The Utility of Protocol Biopsies in the Follow-up of Acute AMR and in the Detection of Chronic AMR

What do we know about histology and AMR clinically?

Tailored Immunosuppression Based on Routine DSA Monitoring (both in sensitized and nonsensitized patients)

Is there a standard of care regarding therapeutic management?

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Departments of Surgery and Immunology

Disclosures

- Ad Board—Novartis, Roche, Astellas
- Mayo Contract—Transplant Genomics, Inc.
- FDA—flight to DC and 1 night’s lodging

Goals of the Workshop:

1) *Examine and emphasize the importance of immunosuppressive medication nonadherence in the development of de novo donor specific antibodies (DSA) and subsequent antibody mediated rejection (AMR)*

- Agree, but not all patients are non-adherent
- Non-adherent→
- Treat cellular rejection and put back on immunosuppression
- ?primary problem is persistent ABMR leading to graft loss (evidence from histology)

Goals of the Workshop

2) Discuss the new developments in transplantation and their impact on patient management such as pretransplant sensitization not manifested by DSA, donor/recipient HLA epitope matching, routine posttransplant DSA monitoring

Sensitization not manifested by DSA—Hypothesis vs Memory?

Post-Transplant DSA monitoring—would be more important if there was effective therapy

Goals of the Workshop

3) Discuss the natural course of the acute-chronic AMR continuum and its temporal association with cellular rejection and changes in GFR

This is a major source of confusion. Current terminology is poor.

Antibody Mediated Rejection

American Journal of Transplantation 2007; 7: 2124–2132
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2007.01895.x

Transplant Glomerulopathy: Subclinical Incidence and Association with Alloantibody

American Journal of Transplantation 2008; 8: 1367–1373
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2008.02262.x

Minireview

The Spectrum of Antibody-Mediated Renal Allograft Injury: Implications for Treatment

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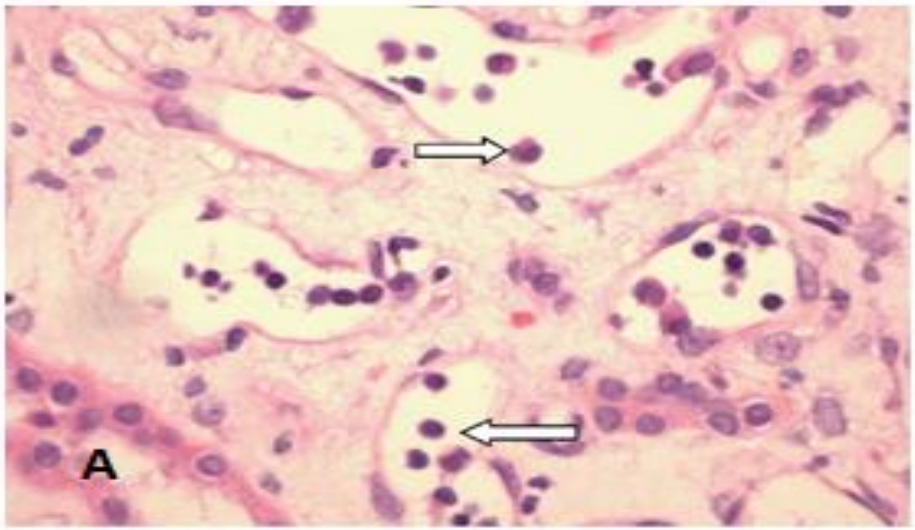
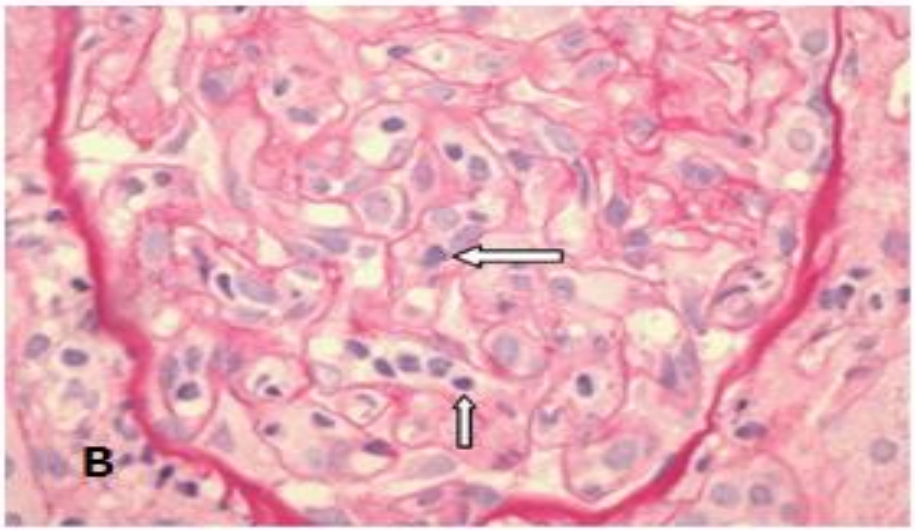
rejection owing in part to four factors. First, there has been a dramatic improvement in the technology of antibody detection. Newer assays incorporating purified HLA antigens bound to solid phase substrates permit identification of previously undetectable levels of donor-specific antibodies (DSA) with accuracy unobtainable using donor-cell-based assays (1). Secondly, the histologic appearance of acute antibody-mediated rejection (AMR) has been more clearly delineated, following the recognition of the importance of the complement degradation factor C4d as a histologic marker (2–4). Third, protocols incorporating pre- and post-

All Prior to DSA testing with Solid Phase/LabScreen

Microvascular inflammation

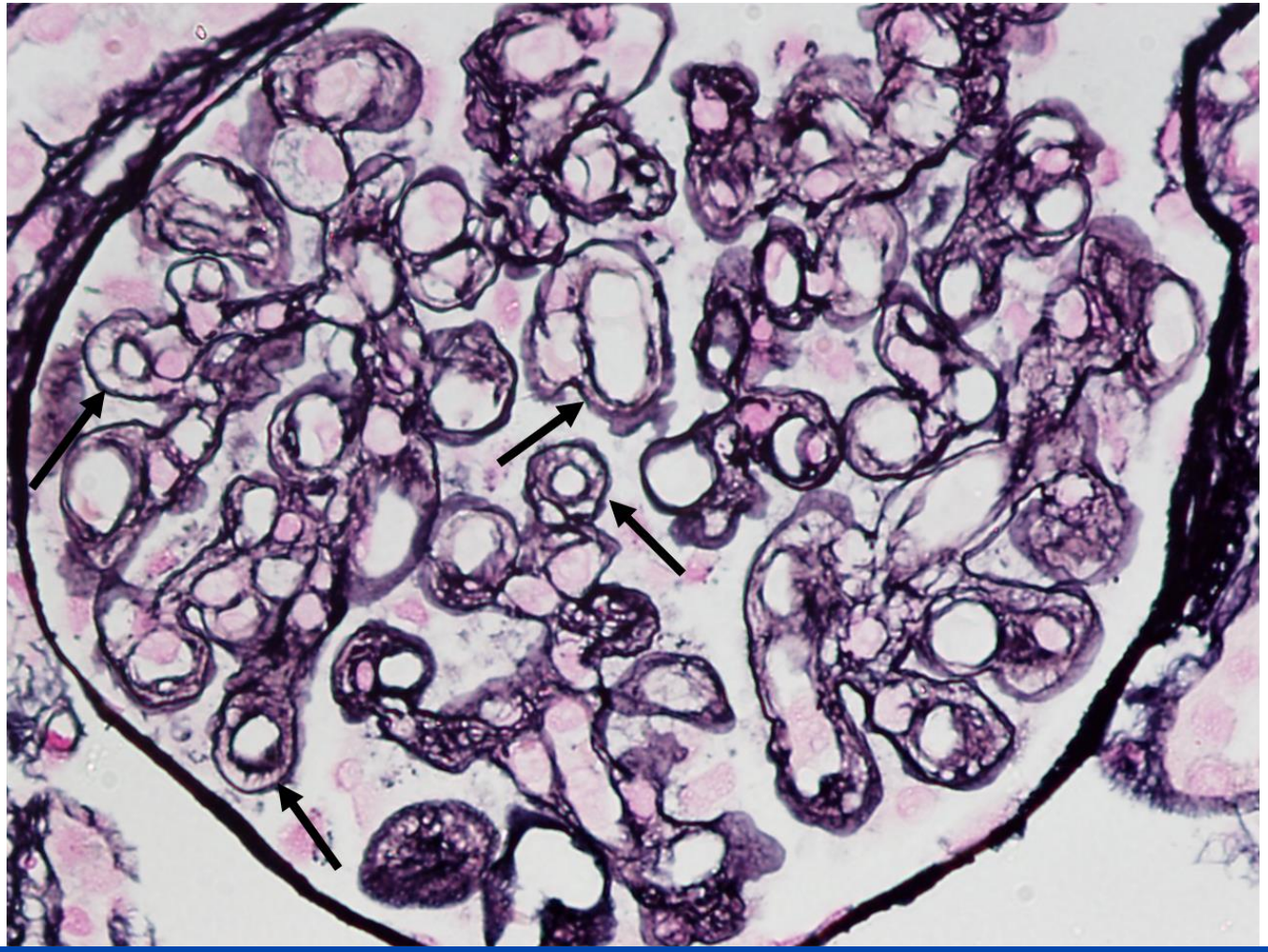
Acute, active antibody mediated rejection





Peritubular capillaritis (leftl A) and glomerulitis (right B) are hallmark histologic features of antibody mediated rejection.

Chronic ABMR = cg
chronic transplant glomerulopathy



American Journal of Transplantation 2014; 14: 272–283
Wiley Periodicals Inc.

doi: 10.1111/ajt.12590

Meeting Report

Banff 2013 Meeting Report: Inclusion of C4d-Negative Antibody-Mediated Rejection and Antibody-Associated Arterial Lesions

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

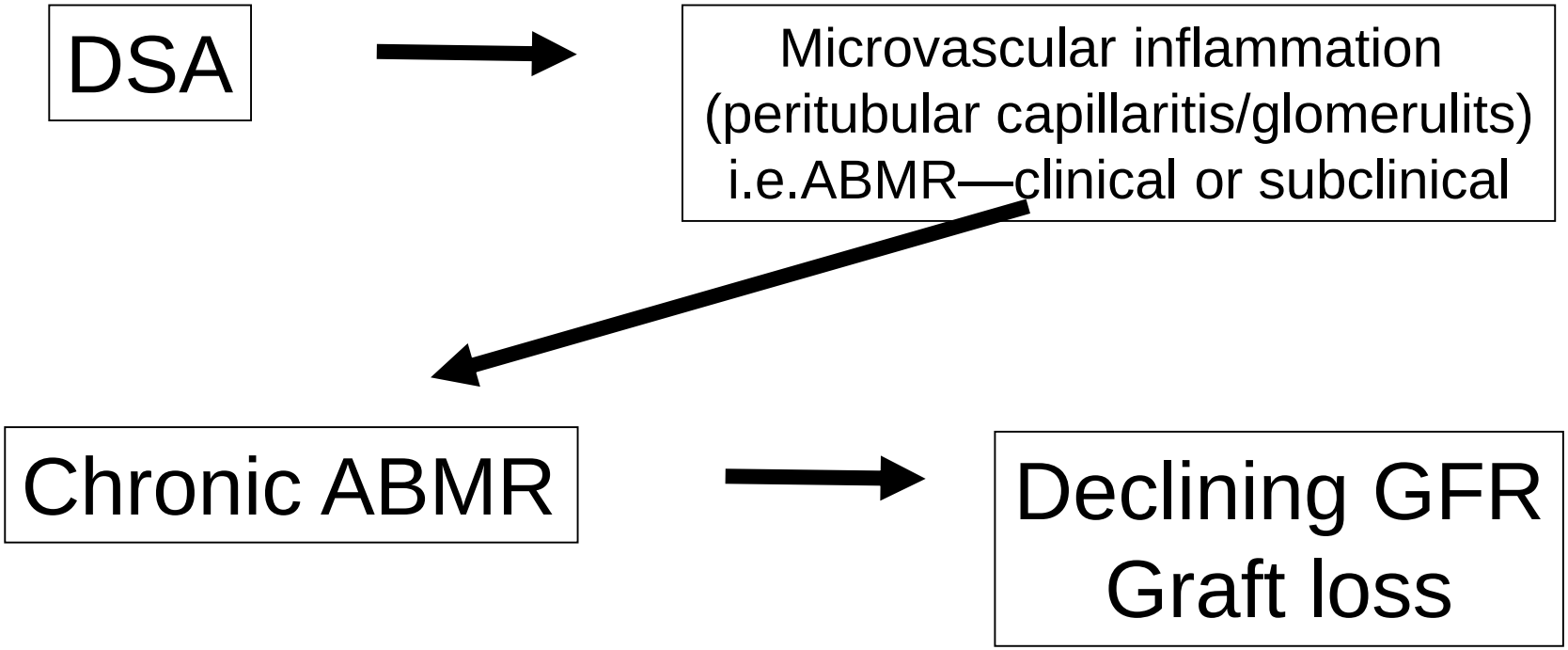
Acute/active ABMR; all three features must be present for diagnosis[1,2]

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)

Chronic, active ABMR; all three features must be present for diagnosis[1,7]

1. Morphologic evidence of chronic tissue injury, including one or more of the following:
   Transplant glomerulopathy (TG) ($cg > 0$)[8], if no evidence of chronic thrombotic microangiopathy
   Severe peritubular capillary basement membrane multilayering (requires EM)[9]
   Arterial intimal fibrosis of new onset, excluding other causes[10]
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 DSAs (HLA or other antigens)

Paradigm


DSA
Microvascular inflammation
(peritubular capillaritis/glomerulits)
i.e.ABMR—clinical or subclinical
Chronic ABMR
Declining GFR
Graft loss

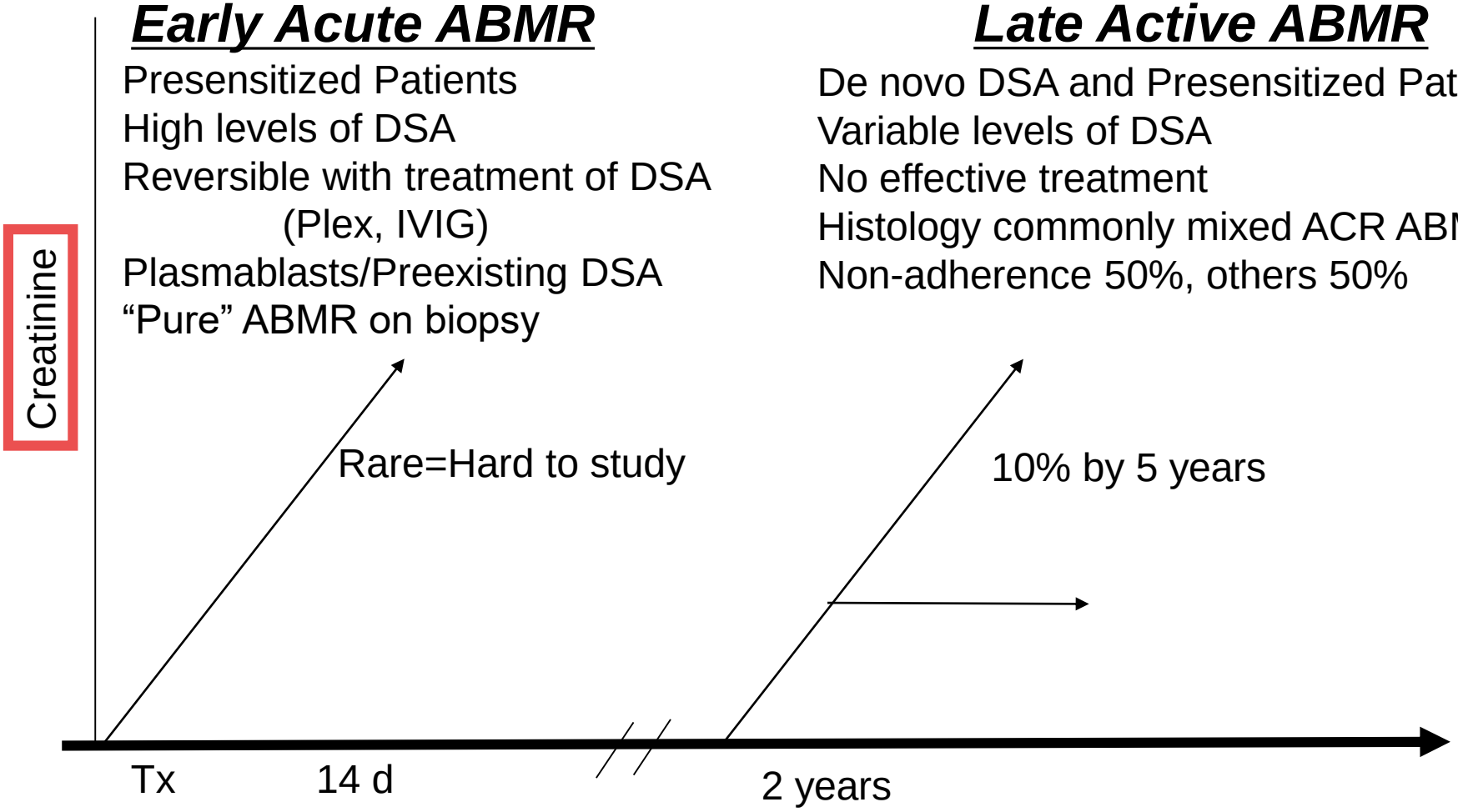
Different Clinical Scenarios

Early Acute ABMR

Presensitized Patients
High levels of DSA
Reversible with treatment of DSA
(Plex, IVIG)
Plasmablasts/Preexisting DSA
"Pure" ABMR on biopsy

Late Active ABMR

De novo DSA and Presensitized Patients
Variable levels of DSA
No effective treatment
Histology commonly mixed ACR ABMR
Non-adherence 50%, others 50%



Different Clinical Scenarios

Early Acute ABMR

Late Active ABMR

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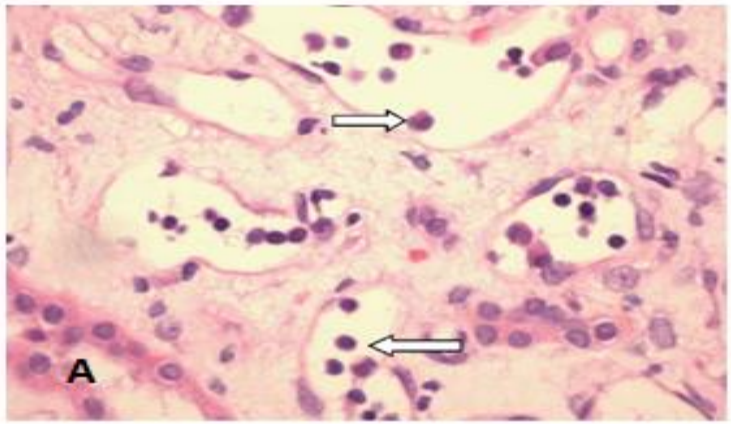
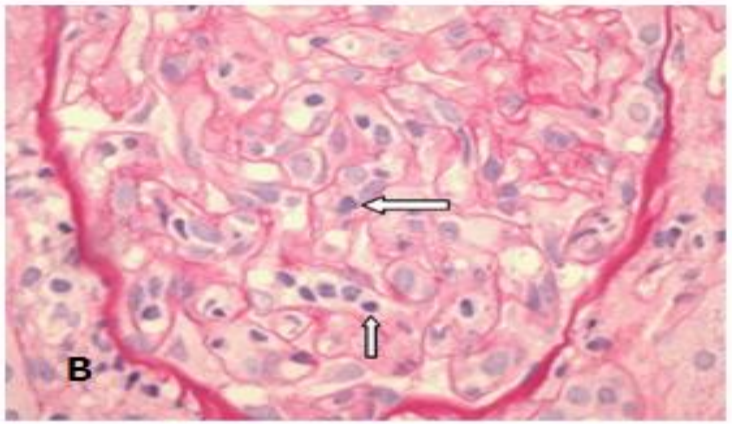
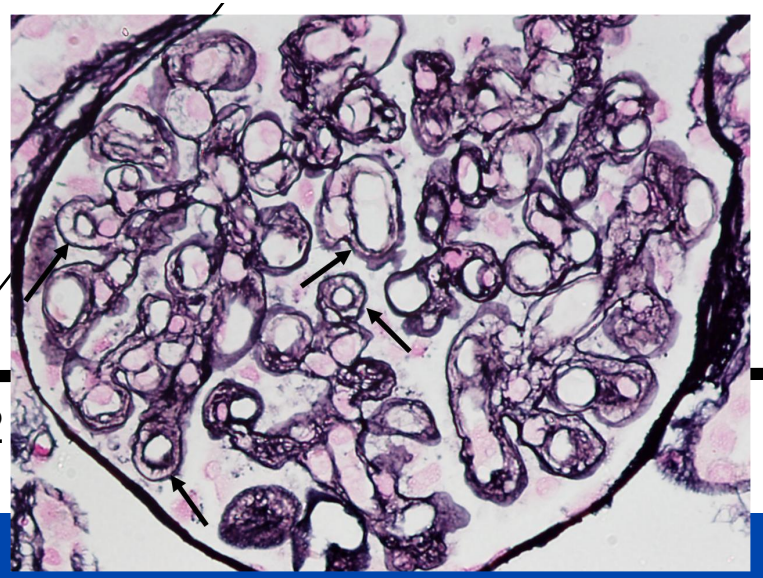




Rare=Hard to study



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Banff 2013 criteria: ABMR

- 1) Histologic evidence of acute tissue injury resulting from ABMR and includes glomerulitis (Banff g score >0) and/or peritubular capillaritis (Banff ptc score >0), intimal or transmural arteritis (Banff v score>0), thrombotic microangiopathy, or 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 (Banff C4d score ≥2 with immunofluorescence on frozen section or Banff g+ptc score ≥2), and
- 3) Serologic evidence of donor-specific antibodies.
- Haas M, Sis B, Racusen LC, et al. Am J Transplant 2014; 14 (2): 272.

Very Important in Prognosis

Banff 2013 criteria

- 1) Histologic evidence of acute tissue injury resulting from ABMR and includes glomerulitis (Banff g score >0) and/or peritubular capillaritis (Banff ptc score >0), intimal or transmural arteritis (Banff v score>0), thrombotic microangiopathy, or acute tubular injury, in the absence of any other apparent cause
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- Haas M, Sis B, Racusen LC, et al. Am J Transplant 2014; 14 (2): 272.

Misses Many Grafts that Progress

Banff 2013 criteria

- 1) Histologic evidence of acute tissue injury resulting from ABMR and includes glomerulitis (Banff g score >0) and/or peritubular capillaritis (Banff ptc score >0), intimal or transmural arteritis (Banff v score>0), thrombotic microangiopathy, or acute tubular injury, in the absence of any other apparent cause
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- Haas M, Sis B, Racusen LC, et al. Am J Transplant 2014; 14 (2): 272.

Possibly not relevant to outcome

Variable Presence, but high levels are bad

Banff 2013 criteria

- 1) Histologic evidence of acute tissue injury resulting from ABMR and includes glomerulitis (Banff g score >0) and/or peritubular capillaritis (Banff ptc score >0), intimal or transmural arteritis (Banff v score>0), thrombotic microangiopathy, or acute tubular injury, in the absence of any other apparent cause
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- Haas M, Sis B, Racusen LC, et al. Am J Transplant 2014; 14 (2): 272.

Nothing is perfect

- Microvascular inflammation has the highest correlation with graft loss/50% decline in eGFR in the following 2-5 years
- DSA has a lower correlation—i.e. not all people with DSA have inflammation
- Non-HLA antibody—is this just a case where the DSA is no longer detectable in the serum?

Other Biopsy Issues: C4d and ACR

- C4d+ has a higher correlation but it may be negative in patients that progress
- All DSA is the product of a T cell dependent immune response, but we may not detect ACR on biopsy
- T cells home to sites of inflammation in ABMR
- Borderline ACR has a generally good prognosis compared to ABMR

The Utility of Protocol Biopsies in the Follow-up of Acute AMR and in the Detection of Chronic AMR

Does Early Acute → Late Chronic?

Early Acute ABMR

Presensitized Patients
High levels of DSA
Reversible with treatment of DSA
(Plex, IVIG)
Plasmablasts/Preexisting DSA
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Late Active ABMR

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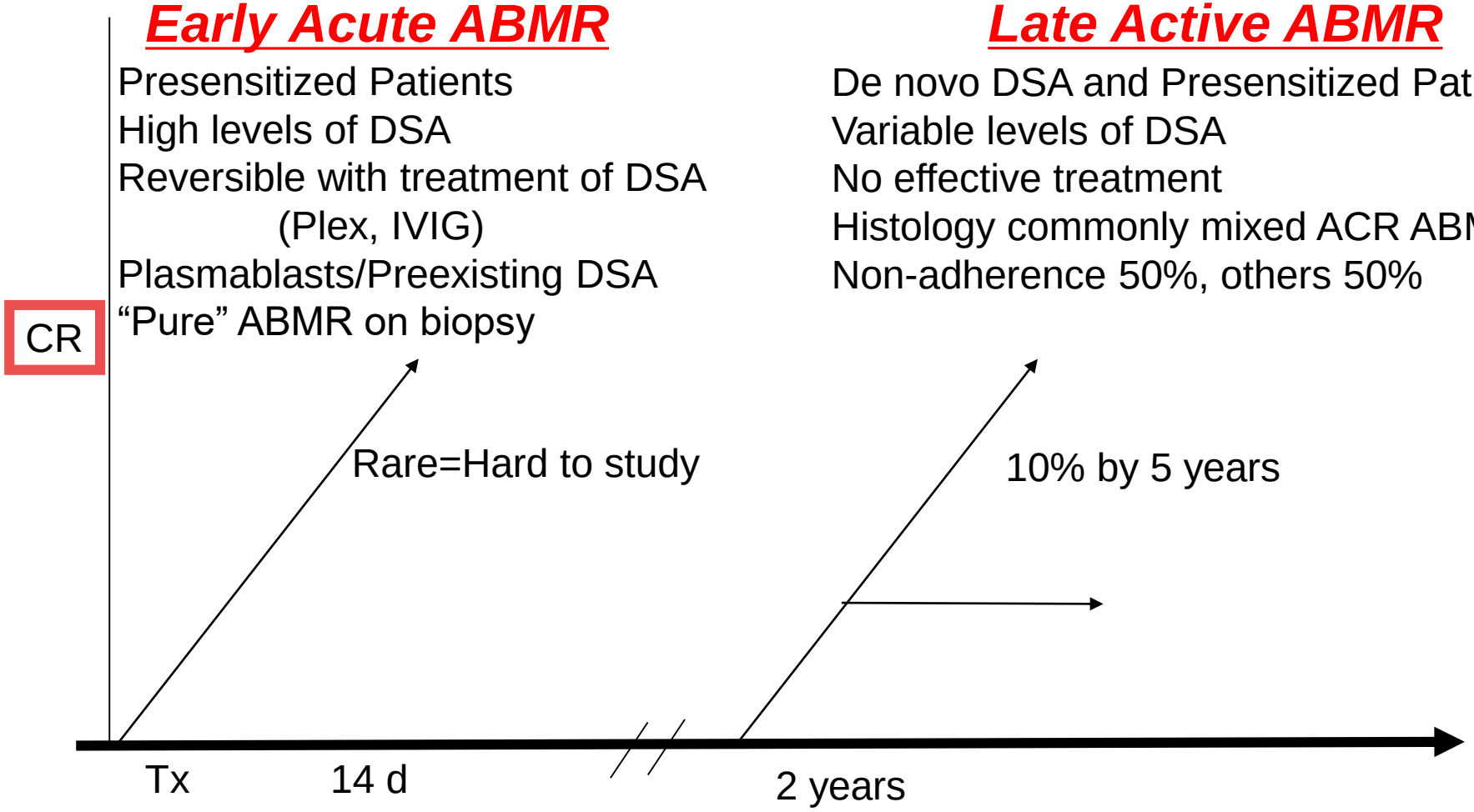


Preventing Early Acute ABMR does not prevent chronic ABMR

American Journal of Transplantation 2015; 15: 1293–1302
Wiley Periodicals Inc.

doi: 10.1111/ajt.13168

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,*]

Introduction

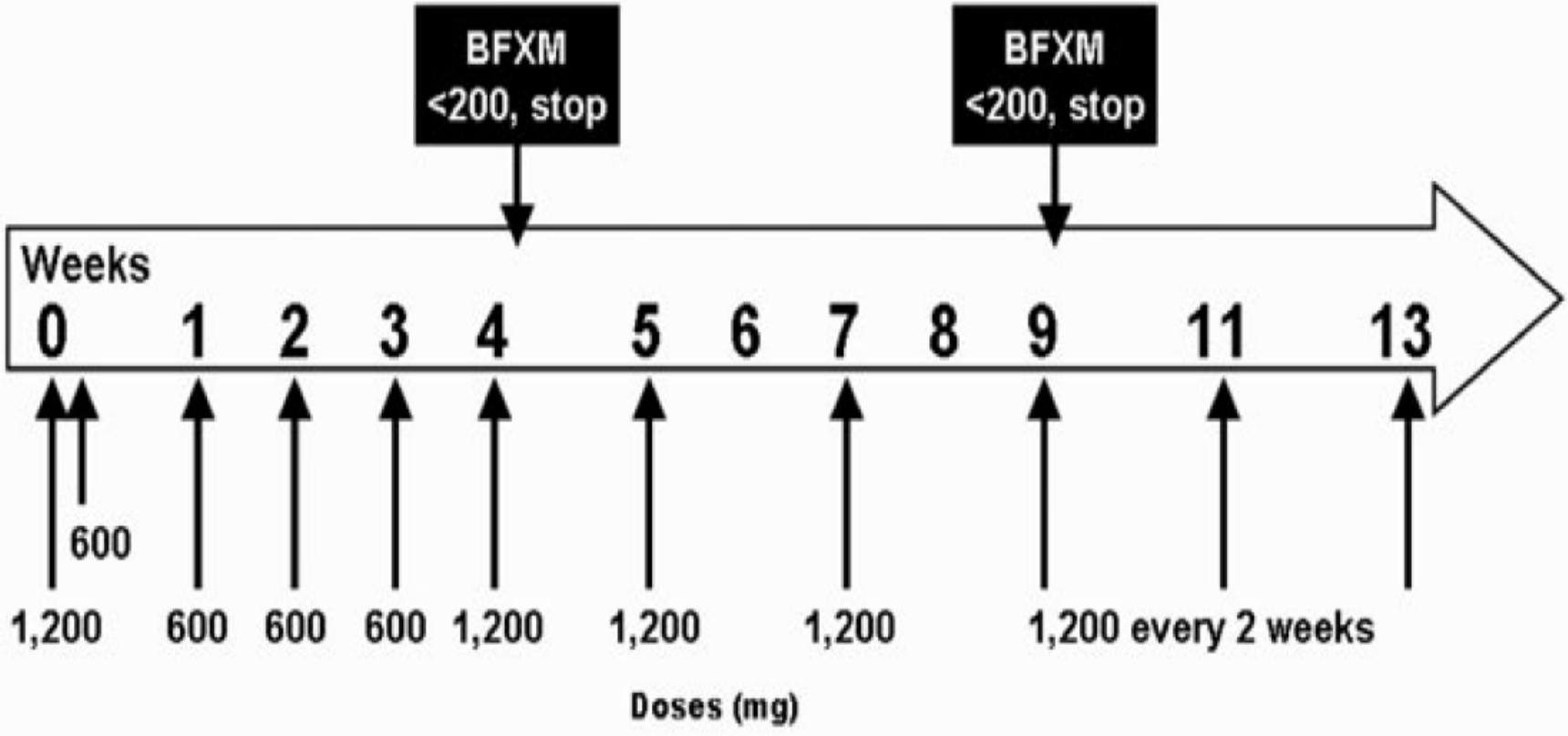
Renal transplant candidates with high levels of antibody against a broad spectrum of HLA are very difficult to transplant. Despite receiving high priority for deceased

Table 1: Baseline characteristics

	Eculizumab group n = 30	Control group n = 48	p-value
Age at transplant	47.8 (±1.2.7)	47.9 (±11.0)	p = 0.91
Female (%)	71.0%	78.0%	p = 0.36
Race[1] (%)			p = 0.24
Caucasian	96.8%	91.1%	
African American	0%	6.7%	
Hispanic	0%	2.2%	
Asian	3.2%	0%	
Cause of renal failure (%)			p = 0.14
Glornerulonephritis	29.0%	33.3%	
Other	25.8%	24.4%	
Cystic kidney disease	12.9%	13.3%	
Diabetes mellitus	9.7%	15.6%	
Hypertension	9.7%	0%	
Congenital	6.5%	8.9%	
Urological	6.5%	4.4%	
Baseline B flow crossmatch mean ± SD	305.5 ± 91.8	322.9 ± 78.5	p = 0.35
HLA mismatch mean ± SD	3.9 ± 1.3	3.3 ± 1.4	p = 0.34
Retransplant (%)	54.8%	42.0%	p = 0.52
Class I DSA	36.7%	38.6%	p = 0.89
Class II DSA	30.0%	25.0%	
Class I+II DSA	33.3%	36.4%	
Class I DSA MFI2 mean ± SD	4193.3 ± 4889.0	4556.68 ± 5083.0	p = 0.76
Class 2 DSA MFI mean ± SD	4037.07 ± 5183.3	3128 ± 4141.2	P = 0.40
Total DSA MFI mean ± SD	11 905.0 ± 8985.32	9592.51 ± 7806.15	p = 0.24
Number of pretransplant plasmapheresis mean ± SD	4.6 ± 1.3	4.4 ± 1.4	p = 0.78
Length of follow-up (months) mean ± SD (range)	38.2 ± 10.2 (24.1–59.8)	73.0 ± 2.5.0 (41.3–105.0)	p = 0.01

[1]Race or ethnic group was self-reported.

Anti-C5 Treatment Protocol



Biopsy Proven Acute Clinical ABMR

- Increase in serum creatinine >0.3mg/dl from nadir
- Biopsy showing ABMR
- First 3 months
- 43.8% controls vs 6.7% Eculizumab
- Eculizumab given for a minimum of 1 month and continued when BFXM >200 for up to 1 year

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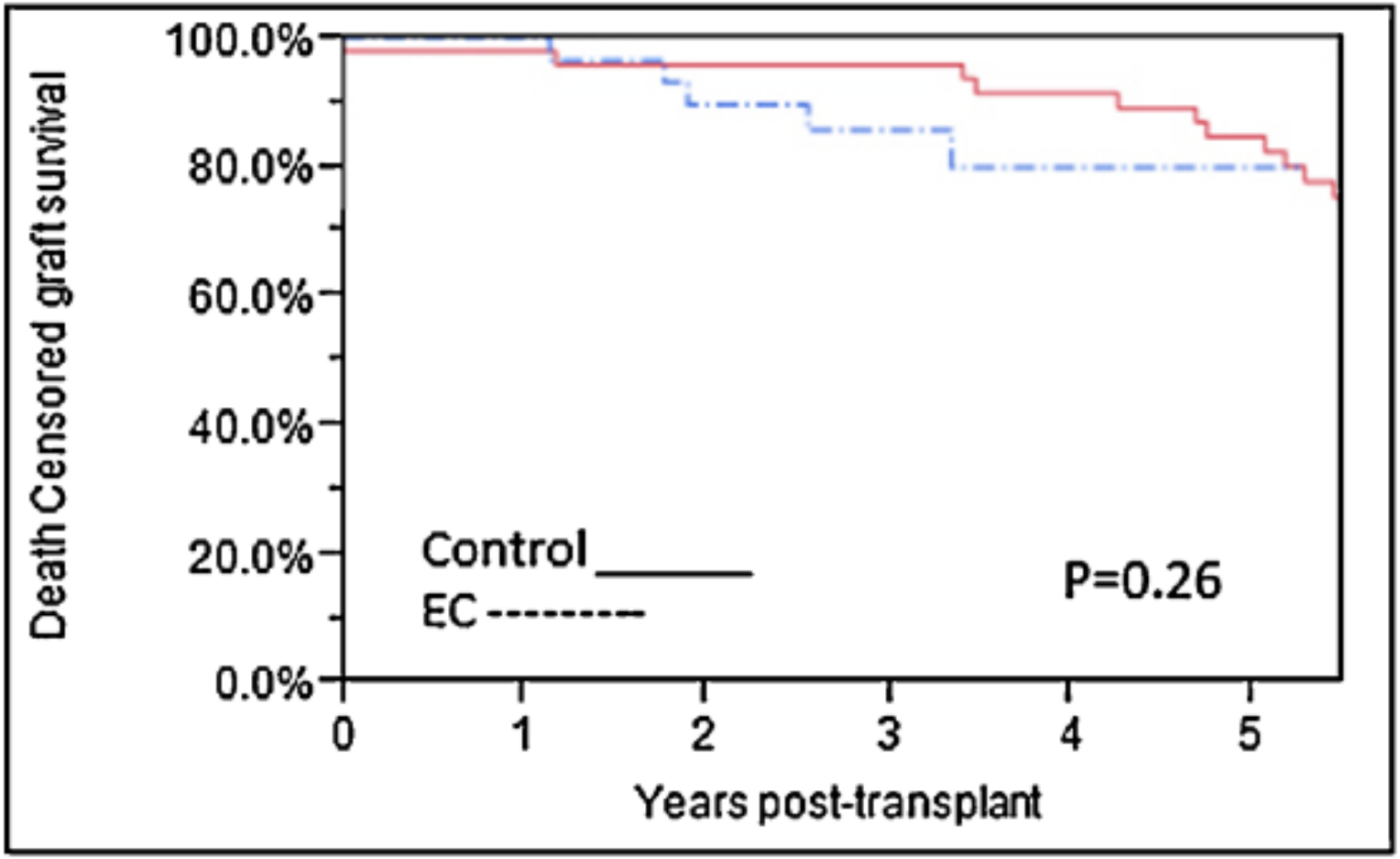
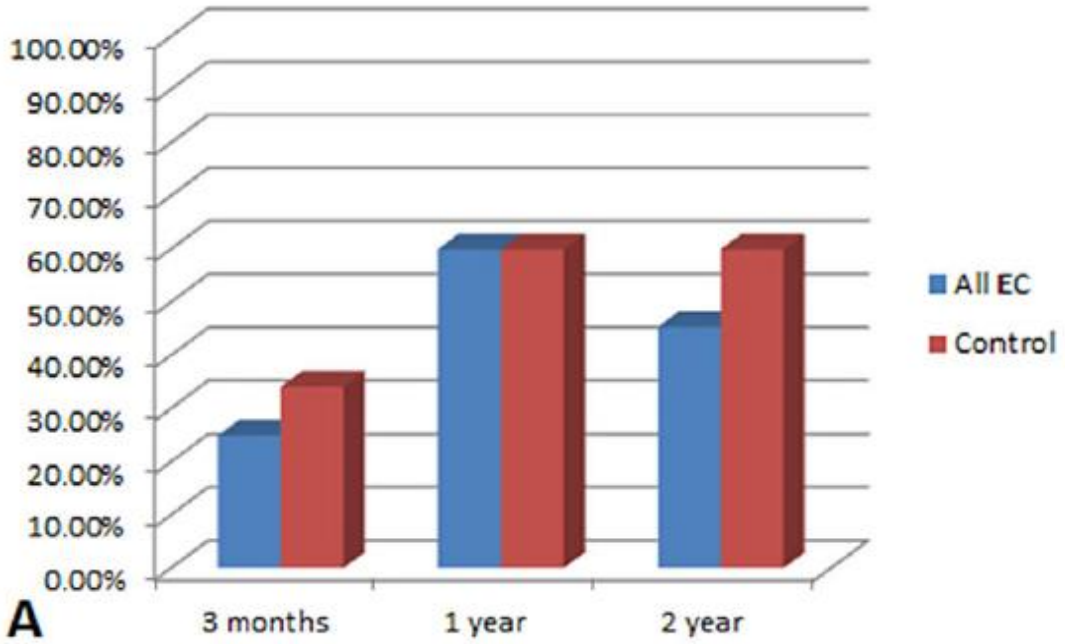


At risk	0	1	2	3	4	5
Control	48	46	46	45	40	37
EC	30	30	26	21	8	2



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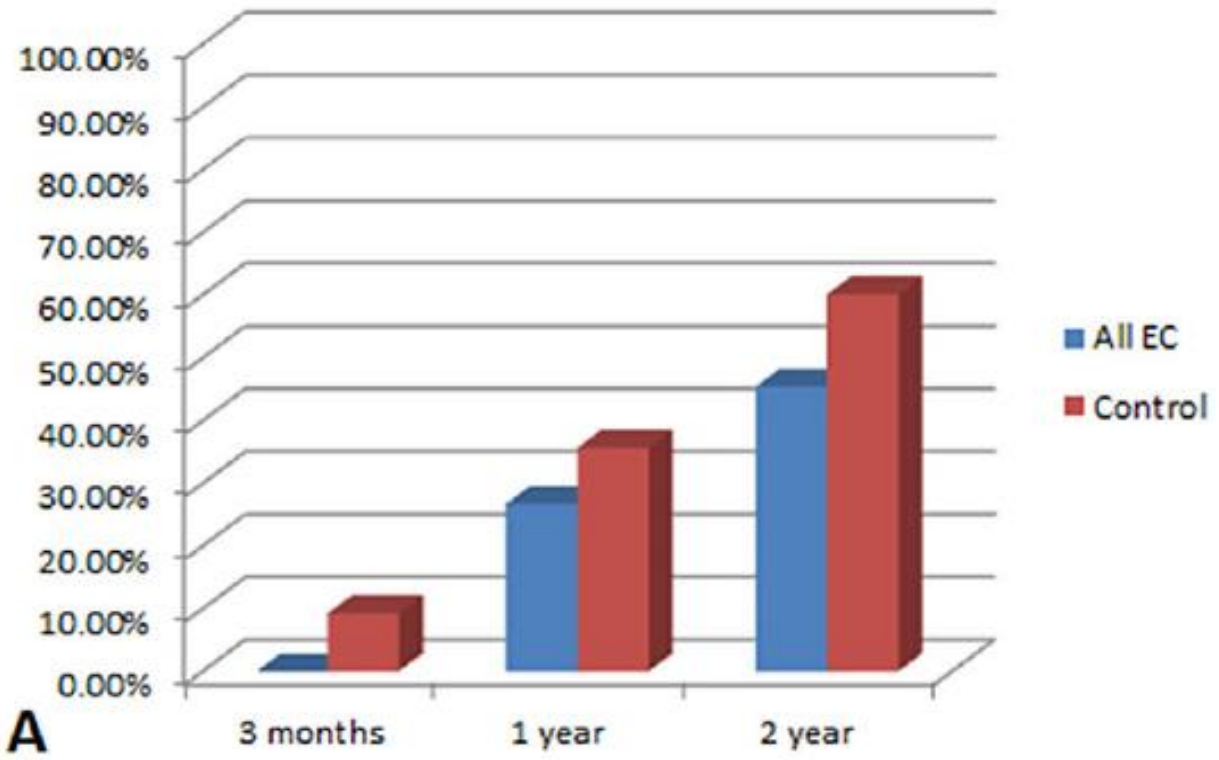
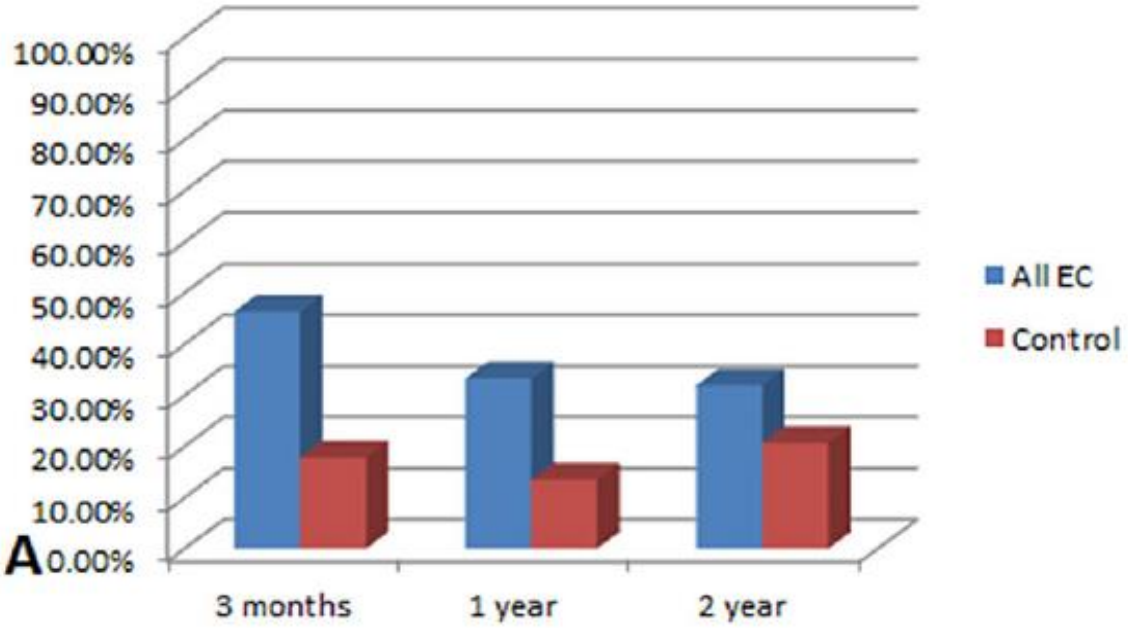
Moderate-to-Severe Peritubular capillaritis in Controls vs. Eculizumab			
	3-4 months	1 year	2 year
All EC	25.0% (7/28)	60.0% (18/30)	45.4% (10/22)
Control	34.1% (14/41)	60.0% (21/35)	60.0% (15/25)
p-value (control vs. EC)	P= 0.59	P=1.00	P=0.39



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



C4d in Controls vs. Eculizumab			
	3-4 months	**1 year**	**2 years**
All EC	46.4% (13/28)	33.3% (10/30)	31.8% (7/22)
Control	17.9% (7/39)	13.5% (5/37)	20.7% (6/29)
p-value (EC vs. control)	P= 0.02	P=0.08	P=0.52

Early C5 Blockade Prevents Late Transplant Glomerulopathy?

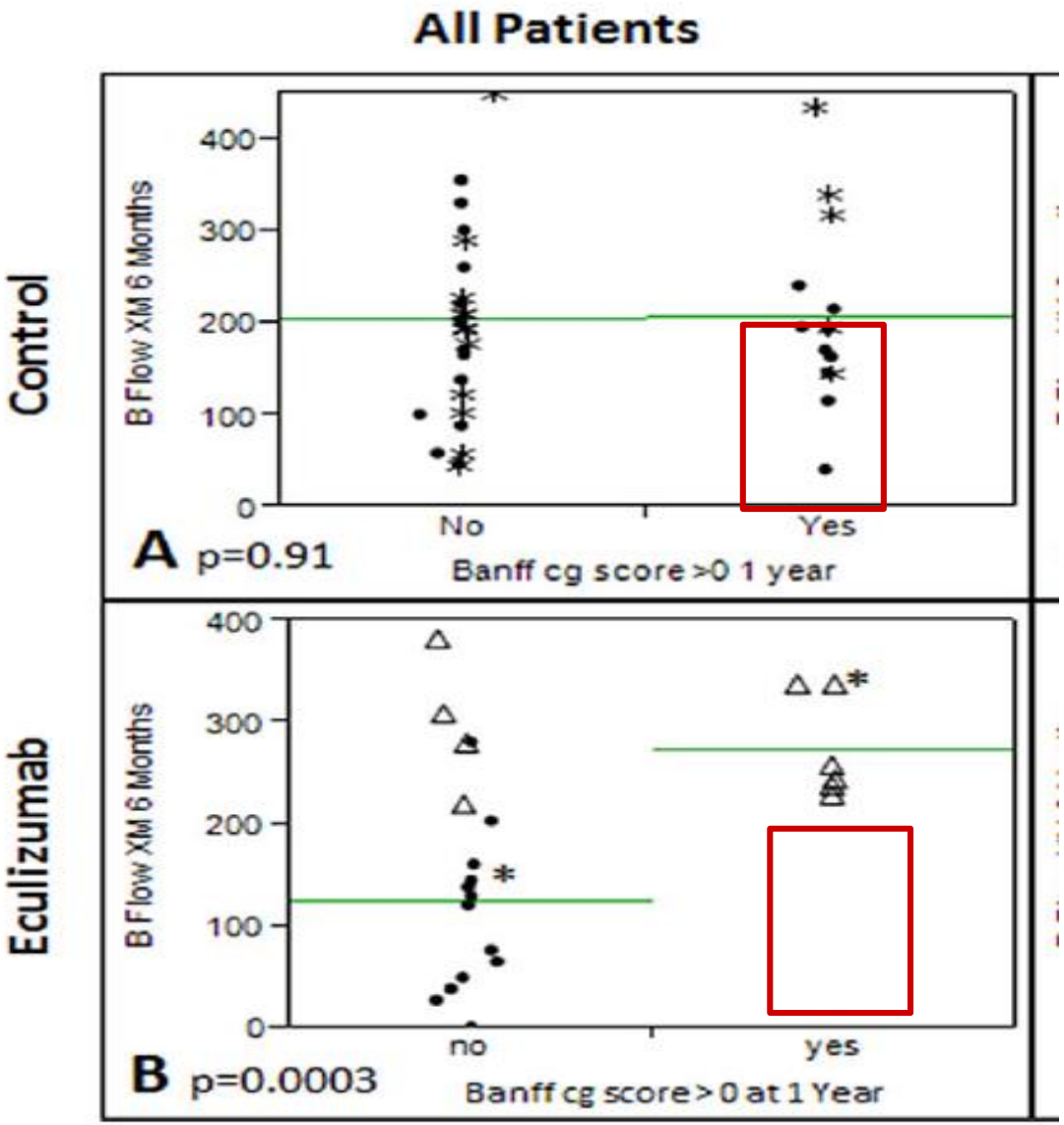


Figure 7: Transplant glomerulopathy at 1 year

Lessons Learned from Eculizumab Experience

- Preventing early clinical ABMR does not prevent chronic ABMR
- Complement blockade may prevent injury in patients with low levels of DSA, but high levels of DSA are not as complement dependent
- Protocol biopsies help to delineate progression of chronic injury

Goals of the Workshop

3) Discuss the natural course of the acute-chronic AMR continuum and its temporal association with cellular rejection and changes in GFR

Emerging Paradigm:

Late after transplantation

Many patients present with a combination of ACR and ABMR on biopsy

ACR is the primary cause of acute rise in creatinine

ABMR is the primary cause of late graft loss in this setting (ptcitis→ cg → graft loss)

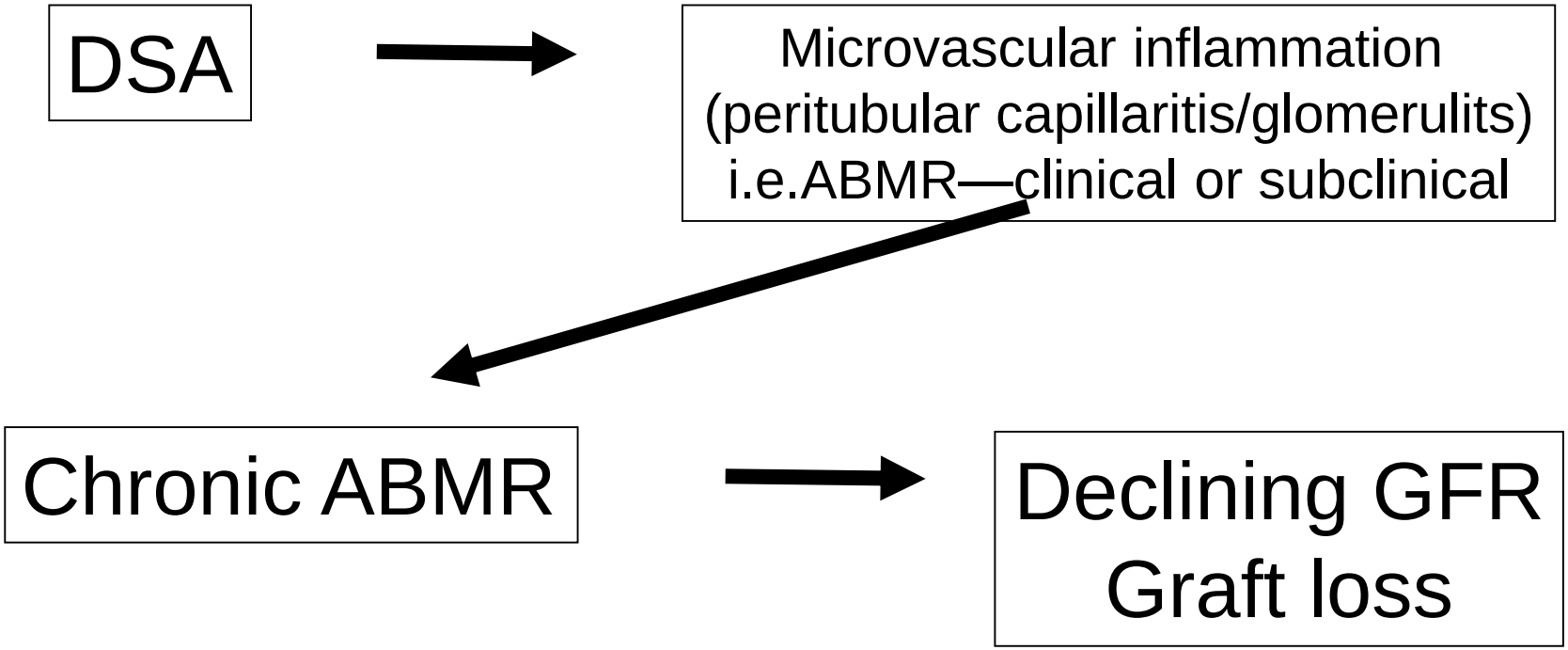
Mechanism of DSA Development

- T cell dependent immune response
- Non-adherence (commonly combined with T cell mediated rejection)→ may persist after treatment/resolution of the cellular response
- Planned reduction in immunosuppression—Polyoma virus, cancer or minimization/tolerance protocols
- Subclinically in otherwise adherent patients (?50% in our series)
- Treating the ACR does not prevent late graft loss from ABMR

What you are left with

- Patient with DSA and the other problems are taken care of
- Now we can go to work

Paradigm

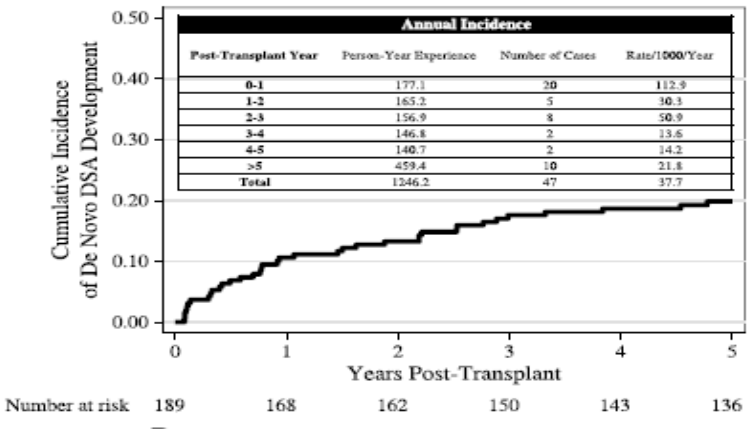

DSA
Microvascular inflammation
(peritubular capillaritis/glomerulits)
i.e.ABMR—clinical or subclinical
Chronic ABMR
Declining GFR
Graft loss

De Novo DSA

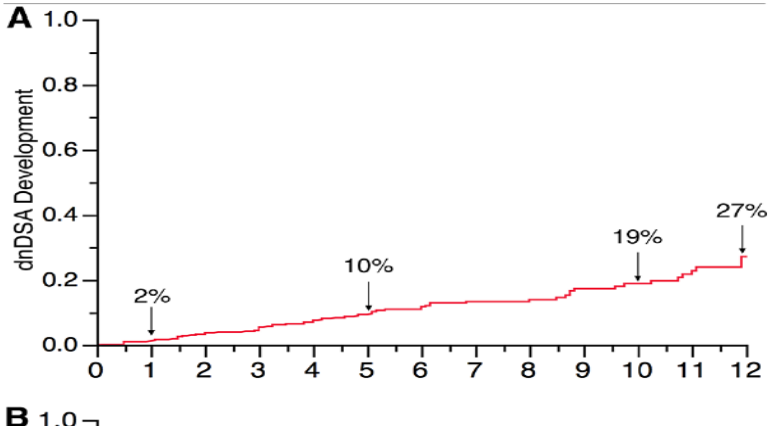
de Novo DSA

- The incidence varies with the patient population studied and how strictly it is defined.
- 5 years after kidney transplantation, cumulative incidence ranged from 13% (14) to 22% (15).
- Weibe C and Nickerson P. Curr Opin Organ Transp;ant 2013; 18:470-477.

De Novo DSA—two studies



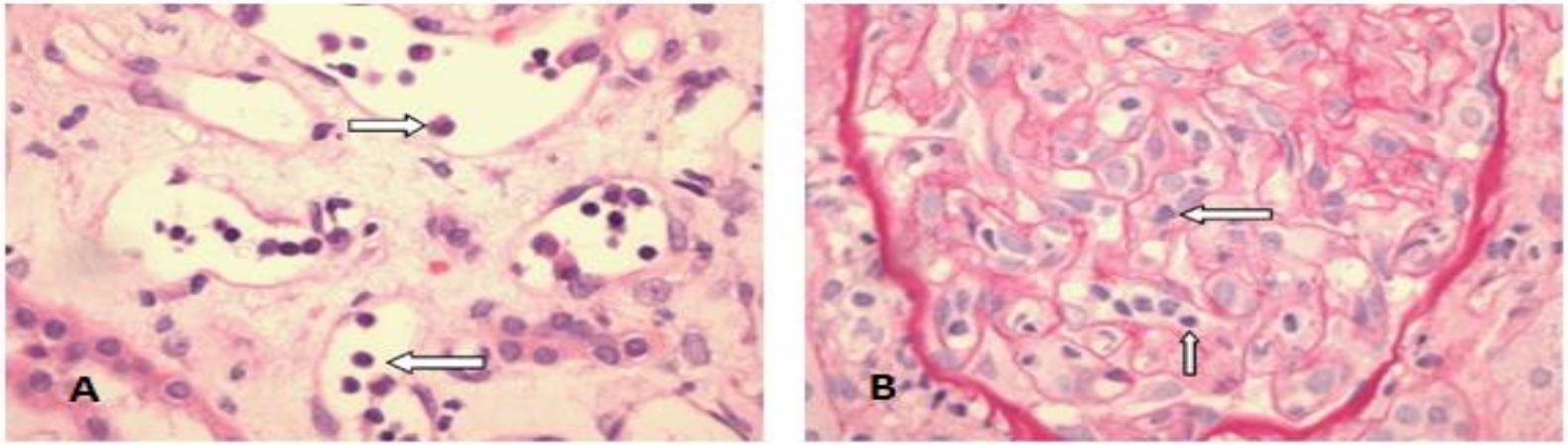
Everly MJ, Rebellato LM, Haissch CE, et al. Incidence and impact of de novo donor-specific alloantibody in primary renal allografts. Transplantation 2013; 95:410-417.



Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. Am J Transplant 2012; 12: 1157.

Not all patients with DSA lose their grafts

- Graft loss is more common when secondary to non-adherence
- Weibe AJT 2012
- Raises the question of the actual cause of graft loss in some patients
- DSA+ patients who do not develop ABMR on biopsy do well



Histologic features of Antibody Mediated Rejection. Peritubular capillaritis (leftl A) and glomerulitis (right B) are hallmark histologic features of antibody mediated rejection.

Paradigm

DSA → Microvascular inflammation (peritubular capillaritis/glomerulits) i.e.ABMR—clinical or subclinical

- 50% of patients with DSA develop ABMR
- More common with higher levels/C1q+
- More common with anti-Class II DSA (?Dq)
- DSA+/ABMR- patients do well

American Journal of Transplantation 2017; XX: 1–11
Wiley Periodicals Inc.

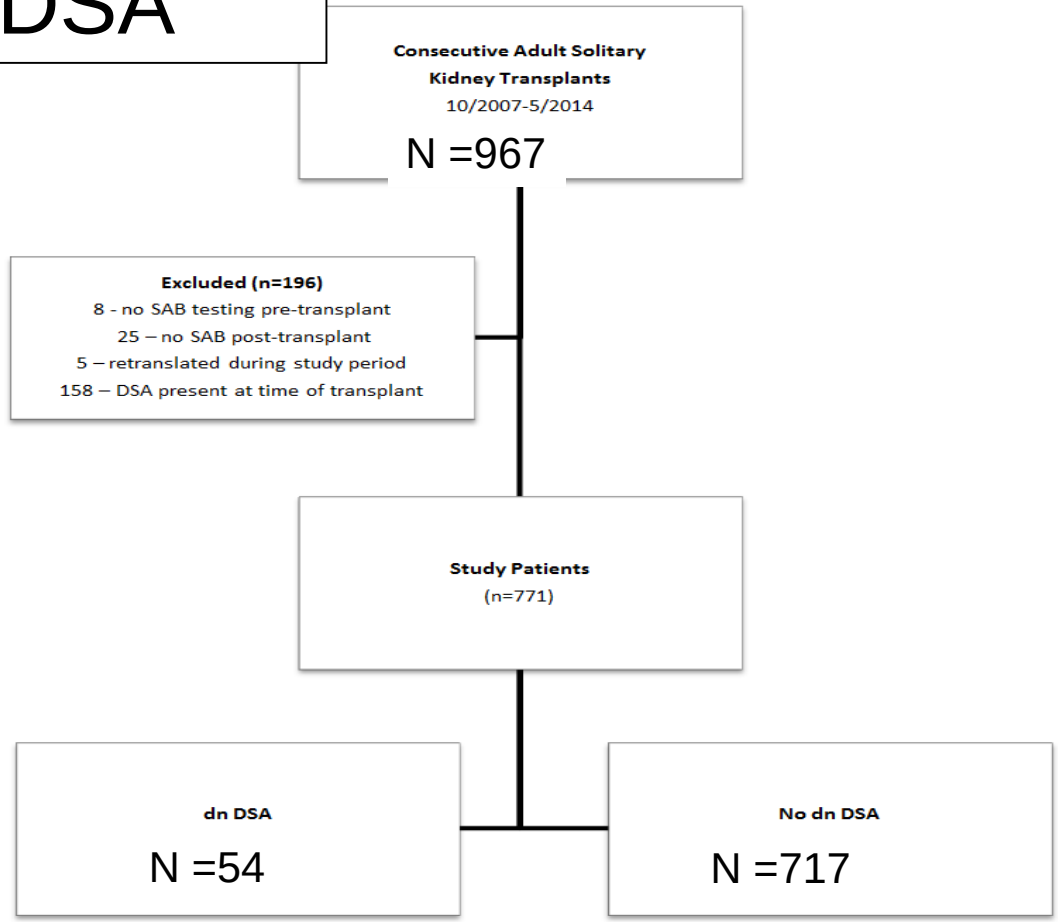
doi: 10.1111/ajt.14161

The Value of Protocol Biopsies to Identify Patients With *De Novo* Donor-Specific Antibody at High Risk for Allograft Loss

C. A. Schinstock[1,*], F. Cosio[1], W. Cheungpasitporn[1], D. M. Dadhania[2], M. J. Everly[3], M. D. Samaniego-Picota[4], L. Cornell[5] and M. D. Stegall[1]

eGFR, estimated GFR; ESRD, end-stage renal disease; IQR, interquartile range; IVIG, intravenous immunoglobulin; MFI, mean fluorescence intensity; NA, not assessed; OR, odds ratio; SAB, single antigen bead; SD, standard deviation

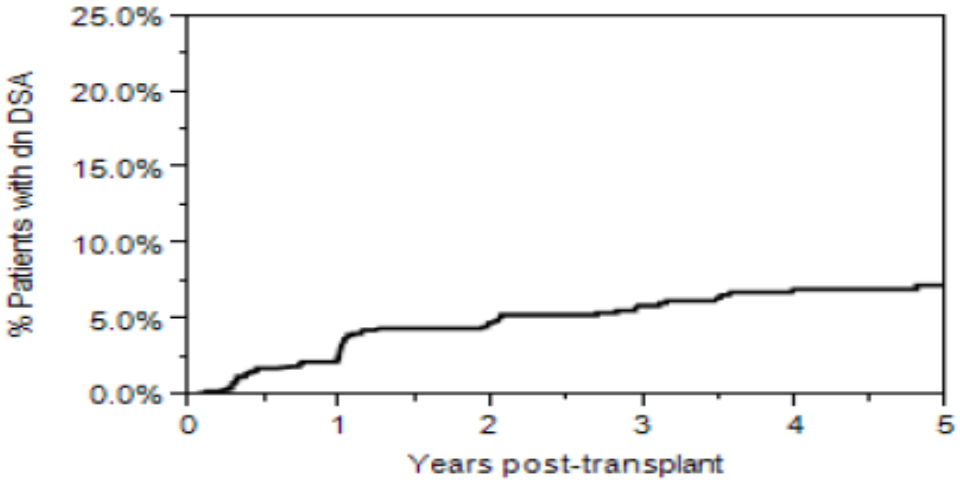
De Novo DSA



Yearly DSA testing
Surveillance biopsies
1, 2, 5 years and when DSA detected

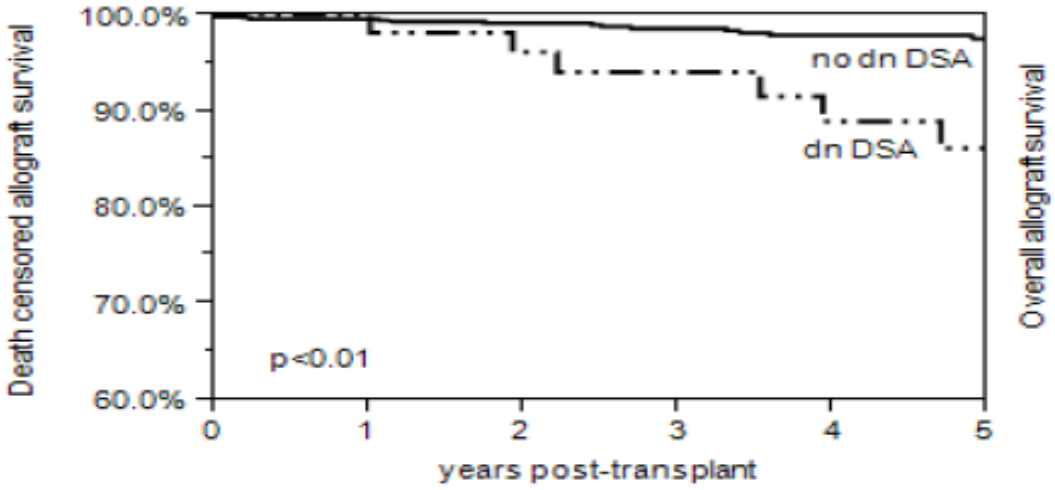
Mean Follow-Up
4.2±1.9 years

Time to de novo DSA detection



Is dnDSA lower in Tacrolimus-treated patients than in cyclosporine-treated patients? Unknown

Death-Censored Allograft Survival



Surveillance Biopsies
1 year after dnDSA detection

- 53% had acute, active ABMR (normal Creatinine)
- 37% had cABMR (cg>0)

De No

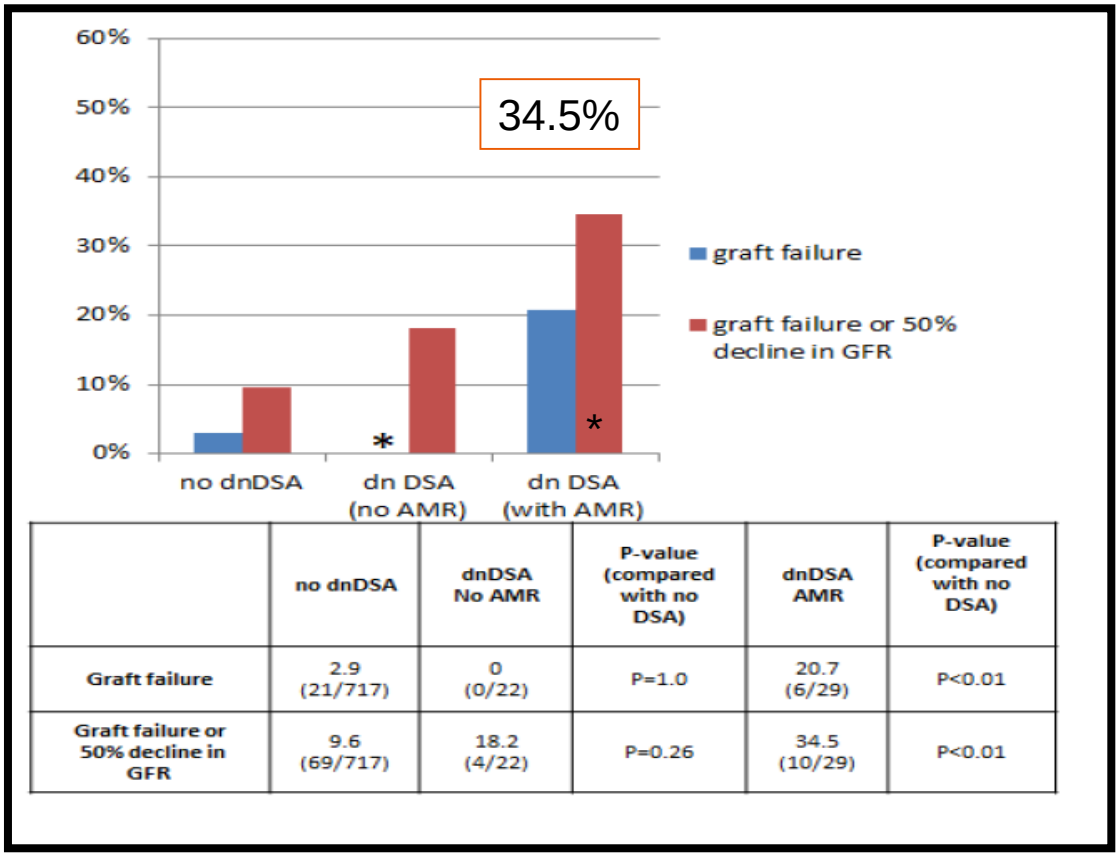
Important for study design:

Prevention—treat all, graft loss rates are lower

Intervention—Enriched population, graft loss rates are higher

Easier to show an effect

ection



	no dnDSA	dnDSA No AMR	P-value (compared with no DSA)	dnDSA AMR	P-value (compared with no DSA)
Graft failure	2.9 (21/717)	0 (0/22)	P=1.0	20.7 (6/29)	P<0.01
Graft failure or 50% decline in GFR	9.6 (69/717)	18.2 (4/22)	P=0.26	34.5 (10/29)	P<0.01

Mean f/u after DN DSA Detection 3.5+2.0 years

Treatment of ABMR

- None proven effective
- Optimize tacrolimus, mmf
- Only use IVIG or plasma exchange in acute graft dysfunction

Treatment of ABMR

CLINICAL AND TRANSLATIONAL RESEARCH

(*Transplantation* 2014;97: 1240–1246)

Late Antibody-Mediated Rejection in Renal Allografts: Outcome After Conventional and Novel Therapies

Gaurav Gupta,[1] Bassam G. Abu Jawdeh,[2] Lorraine C. Racusen,[3] Bhavna Bhasin,[4] Lois J. Arend,[3] Brandon Trollinger,[5] Edward Kraus,[4] Hamid Rabb,[4] Andrea A. Zachary,[4] Robert A. Montgomery,[6] and Nada Alachkar[4,7]

CLINICAL AND TRANSLATIONAL RESEARCH

(*Transplantation* 2014;97: 1253–1259)

High Dose Intravenous Immunoglobulin Therapy for Donor-Specific Antibodies in Kidney Transplant Recipients With Acute and Chronic Graft Dysfunction

James E. Cooper,[1,4] Jane Gralla,[2] Patrick Klem,[3] Laurence Chan,[1] and Alexander C. Wiseman[1]

Transplantation 2008; 86:1754.

Bortezomib Provides Effective Therapy for Antibody- and Cell-Mediated Acute Rejection

Matthew J. Everly,[1] Jason J. Everly,[1] Brian Susskind,[2] Paul Brailey,[2] Lois J. Arend,[3] Rita R. Alloway,[4] Prabir Roy-Chaudhury,[4] Amit Govil,[4] Gautham Mogilishetty,[4] Adele H. Rike,[1] Michael Cardi,[5] George Wadih,[5] Amit Tevar,[1] and E. Steve Woodle[1,6]

Goals of the Workshop

4) Discuss unmet medical needs and potential clinical trial design challenges for the prevention and treatment of AMR

Is there hope?

- What would a clinical trial look like?

The Problem is “Thorny”
Who to include in the study?

- ? 50% caused by non-adherence (Dr. Nickerson will cover this)
- Some secondary to necessary immunosuppressive withdrawal (polyoma virus, cancer
- Mixed cellular and humoral rejection is common
- ? Treated cellular rejection→ persistent ABMR

- **A conservative estimate that we used in power calculations for our proposed study is a rate of DSA detection in the overall transplant population of 2%/year after transplantation.**
- This correlates to a 10% incidence at 5 years.

Combined Clinical Endpoints

- Graft loss
- 50% decline in eGFR

Surrogate endpoints

- The histologic changes of cABMR are a good surrogate biomarker for allograft loss because they precede allograft loss by years, are not seen in other conditions that affect the allograft, and are highly predictive of the outcome.
- Alternatively, just use DSA alone
- Prevention of graft loss or decline in eGFR is the ultimate goal

Chronic Irreversible Changes need to be considered in treatment

- CG3
- Ci3
- If a biopsy has a lot of chronic changes, we are less likely to treat
- Retransplantation is a better option

DSA as the inclusion criteria: Weibe et al

- 40% lost their graft by **5 years** post-dnDSA.
- RCT expected to improve 5 year graft survival by 25% would require 150 recipients (power =80%, drop out 10%, p,0.05)
- Declining GFR as an endpoint also suggested

Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. Am J Transplant 2012; 12: 1157.

What about a surrogate endpoint study? Shorten time to show efficacy

Surrogate=resolution of DSA

or

Surrogate=resolution of cAMR on biopsy

Design #1
DSA as the inclusion criteria Intervention Trial

- MFI >1000
- 6 months treatment and recheck DSA
- Treat→ MFI <1000
- Incidence of graft loss with MFI 1000 at **2 years** is 18%C1q might be better, but not FDA approved

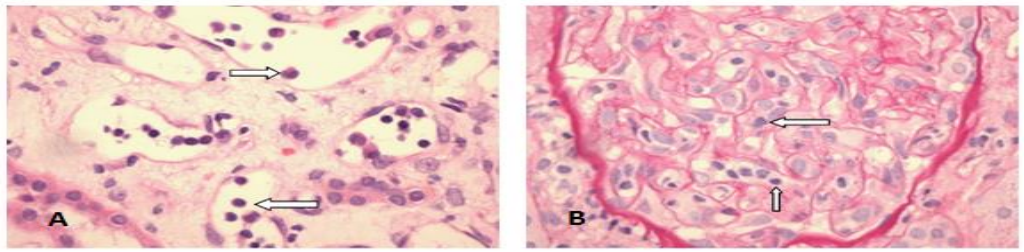
Wiebe et al. Am J Transplant 2016;

	DSA Decrease	80%	90%	Clinical Endpoint	80	90%
CTL	20%	43	58	18%	230	308
Rx	50%	43	58	9%	230	308
Total		84	116		460	608

Two big problems:
DSA can resolve without treatment
Rate of graft loss is low

Intervention Trial Design #2

- Identify patients with de novo DSA
- Biopsy
- If ABMR→ Enter into trial
- If no ABMR→ follow and rebiopsy



Peritubular capillaritis Glomerulitis

cABMR Study: Power Calculations

- cABMR does not spontaneously resolve
- 35.7% lose grafts at 2 years

	Histologic Response	80%	90%	Clinical Endpoint	80	90%
CTL	0%	11	14	35.7%	96	128
Rx	50%	11	14	17.9%	96	128
Total		22	28		192	256

Adaptive Trial Design

- A methodology in which a clinical trial evolves or adapts as the trial proceeds depending on the outcomes of patients enrolled. T
- The criteria for these decisions are set prior to the beginning of the studies.
- An adaptive design may use of standard statistical methods (i.e. frequentist) to halt the trial early for toxicity (dangerous substance), futility (no improvement over a control), or efficacy (great improvement over a control).

Adaptive Trial Design

- can “learn” from relatively small numbers of study subjects.
- In our calculations, as few as 8 patients can be used to decide if a therapy is ineffective.
- Another aspect of ATD that enhances efficiency is that it uses a single ongoing control group rather than having a different control group for each experimental group. T
- The vast majority of patients can be assigned to an experimental group. This maximizes the number of different studies that can be performed in a small population of patients

Adaptive Trial Design

- Minimizes the number of patients receiving ineffective treatments and thus limits unnecessary treatment risks in study patients. FDA like it
- Cheaper—drug companies like it

cABMR Study: Power Calculations

Treatment	Histologic Response	Sample Size		Clinical Endpoint	Sample Size	
		80%	90%		80%	90%
Control	0%	11	14	35.7%	96	128
Drug A	50%	11	14	17.9%	96	128
Total		22	28			

	Single Therapy [No Dual therapy]				Dual Therapy [ALL Single therapy fail]			
Therapy	ALL FAIL	1 Works	2 Works	3 Works	ALL FAIL	1 Works	2 Works	3 Works
Control	8	17	17	17	17	17	17	17
Treatment								
1	8	17	17	17	8	8	8	8
2	8	8	17	17	8	8	8	8
3	8	8	8	17	8	8	8	8
Treatment								
1+2					8	17	17	17
1+3					8	8	17	17
2+3					8	8	8	17
	32	50	59	68	65	74	83	92

Need 7/14 to respond

Summary

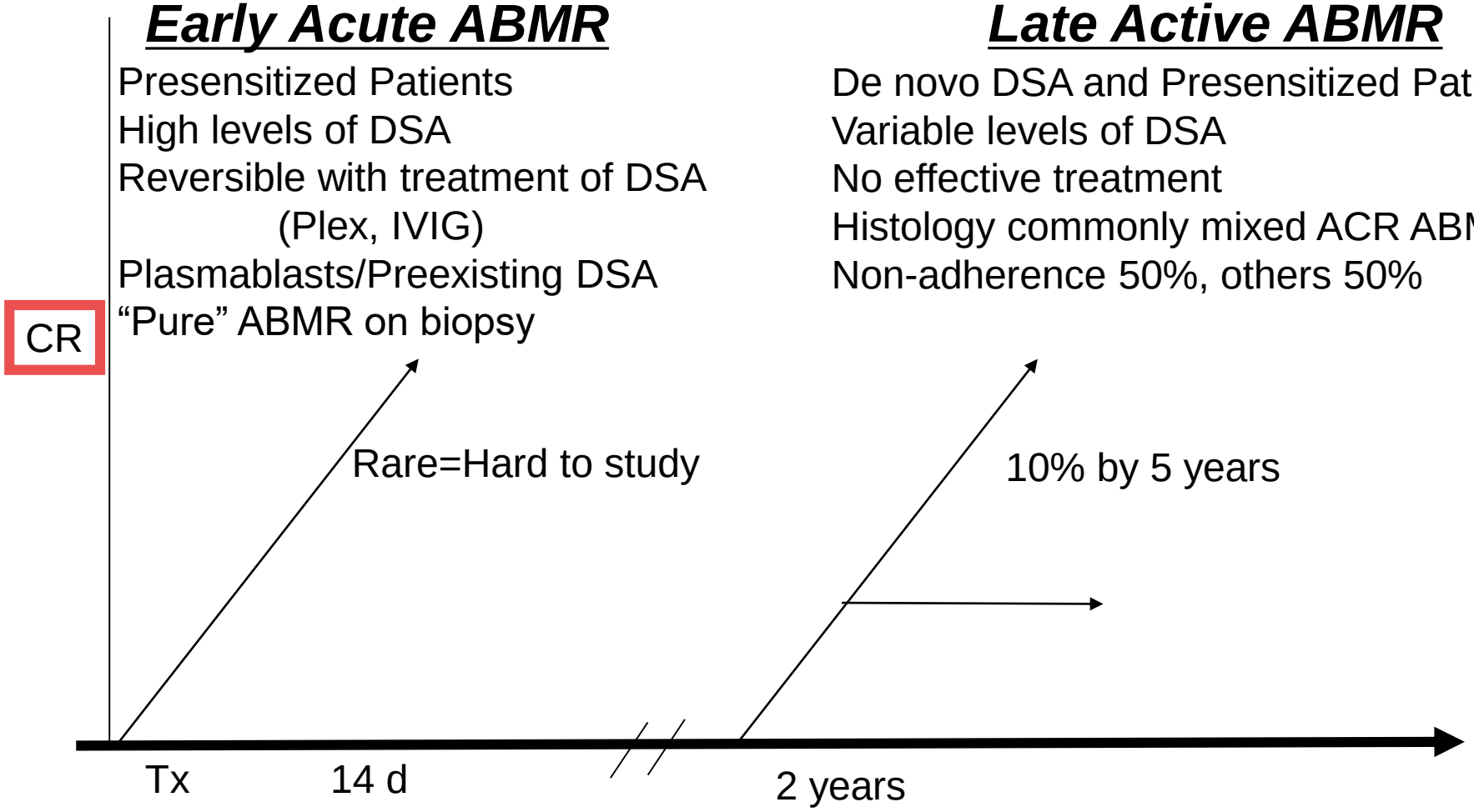
Different Clinical Scenarios

Early Acute ABMR

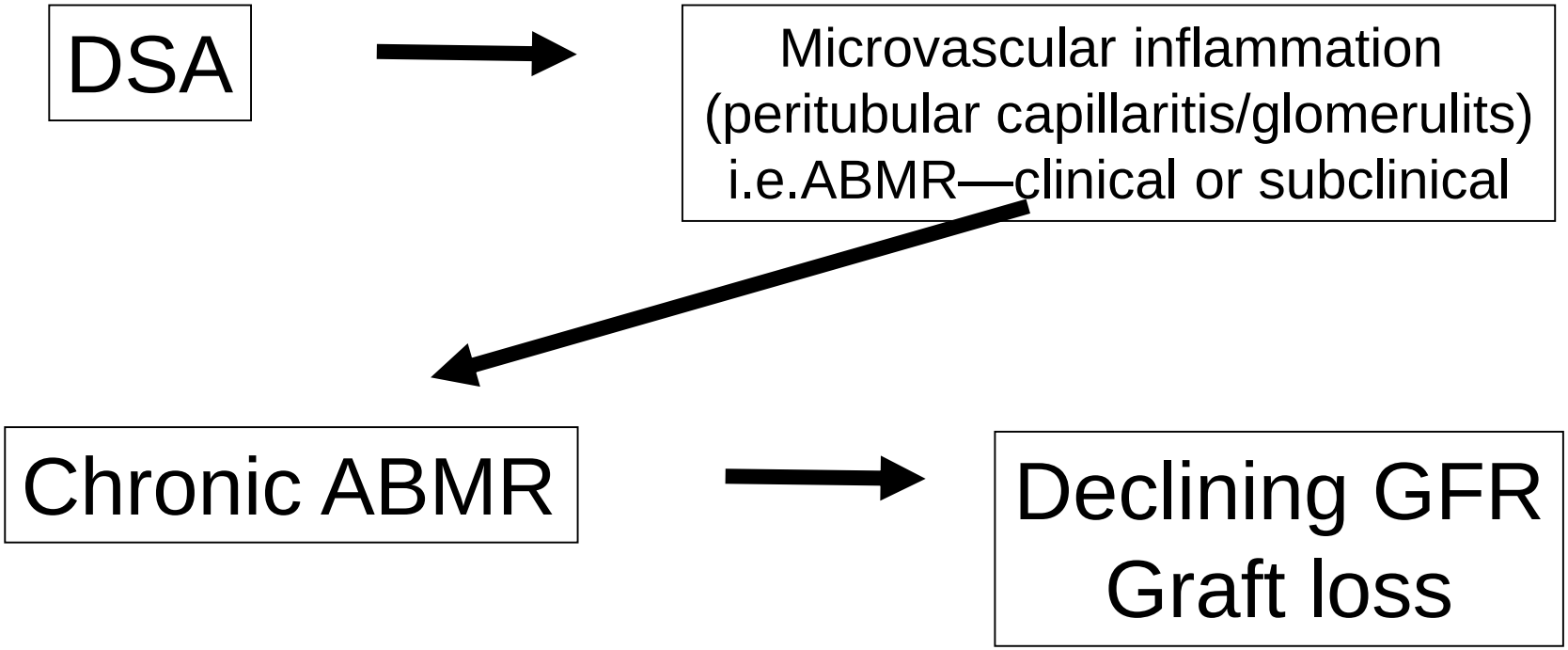
Presensitized Patients
High levels of DSA
Reversible with treatment of DSA
(Plex, IVIG)
Plasmablasts/Preexisting DSA
"Pure" ABMR on biopsy

Late Active ABMR

De novo DSA and Presensitized Patients
Variable levels of DSA
No effective treatment
Histology commonly mixed ACR ABMR
Non-adherence 50%, others 50%



Paradigm


DSA
Microvascular inflammation
(peritubular capillaritis/glomerulits)
i.e.ABMR—clinical or subclinical
Chronic ABMR
Declining GFR
Graft loss

Biopsy

- A picture of the past and of the future
- A biomarker—how well does a biopsy finding correlate with subsequent clinical outcomes (graft loss)?

Most Important

- If your biopsy is normal, your chance of graft loss is low

Conclusions

- Developing therapy for cABMR is a major unmet need in kidney transplantation
- Validated surrogate markers are needed (histology is a very good one)
- Clinical trials are feasible
- Best to employ adaptive trial design

Reality

- Improving long-term renal allograft survival is a tough problem
- It will take many years to make improvements
- We need to start now
- I may not see the final product

Subpart H: Accelerated Approval

- Shortens time to approval
- Encourages companies to study long-term outcomes
- Drug gets FDA interim approval because it improves a predictive biomarker
- Drug can then be marked and sold
- Follow-up studies needed to show that it actually improves the clinical endpoint (ex. graft survival)
- May be “pulled” if it does not meet the clinical endpoint