioned	Not done	01, 4, 12 mos and cause	Not done	C4d+ 1 yr protocol bx 3% DSA +, 2%	Not done	Banff 2009 meeting report	Thymo/campath or anti-IL-2	Thymo/campath + tac & MMF or anti-IL-	Yes - 1 yr	17.6% anytime, 8.2% + at 12 mos	All rejection 21% DSA+ vs 17% DSA -	Not reported	58% AMR or mixed DSA+ vs 3% DSA-	61.2 DSA+, 62 ml/min/1.73 m2	Not reported	Not reported	DSA 1st yr frequently transient,
Not reported	Single antigen beads (?type or	Not reported	Not reported	For cause at time of bx	Not done	Not done	Not done	Banff 2007	Not Reported	Not reported	No - for cause only	Described as DSA not detected pre	Y (ACMR, AMR, MIXED)	33% (inlcudes BR); 2% mixed	8.20%	Not reported	Not reported	reduced survival in dn DSA 47.6%	49/89 (55%) late bx were DSA +; dn
Labscreen SAB (one Lamda)	SAB	Not done	Not done	6 mos, annually & for cause	Not done	C4d all biopsies. AAMR & CAMR	Not done	Banff 2009	Anti-IL-2, rituximab and PP ABO	CNI, antimetabolite, steroids	6 mos and 1 yr	4.8%	Prior to 6 mos 14.8 & 12.1% dnDSA +	0after 6 mos 25.9 dnDSA VS 3.9% no	AANR14.8 vs 1.5% & CAMR 22.2 vs	Cr 2&3 yrs 1.35 & 1.46 dnDSA+ vs	Not reported	Stat sig, shown in figure numeric	Rituximab may decrease dnDSA
Luminex	Single antigen flow bead assay (One	Not reported	ND	Protocol: M 3, 6, 9, 18	ND	ND	ND												
Luminex	SAB One Lambda, >500 MFI + DSA	ND	ND	For cause at time of bx	ND	ND	ND	Banff 2009	Not reported	Not reported	ND	Frequency of DSA not reported	302/2079 (15%)	TC vascular 9%; TC no vascular 46%	AM vascular 21%; TC no vascular	Not reported	Not reported	TC no vascular 93.2%, TC vascular	Reports a new type of rejection -
Luminex	LABScreen Mixed beads - One	ND	ND	ND	ND	ND	ND	Banff 2009	basiliximab	CSA, EC MPA, steroids	No - for cause only	21/127	Overall rate of BPAR not stated	Rate of TCMR not stated	2/66 CSA + AMR vs 8/61 everolimus	eGFR not reported stratified for	Not reported stratified for	Not reported stratified for	Everolimus associated with
Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Banff 2013 for AMR; Banff 2009 for BK	Mixed use of thymo, campath,	Mixed with reductions and	N	Y	Y	Not reported	11/69 PVN with AMR	Not reported	Not reported	Worse survival with SCR > 2 mg/dL,	BKPVN with AMR patients were more
Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Varies	Varies	Varies	Varies	yes, and some individuals were	Y	Not reported	DSA more frequently	Not reported	Not reported	DSA more frequently	There is a signficantly
Luminex	Single antigen flow bead assay (One	ND	ND	Tx day 0 and 1 year as well as for	Yes - C1qScreen TM, One Lambda	ND	ND	Banff 2009	In supplemental appendix	In supplemental appendix	Yes - 1 yr	N=196 (19% overall), 128 with	171 of 1016 total pts	96 of 1016 total pts	75 of 1016 total pts	C1q binding DSA eGFR at 1 yr 42+22	Not reported	5 yr survival with DSA 83% vs 94%	complement binding DSA are
Flow & Luminex	Screening flow, single antigen	Not reported	ND	Not reported	Not reported	Not reported	Not reported												
Luminex	Single antigen flow bead assay (One	Not reported	Not reported	0, 4m, 1y, yearly	ND	ND	ND	Banff 2013	Mixed; thymo (50%), campath (20%) and	Triple but steroid free with campath	at 4, 12, 24 and 60m	Yes, in 7% of all recipients; mostly	Y (ACMR, AMR, MIXED)	Yes (20% TCMR at time of dn DSA)	Yes (25% AMR at time of dn DSA);	Fell over time with dn DSA (53 down to		13% graft failure with dnDSA versus	Suggests testing at intervals with
Luminex	Single antigen flow bead assay (One	EDTA treatment	ND	Protocol: 0, 1 yr, 2 yrs, at time of	Yes - C1qScreen TM, One Lambda	ND	Yes												
Flow & Luminex Pos cutoff >300 MFI	Screening flow, single antigen flow,	Not reported	ND	Protocol: 0,1, 2, 3, 6, 12, 18 and 24	ND	ND	ND	Not reported											
Flow & Luminex Pos cutoff >300 MFI	Screening flow, single antigen flow,	Not reported	ND	Protocol: 0,1, 2, 3, 6, 12, 18 and 24	ND	ND	ND	Banff 2009	32% of patients; 9% rATG and 23%	Triple therapy	Y with dnDSA only	64 of 508 dn DSA (13%); 2% year 1,	Y	associated but rates not provided	76% of AMR with dnDSA (48%	Fall in GFR - 65 ml/min versus -3.63	Not reported	5y gs 28% with clinical dnDSA;	Risk for graft dysfunction with dn
Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported												

Frequency of De Novo DSA Development Varies from 2-27%

Group	1st Tx	Pre-Txp Technique	De novo DSA		
			1st Month	1st Year	>1st Year
Cooper	NA	FCXM	15.6%	27%	0%
DeVos	93%	>2000 MFI	8.0%	20%	5% / y
Heilman	91%	>1000 MFI	8.2%	17.6%	NA
Everly	100%	>1000 MFI	3.0%	11.0%	2.3% / y
Wiebe	95%	>500 MFI	0.0%	2.0%	2.0% / y

Frequency varies based on measuring technique, frequency of measures, baseline immunosuppression and patient type.

Rates and Determinants of Progression to Graft Failure in Kidney Allograft Recipients With *De Novo* Donor-Specific Antibody



76% Stable

9 % Subclinical DSA

11 % Dysfunction/ no DSA

4 % Clinical DSA

11 % Other =

GN+IFTA (n=20)
TCMR+IFTA (n=10)
IFTA (n=8)
BKPVN (n=2)
Other (n=6)
Not bx (n=10)

Clinical DSA Outcome Worse than Subclinical DSA:
- Loupey JASN 2015;
- Orandi Transplantation 2015

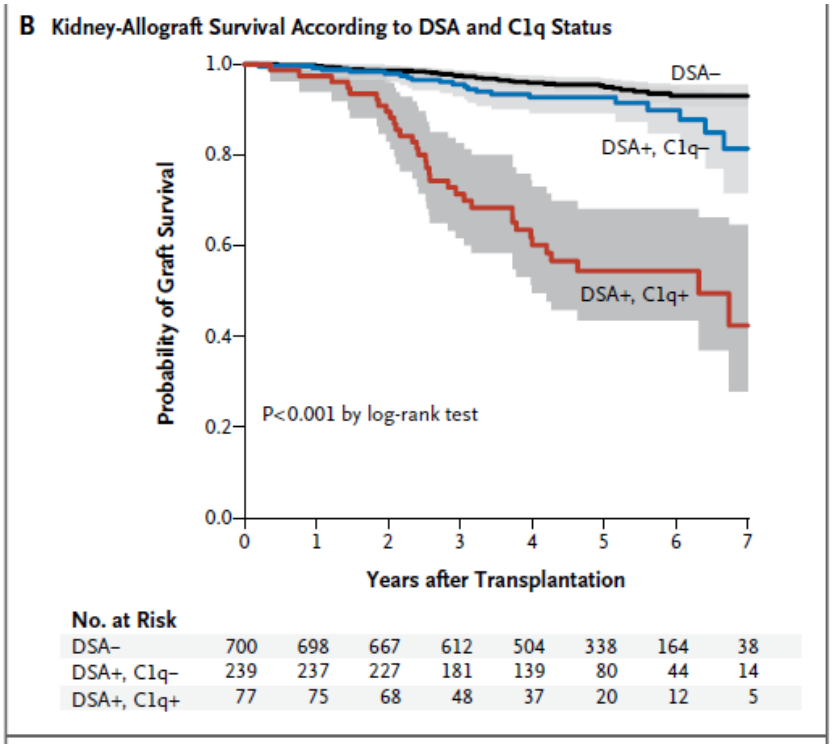
Wiebe et al. Am Jnl Transplant 2012; 12(5):1157

DNDSA and therapy conversion or minimization –the other adherence

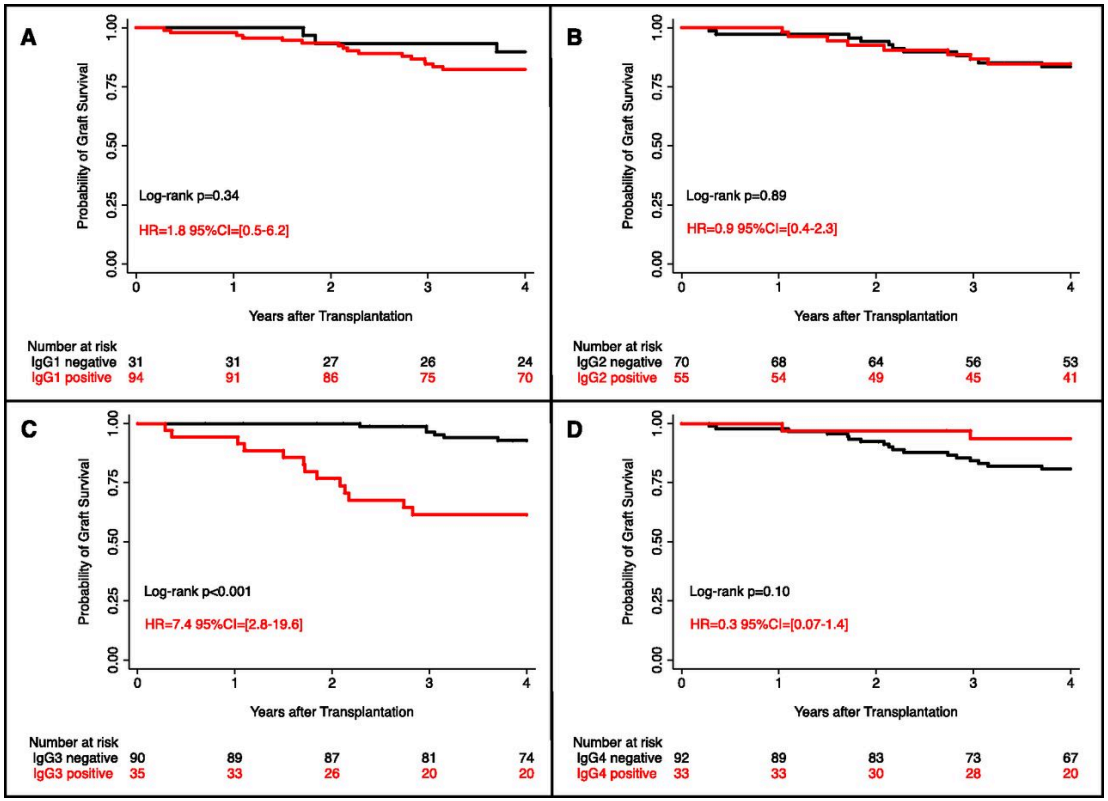
- Liefeldt Am Jnl Transplantation 2012; 12(5): 1192 :: CSA conversion to mTORi
- Hricik et al. JASN 2015; 26:3114:: tac minimization/withdrawal
- Shapiro Transplantation 2008; 85:1125:: tac weaning
- Hoshino Transplantation 93: 1173:: LD with clonal deletion protocol
- Dorje C Transplantation 2013; 96:79:: Late AbMR with MNZA or physician minimization
- Gupta G Transplantation 2014; 97:1240:: Late AbMR with MNZA or physician minimization

Other considerations about DSAs: C1q Binding

C1q binding of DSA associated with worse outcomes (Loupey NEJM 2013; 369:1215)

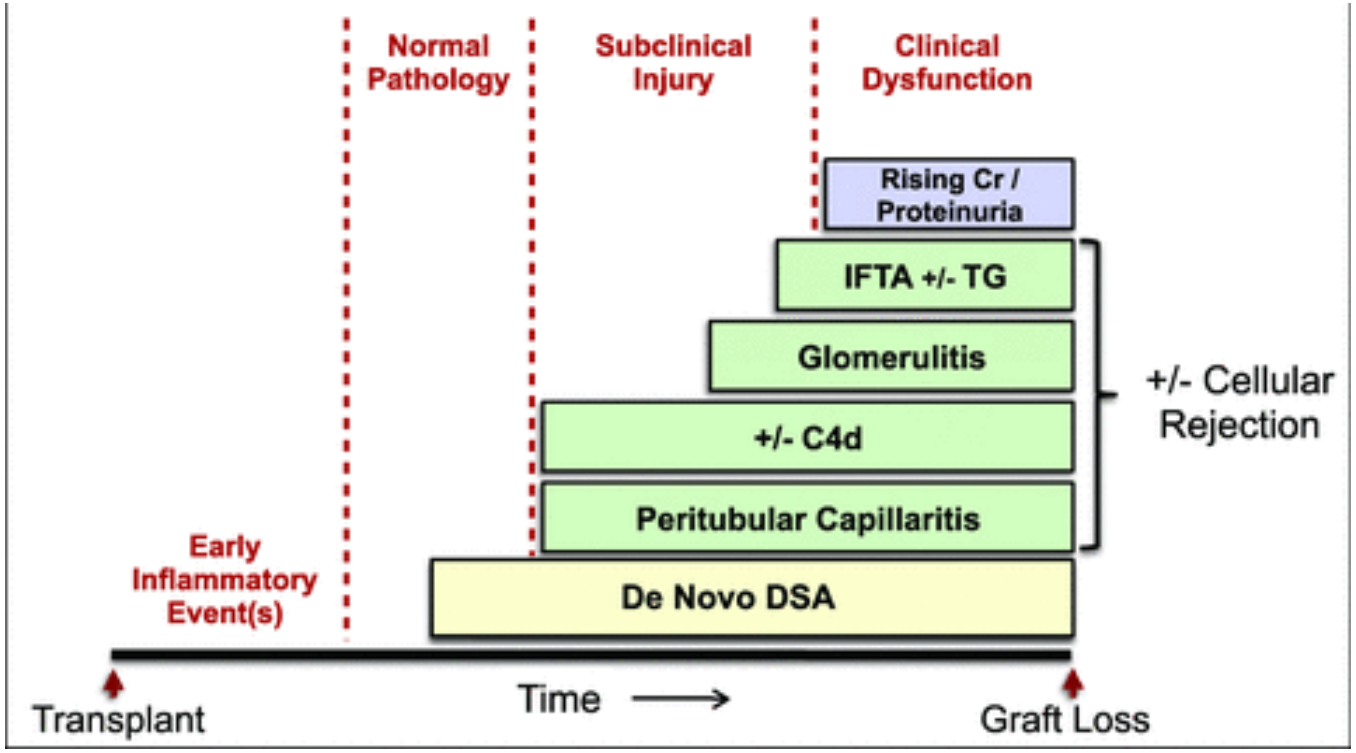


Death Censored Kidney Allograft Survival According DSA IgG Subclass



Carmen Lefaucheur et al. JASN 2016;27:293-304

Natural History of Alloantibody Injury



Wiebe et al. Am Jnl Transplant 2012; 12(5):1157

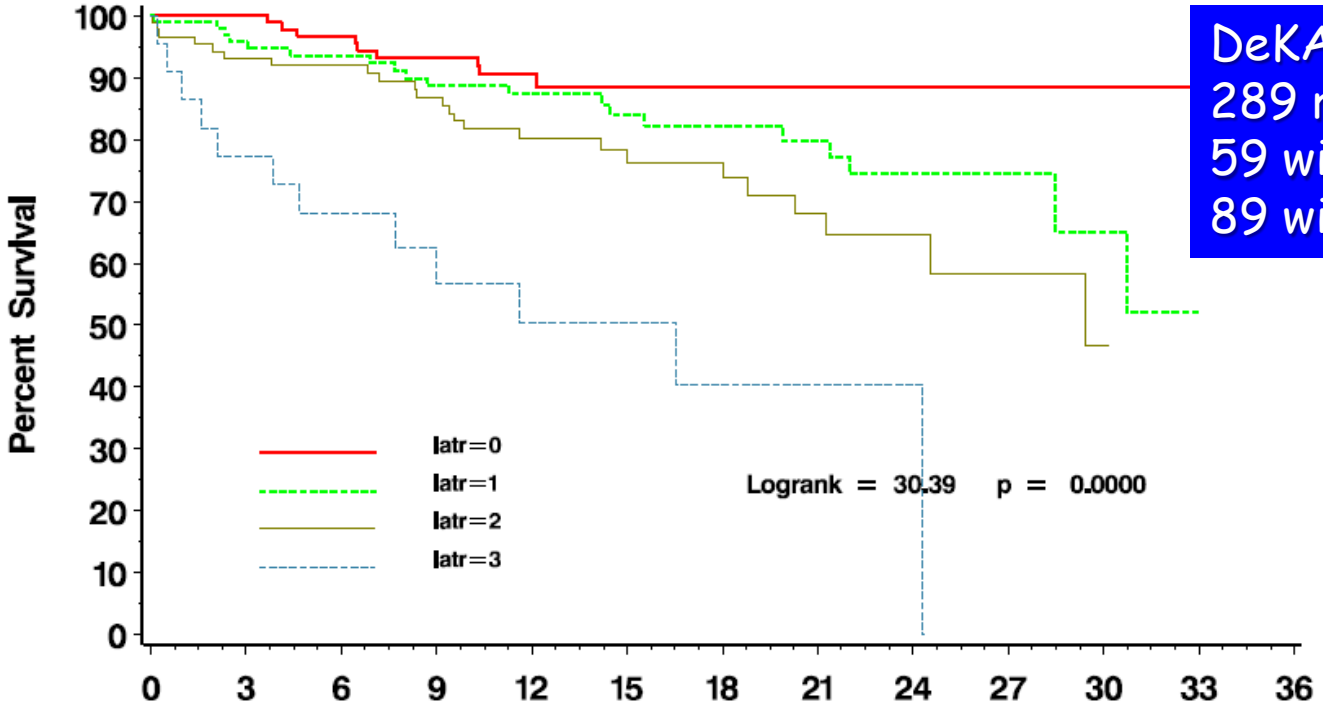
Banff ti Score Defined in Banff 2007 Revisited in Banff 2017

Table 4: Quantitative criteria for mononuclear cell interstitial inflammation ('ti') in total parenchyma (scarred and unscarred) scores—to be evaluated over next two years. Not incorporated into classification yet

ti0	No or trivial interstitial inflammation (<10% of parenchyma)
ti1	10–25% of parenchyma inflamed
ti2	26–50% of parenchyma inflamed
ti3	>50% of parenchyma inflamed

- Should the ti score be included in the classification for TCMR diagnosis?
  - As a replacement for the i score
  - As part of a new category of chronic/active TCMR
  - Recommend inclusion of ti score in the diagnosis line, possibly with a comment as to its prognostic significance, but do not change the
  - current TCMR classification

Inflammation in Areas of Atrophy: Strong Negative Predictor of Outcome



DeKAF Study:
289 recipients in cohort
59 with graft loss
89 with i=0, and iatr>1

iatr= i-IFTA

"iatr"—inflammation in areas of tubular atrophy
0 = inflammation in less than 10% of atrophic regions
1 = inflammation in 10-25% of atrophic regions;
2 = inflammation in 26-50% of atrophic regions;
3 = inflammation in >50% of atrophic regions.

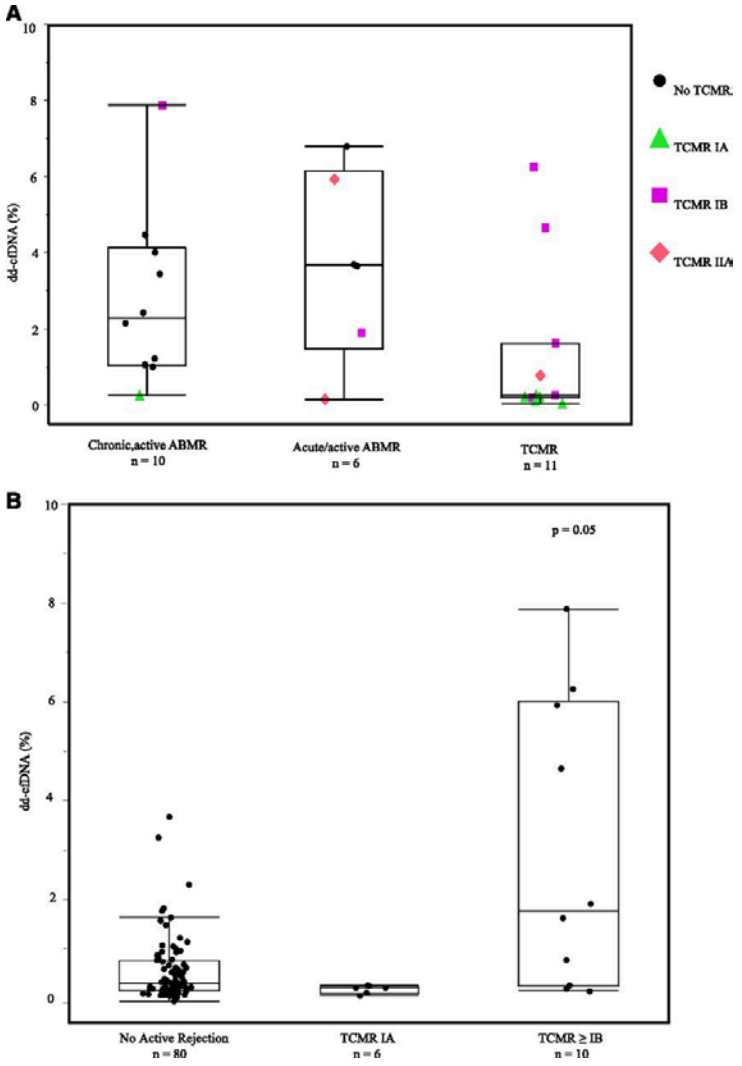
Mannon RB. Am Jnl Transplant 2010; 10: 2066-2073

i + IFTA is Bad News

- Tubulointerstitial inflammation in early surveillance biopsies is associated with progression of IF and decreased allograft survival [*Nankivell et al. Transplantation 2004; Choi et al. AJT 2005*].
- Surveillance biopsies with i in nonscarred areas and IFTA [i+IFTA] are associated with shorter graft survivals [*Shishido et al. JASN 2003; Moresco et al. AJT 2006; Park et al. JASN 2010*]
- Surveillance biopsy at 6w with i+IFTA is an independent risk factor for dnDSA development with an incidence of 9% at 1y *[Garcia-Carro et al. Transplantation 2016; PMID 27163535]*

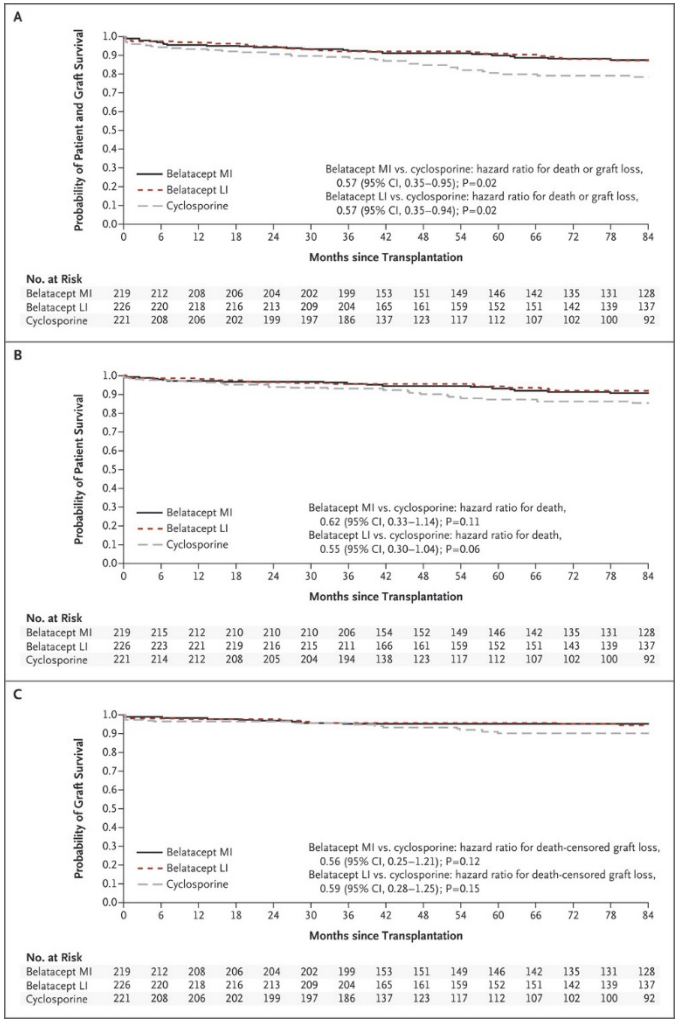
Molecular Classifiers of Inflammation/Injury

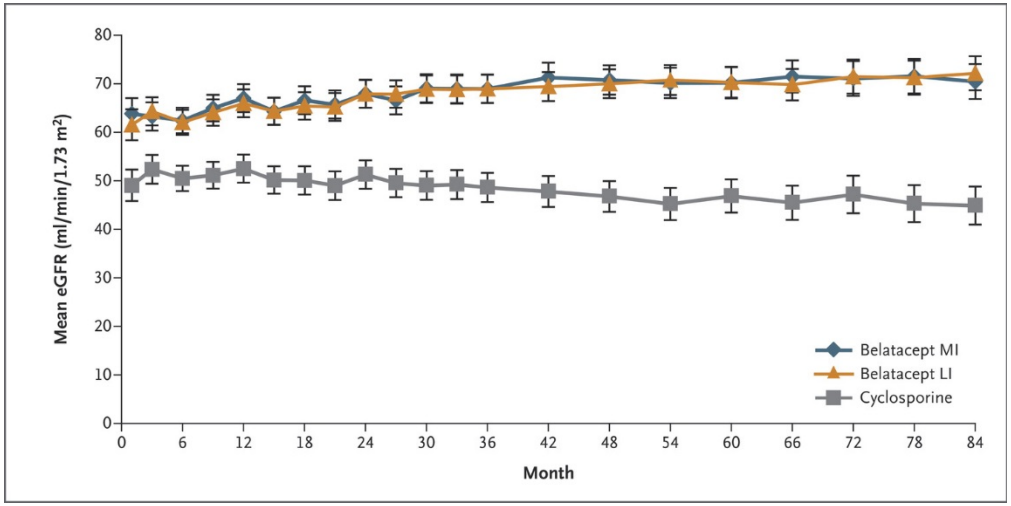
- PBMC
  - Transplant Genomics Inc: Tx status (Peripheral blood; transplant excellence)
  - Immuncor—15 gene transcripts indicating acute cellular rejection
  - AlloSure™ Cell Free DNA measurements
- Urine
  - Urinary markers of acute rejection (mRNA expression of CD3ε chain, perforin, granzyme B, proteinase inhibitor 9, CD103, interferon-inducible protein 10 (IP-10), and the chemokine receptor CXCR3)
- Cell Free DNA
  - AMR and CAMR discrimination from TCMR [Bloom et al. JASN 2017; in press.]

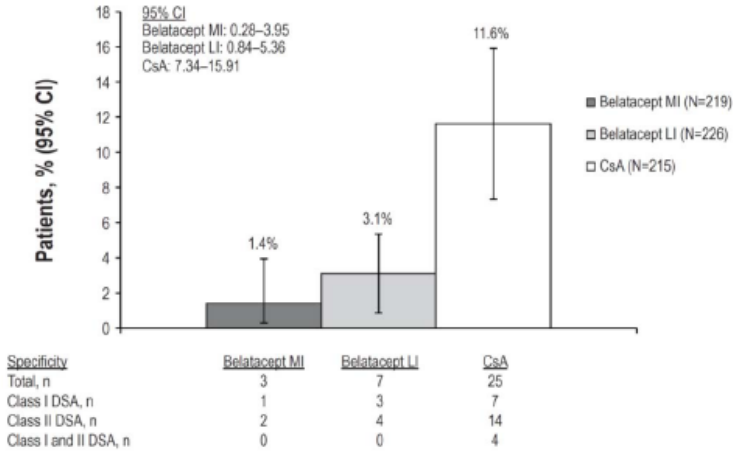


Belatacept Approved 2012

Vincenti et al. NEJM 2016; 374:333

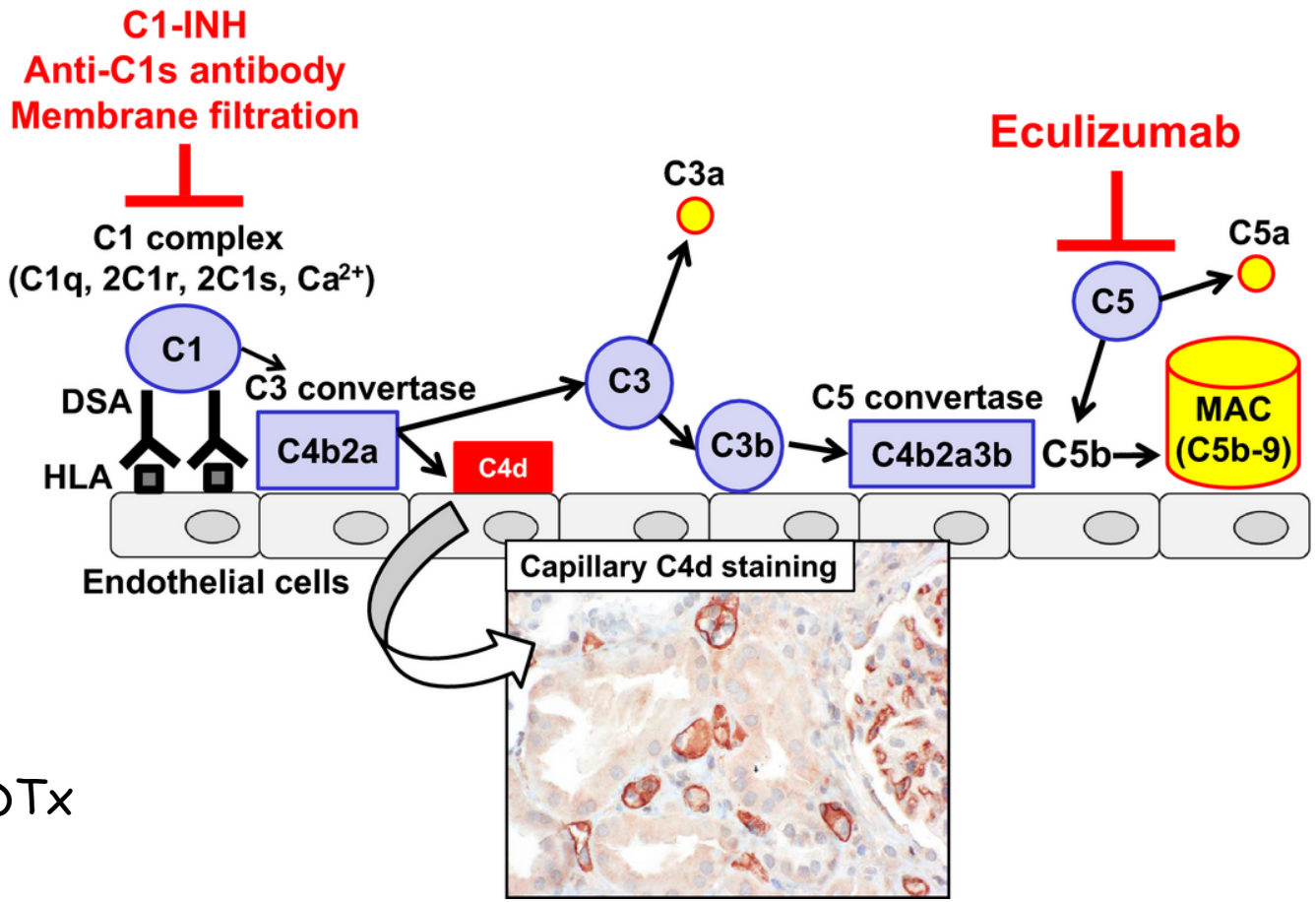






Specificity	Belatacept MI	Belatacept LI	CsA
Total, n	3	7	25
Class I DSA, n	1	3	7
Class II DSA, n	2	4	14
Class I and II DSA, n	0	0	4

Complement Inhibition as Potential New Therapy for Antibody-Mediated Rejection



HLAi LDTx
DGF
AMR

Transplant International 2016; 29(4): 392

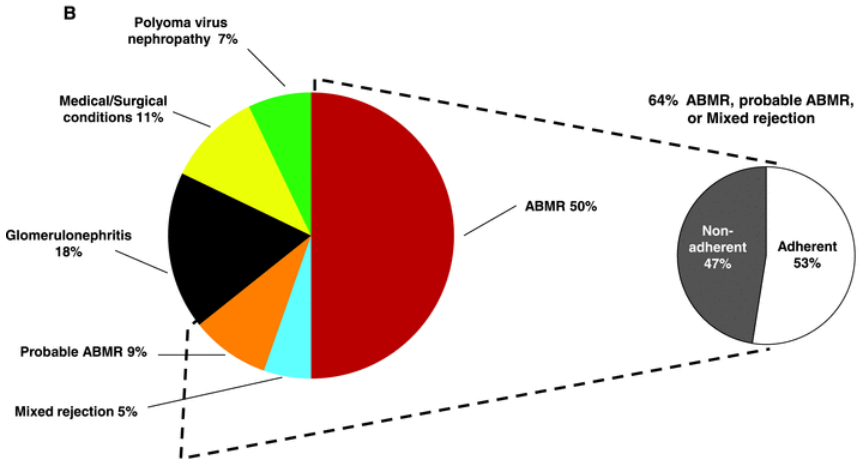
Risk of Nonadherence on Outcomes

A

Histological diagnosis	n	Attributed causes of allograft failure: Antibody-mediated rejection	Probable ABMR	Mixed rejection	Polyoma virus nephropathy	Glomerulone-phritis	Medical causes	Missing data	Non-adherence
Antibody-mediated rejection	28	26	–	–	–	–	2	–	11
Probable ABMR	2	–	2	–	–	–	–	–	1
Mixed rejection	6	2	–	3	–	–	1	–	2
T cell-mediated rejection	1	–	1	–	–	–	–	–	1
Borderline	1	–	1	–		–	–	–	1
Polyoma virus nephropathy	1	–		–	1	–	–	–	0
Glomerulonephritis	12	–	1	–	–	9	2	–	2
No major abnormalities	3	–	–	–	–	–	1	2	1
Atrophy-fibrosis	3	–	–	–	–	1	–	2	0
Other	3	–	–	–	3[a]	–	–	–	0
Total	60	28	5	3	4	10	6	4	19

[a] Patients whose biopsies showed histologic changes highly suggestive of polyoma virus nephropathy, although the IC/in situ hybridization was reported either inconclusive (n=1) or negative (n=2)

B



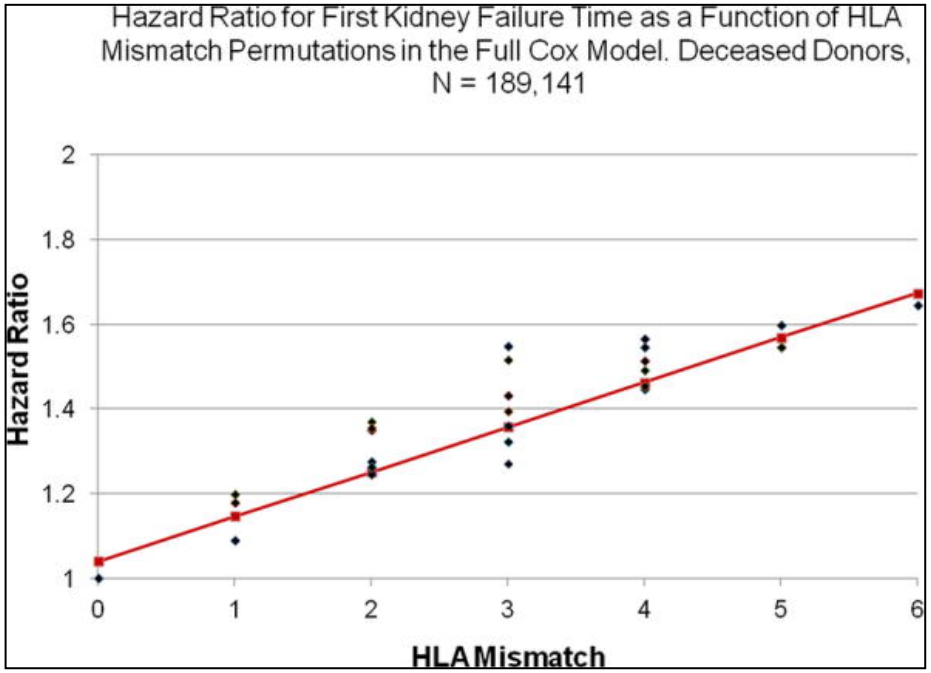
Sellares et al Am Jnl Transplant 2012; 12:368

Table 2: Clinical pathologic course before dnDSA detection

	No dnDSA (n = 268)	Total dnDSA (n = 47)
Non-adherence	8%	49%***
DGF requiring dialysis	12%	11%
Clinical rejection, 0–6 months	13%	28%*
Subclinical rejection, 0–6 months	15%	26%

Wiebe et al. Am Jnl Transplant 2012; 12: 1157

HLA Mismatch Has a Graded Effect on Transplant Survival

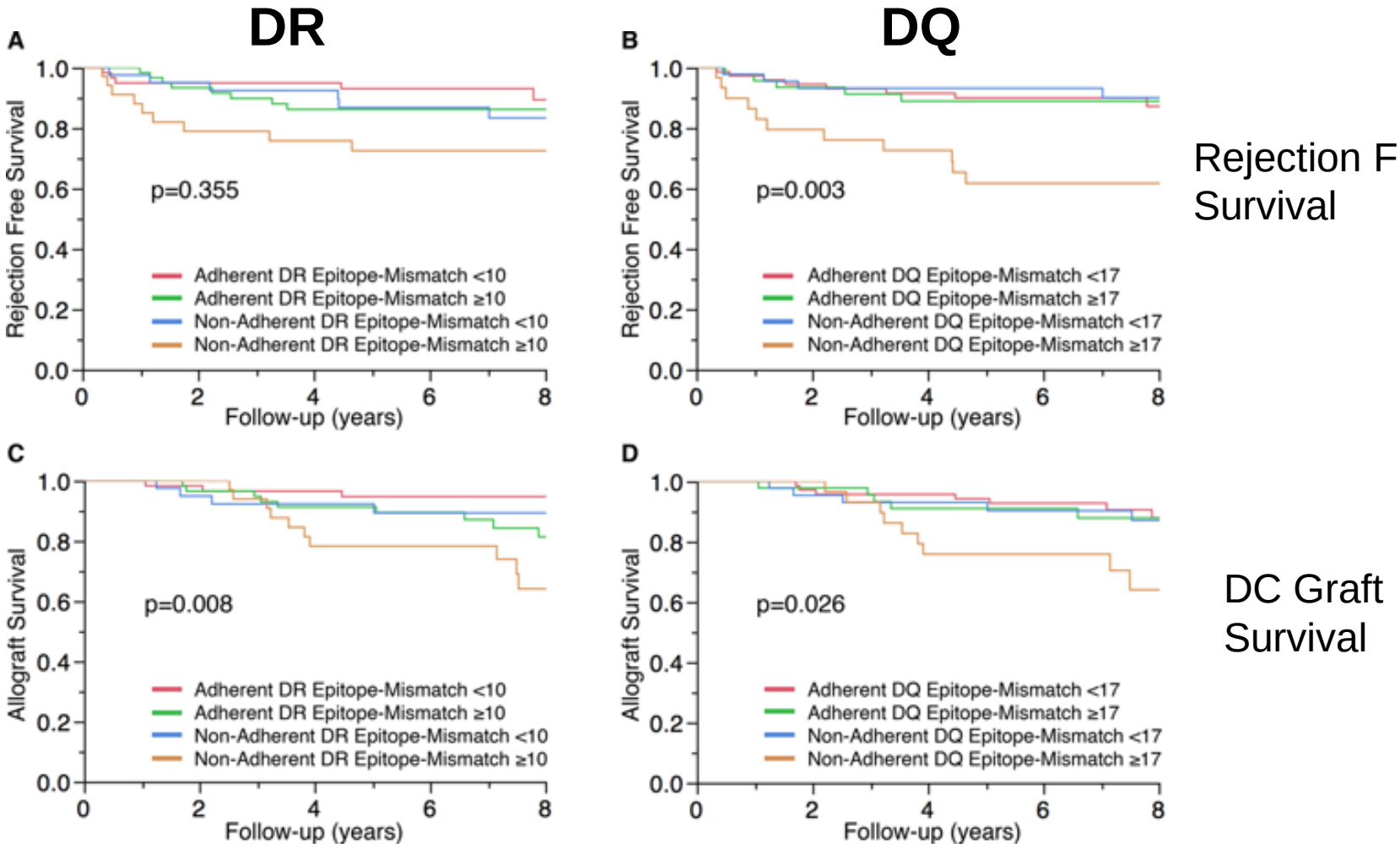


HLA mismatch	Reduced model[a]	P	Full model[b]	P
1	1.17 1.10, 1.25	<0.0001	1.13 1.06, 1.21	<0.0002
2	1.38 1.31, 1.46	<0.0001	1.29 1.23,1.37	<0.0001
3	1.51 1.44, 1.58	<0.0001	1.36 1.30, 1.43	<0.0001
4	1.69 1.61, 1.77	<0.0001	1.48 1.41, 1.55	<0.0001
5	1.84 1.75, 1.92	<0.0001	1.56 1.49, 1.64	<0.0001
6	1.98 1.88, 2.08	<0.0001	1.64 1.56, 1.73	<0.0001

[a]Adjustment for recipient age, recipient sex, transplant era.
[b]Adjustment for recipient age, donor age, donor sex, transplant era, recipient ethnicity, recipient diabetes, cold ischemia time, recipient peak PRA, recipient education, recipient BMI, donor BMI, recipient working for income at transplant, recipient COPD, recipient dialysis type, induction and immunosuppression at discharge.
PRA, panel-reactive antibody.

Harini et al. Transplantation 2016; 100(5):1094-1102

The Synergistic Effect of Class II HLA Epitope-Mismatch and Non-adherence on Acute Rejection and Graft Survival



Rejection Free Survival

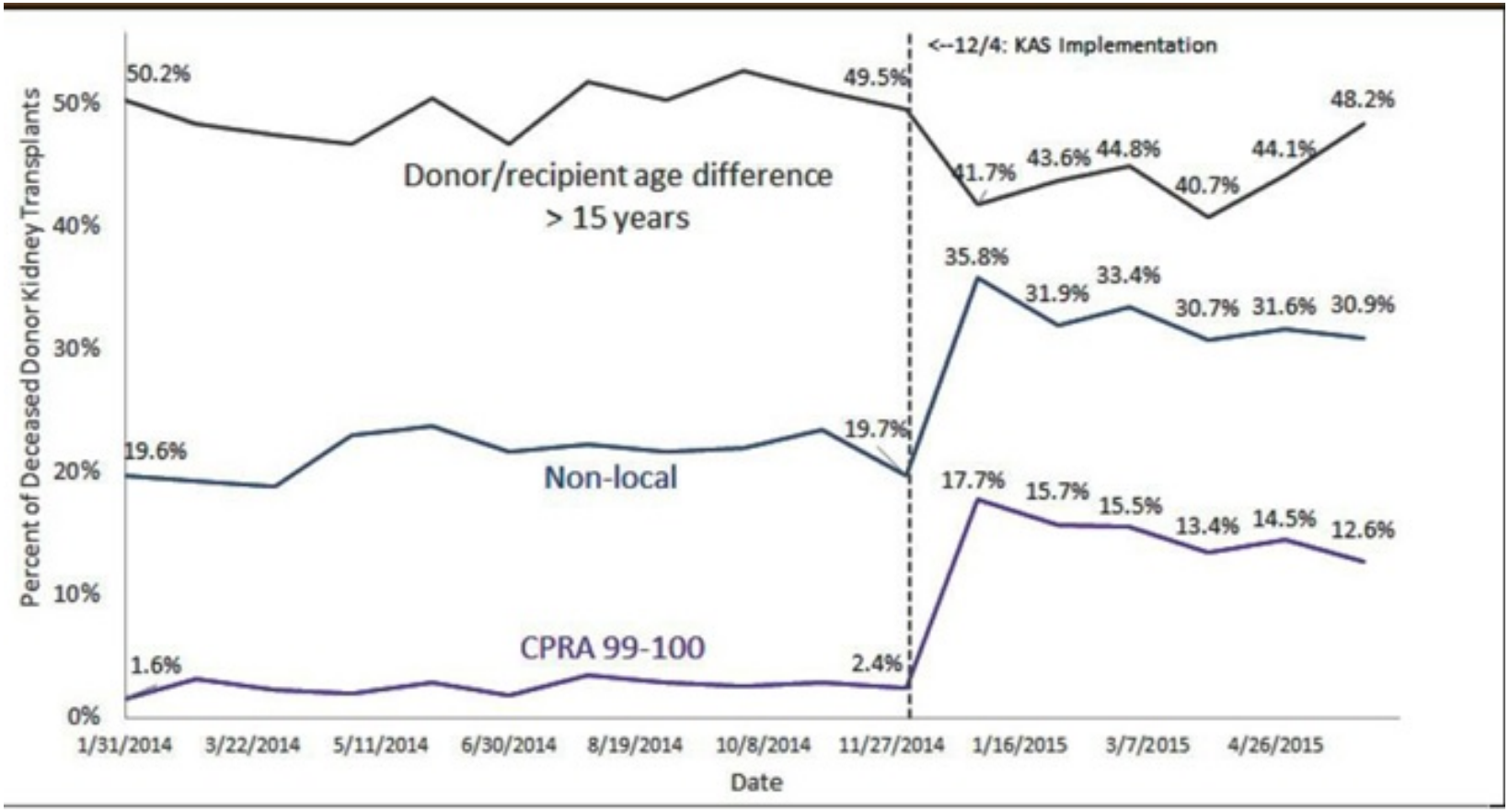
DC Graft Survival

Wiebe at al. Am Jnl Transplantation 2015; 15(8): 2197.

Kidney Allocation System December 4, 2014

- Changed prior algorithm from first-come, first-serve, to a scheme where balanced equitable distribution of deceased donor kidneys with maximal utility.
- Improvement in utility: kidney donor risk index (KDRI) based on donor age , height, weight race/ethnicity, hypertension, diabetes, cause of death, serum creatinine, hepatitis C status, and donation after circulatory death status and converted to KD Profile Index of 0-100% (KDPI).
- Kidneys in 20% of expected post-transplant allograft survival are offered first to recipients in the highest 20% of estimated post-transplant survival (EPTS)[age, duration dialysis, prior transplant, diabetes].
- Equity is addressed by increased national and regional sharing, and priority given to those waiting for multi-organ transplants, calculated panel-reactive antibody (cPRA) of 98% or higher (more sensitized), zero-HLA mismatched kidneys, pediatric candidates and prior living donors.
  - Listing after dialysis still accrues time on dialysis!

Pre and Post KAS Deceased Donor Kidney Transplant Recipient Characteristics 01/01/2014-05/31/015



And impacts on AA recipients, peds, DGF, and graft survival

Other New Concepts in Kidney Transplantation

- Use of HIV positive donor organs
- Hepatitis C treatment: before or after kidney transplantation
  - Use of HepC^{+} kidneys in high EPTS recipients
- Potential role of *APOL1* mutations in either living donor or recipient outcomes

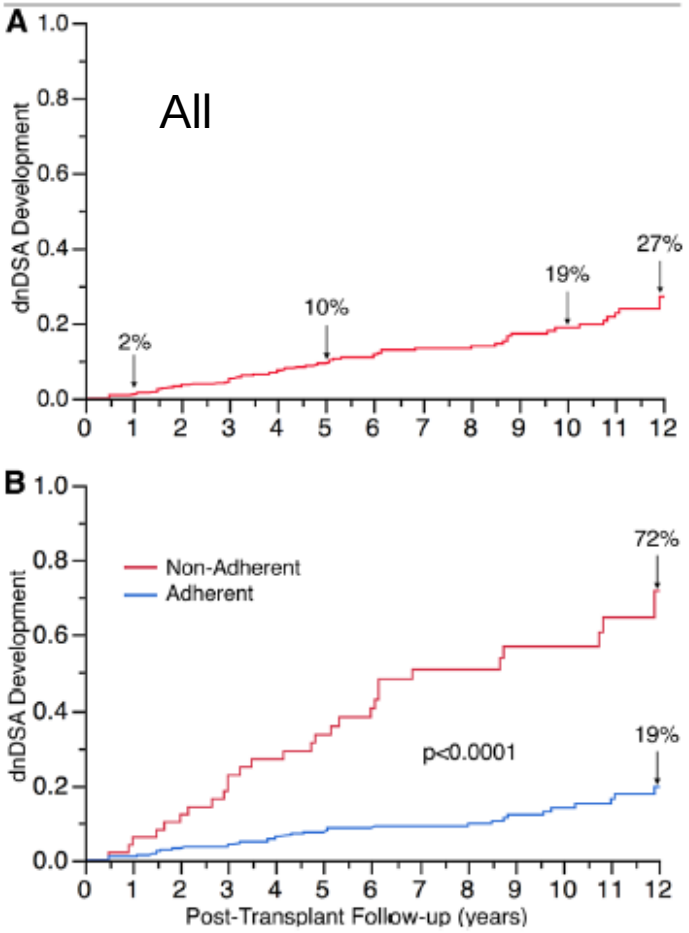
Conclusion

Since 2010, there has been remarkable progress in the field of AMR and CAMR.

- We have yet to develop consensus on monitoring (close), or validated biomarkers.
- These will assist in endpoint development and facilitate the identification of new therapeutics in this unmet need in solid organ transplantation.

De Novo DSA is Associated with Worse Kidney Allograft Survival

DSA free Survival



Wiebe et al. Am Jnl Transplant 2015; 15:2921