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Pushing the Boundaries of ABOi: *State of the Art*

Jayme E. Locke MD MPH FACS FAST
Mark H Deierhoi Endowed Professor
Director, Comprehensive Transplant Institute
University of Alabama at Birmingham, Birmingham, AL, USA

Disclosures

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  - NIDDK – K23DK103918 (PI, mentored)
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    R01DK111966 (site PI)
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    U01AI118594 (site co-PI)

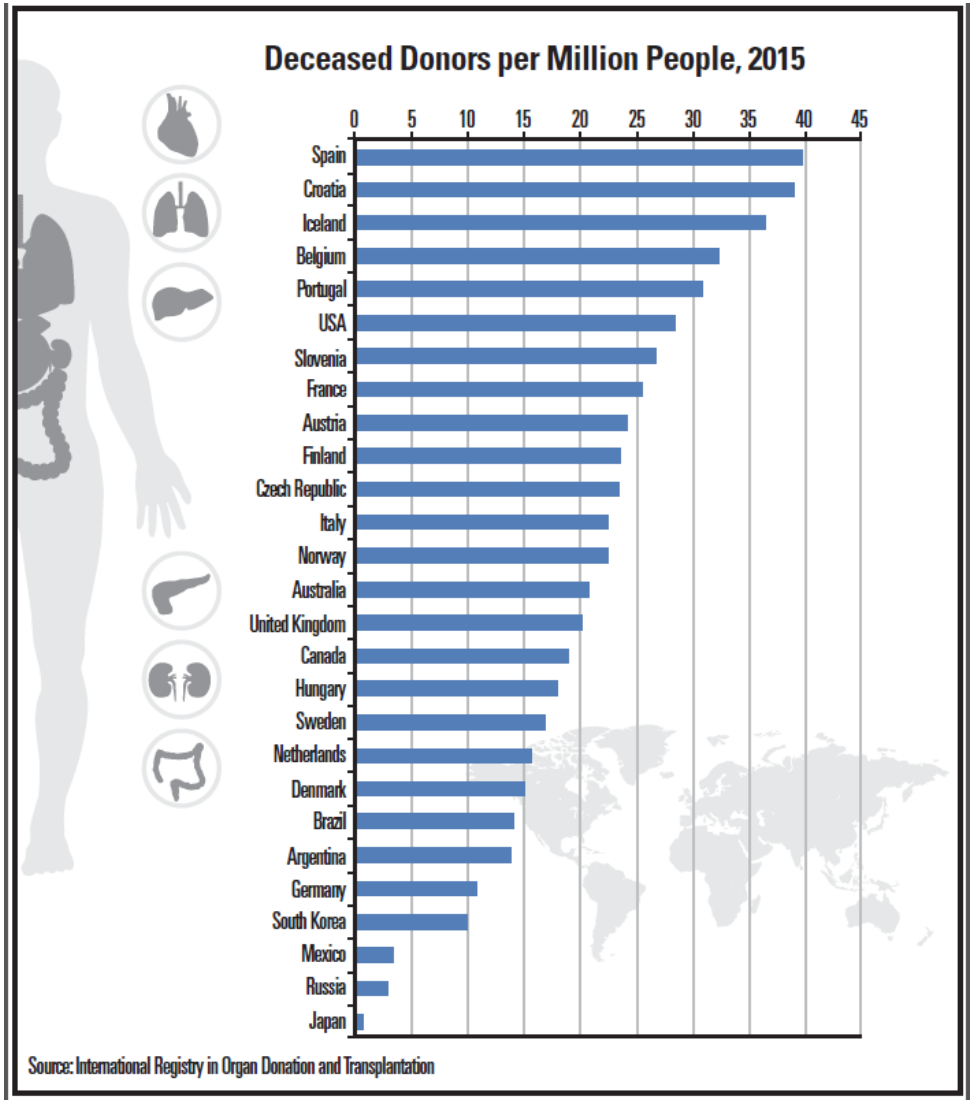
Objectives

- Rationale for ABO-incompatible transplantation
- The How To – Methods and Pitfalls
  - Desensitization
  - Understanding titer methods
- The Good and the Bad – US National Results
- Personalized Medicine - Balancing Risk vs. Benefit *(e.g. What's the best path for your patient?)*

Rationale

Global Organ Shortage

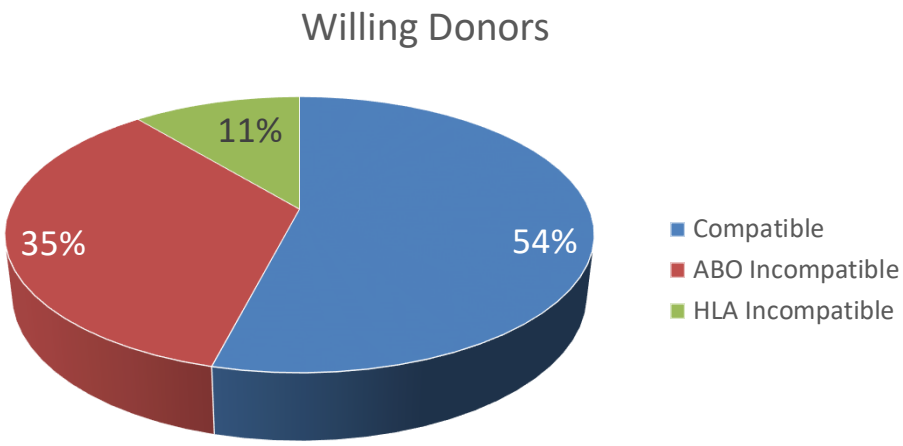
<10% of the global need



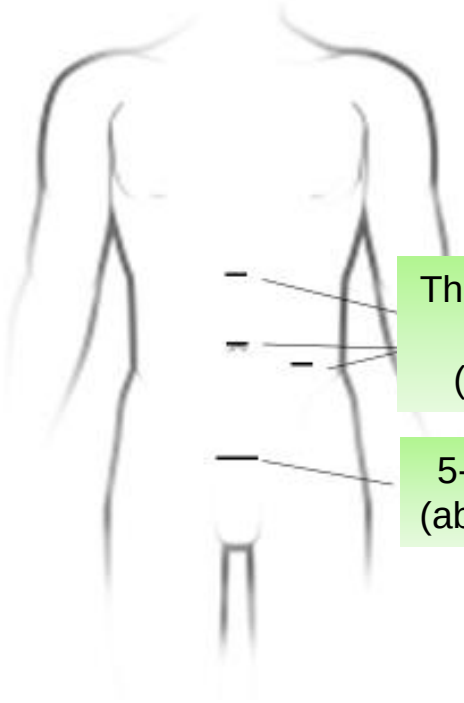
Rationale

Global Organ Shortage

Donor-Recipient Compatibility



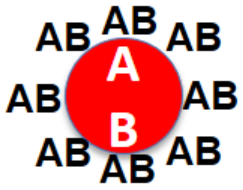
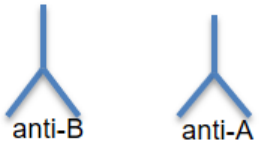
Living Donor Nephrectomy



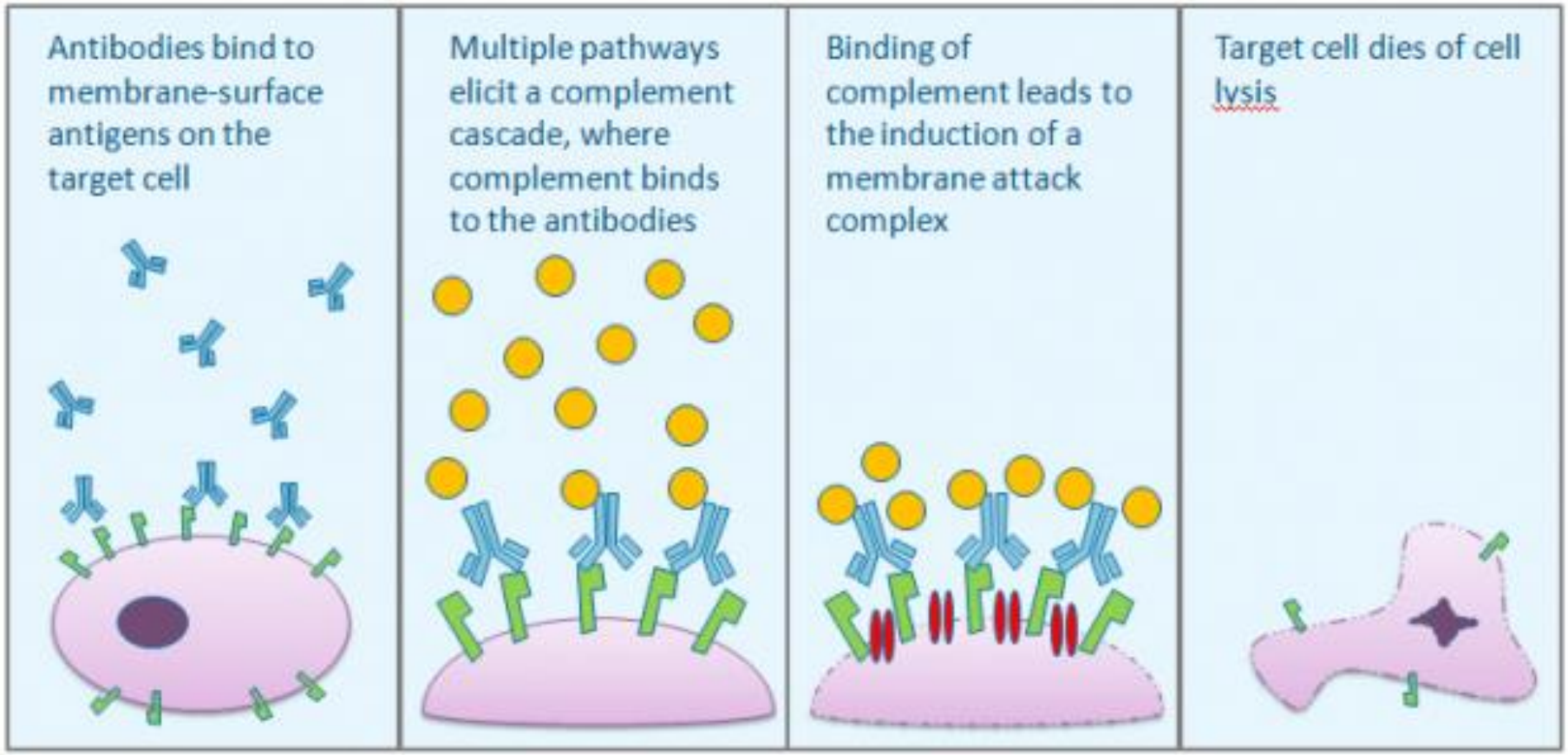
Three small incisions[3]
1-1.5 cm
(less than ½ inch)

5-cm incision[3]
(about 2 inches)

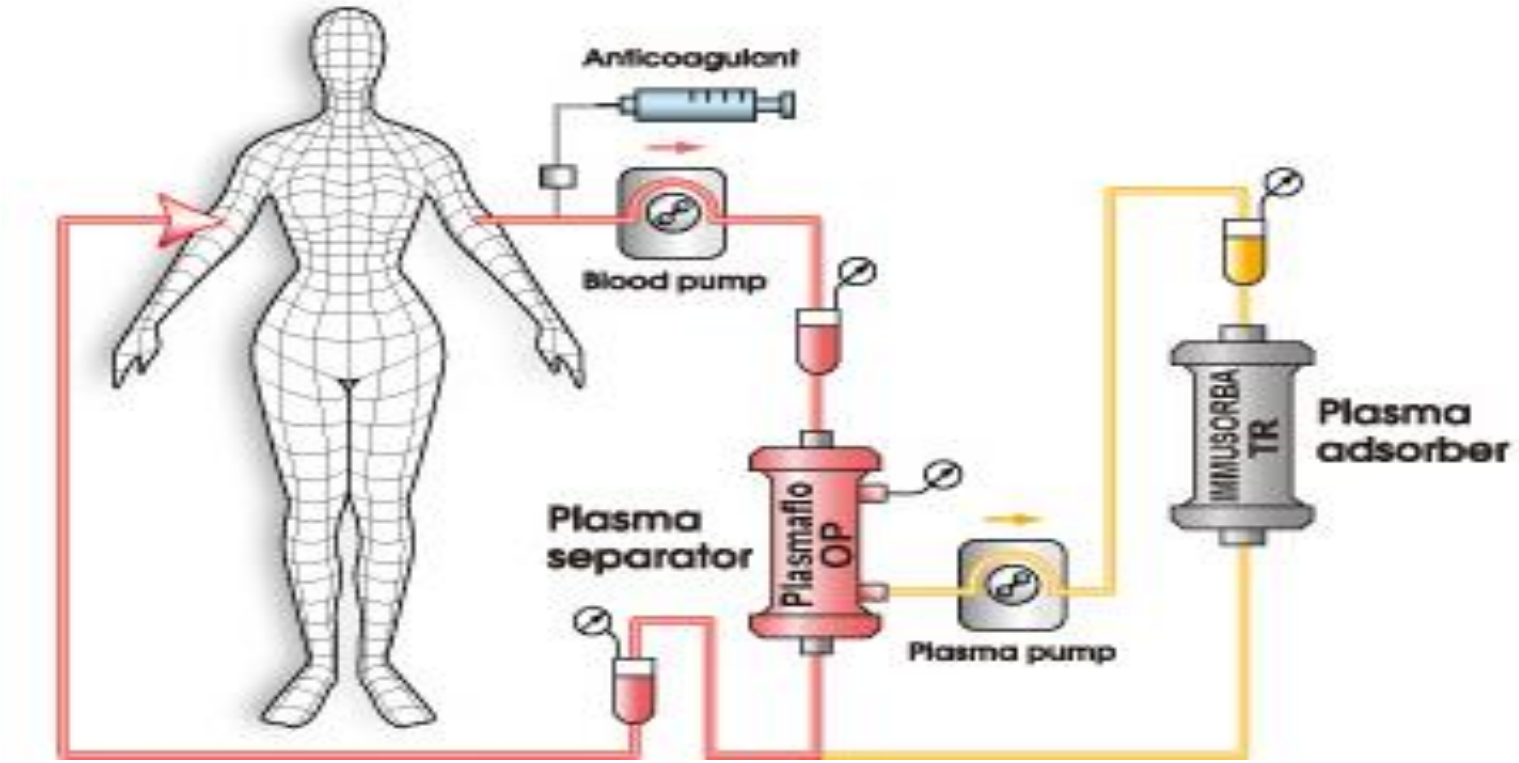
The How To - METHODS

RED BLOOD CELLS		PLASMA
	→	
	→	
	→	**no** antibodies universal *plasma* donor
 **no** antigens universal *blood* donor	→	

The How To - METHODS



The How To - METHODS

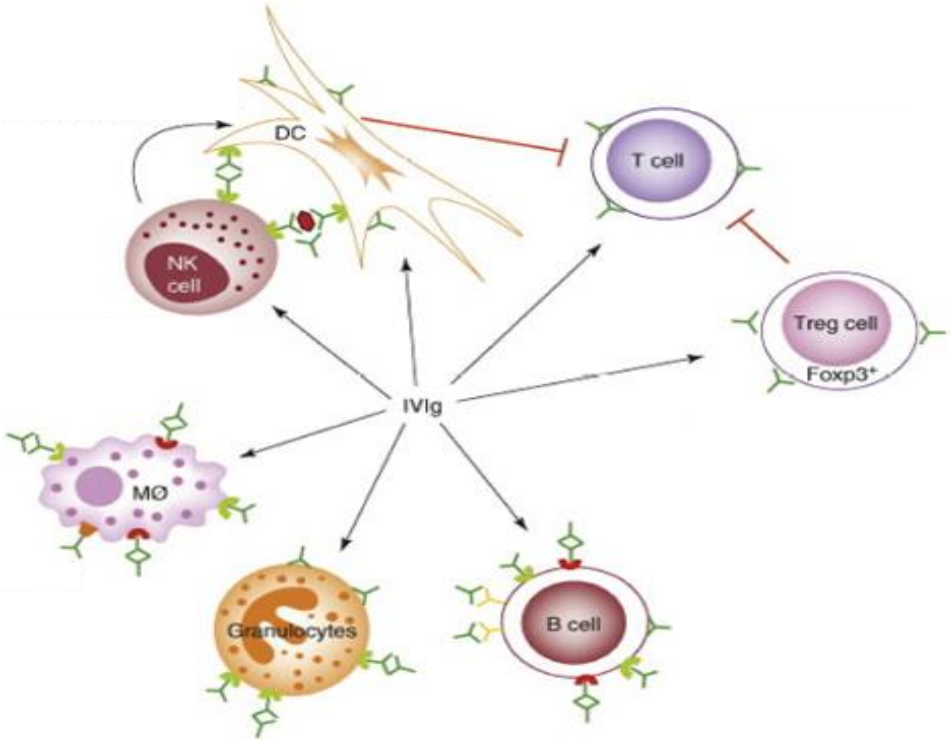


- TPE: Plasma is separated from blood via centrifugation
- IA: Ig is removed from plasma via protein A /G column
- IA more efficient than TPE
  2 sessions within 48 h, reduces serum IgG level by >95%

Asahi Kasei Medical Co. Website
Rummler & Barz & Transfus Med Hemother 2012;39:234–240

The How To - METHODS

IVIg – Mechanism of Action



- Anti-idiotypic Ab
- Inhibits cytokine gene activation, blocks cytokine action
- Blocks T cell activation
- Inhibits complement
- Induces B cell apoptosis
- Interaction with inhibitory FcRs – affect lymphocytes and MΦs

Trends Immunol. 2008;29:608-615

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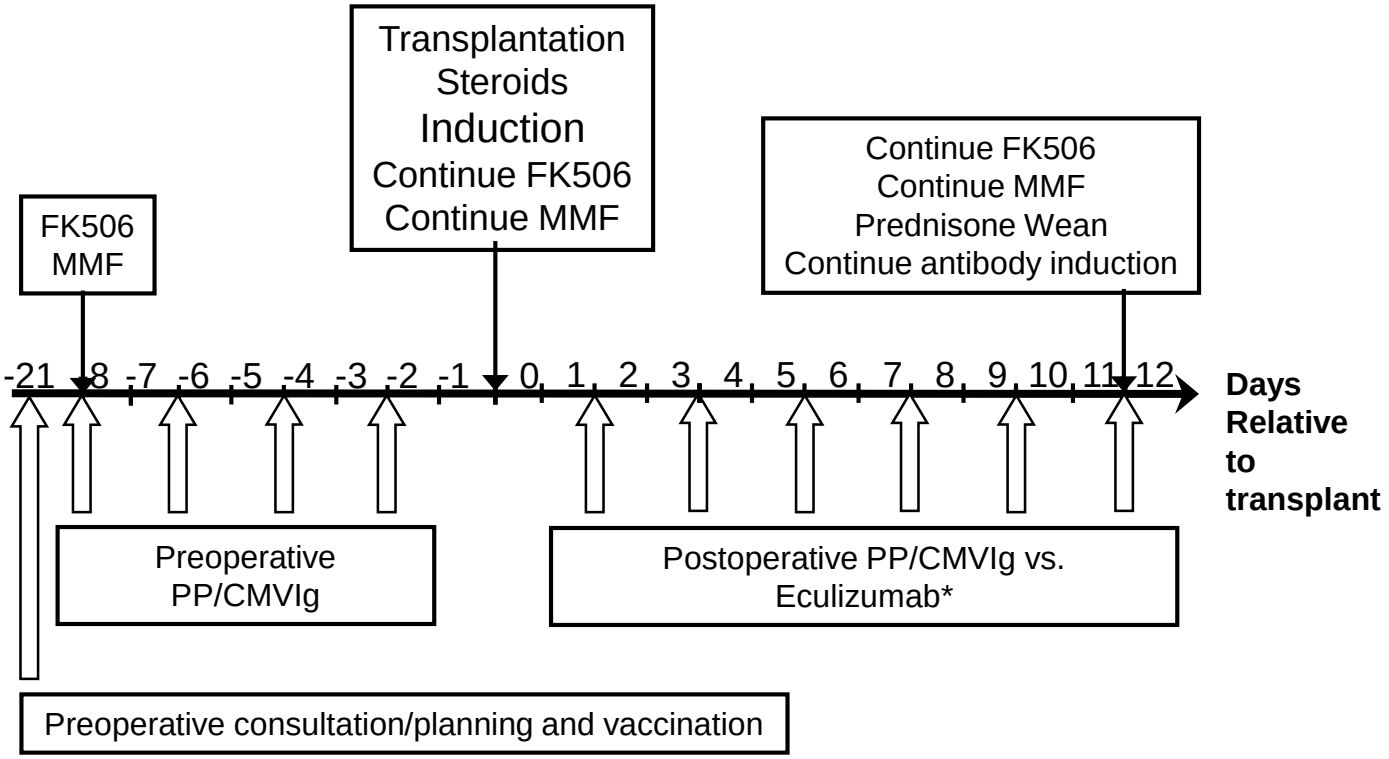
The How To - METHODS



The How To - METHODS

TABLE 1. The number of planned pre- and posttransplant PP/IVIg treatments correlate with the starting isohemagglutinin titer

Starting isoagglutinin AHG titer	Pretransplant PP/IVIG treatments	Posttransplant PP/IVIG treatments
<16	2	2
16–32	3	2–3
64	4	3
128	5–6	4
256	7–8	4
512	9–10	5
>512	>10	6

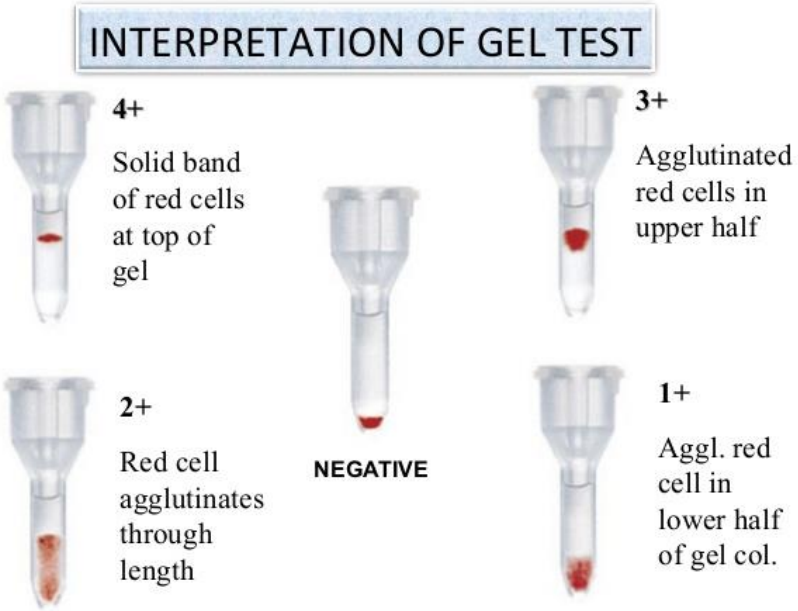
PP, plasmapheresis; AHG, anti-human globulin.

Montgomery RA, Locke JE, et al. ABO incompatible renal transplantation: a paradigm ready for broad implementation. *Transplantation. 2009; 87: 1246-55.*

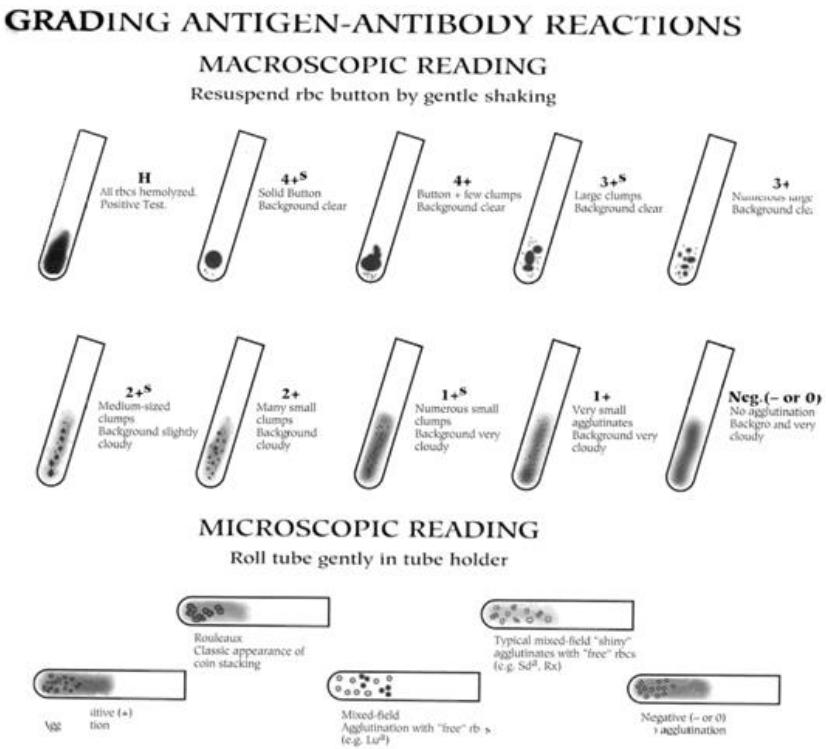
The How To - Pitfalls

Column Agglutination Test

a.k.a. "Gel Method"



Tube Test



The How To - Pitfalls

Table 3. Distribution of ABO antibody titers according to titration methods

Blood group antibodies (N of samples)	Median (interquartile range) of antibody titer for each method			
	IS tube	AHG tube	CAT without DTT	CAT with DTT
Anti-B in blood group A (60)	16 (2-256)	8 (1-512)	8 (1-64)	2 (1-16)
Anti-A in blood group B (60)	16 (2-128)	8 (2-64)	8 (1-256)	4 (1-128)
Anti-B in blood group O (60)	16 (4-128)	32 (4-256)	128 (8-2,048)	64 (2-1,024)
Anti-A in blood group O (60)	16 (4-128)	32 (8-256)	256 (16-2,048)	128 (16-2,048)

Abbreviations: IS, immediate spin; AHG, anti-human globulin; CAT, column agglutination technique; DTT, dithiothreitol.

- IgM is the predominant isotype found in group A and group B serum
- IgG is the major isotype for anti-A and anti-B in group O serum
- Activity of IgG is enhanced by AHG especially in the column agglutination method
- CAT more sensitive than tube in blood group O individuals

Park ES, et al. Annals of Laboratory Medicine, 2014; 34: 223-229.v

The Good

ABO Incompatible Transplant Outcomes			
	Years post-transplant	Graft Survival (%)	Patient Survival (%)
Johns Hopkins Hospital (1999-2007) N=60	1	98.3	96.3
	3	92.9	96.3
	5	88.7	89.4
Mayo Clinic (1999-2001) N=18	1	88.9	94.4

Montgomery RA, Locke JE, et al. ABO incompatible renal transplantation: a paradigm ready for broad implementation. *Transplantation. 2009; 87: 1246-55.*
Gloor, J.M., et al., *ABO-incompatible kidney transplantation using both A2 and non-A2 living donors.* Transplantation, 2003. **75**(7): p. 971-7.

The Good

Graft Loss, ABO Incompatible vs. ABO Compatible Transplants

	Days 0-14		Days >14	
Era	SHR	P value	SHR	P value
All	2.34	0.001	1.28	0.06
1995-2002	3.45	0.01	1.97	0.01
2003-2010	2.05	0.02	1.31	0.10

Montgomery JR, et al. Outcomes of ABOi Transplantation in the US. *Transplantation,* 2012; 93(6): 603-609.

The Good

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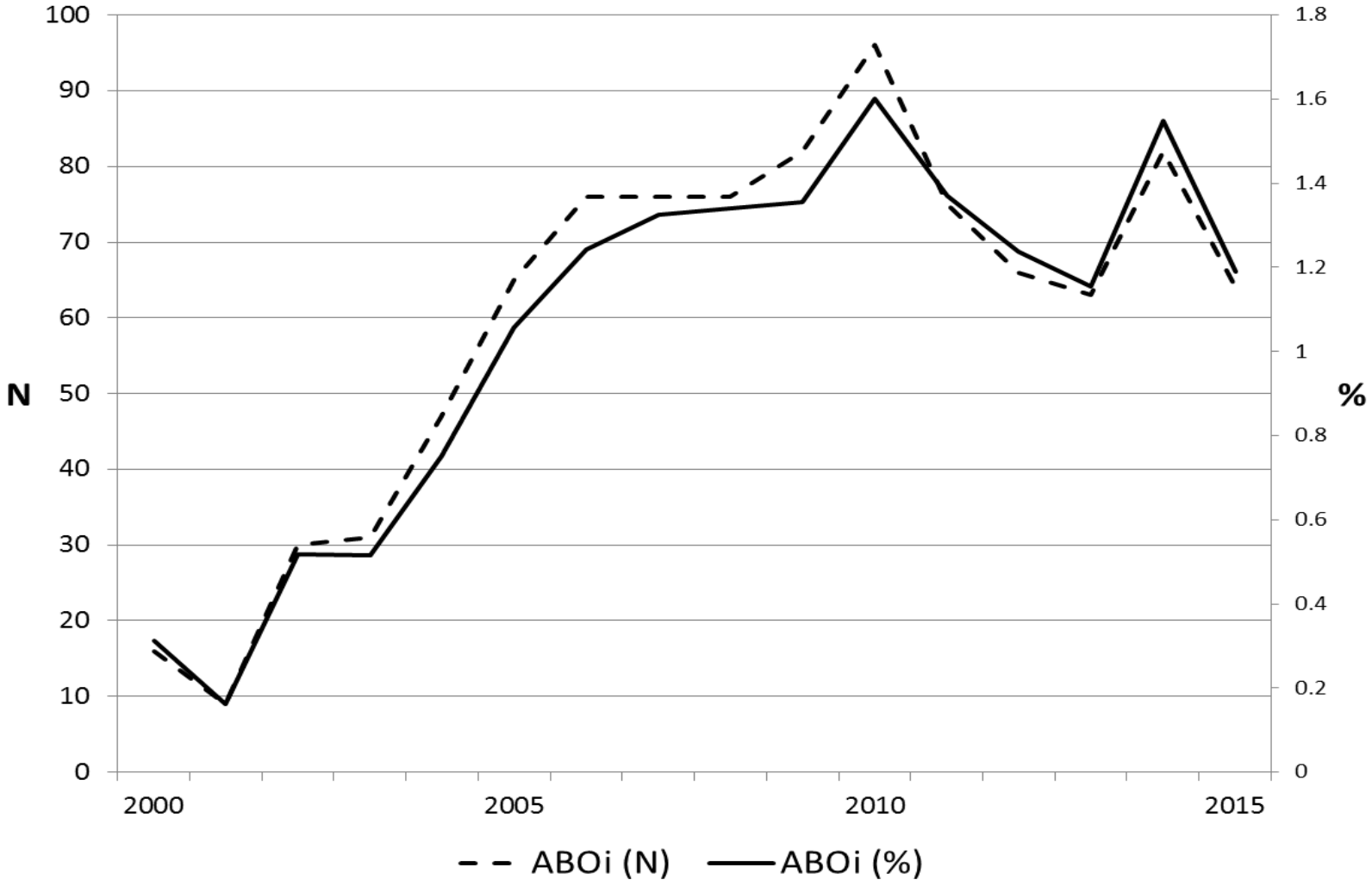
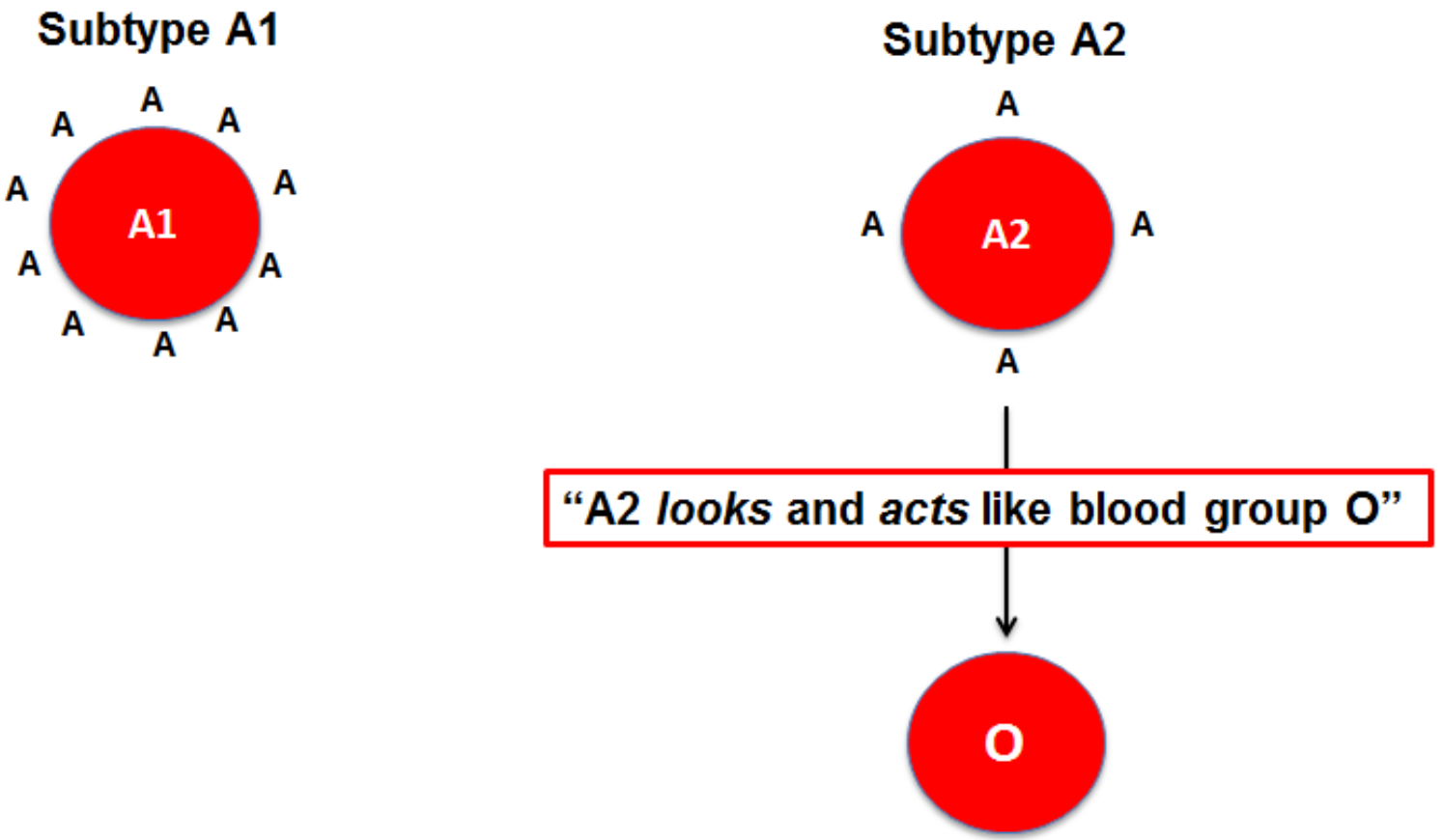
The Good



Mustian et. al. JACS, 2018; 226(4): 615-621.

The Not So Good



The Not So Good

Characteristic	ABOi (N=930)	ABOc (N=89713)	P-value
Donor age > 50	281 (30.2)	20,573 (22.9)	<0.0001
Recipient age > 50	449 (48.3)	39,398 (43.9)	0.008
Male recipient	559 (60.1)	54,355 (60.6)	0.77
Recipient race			0.02
White	713 (76.7)	72,030 (80.3)	
Black	159 (17.1)	12,700 (14.2)	
Asian	48 (5.2)	3,771 (4.2)	
Other/unknown	10 (1.1)	1,212 (1.4)	
Max PRA >80	105 (11.3)	3,719 (4.2)	<0.0001
HLA mismatch	659 (71.3)	61,824 (69.5)	0.24
Previous KT	164 (17.6)	9,541 (10.6)	<0.0001
AR within 1 year	180 (19.4)	9,383 (10.5)	<0.0001

Mustian et. al. JACS, 2018; 226(4): 615-621.

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The Not So Good

Crude and adjusted RRs and 95% CIs for the association between acute rejection within 1-year of transplant, 2000-2015		
Risk Factor	RR (95% CI)	aRR (95% CI)
ABOi	**1.85 (1.62-2.12)**	**1.76 (1.54-2.01)**
Donor age > 50	**1.15 (1.10-1.20)**	**1.23 (1.18-1.29)**
Recipient age > 50	**0.74 (0.71-0.77)**	**0.71 (0.68-0.74)**
Recipient race		
White	Ref	Ref
Black	**1.16 (1.10-1.22)**	**1.12 (1.06-1.18)**
Asian	**0.74 (0.66-0.83)**	**0.73 (0.66-0.82)**
Other/unknown	0.96 (0.81-1.13)	0.97 (0.82-1.15)
Max PRA > 80%	**1.51 (1.40-1.63)**	**1.51 (1.40-1.64)**
HLA mismatches ≥ 3	**1.58 (1.51-1.66)**	**1.60 (1.53-1.68)**
Previous KT	**1.14 (1.08-1.21)**	1.02 (0.99-1.09)

Mustian et. al. JACS, 2018; 226(4): 615-621.

The Not So Good

Crude and Adjusted Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) for Live Donor ABO Incompatible Transplantation 2000-2015, and Patient Survival, All-cause Graft Failure, and Death Censored Graft Failure

	Patient survival		All-cause graft failure		Death censored graft-failure	
Follow-up	Crude HR (95% CI)	aHR (95% CI)	Crude HR (95% CI)	aHR[2] (95% CI)	Crude HR (95% CI)	aHR[2] (95% CI)
1-year	1.81 (1.26-2.60)	1.74 (1.15-2.63)	2.23 (1.78-2.79)	2.27 (1.76-2.93)	2.42 (1.85-3.17)	2.34 (1.85-2.96)
3-year	1.55 (1.21-1.98)	1.51 (1.15-1.99)	1.71 (1.44-2.03)	1.70 (1.41-2.06)	1.83 (1.47-2.26)	1.82 (1.45-2.27)

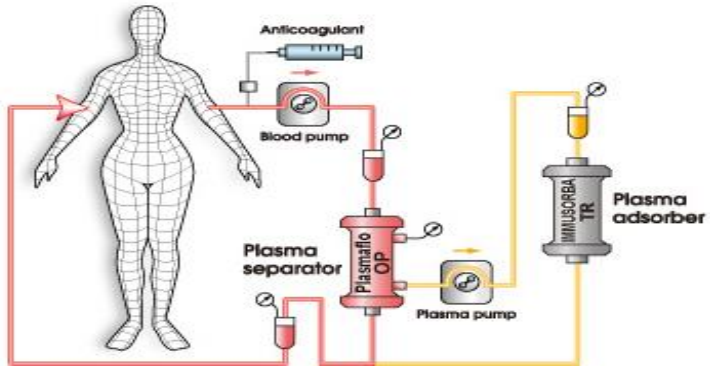
Mustian et. al. JACS, 2018; 226(4): 615-621.

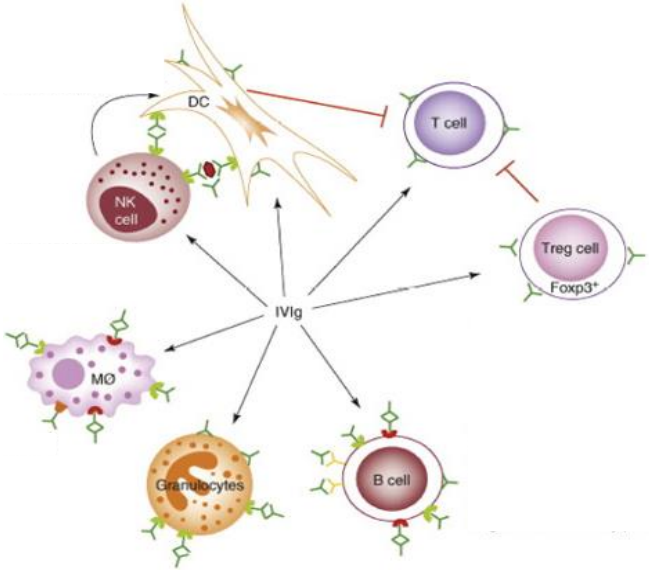
US National Outcomes

- ABOi LDKT associated with a **1.76-fold increased risk for acute rejection** compared to ABOc LDKT
  - Risk higher than the risk posed by either high level of panel reactive antibody or HLA mismatch
- ABOi LDKT associated with a **2.34-fold increased risk for death-censored graft loss** at 1-year post-transplant compared to ABOc LDKT
- ABOi LDKT associated with **1.74-fold increased risk for mortality** compared to ABOc LDKT

Mustian et. al. JACS, 2018; 226(4): 615-621.

The Bad



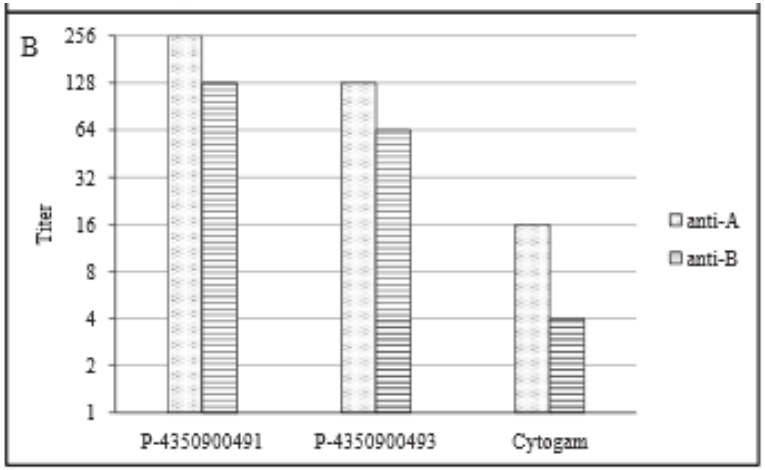


RED BLOOD CELLS → **PLASMA**

- A → anti-B
- B → anti-A
- AB → **no** antibodies, universal *plasma* donor
- O → **no** antigens, universal *blood* donor → anti-B, anti-A

If your patient needs blood, then give their blood type

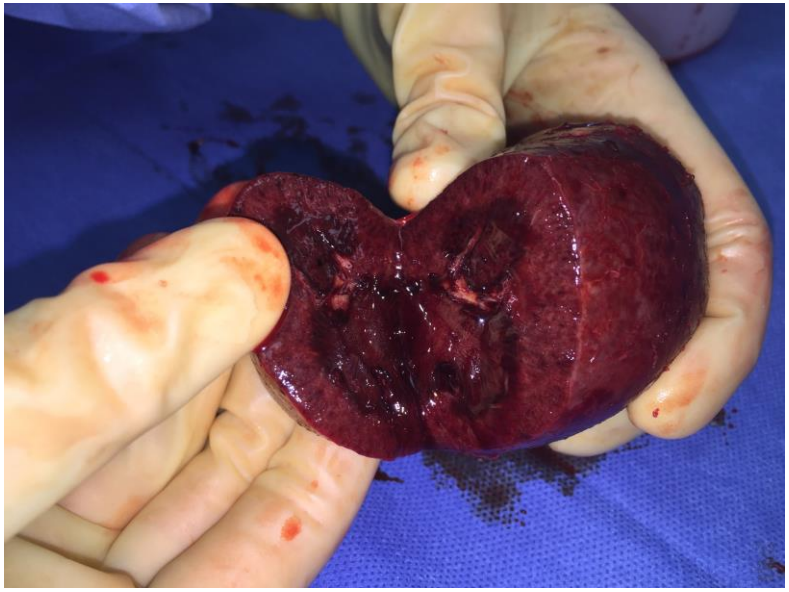
If your patient needs plasma (FFP), then give donor blood type

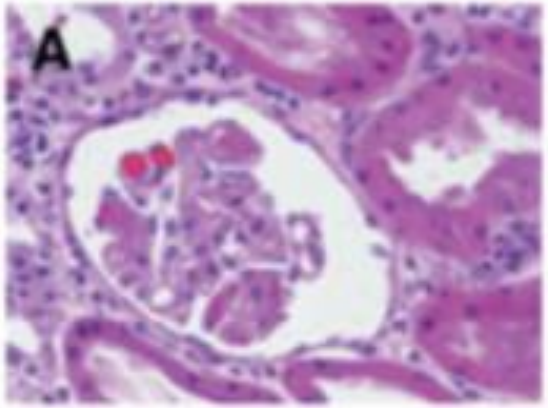


Staley, et al. AJT, 2016; 16: 2483-2486

The Bad

Elevated resistive indices of 1.00 are obtained throughout the upper, mid, and lower pole of the allograft. There is probable **reversal of diastolic flow** within the upper pole the right kidney. The **main renal vein is grossly patent at the hilum**; however, it is not well visualized beyond this point. **Peak systolic velocity at the main renal anastomosis is 2.4 m/sec** and peak systolic velocity of the ipsilateral external iliac artery is 1.0 m/sec.

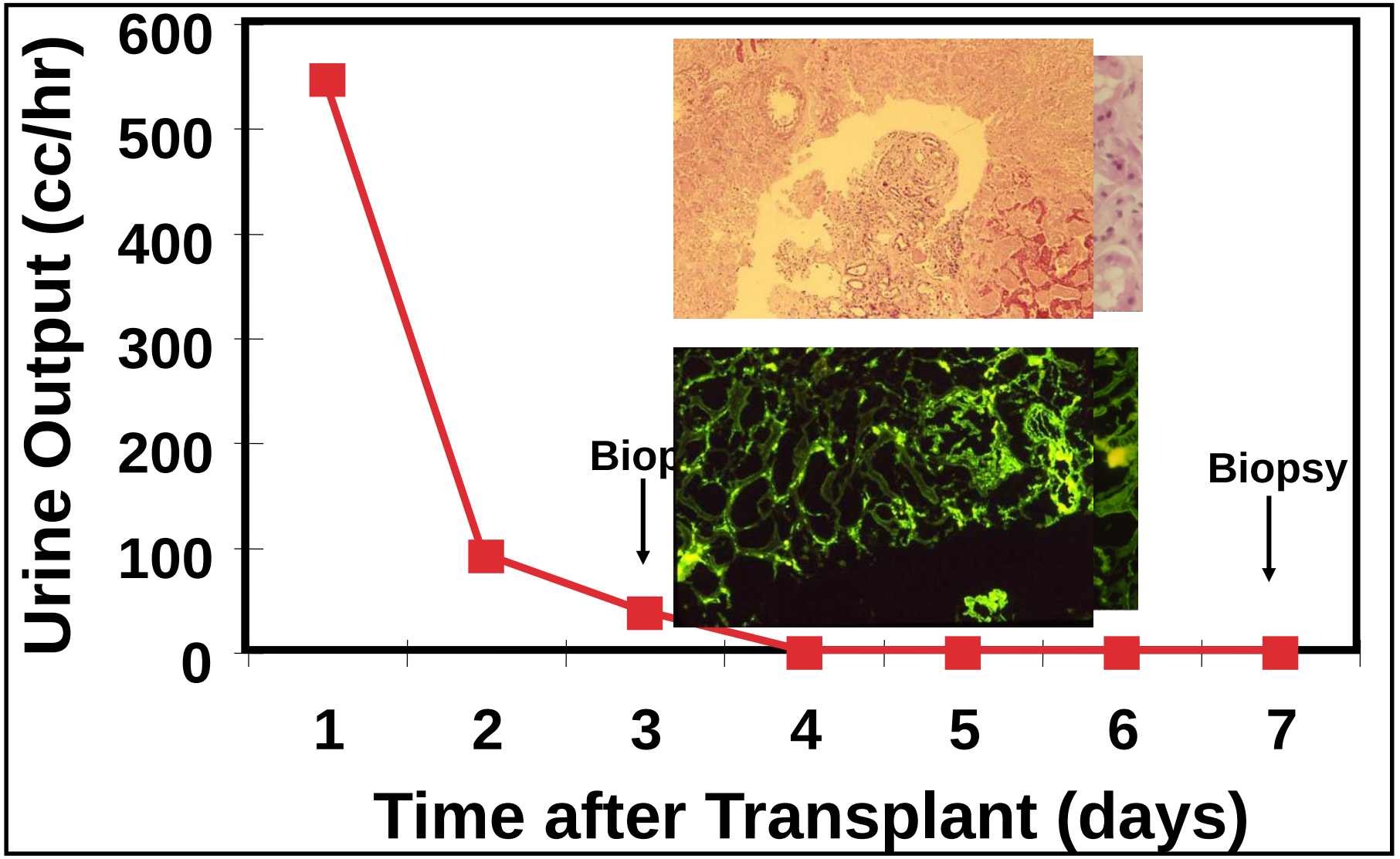




HYPERACUTE REJECTION

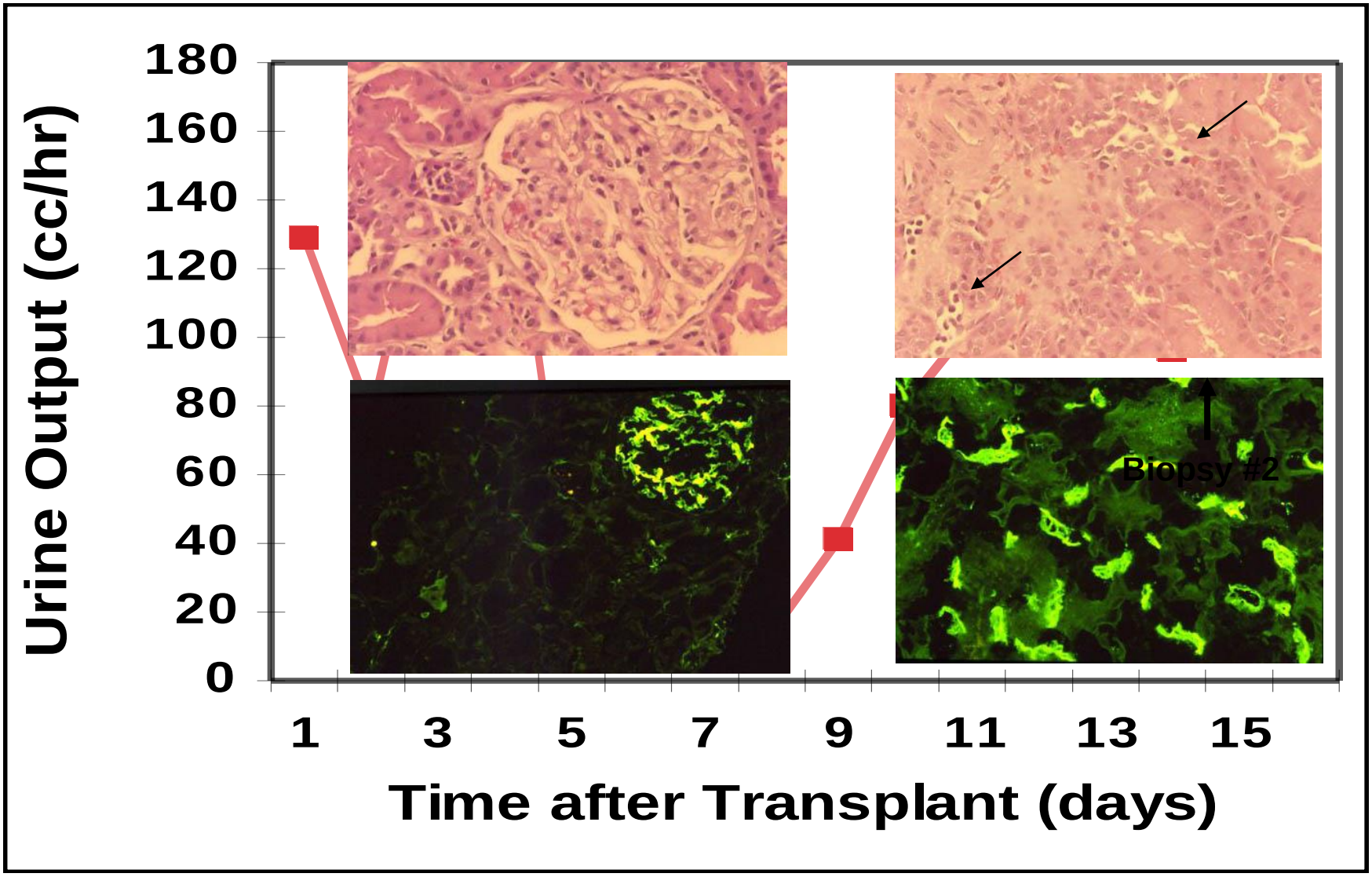
Staley, et al. AJT, 2016; 16: 2483-2486

The Bad



Locke JE et al. *AJT*. 2007; 4: 842-846.

The Bad



Locke JE et al. *AJT*. 2007; 4: 842-846.

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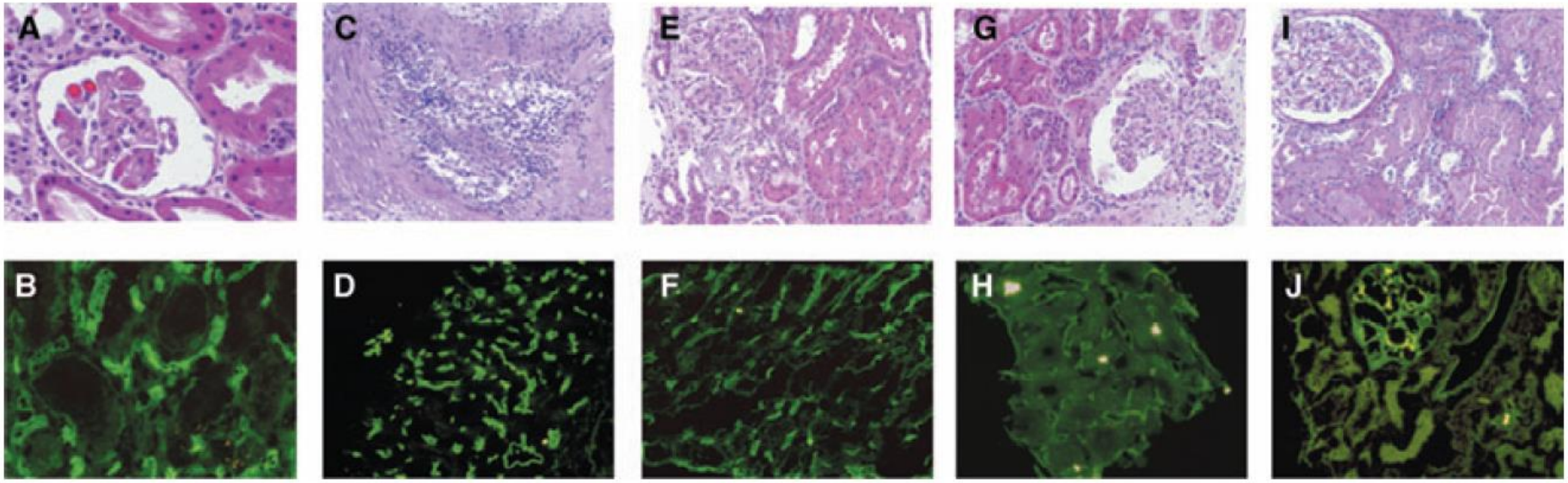
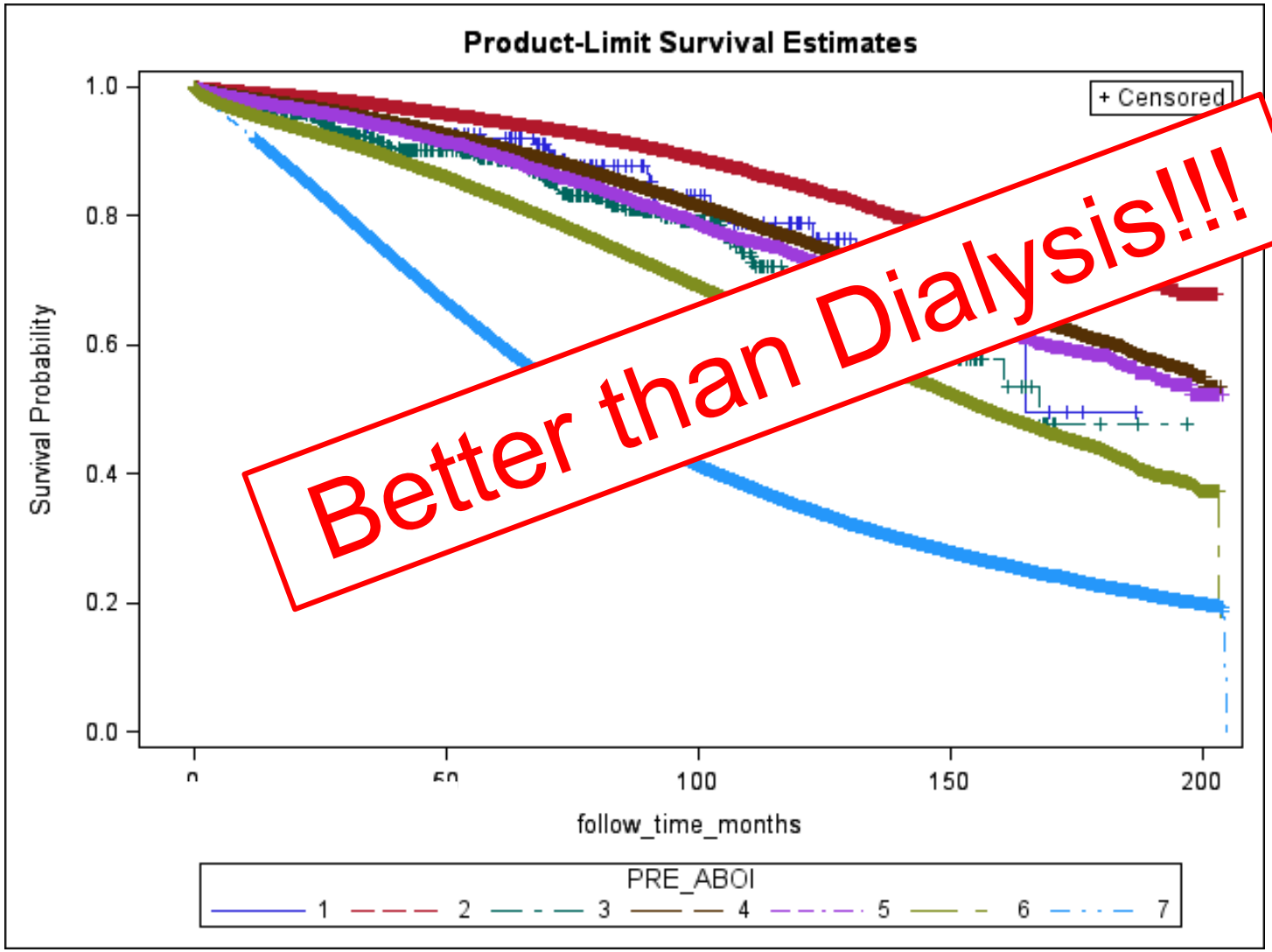


Figure 2: Development, progression and resolution of severe antibody-mediated rejection (AMR) over time. (A) H&E on the day of severe AMR diagnosis, postoperative day (POD) 10, demonstrating thrombotic microangiopathy and peritubular capillary (PTC) neutrophil margination. (B) C4d immunofluorescence staining at the time of AMR diagnosis (POD 10) demonstrating 3 + diffuse PTC C4d deposition. (C) H&E from POD 13 with evidence of transmural arteritis and PTC leukocyte margination. (D) Immunofluorescence staining on POD 13 demonstrating 2–3 + C4d staining. (E) H&E of tissue from biopsy performed on POD 28 with evidence of residual intimal arteritis and clearing of glomerular fibrin thrombi. (F) Immunofluorescence staining on POD 28 demonstrating 1–2 + C4d staining. (G) H&E with evidence of mild glomerulitis. (H) Immunofluorescence staining of POD 33 biopsy demonstrating weakly positive C4d staining. (I) H&E POD 48 demonstrating complete resolution of AMR. (J) Immunofluorescence staining on POD 48 shows resolution of C4d (glomerular staining is nonspecific).

Locke JE et al. *AJT*. 2009; 9: 231-235.

The Good

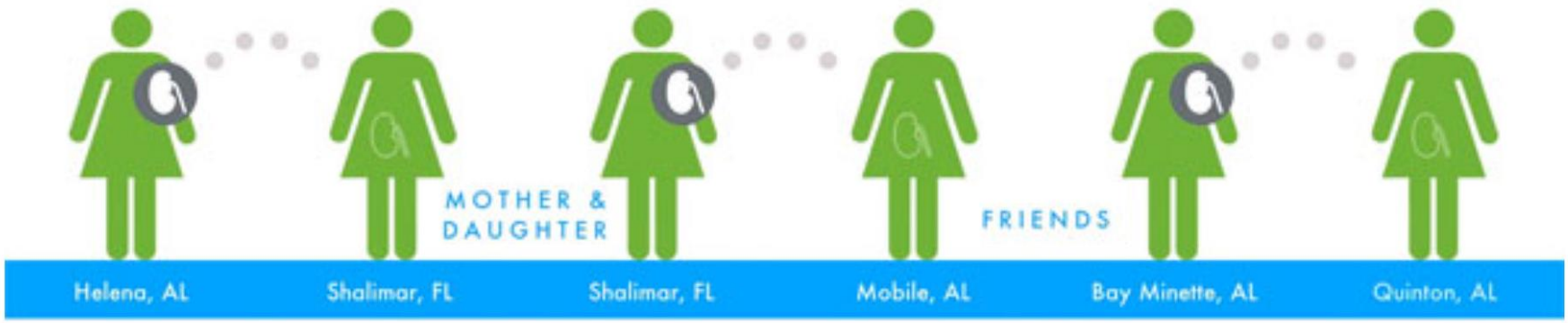


1= Preemptive ABOi LDKT
2= Preemptive ABOc LDKT
3= ABOi LDKT (previous dialysis)
4= ABOc LDKT (previous dialysis)
5= Preemptive DDKT
6= DDKT (previous dialysis)
7= Waitlist candidates

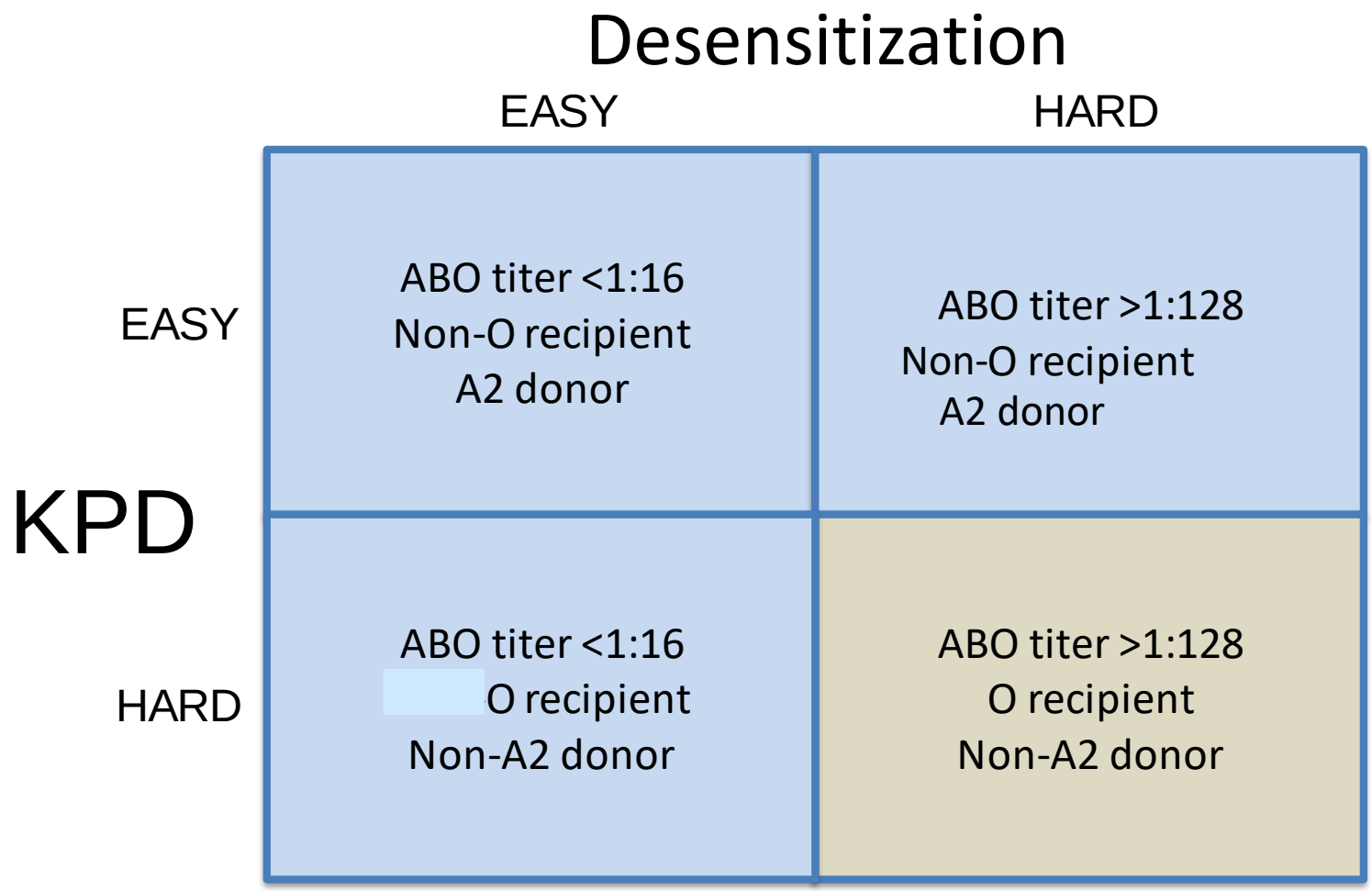
Personalized Medicine

70. Jonathan Quinn	A+	A2 B44 DR7	14. Lucia Davis	O-	A2 B44 DR7
71. Sherri Maldonado	O+	A2 B62 DR4	15. Dave Newton	O+	A2 B62 DR4
72. Alice Gibson	O-	A23 B44 DR7	16. Hattie Washington	O+	A23 B44 DR7
73. Becky Barton	A+	A1 B8 DR3	17. Virgil Stewart	O-	A1 B8 DR3
74. George Parks	B-	A29 B44 DR7	18. Beulah Evans	A+	A29 B44 DR7
75. Shari Harris	O	A3 B7 DR15	19. Vivian Valdez	B-	A3 B7 DR15
76. Gordon Medina	A-	A2 B7 DR15	20. Meredith Manning	O	A2 B7 DR15
77. Bonnie Hicks	A+	A1 B52 DR15	21. Allan Lewis	A-	A1 B52 DR15
78. Pablo Waters	AB+	A2 B44 DR7	22. Sandra George	A+	A2 B44 DR7
79. Grant Campbell	A-	A2 B62 DR4	23. Lloyd Ramos	AB+	A2 B62 DR4
80. Jenna George	A+	A23 B44 DR7	24. Lorenzo Gutierrez	A-	A23 B44 DR7
81. Sara Gibbs	A+	A1 B8 DR3	25. Grace Jimenez	A+	A1 B8 DR3
82. John Phelps	B-	29 B44 DR7	Fuller		A29 B44 DR7
83. Lowell Guzman	O	B7 DR15	Orville Lon		A3 B7 DR15
84. Ida Horton		7 DR15	Heidi Lo		A2 B7 DR15
85. Samantha Robin		2 DR15	Alton W ms		A1 B52 DR15
86. Brooke Hudson		DR7	Miriam s		A2 B44 DR7
87. Jimmie Harrison		R4	Clark Ki		A2 B62 DR4
88. Bertha Butler	A+	R7	Whitney ton		A23 B44 DR7
89. Cary Fernande	B-	A1 B8	Vanessa E		A1 B8 DR3
90. Dana Webste	O	A29 B44	Laurie Davids		A29 B44 DR7
91. Joel Phillips	A-	A3 B7 DR15	35. Esther Moore	O	A3 B7 DR15
92. Larry Mcdonald	A+	A2 B7 DR15	36. Joshua Mendez	A-	A2 B7 DR15
93. Ira Yates	O+	A1 B52 DR15	37. Sammy Cain	A+	A1 B52 DR15
94. Marion Abbott	O-	A2 B44 DR7	38. Marco Summers	AB+	A2 B44 DR7
95. Norma Black	A+	A2 B62 DR4	39. Alfred Lawson	A-	A2 B62 DR4

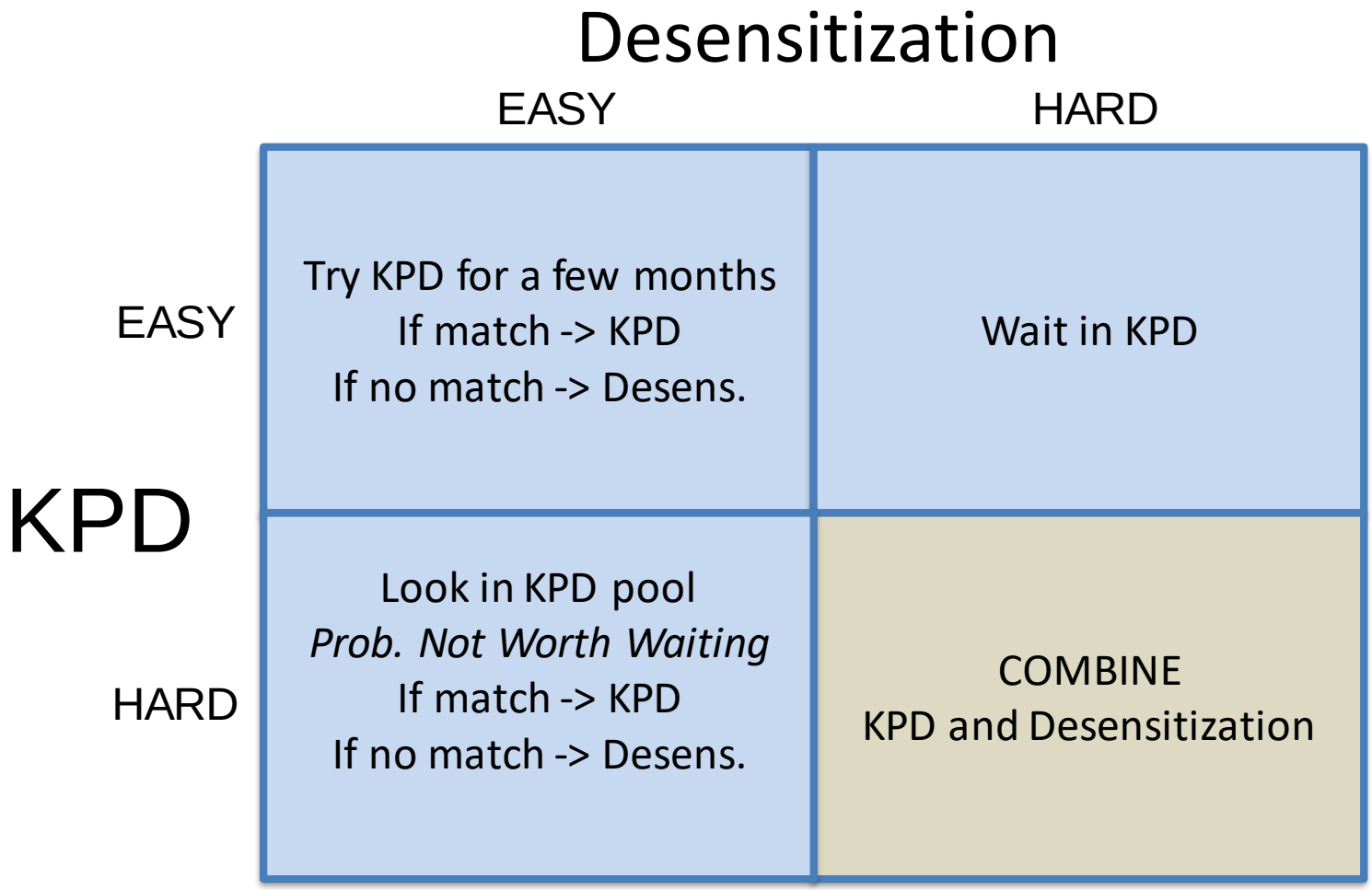
MATCH



Personalized Medicine



Personalized Medicine



Concluding Remarks

Summary - rationale

- Deceased donations meet <10% of the global need for organs
- Living donors are needed to narrow the gap in organ supply and demand
- 35% of living donors will be blood group incompatible with their intended recipient

Concluding Remarks

Summary – methods and pitfalls

- ABO antibodies can be removed through a process known as desensitization (TPE ± IVIg)
- Measuring antibody titers is cumbersome and fraught with inter and intra user variability
- Understanding the starting ABO titer is a prerequisite for correct assessment and implementation of peri-transplant desensitization

Concluding Remarks

Summary – US national results

- Early single center studies concluded ABOi LDKT outcomes were similar to ABOc LDKT
- Reported results may have been skewed by inclusion of A2 donors into non-A recipients
- Most recent national data indicates higher acute rejection, graft loss and mortality with ABOi LDKT vs. ABOc LDKT

Concluding Remarks

Summary – balancing risk vs. benefit

- ABOi LDKT is associated with worse outcomes and technical issues
- ABOc LDKT is always best option. . . ***BUT***. . . ABOi LDKT is associated with a survival benefit over remaining on dialysis
- What's right for your patient requires individualized assessment of likelihood to match in KPD