

Unmet Needs in Kidney Transplantation: Desensitization



Transplant Immunotherapy Program

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Unmet Needs in Kidney Transplantation: Desensitization

- Objectives:
 - Discuss current desensitization therapies as a means to improve transplantation for highly-HLA sensitized patients.
 - Discuss clinically relevant end points that allow successful transplantation to occur.
 - Discuss potential surrogate end points for studies that could benefit adult and pediatric patients.
 - Discuss unmet needs in desensitization for adult and pediatric patients.



Unmet Needs in Kidney Transplantation: Desensitization

- The purpose of DES therapy is to accomplish antibody reduction to an acceptable level that allows for successful transplant.
- **Complete elimination of all DSAs is not required and not desirable** as excessive reductions in total IgG would be likely exposing the patients to increased infection risk.



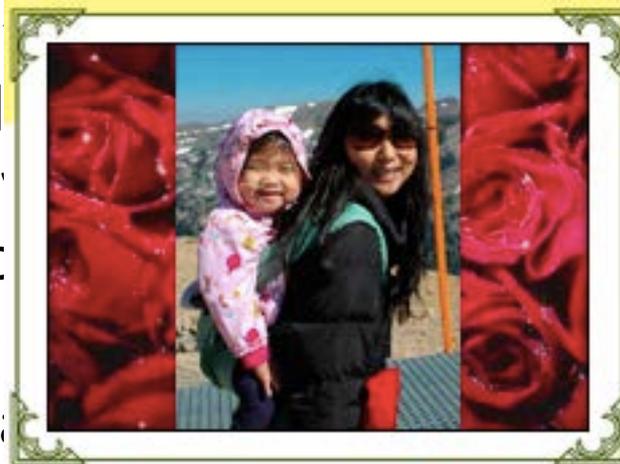
Unmet Needs in Pediatric Kidney Transplantation

- Case Report: CC is a 2.5 y.o. Asian female with ESRD secondary to congenital obstructive uropathy. Patient had 1 failed DD transplant at age 1 y.o. and became sensitized. Mother came forward as a potential donor, but work up revealed the following: DSA: **B60 strong, C10 moderate DR12, DQ7, DR52** weak to moderate. DSA RIS score was 21. FCMX was **T-200 CS, B-352 CS**.
- What would you do?
 - Have child remain on dialysis?
 - Paired exchange?
 - Attempt desensitization?



Unmet Needs in Pediatric Kidney Transplantation

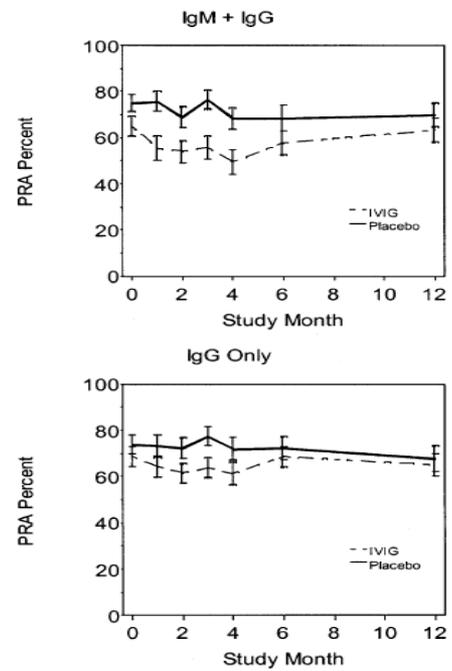
- Patient underwent desensitization with IVIG + Rituximab without successful reduction of DSAs. After 6M, the patient received Rituximab and was transplanted at BCMX 200, BCMX 283. Patient received tacrolimus, cyclosporine, mycophenolate mofetil, and prednisone. Patient maintained clinical remission.
- At 1M post-transplant, DQ7. DSAs have not been detected. A present was a weak DQ7. Patient is now 5.5 years post-transplant with SCr 0.9mg/dl. Biopsy in 2014 showed no evidence of ABMR or TG. Patient now in second grade doing well!



: The NIH IG02 Study



Transplant Immunotherapy Program



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Rituximab and Intravenous Immune Globulin for Desensitization during Renal Transplantation

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ABSTRACT

BACKGROUND

Few options for transplantation currently exist for patients highly sensitized to HLA. This exploratory, open-label, phase 1–2, single-center study examined whether intravenous immune globulin plus rituximab could reduce anti-HLA antibody levels and improve transplantation rates.

METHODS

Between September 2005 and May 2007, a total of 20 highly sensitized patients (with a mean \pm SD T-cell panel-reactive antibody level, determined by use of the complement-dependent cytotoxicity assay, of $77\pm 19\%$ or with donor-specific antibodies) were enrolled and received treatment with intravenous immune globulin and rituximab. We recorded rates of transplantation, panel-reactive antibody levels, cross-matching results at the time of transplantation, survival of patients and grafts, acute rejection episodes, serum creatinine values, adverse events and serious adverse events, and immunologic factors.

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EDITORIAL



Reducing Antibody Levels in Patients Undergoing Transplantation

Ron Shapiro, M.D.

The advent of solid-organ transplantation for the treatment of patients with end-stage organ failure has been one of the most exciting medical advances in the late 20th and early 21st centuries. Thousands of lives have been saved or improved by transplantation, allowing terminally ill patients to rejoin society, work productively, and have a meaningful life.^{1,2}

Unfortunately, transplantation has been an imperfect and expensive therapy. The financial burden of transplantation has limited its widespread application in the developed world; furthermore, therapeutic failure occurs all too often, owing to side effects or inadequacy of immunosuppression. Fortunately, in recent years, the potency of the newer immunosuppressive medications has improved, and the ability to prevent or treat acute cellular (i.e., T-cell-mediated) rejection has led to

on renal-transplant waiting lists. Waiting times for such patients are much longer than those for nonsensitized patients, and the immunologic obstacle to transplantation in such patients often becomes a death sentence, as they remain, and die, on dialysis.

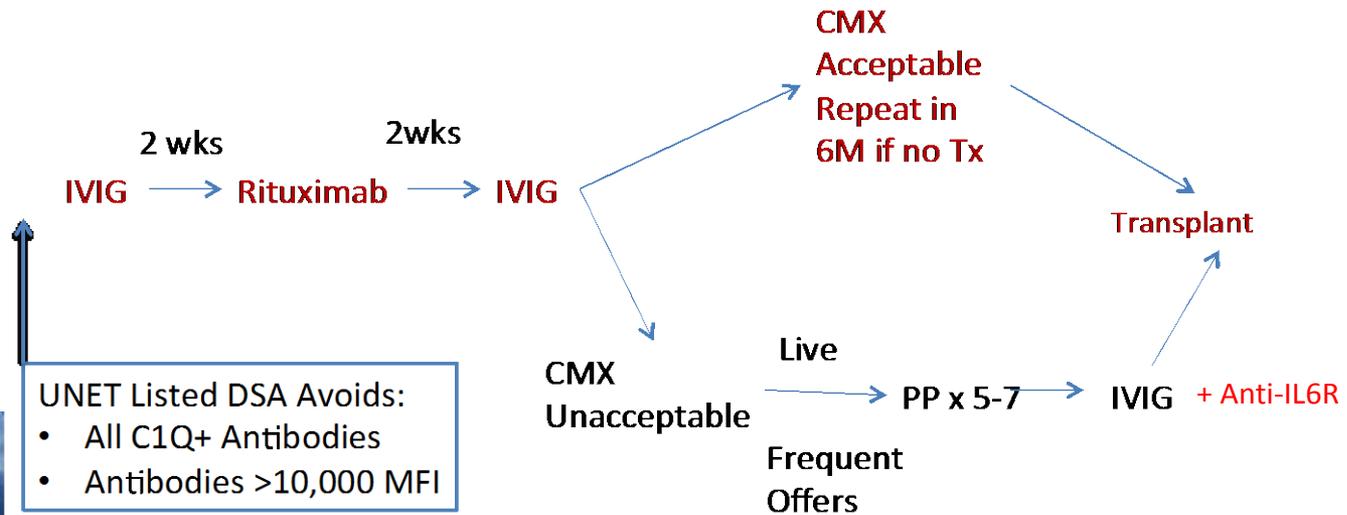
Attempts to reduce antibody levels in candidates for transplantation with high titers are therefore important. Methods used have included plasmapheresis,^{3,4} protein A immunoadsorption,⁵ intravenous immune globulin,⁶ immunosuppression with B-cell-specific agents,⁷ or various combinations of these.^{3,8} The two most popular and successful therapies have included the combination of plasmapheresis and low-dose (100 mg per kilogram of body weight per dose) intravenous immune globulin,^{3,9} or the use of high-dose (2 g per kilogram per dose) intravenous immune globulin.^{4,10}



<http://online.wsj.com/article/SB121623403383459229.html>

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Desensitization Protocols: Cedars-Sinai Medical Center

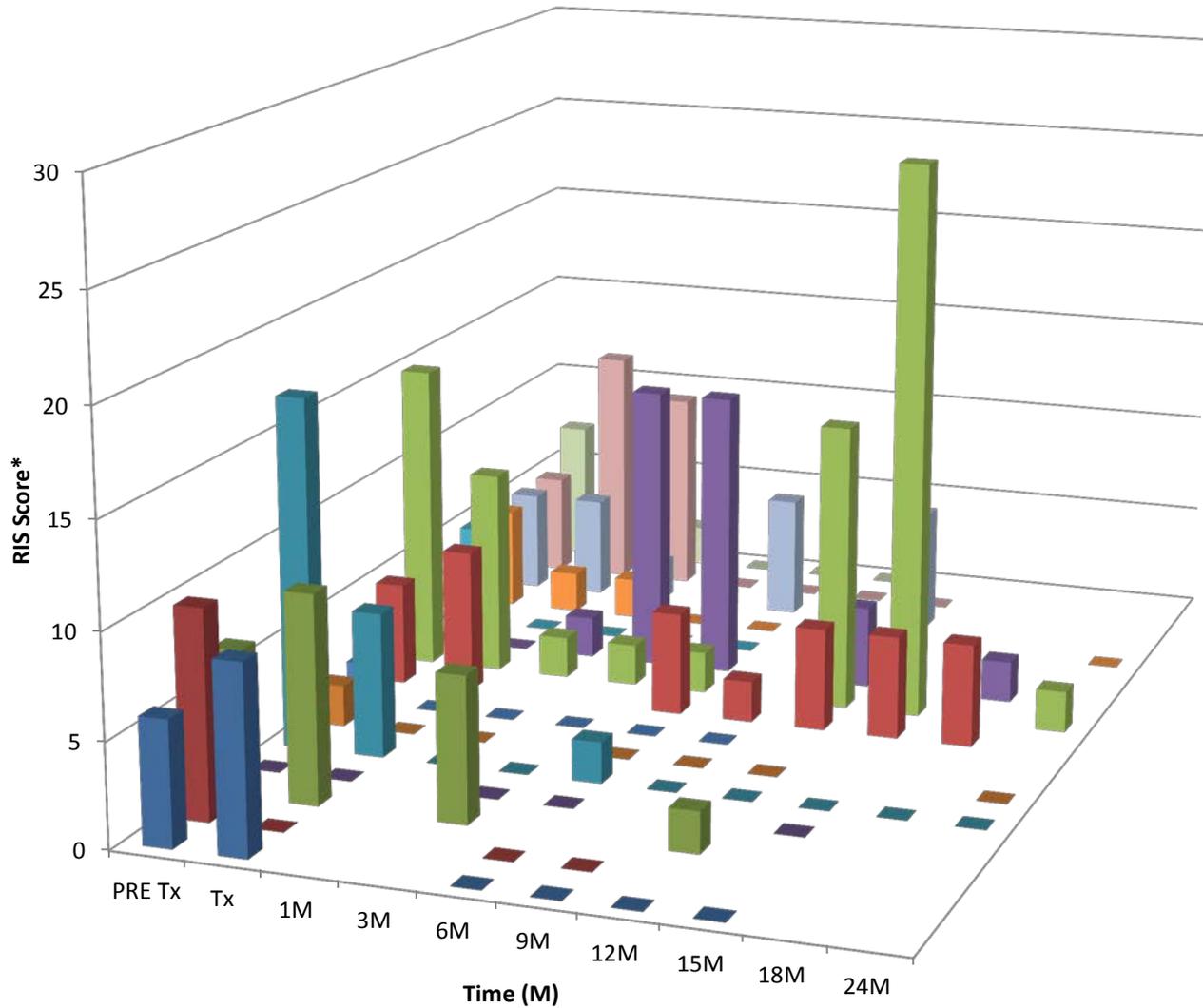


Unmet Needs in Kidney Transplantation: Desensitization

Data From HS-Pediatric Transplant Patients at Cedars-Sinai

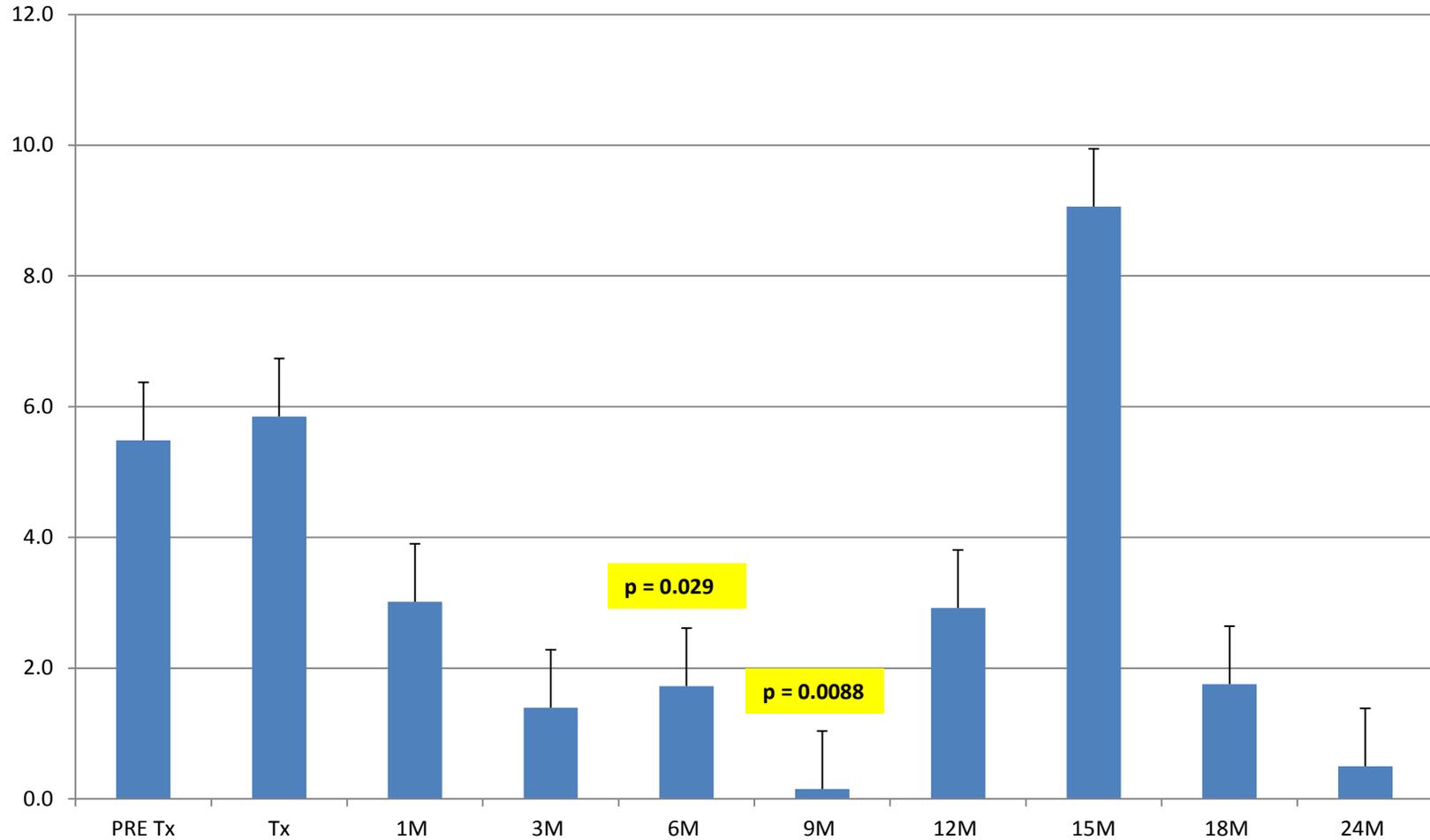


DSA RIS Trends of HS Pediatrics Patients (N=16)



*Relative Intensity Scale (RIS) [0 points = No DSA; 2 points = <5000MFI {weak}; 5 points = 5000-10,000 MFI {moderate}; 10 points = >10,000MFI {strong}].

Average DSA RIS score of Pediatric HS Patients (N= 16)



*Relative Intensity Scale (RIS) [0 points = No DSA; 2 points = <5000MFI {weak}; 5 points = 5000-10,000 MFI {moderate}; 10 points = >10,000MFI {strong}].

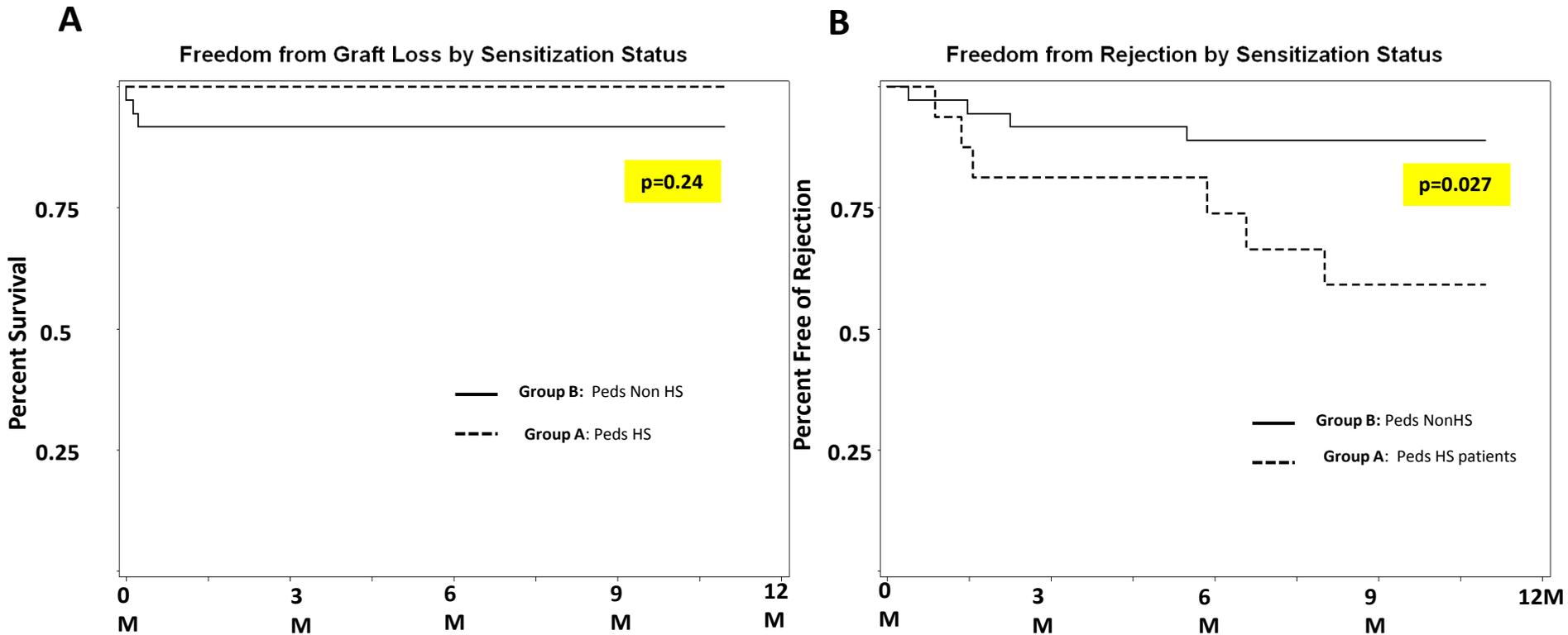
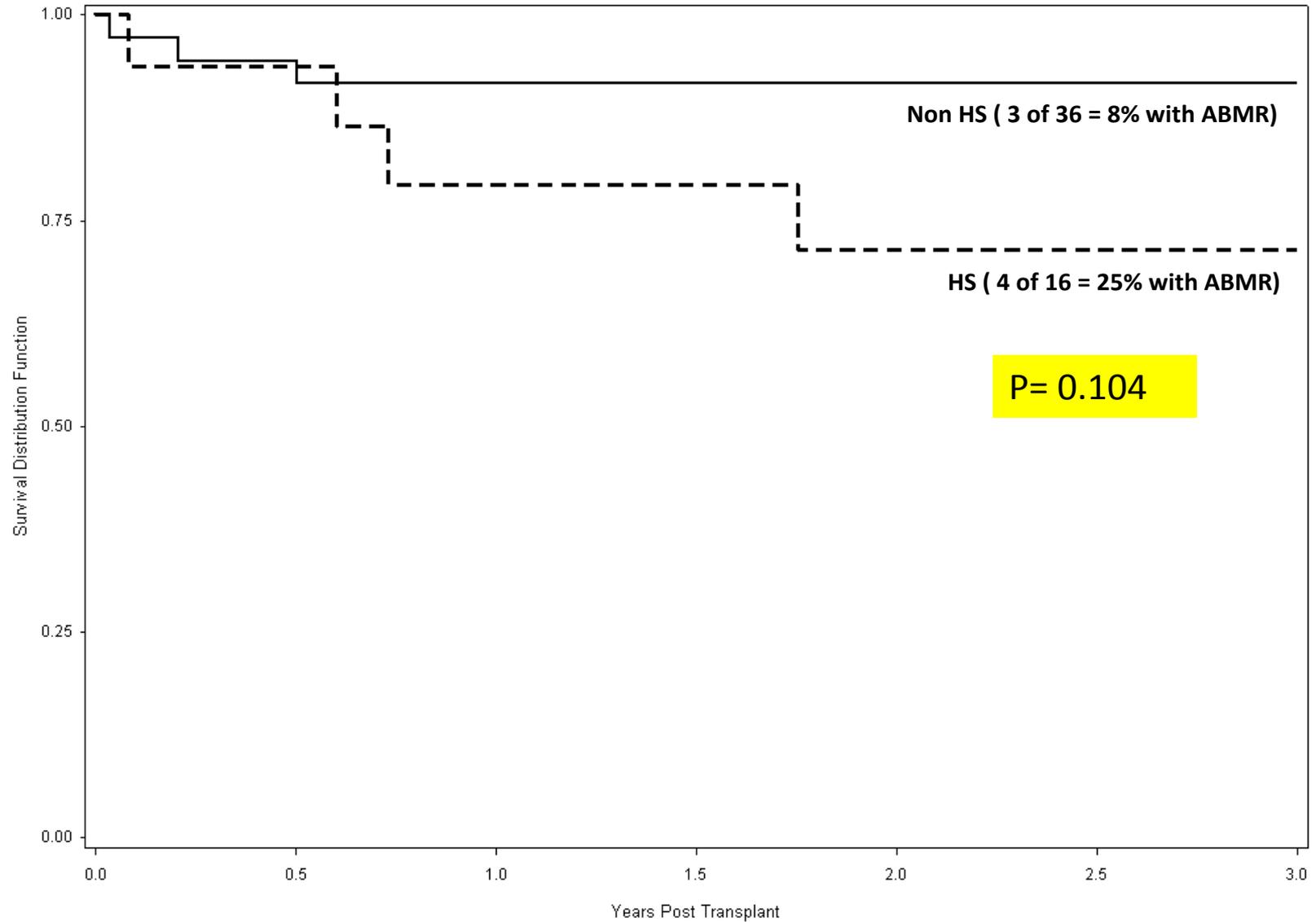
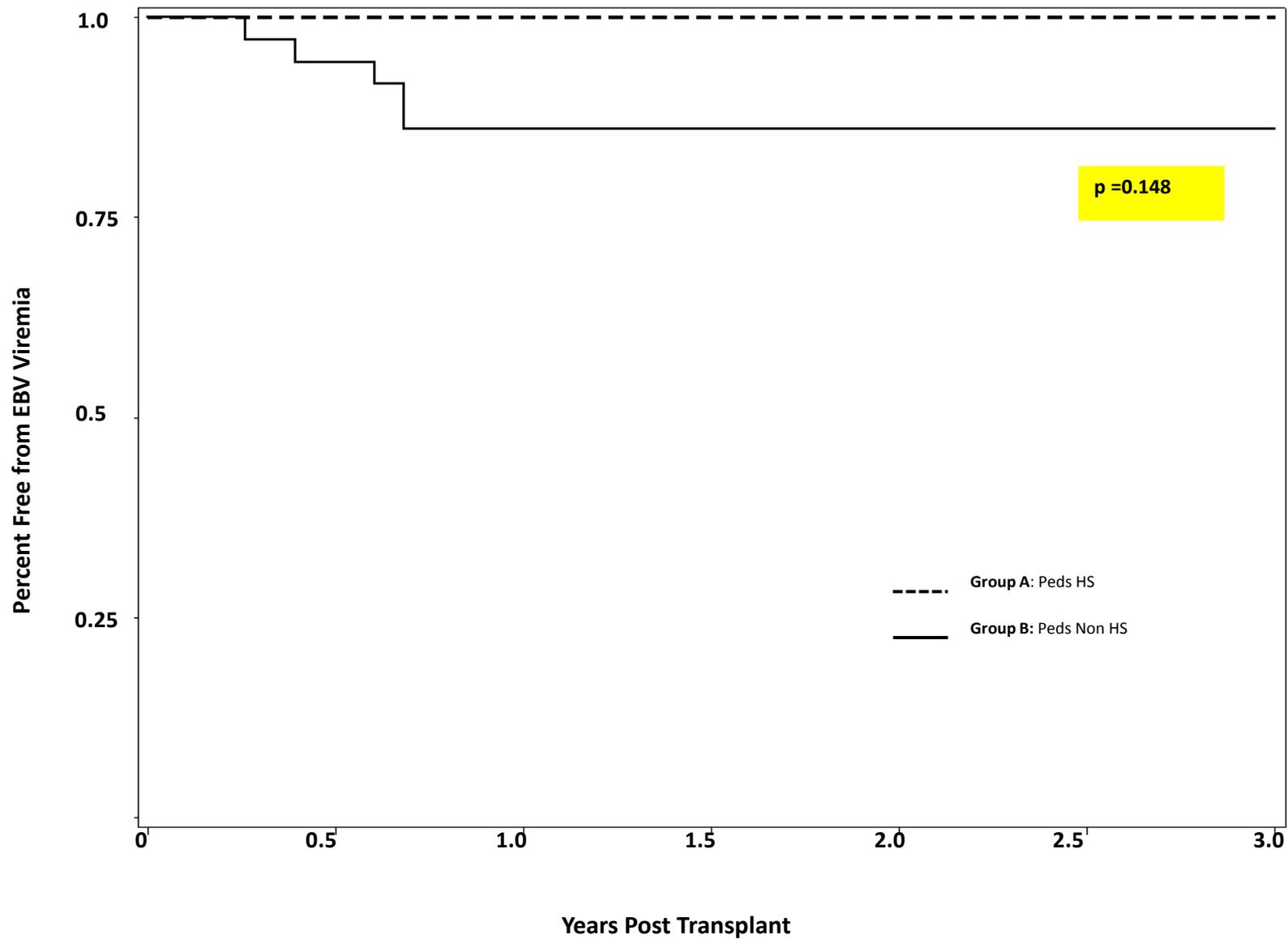


Figure 1: Kaplan-Meier curves out to 1 year post-transplant. Figure A demonstrates no difference in graft loss between HS patients who received alemtuzumab, compared to non-sensitized patients receiving anti-IL-2R induction. Figure B shows a statistically significant increase in graft rejection in HS group receiving alemtuzumab compared to non-sensitized pediatric patients receiving anti-IL-2R induction.

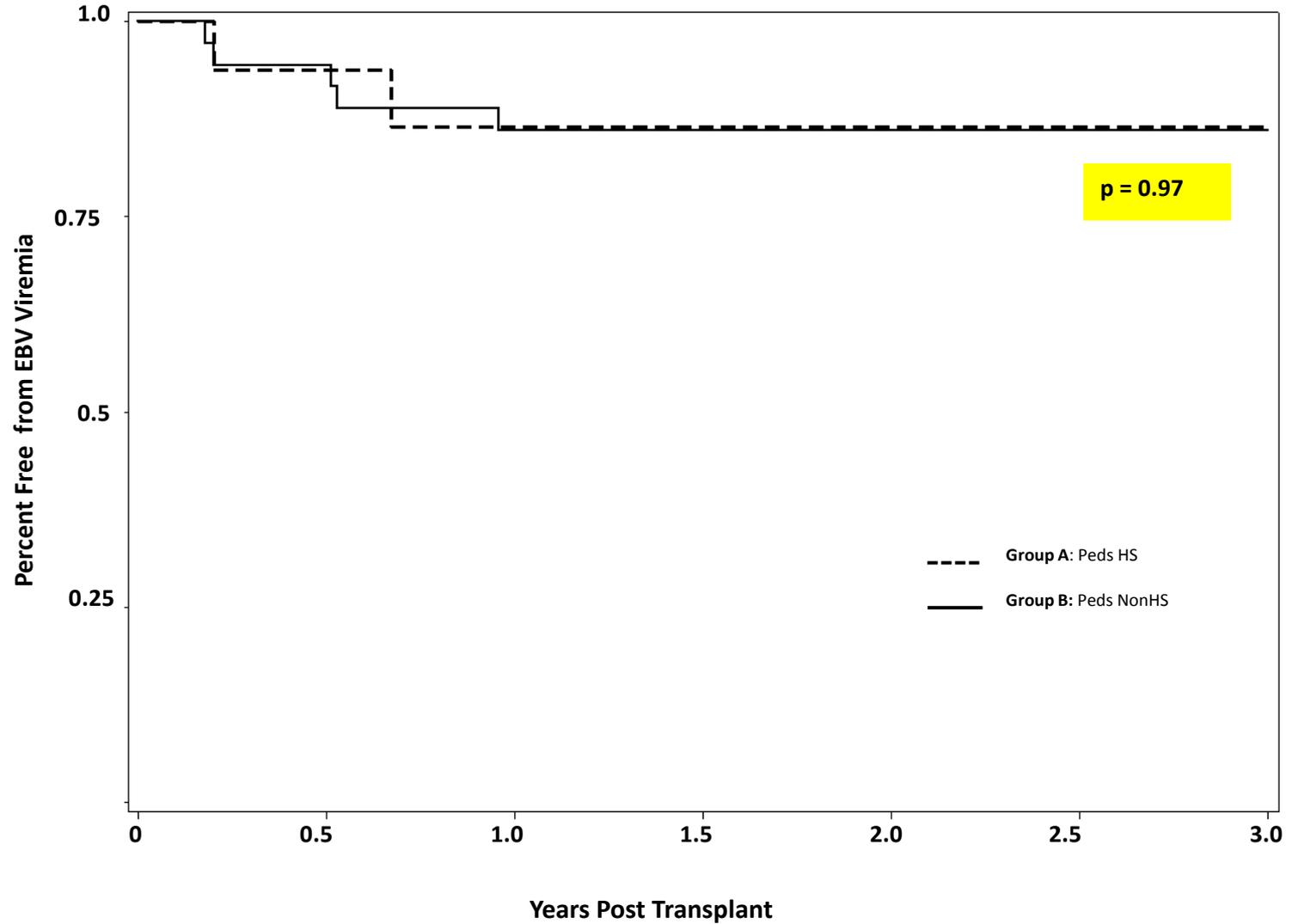
Freedom from ABMR Highly Sensitized (HS) vs Non-HS Pediatric Patients



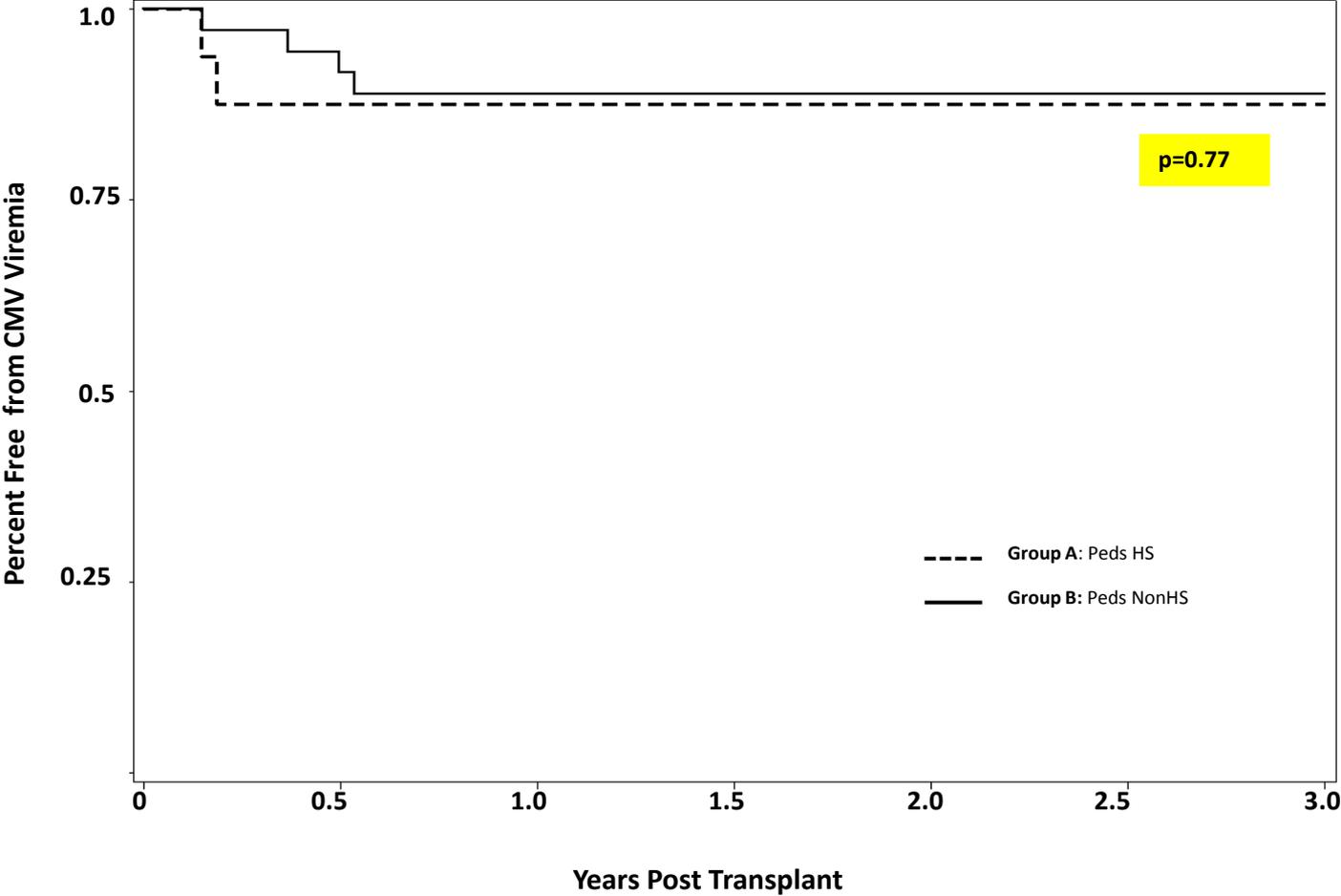
Freedom from EBV by Sensitization Status



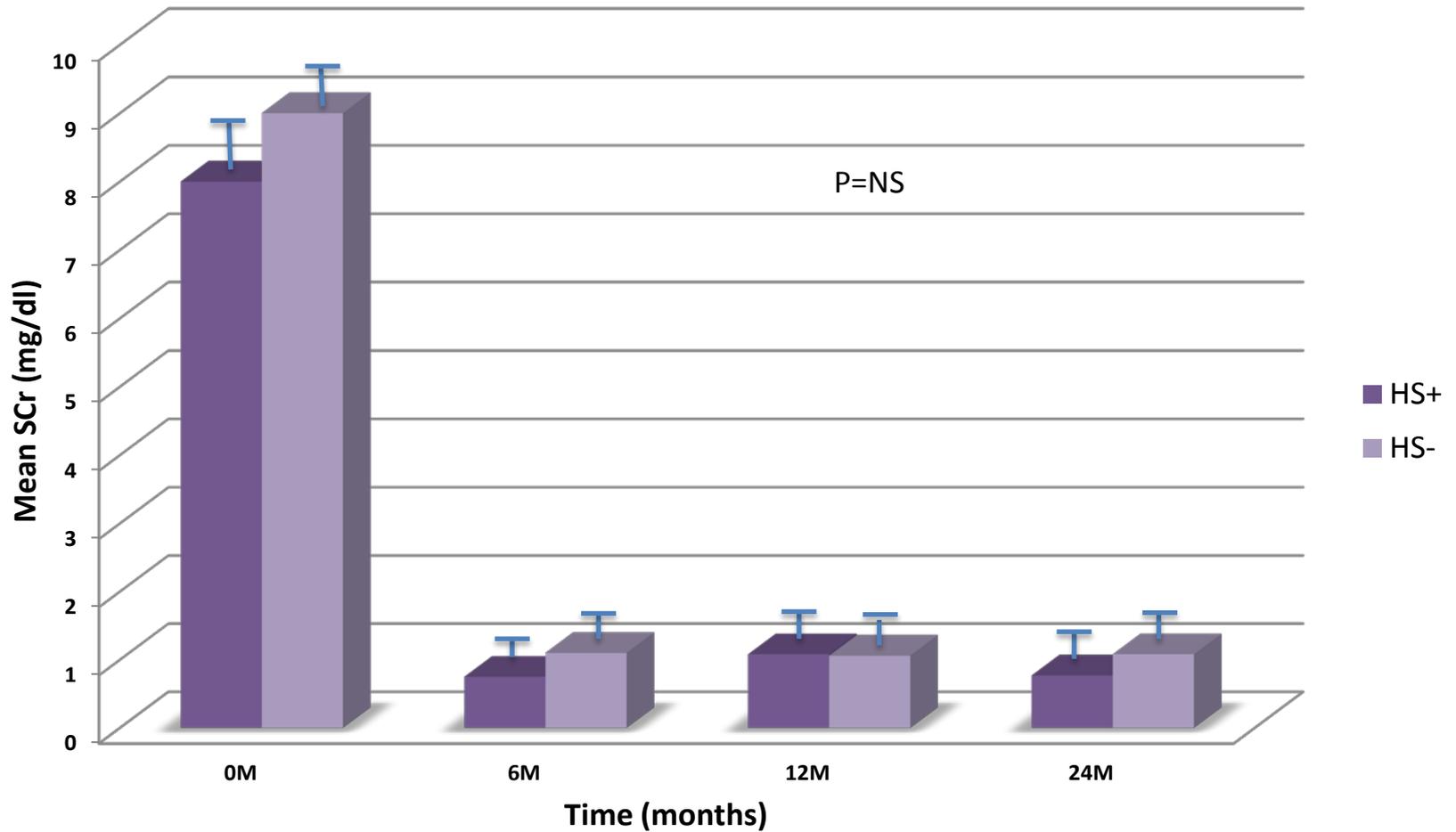
Freedom from BK Viremia by Sensitization Status



Freedom from CMV by Sensitization Status



Renal Function in HS- v. HS+ Patients Transplanted After Desensitization



Navigating Donor Antibodies for Best Outcomes

- Aims:

The aim of our study was to establish an algorithm for assignment of unacceptable antigens (UAs) such that a complement dependent cytotoxicity crossmatch (CDC-XM) would be **negative** and a concomitant flow cytometric crossmatch (FXM) would be **weakly positive (<225 CS)** to allow for successful transplant of sensitized kidney recipients.



Desensitization with IVIG + Rituximab is Effective in Improving DD Transplant Rates for HS Patients with CPRA >80%

Table 1. Deceased Donor Transplant Rates Following Immunomodulatory Therapy.

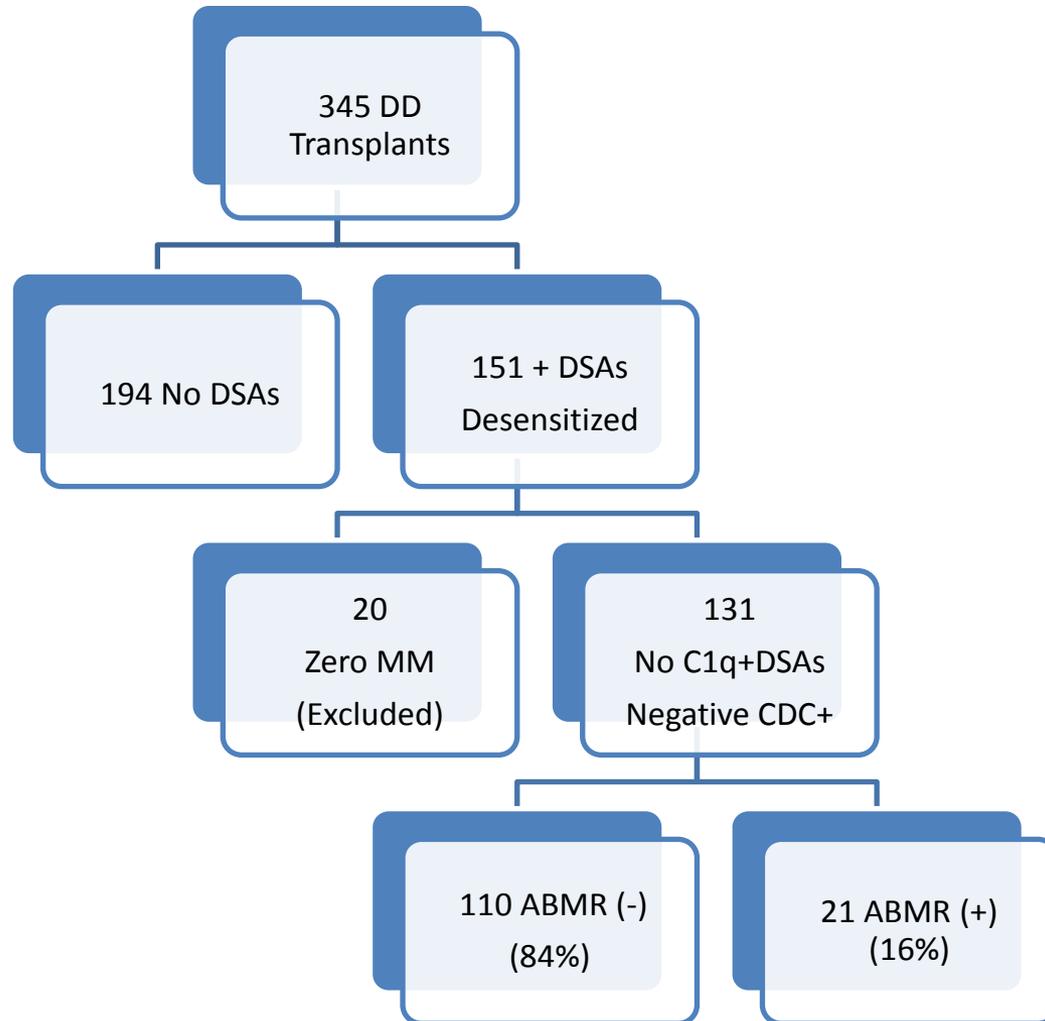
	Total Treated	Total Transplanted	Predicted UNOS Transplant Rates	Rates of Allograft Rejection
Totals	230	143 (62%)	6.5%†	35 (24.4%)
FCMX+@ Transplant		66 (46%)		AMR+23 (16%) AMR-43 (30%)
FCMX-@ Transplant		63 (44%)		CMR+10 (7%) AMR+1 (0.5%) AMR-/CMR-51 (36%)
0 Mismatched @ Transplant		14 (10%)		AMR+1 (0.5%)

Total treated: n=230. CPRA, calculated panel reactive antibody; AMR, antibody-mediated rejection; CMR, cell mediated rejection. Note, transplant rates for patients with CPRAs >80% are 6.5%/year (Montgomery *et al.*, 2011b)†.

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Navigating Donor Antibodies for Best Outcomes





Factors Predicting Risk for Antibody-mediated Rejection and Graft Loss in Highly Human Leukocyte Antigen Sensitized Patients Transplanted After Desensitization

Ashley A. Vo,¹ Aditi Sinha,² Mark Haas,³ Jua Choi,¹ James Mirocha,⁴ Joseph Kahwaji,¹ Alice Peng,¹ Rafael Villicana,¹ and Stanley C. Jordan¹

Background. Desensitization with intravenous immunoglobulin and rituximab (I+R) significantly improves transplant rates in highly sensitized patients, but antibody-mediated rejection (ABMR) remains a concern. **Patients and Methods.** Between July 2006 and December 2012, 226 highly sensitized patients received transplants after desensitization. Most received alemtuzumab induction and standard immunosuppression. Two groups were examined: ABMR⁻ (n = 181) and ABMR⁺ (n = 45, 20%). Risk factors for ABMR, pathology, and outcomes were assessed. **Results.** Significant risks for ABMR included previous transplants and pregnancies as sensitizing events, donor-specific antibody (DSA) relative intensity scores greater than 17, presence of both class I and II DSAs at transplant and time on waitlist. The ABMR⁻ showed a significant benefit for graft survival and glomerular filtration rate at 5 years ($P < 0.0001$). Banff pathology characteristics for ABMR⁺ patients with or without graft loss did not differ. C4d⁺ versus C4d⁻ ABMR did not predict graft loss ($P = 0.086$). Thrombotic microangiopathy (TMA⁺) significantly predicted graft failure ($P = 0.045$). The ABMR episodes were treated with I+R (n = 25), or, in more severe ABMR⁺, plasma exchange (PLEX)+I+R (n = 20). Graft survival for patients treated with I+R was superior ($P = 0.028$). Increased mortality was seen in ABMR⁺ patients experiencing graft loss after ABMR treatment ($P = 0.004$). The PLEX + Eculizumab improved graft survival for TMA⁺ patients ($P = 0.036$). **Conclusion.** Patients desensitized with I+R who remain ABMR⁻ have long-term graft and patient survival. The ABMR⁺ patients have significantly reduced graft survival and glomerular filtration rate at 5 years, especially TMA⁺. Severe ABMR⁺ episodes benefit from treatment with PLEX + Eculizumab. The DSA-relative intensity scores at transplant was a strong predictor

DSA Number & Strength are Strong Predictors of Risk for ABMR

Transplant by ABMR Status

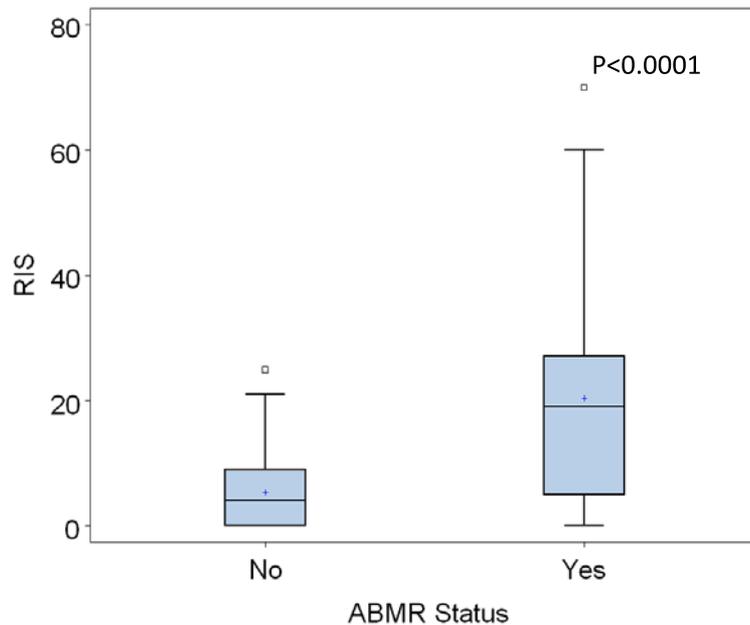


Figure 1C

Positive Predictive Value (PPV) of RIS for ABMR Episodes

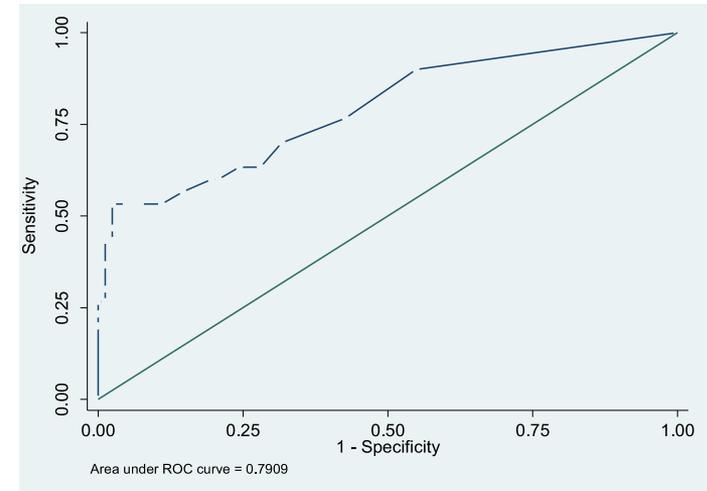
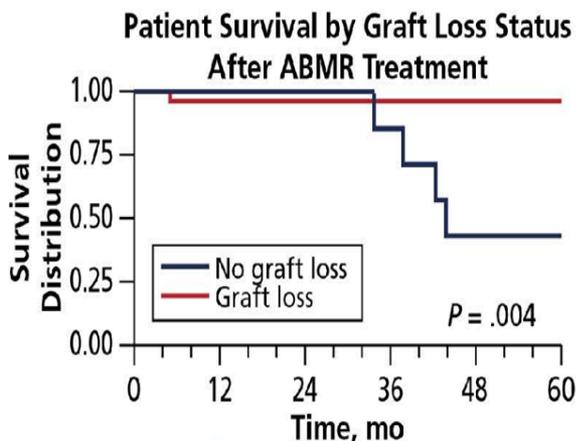
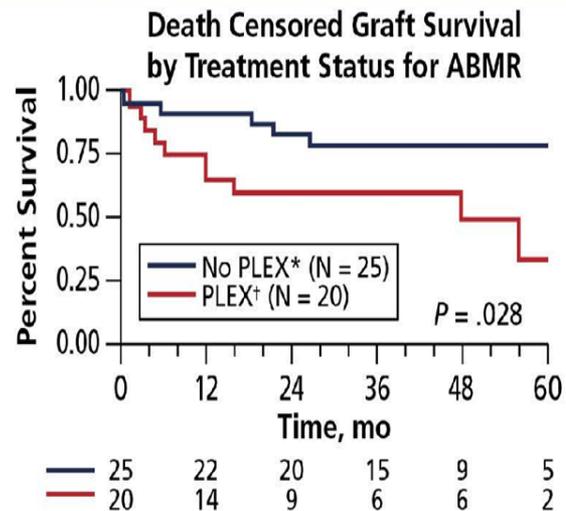
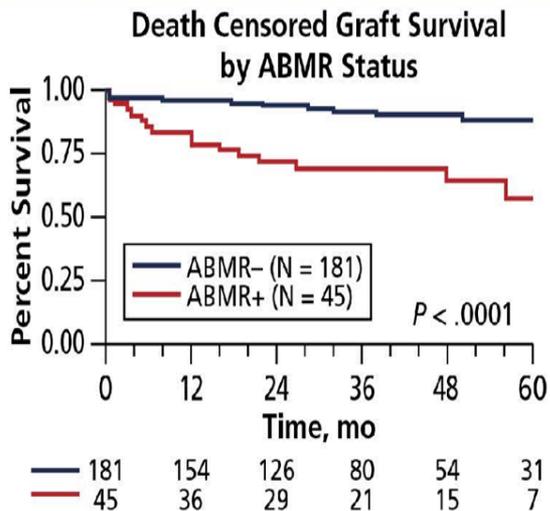


Figure 1D



Factors Predicting Risk for ABMR and Graft Loss in Highly HLA-Sensitized Patients Transplanted After Desensitization¹

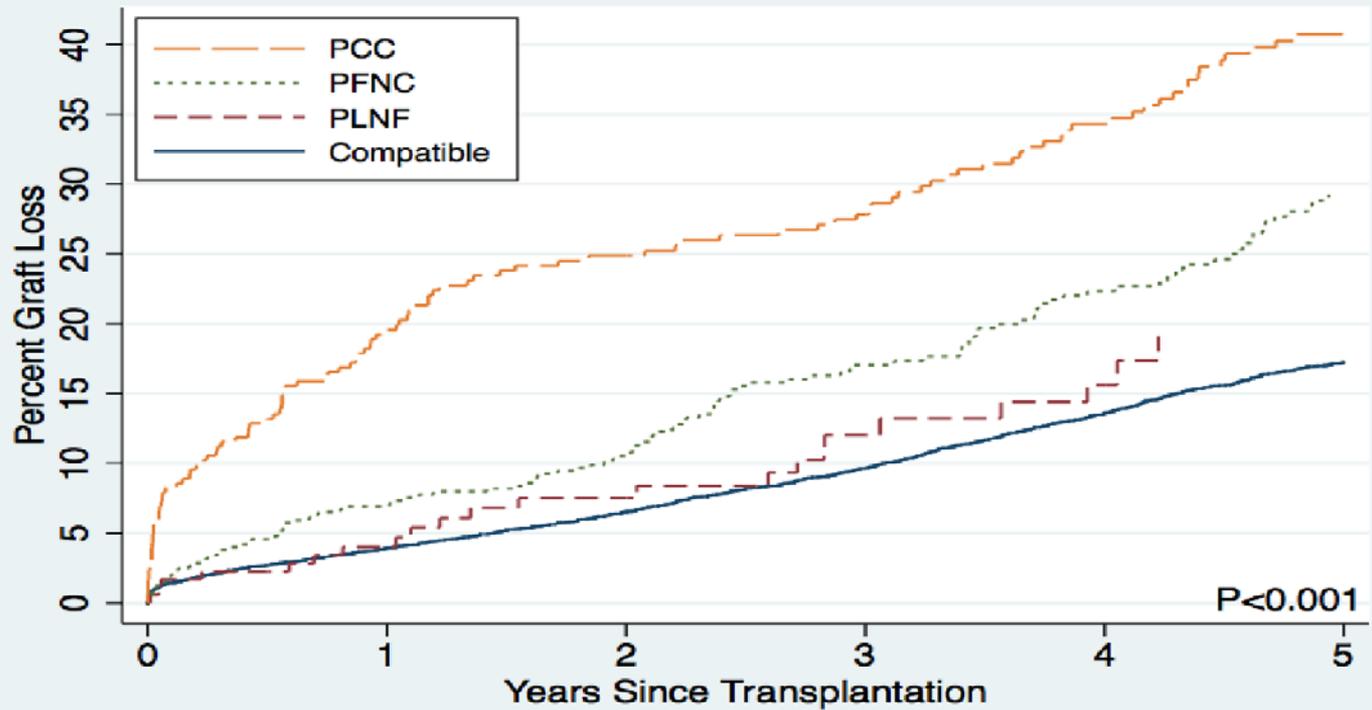


ABMR is associated with high risk for allograft loss and death

* IVIG + rituximab. † PLEX + IVIG + rituximab.

1. Vo AA et al. *Transplantation*. 2015. In press.

Post-Transplant Allograft Survival by CMX Status at Transplant



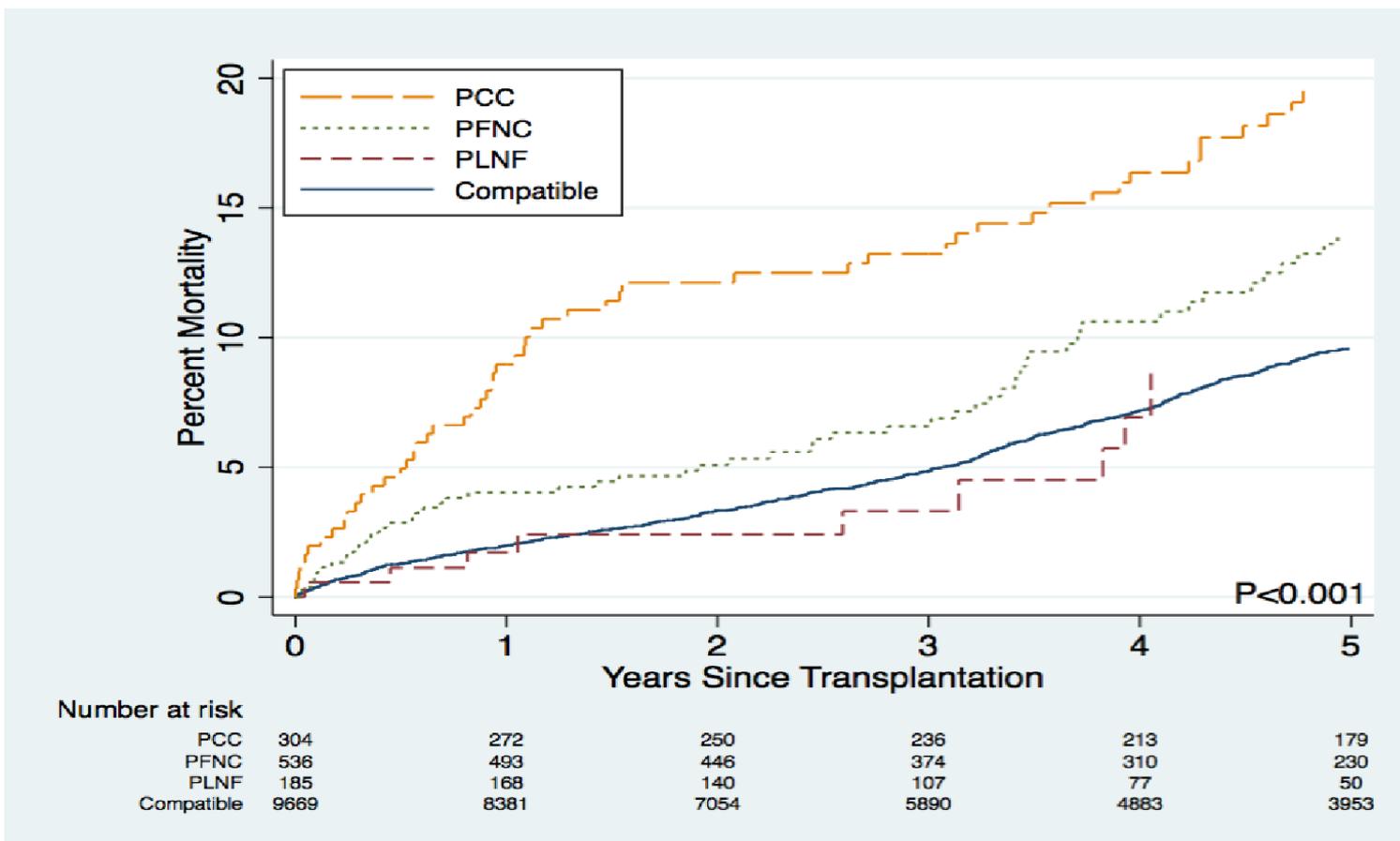
Number at risk

	0	1	2	3	4	5
PCC	304	240	213	194	163	128
PFNC	536	478	420	331	265	185
PLNF	185	164	132	97	71	46
Compatible	9669	8215	6815	5576	4515	3579

Orandi, BJ AJT 2014;14: 1573-80



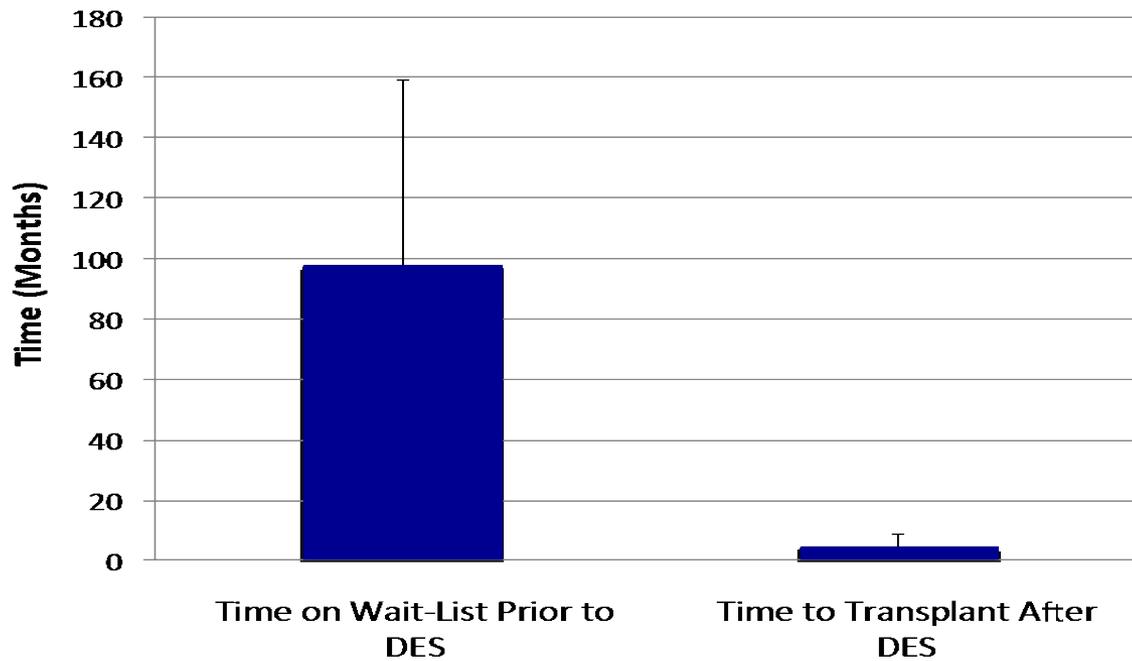
Post-Transplant Mortality by CMX Status at Transplant after Desensitization



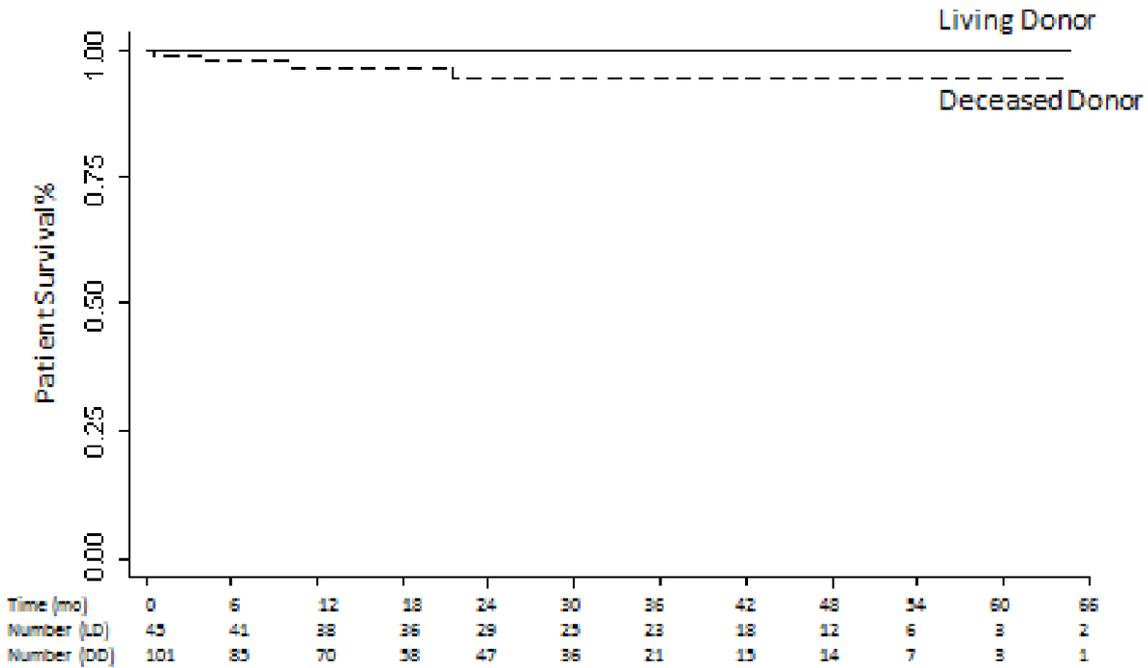
Orandi, BJ AJT 2014;14: 1573-80



Effect of IVIG + Rituximab on Wait-Time to Transplantation for Highly-HLA Sensitized Patients

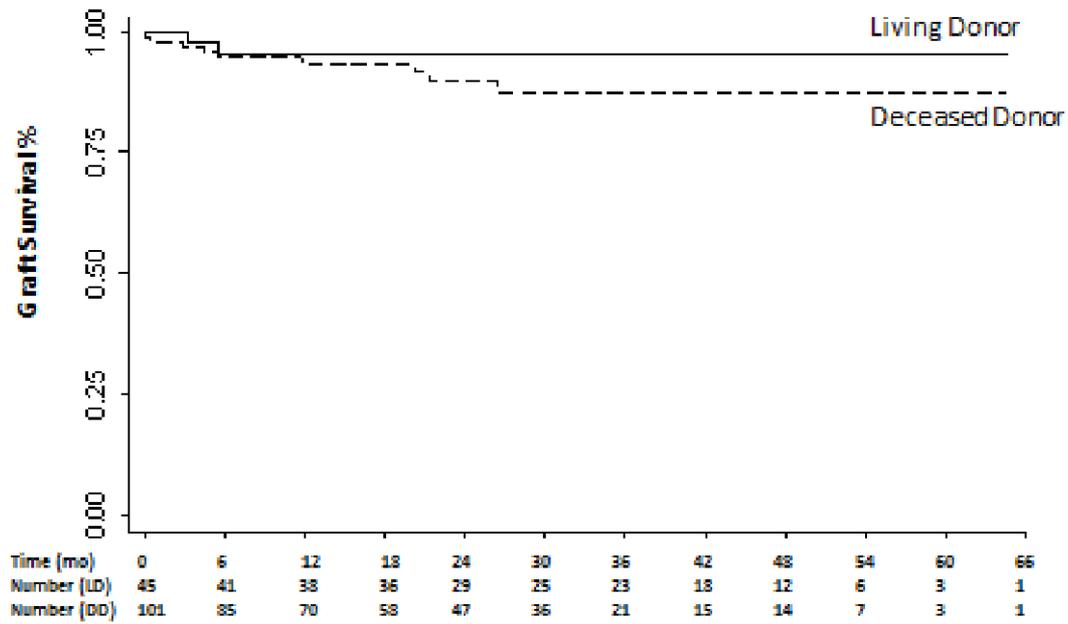


Patient Survival After Desensitization & Transplant for Patients with PRA>80%

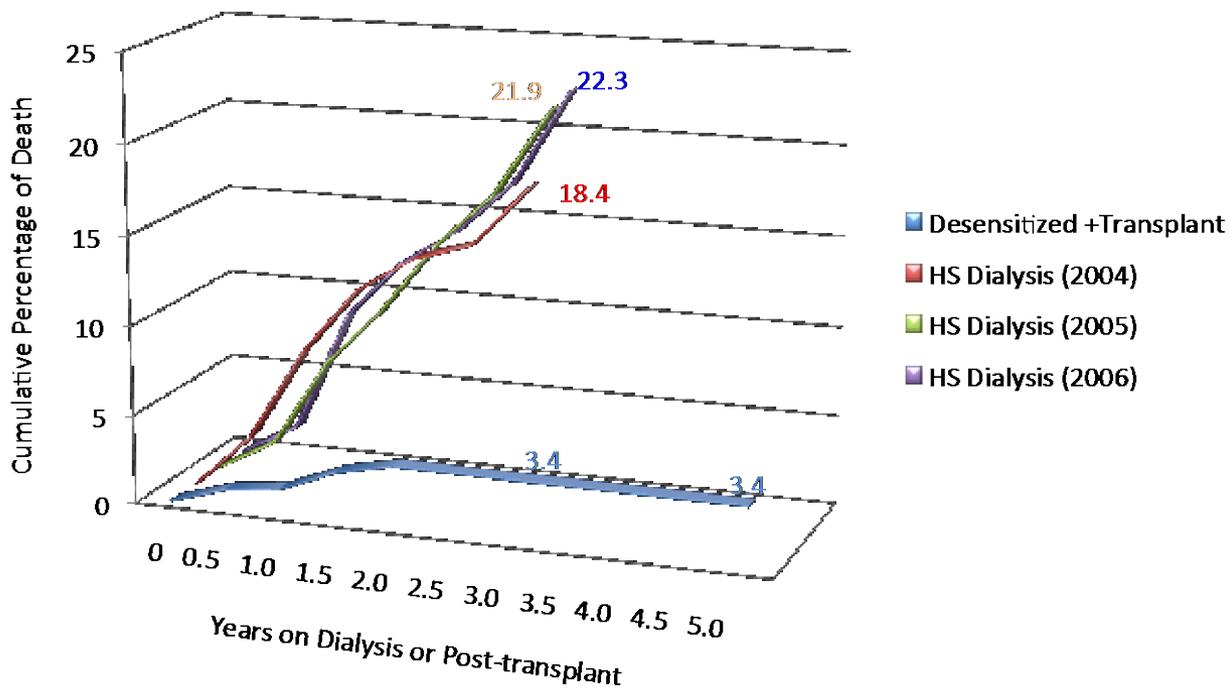


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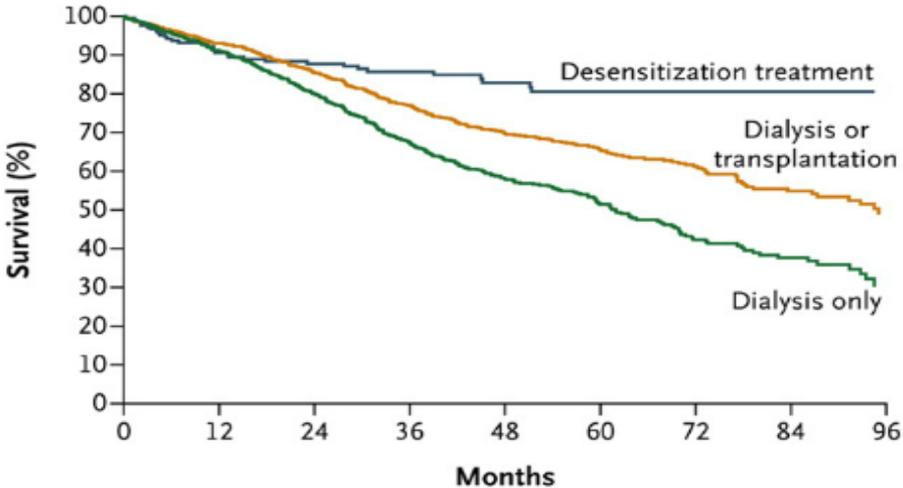
Graft Survival After Desensitization & Transplant for Patients with PRA>80%



Highly-HLA Sensitized Patient Survival by Treatment Type: Dialysis v. Desensitization & Transplantation



splant Recipients

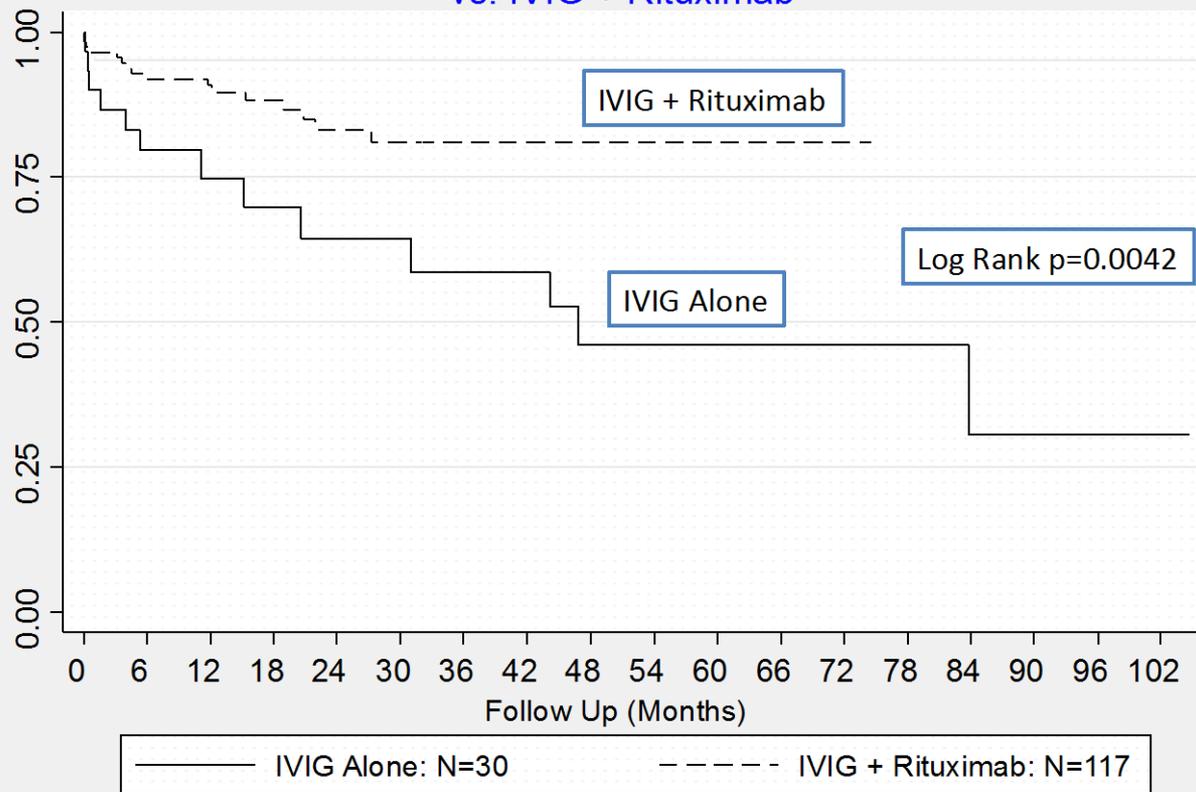


No. at Risk		0	12	24	36	48	60	72	84	96
Desensitization treatment	210	170	143	110	75	58	42	28	14	
Dual therapy	1027	854	688	497	321	230	157	96	41	
Dialysis only	1012	822	626	419	250	159	93	54	17	



Montgomery et al NEJM 2012

Kaplan-Meier Graft Survival in Patients Desensitized with IVIG vs. IVIG + Rituximab



Course of DSAs Pre- & Post-Transplant in IVIG + Placebo

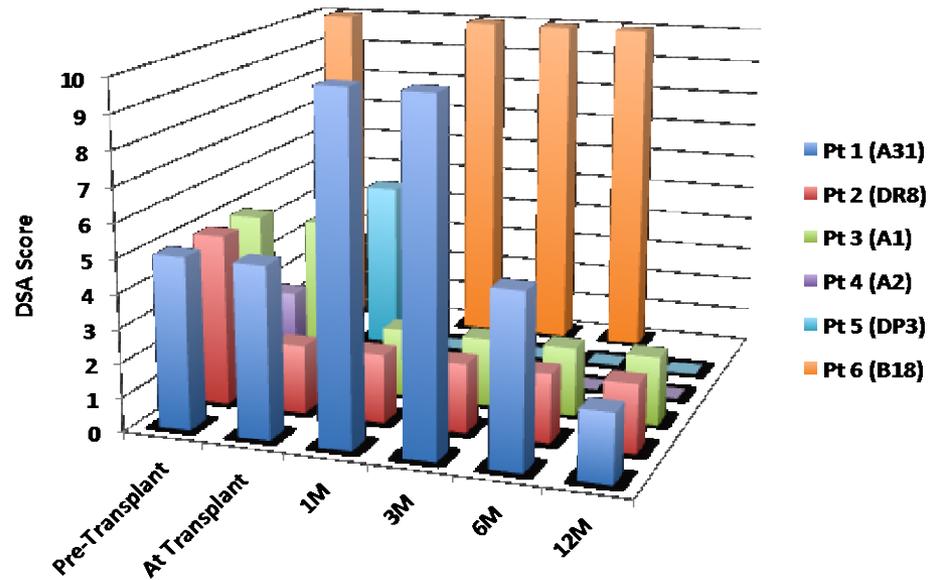
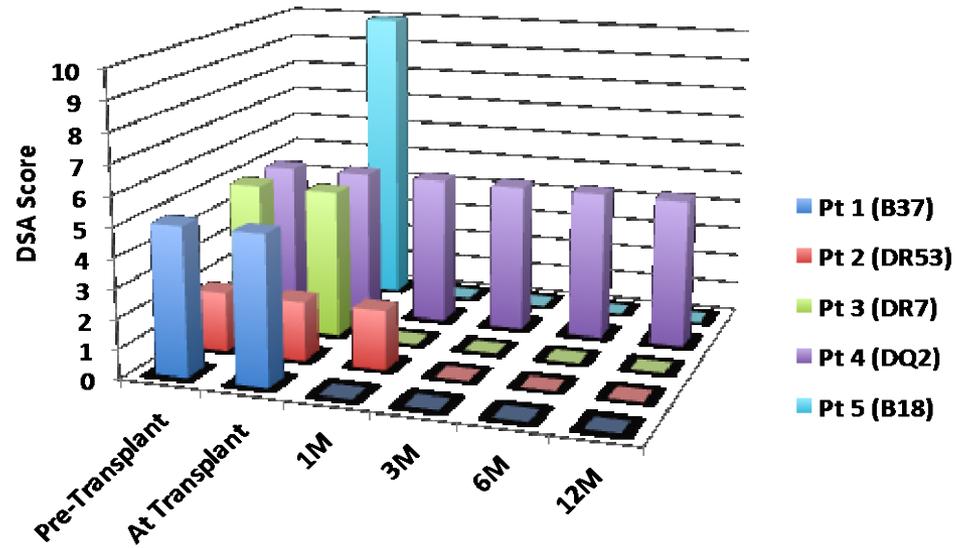


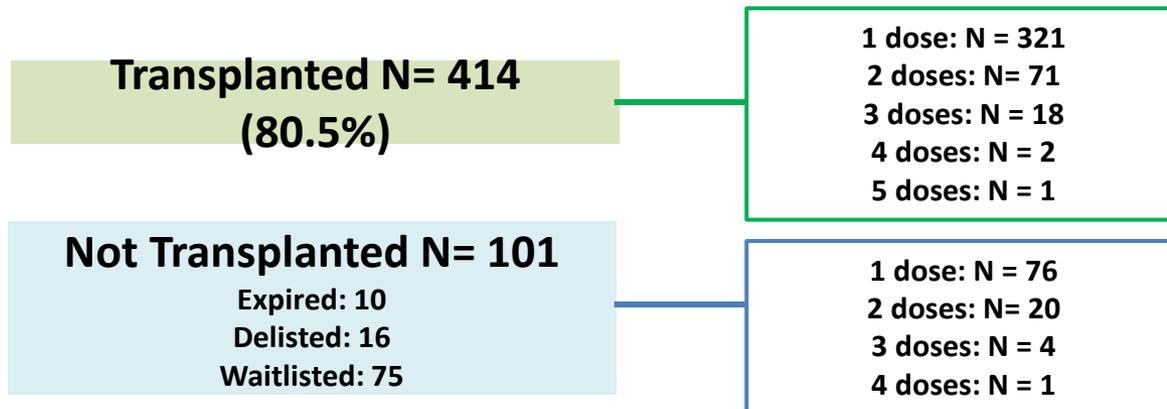
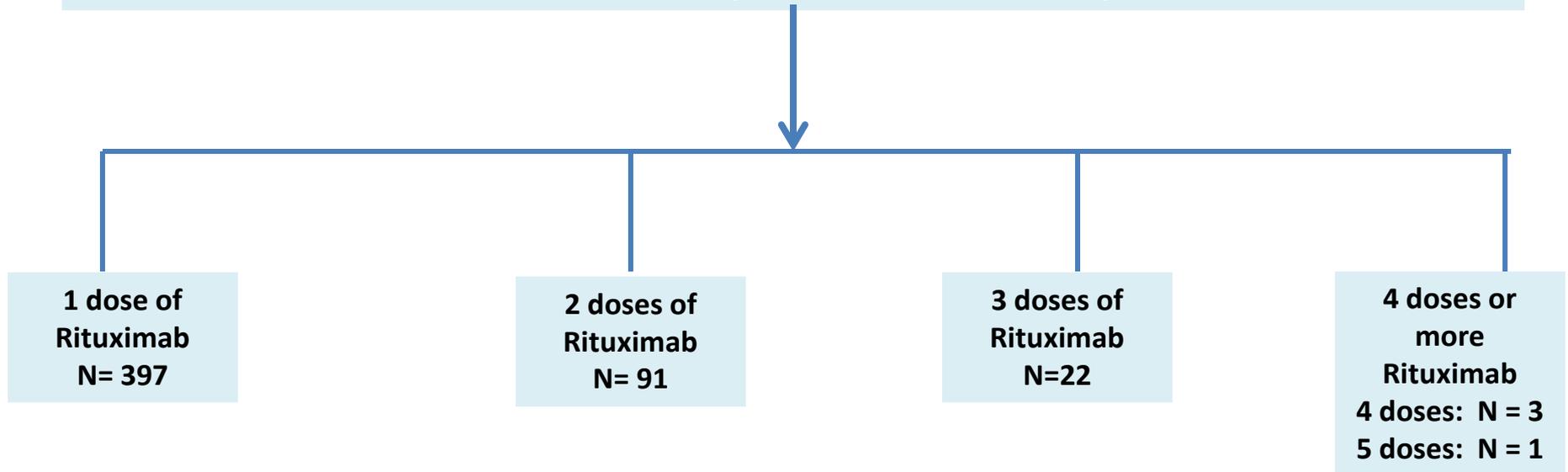
Figure 2A

Course of DSAs Pre- & Post-Transplant in IVIG + Rituximab



Transplant Immunotherapy Program **Figure 2B**

Total Desensitized Patients N= 514 (2007-2015)



CURRENT STATUS OF DESENSITIZATION FOR KIDNEY TRANSPLANTATION

- Desensitization combined with avoidance of C1q+ DSAs can be quite successful with ABMR rates \sim 20% and graft survival rates comparable to non-sensitized patients.
- Patient survival is quite superior for patients desensitized and transplanted v. those HS patients remaining on dialysis
- Current DSA monitoring techniques are problematic in that efficacy of desensitization cannot be discerned by assessment of CPRA values. Cellular assays are essential before proceeding to transplantation.
- Pediatric desensitization appears to yield results and outcomes similar to that for adults.



Unmet Needs in Desensitization

- A recognition by SRTTR that centers performing desensitization are serving a higher risk population than non-sensitized patients and appropriate risk adjustments should be granted.
- Need for increased biotech & transplant center collaboration to improve implementation of novel therapies aimed at modifying antibodies, B-cells, plasma cells and complement
- Current DSA monitoring techniques are problematic in that efficacy of desensitization cannot be discerned by assessment of CPRA values. Cellular assays are essential before proceeding to transplantation. Need for innovative thinking here.
- Pediatric patients represent a growing and underserved population of sensitized patients and should be included in clinical trials.





Thanks for your attention!