Desensitization for living donor kidney transplants

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SATS CONGRESS

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Benefits of Transplantation

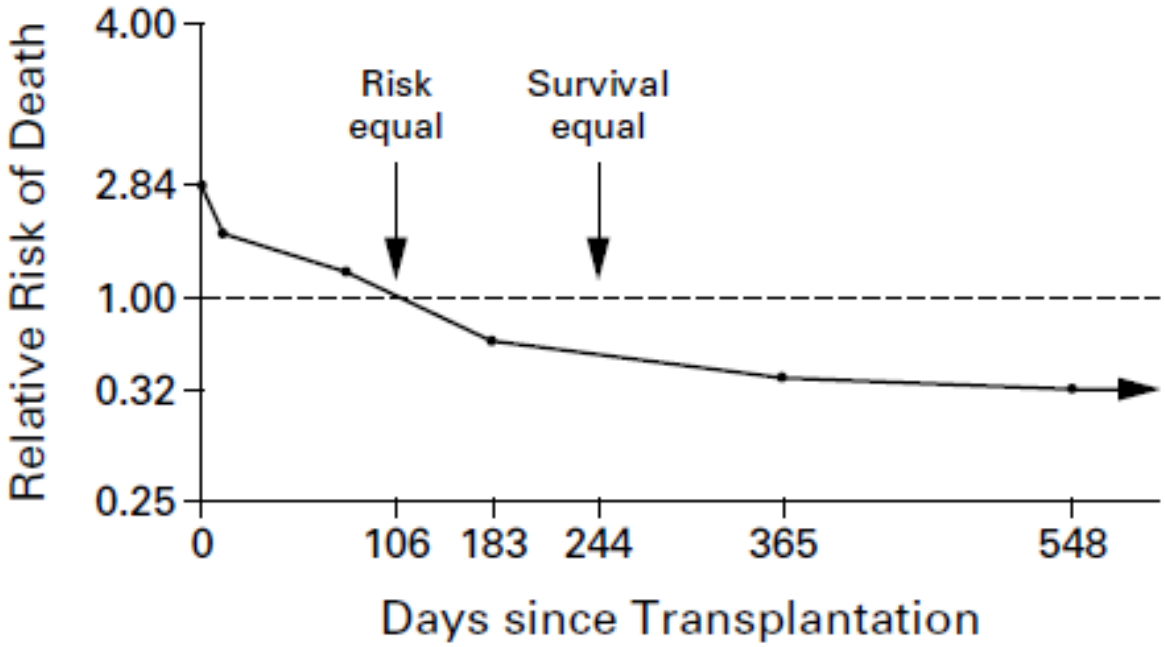


Figure 2. Adjusted Relative Risk of Death among 23,275 Recipients of a First Cadaveric Transplant.

Wolfe RA, Ashby VB, Milford EL, et al. N Engl J Med 1999; 341:1725–1730

The Problem

The New England
Journal of Medicine

Volume 280 APRIL 3, 1969 Number 14

SIGNIFICANCE OF THE POSITIVE CROSSMATCH TEST IN KIDNEY TRANSPLANTATION*

RAMON PATEL, M.R.C.P., AND PAUL I. TERASAKI, PH.D.

Abstract Crossmatch tests of the prospective kidney-transplant donor's lymphocytes with the serum of the prospective recipient in 225 transplants showed that eight of 195 with negative crossmatch failed to function immediately, in contrast to 24 of 30 with positive crossmatch (p less than 0.001). Immediate failure occurred in significantly higher numbers among patients with a higher risk of having antibodies, such as multiparous females and patients receiving secondary transplants. The effect was not a nonspecific one, for more immediate failures occurred among transplants from unrelated than among those from related donors. The corresponding frequency of positive crossmatch was also lower among related donors. The presence of preformed cytotoxic antibodies against the donor appears to be a strong contraindication for transplantation.

PREFORMED allogeneic antibodies present in a recipient were first postulated as being responsible for immediate failure of a kidney transplant in 1964.[1] At that time it was suggested that a crossmatch test of the prospective recipient's serum (80 per cent) when a direct positive crossmatch can be demonstrated.

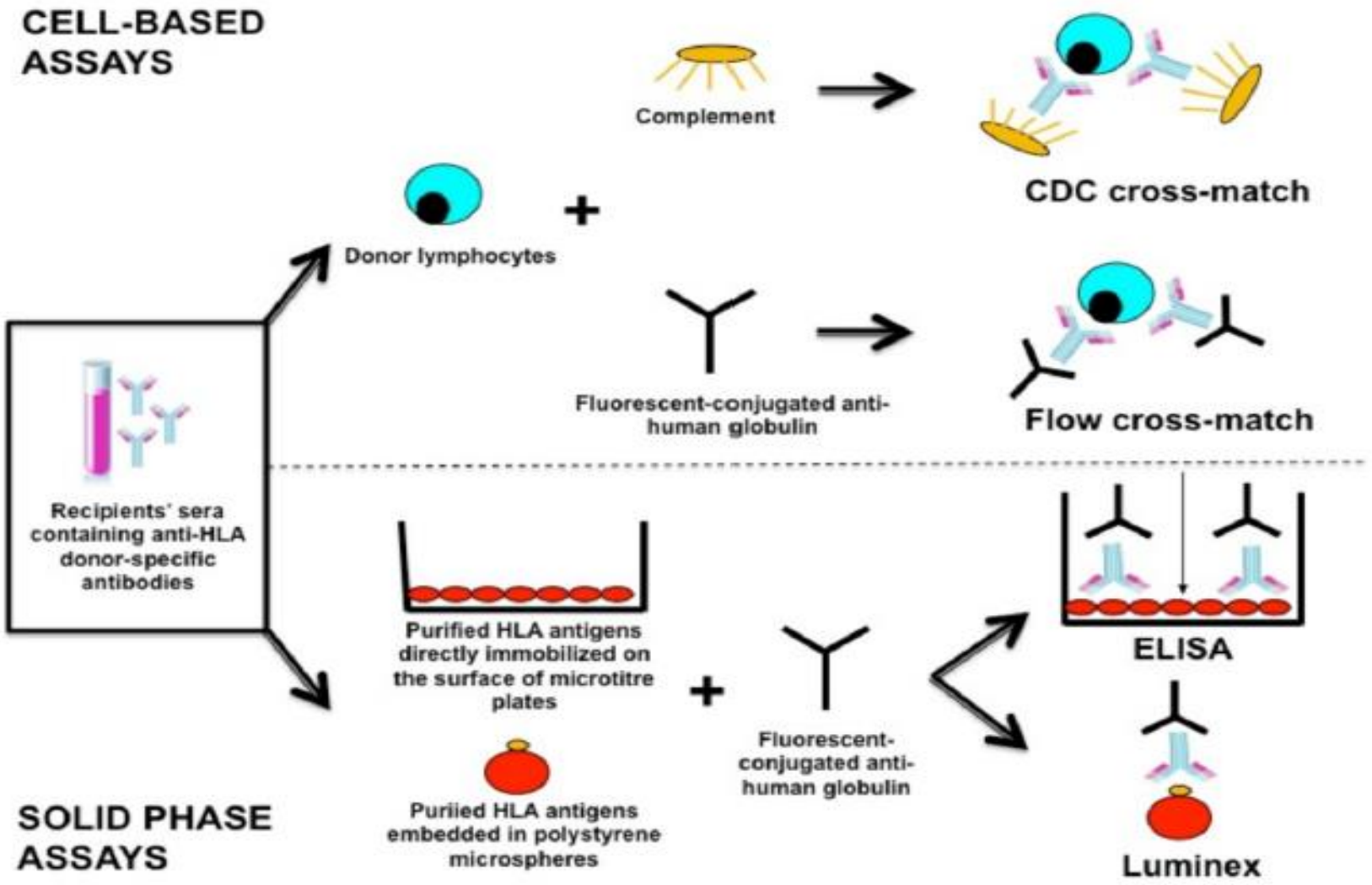
MATERIAL AND METHODS

The 226 kidney-transplant recipients were bled be-

CDC Cross match

- Initial studies evaluating the clinical validity of CDC assays demonstrated that 80% of CDC cross-match–positive kidney transplants rejected
- Only 4% of cross-match–negative kidney transplants were associated with early graft loss

Cross-match techniques



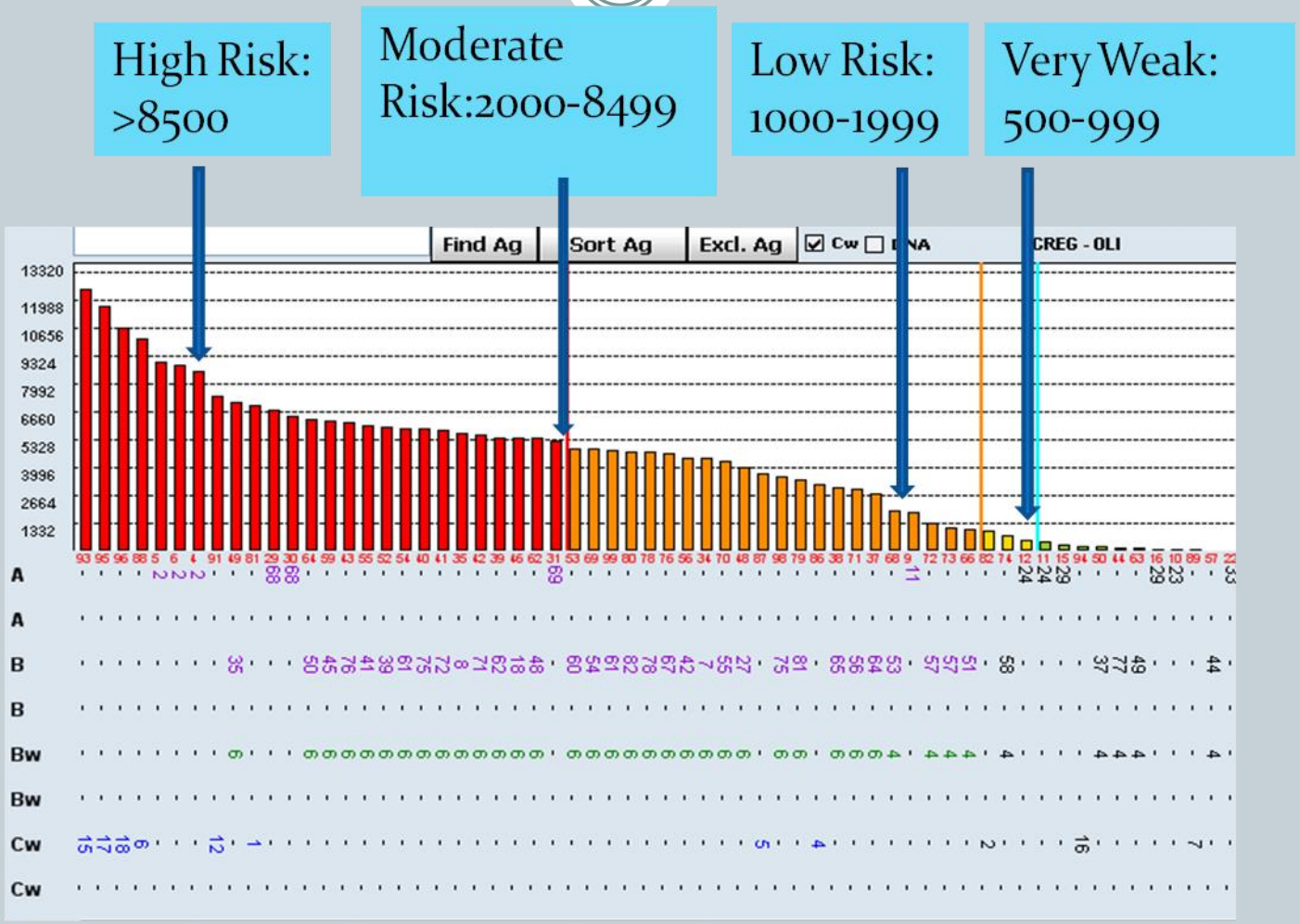
Flow Cytometry

- Quantification of anti-HLA antibodies by flow cytometer expressed as mean channel shifts.
- Unlike CDC cross-match, flow cytometry cross-match (FCXM) identifies both complement-fixing and non-complement-fixing anti-HLA donor-specific antibodies.
- Several studies have shown that the presence of a positive FCXM with a negative CDC cross-match is associated with a significantly greater risk of AMR and early graft rejection

Virtual Cross-Match

- Donor HLA Typing
- Recipient Luminex-based antibody identification
- Donor-Specific Antibody (DSA) = Virtual positive cross-match (above a certain MFI cut-off value: 5000 vs 3000 vs 1000 etc.)

Classification of Antibodies Using Single Antigen Reagents and MFI Values



Concept of Risk

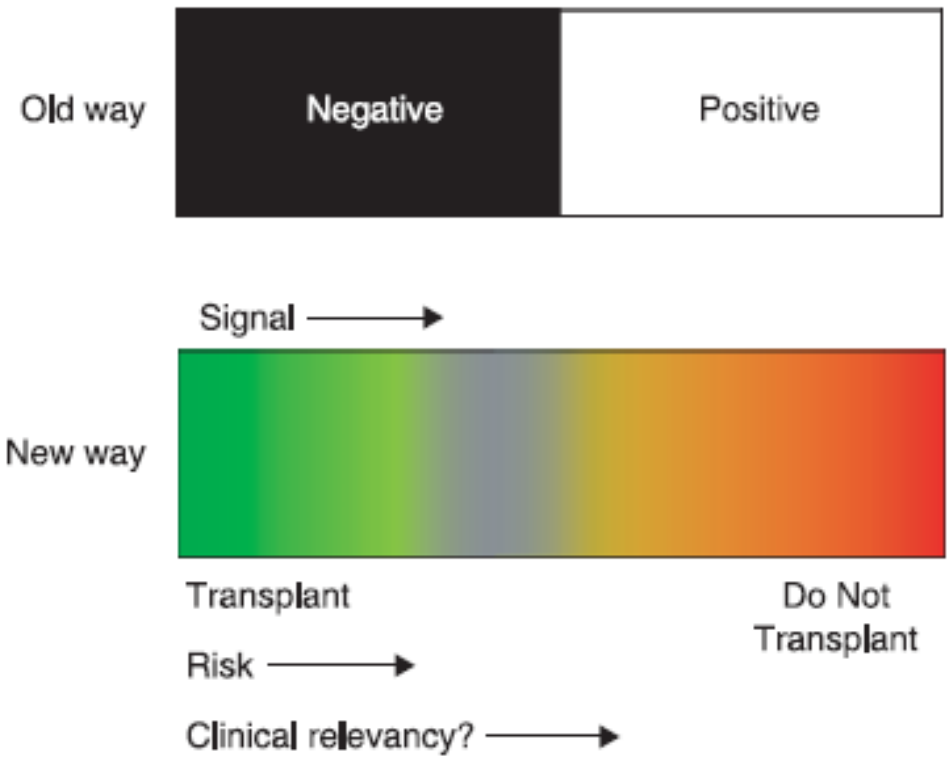
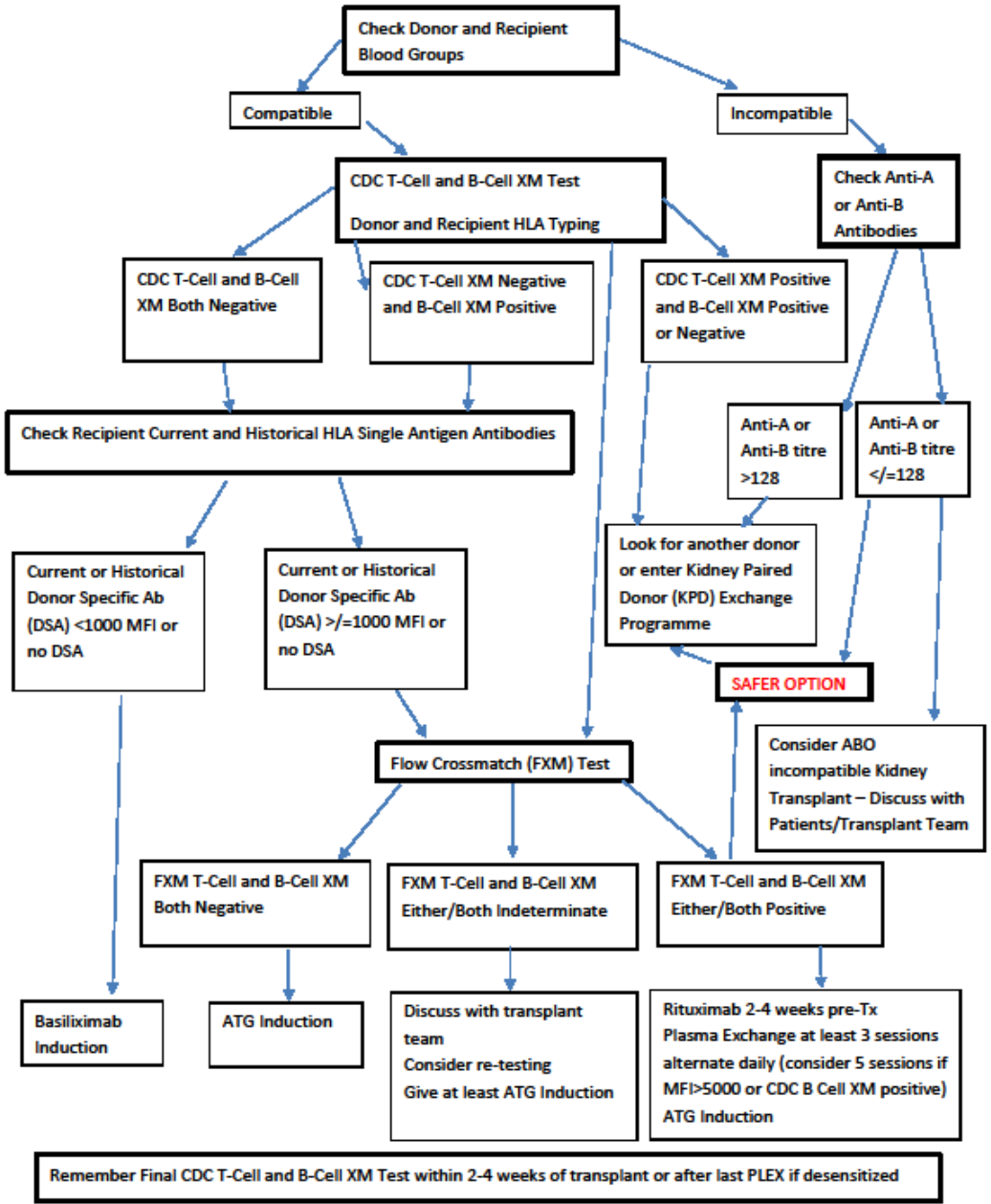


Figure 1. Is a positive cross-match a contraindication to transplant or another risk factor that must be weighed pre-transplant?

UCT Protocol for Tissue Immunology Workup of Living Donor Kidney Transplants

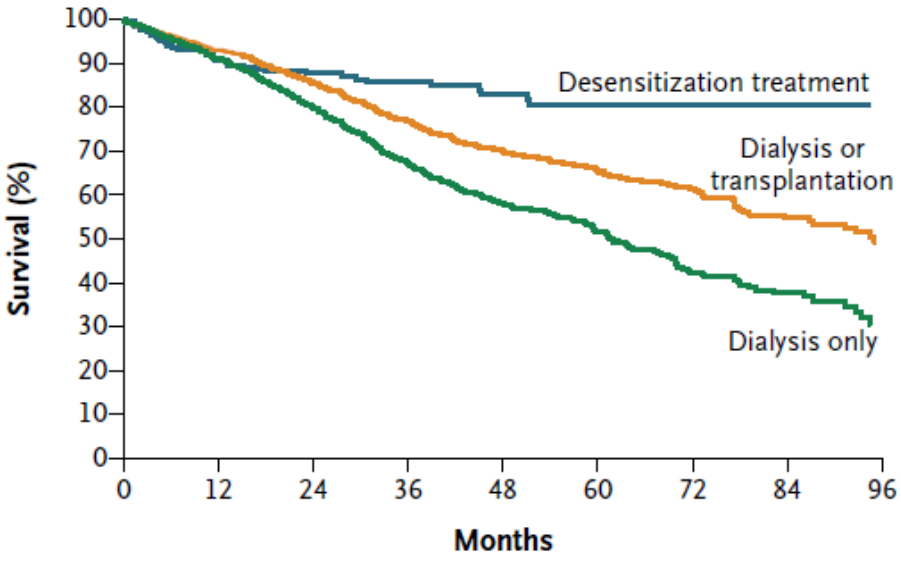


Benefits of Desensitization

- The benefits of desensitization in improving the life expectancy of ESRD patients were shown in at least 2 studies, both published in NEJM:

1. Montgomery et al. “Desensitization in HLA-incompatible kidney recipients and survival”. Vol. 365, no. 4, pp. 318–326, 2011.
2. Orandi et al., “Survival benefit with kidney transplants from HLA-incompatible live donors,”, Vol. 374, no. 10, pp. 940–950, 2016.

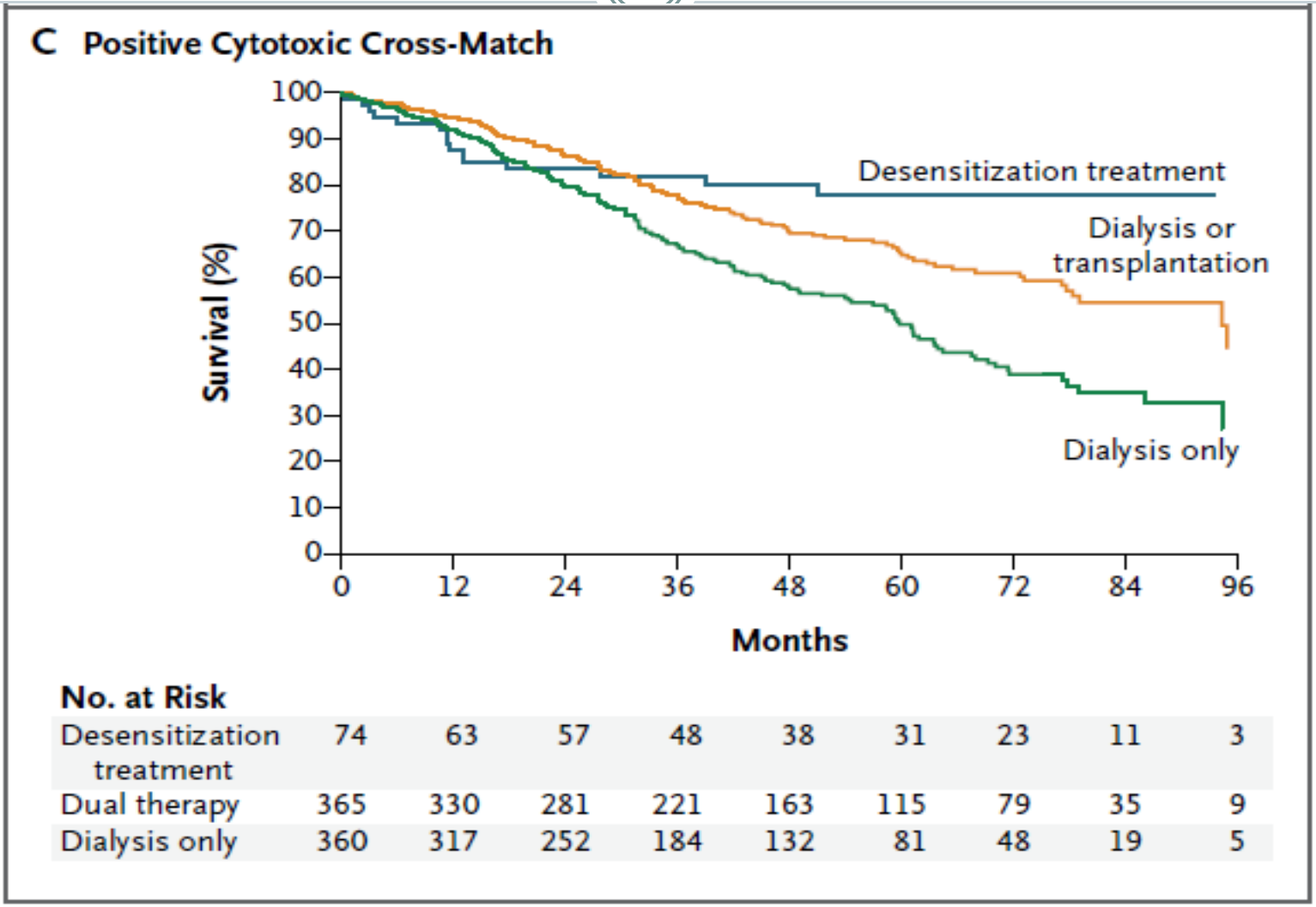
PLEX and IVIG to desensitize 211 HLA-sensitized patients – Montgomery et al 2011



No. at Risk									
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

Figure 1. Survival Benefit of Desensitization in HLA-Incompatible Kidney Recipients.

Positive CDC



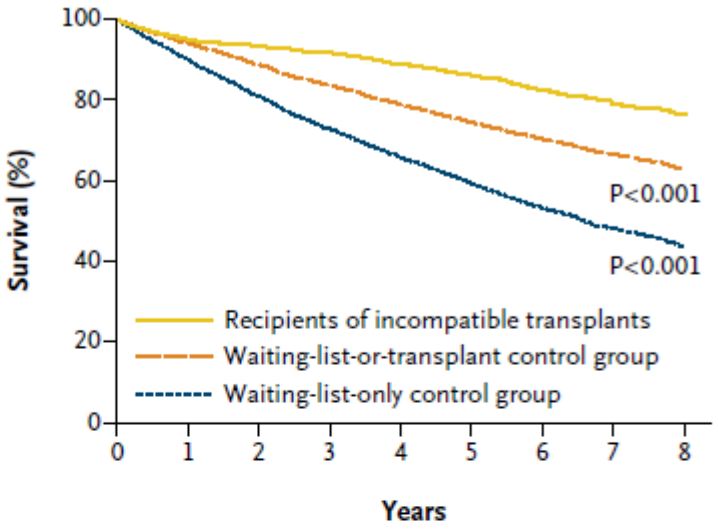
No. at Risk									
Desensitization treatment	74	63	57	48	38	31	23	11	3
Dual therapy	365	330	281	221	163	115	79	35	9
Dialysis only	360	317	252	184	132	81	48	19	5

Plasmapharesis Sessions

Table 1. Baseline Characteristics of HLA-Incompatible Kidney-Transplant Recipients, Stratified According to Strength of Donor-Specific Anti-HLA Antibody.*

Characteristic	All Patients (N=211)	Positive Results on Cross-Matching Assay†		
		CDC (N=74)	FCXM (N=95)	Multiplex Bead (N=42)
Age (yr)	44±13	44±14	46±12	42±14
Female sex (%)	66.8	70.3	66.3	62.0
Race or ethnic group (%)‡				
White	78.2	82.4	81.1	64.3
Black	13.7	10.8	12.6	21.4
Hispanic	1.9	2.7	0	4.8
Asian	0.5	0	0	2.4
Other	5.7	4.1	6.3	7.1
Blood-type incompatibility with donor (%)	10.9	5.4	14.7	11.9
Calculated panel-reactive antibody (%)	82±23	90±15	80±27	73±24
Donor-specific anti-HLA antibody (%)				
HLA class I	41.2	33.8	44.2	47.6
HLA class II	25.6	24.3	25.3	28.6
HLA class I and II	33.1	41.9	30.5	23.8
Previous kidney transplants (%)				
0	45.5	41.9	47.4	47.6
1	39.8	43.2	36.8	28.6
2	12.8	10.8	14.7	11.9
3	1.9	4.1	1.1	0
Plasmapheresis sessions (no.)				
Before transplantation	4±4	6±5	3±2	3±4
After transplantation	5±4	8±6	4±3	5±3

1025 kidney transplant recipients by Orandi et al. 2016

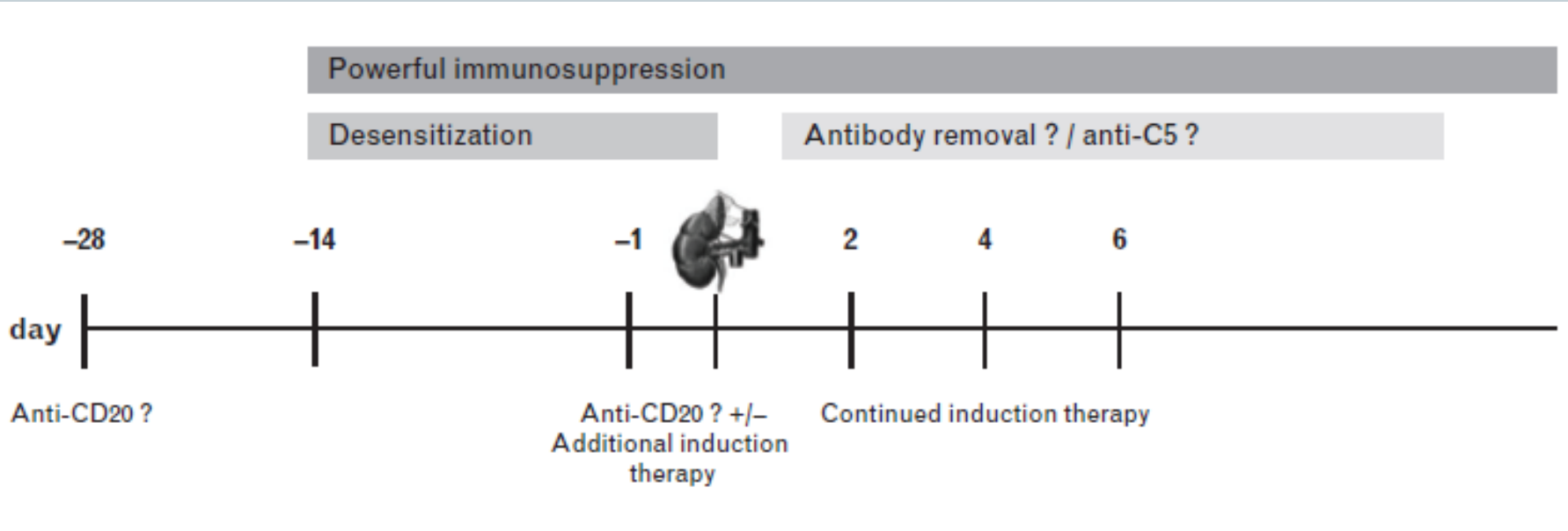


No. at Risk					
Recipients of incompatible transplants	1025	958	832	584	327
Waiting-list-or-transplant control group	5125	4546	3673	2493	1414
Waiting-list-only control group	5125	4141	3024	1810	916

Figure 1. Overall Comparison of Survival between the Group That Received Kidney Transplants from HLA-Incompatible Live Donors and Each Group of Matched Controls.

In one control group, the controls remained on the waiting list or received a transplant from a deceased donor. In the other control group, controls remained on the waiting list and did not receive a transplant from a deceased donor.

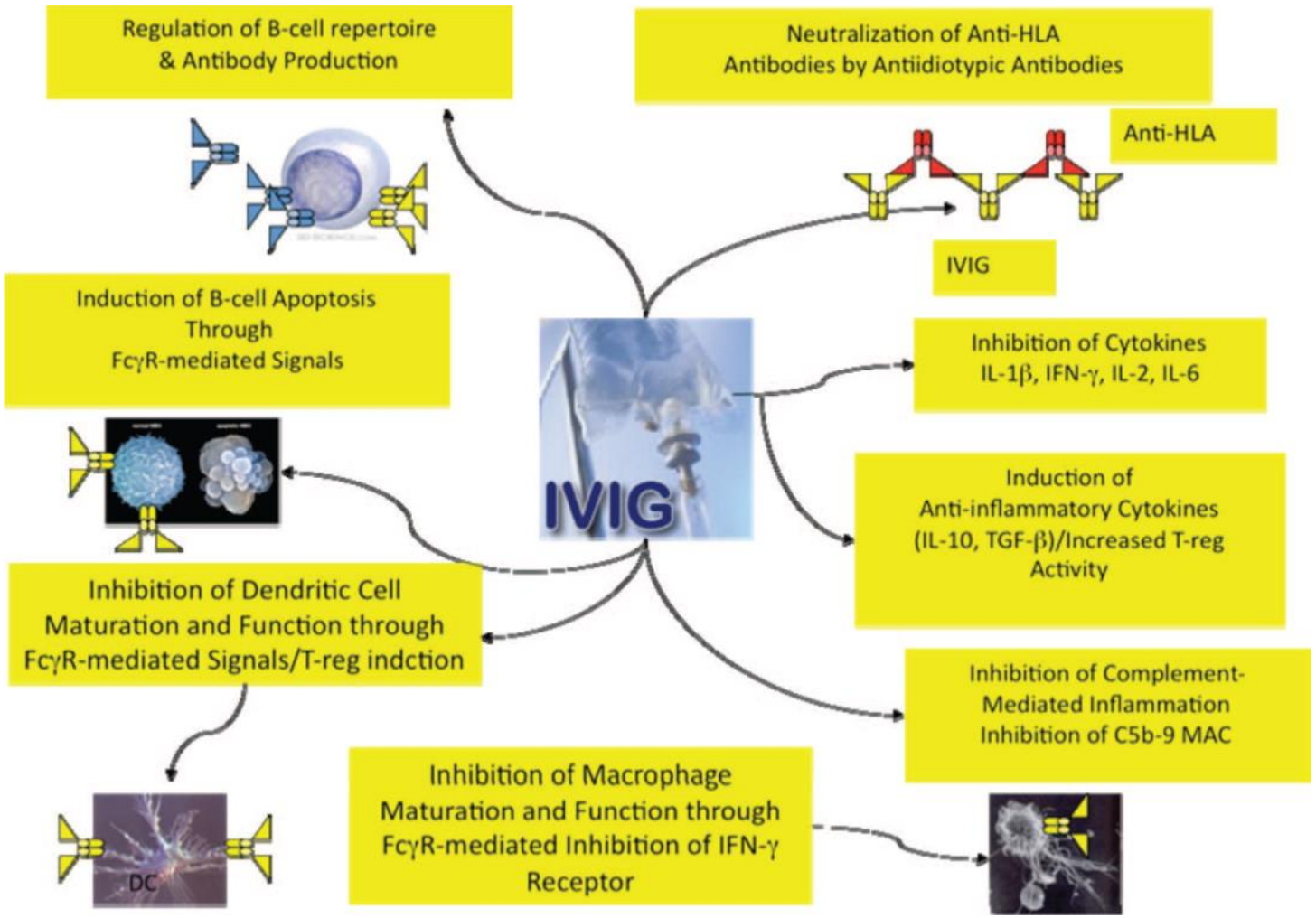
Overview of desensitization/immunosuppressive protocols



Immunosuppressive Strategies

1. Antibody depletion at the time of transplantation using plasmapheresis, immunoadsorption
2. Modulation of the recipient's immune system using intravenous immunoglobulins (IVIg).
3. Reduction of the B lymphocyte pool by splenectomy, more recently substituted in most centres with the anti-CD20 antibody rituximab.
4. Prevention of antibody production by proteasome inhibition (bortezomib).
5. Prevention of the deleterious impact of complement activation upon antibody binding to the graft endothelium (eculizumab).
6. Powerful maintenance immunosuppression

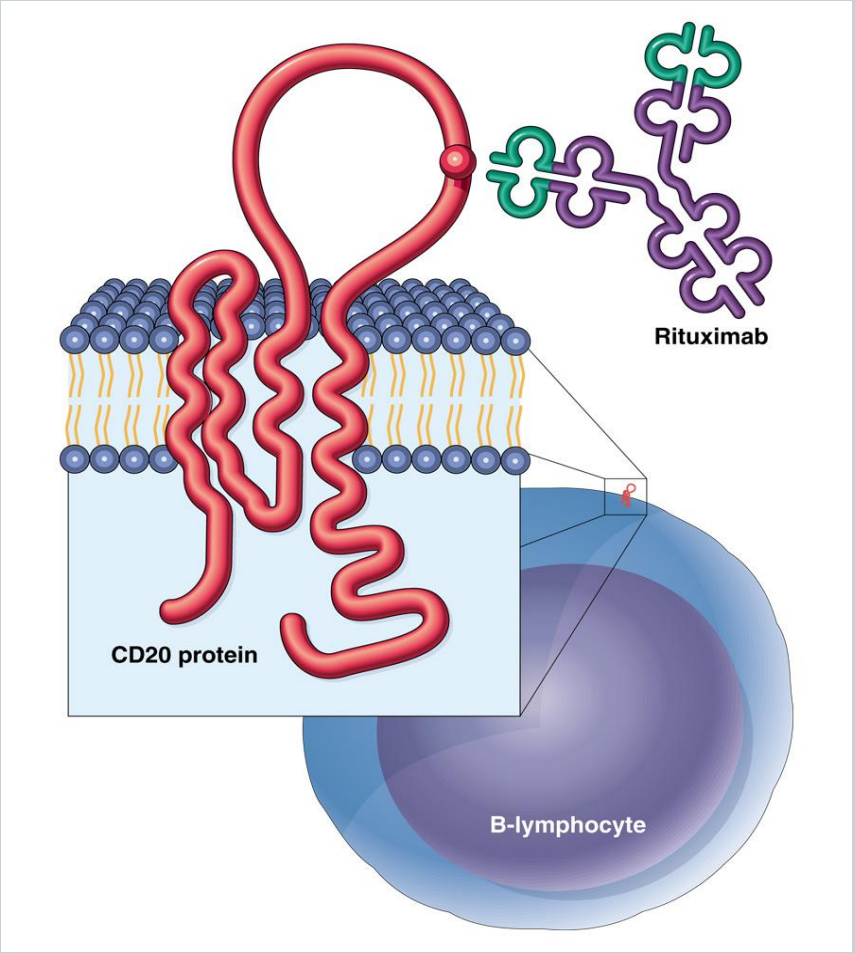
Mechanisms of IVIG



Jordan SC et al. Transplantation 2009; 88:1

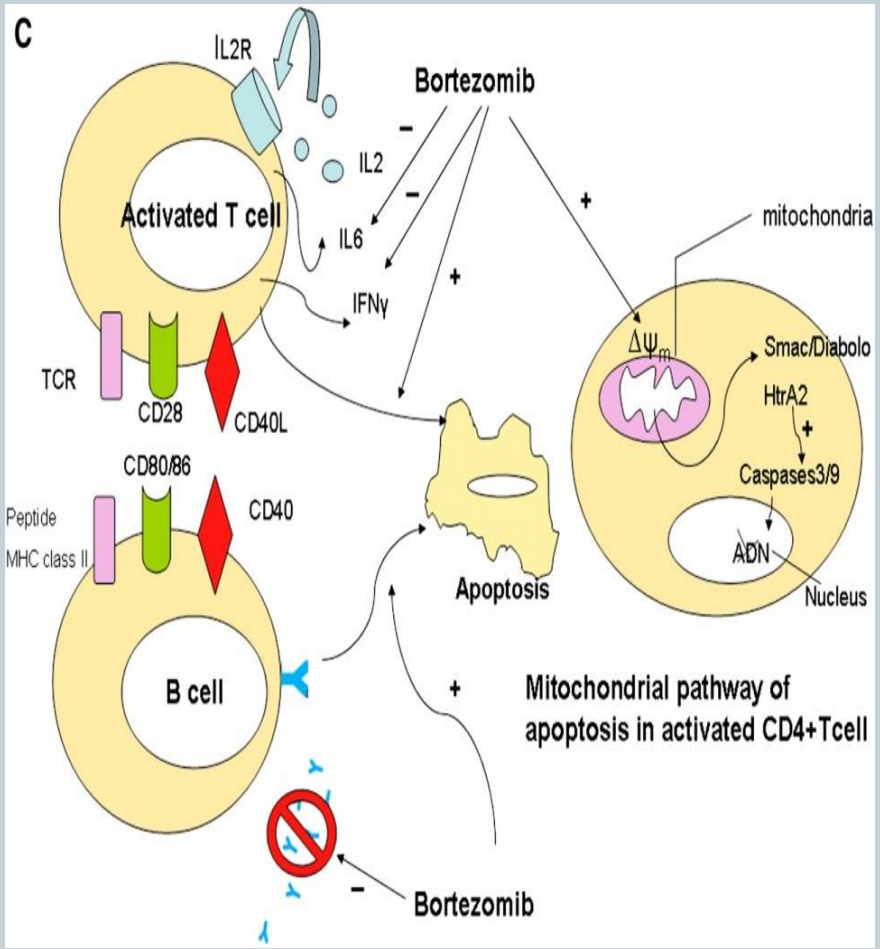
Rituximab

- Genetically engineered monoclonal murine/human antibody
- Anti-CD20
- FDA approved for treatment of lymphoma
- Used for desensitization and ABMR
- Emerging evidence for decrease in
  - ABMR when used in desensitization
  - de novo DSA



Bortezomib

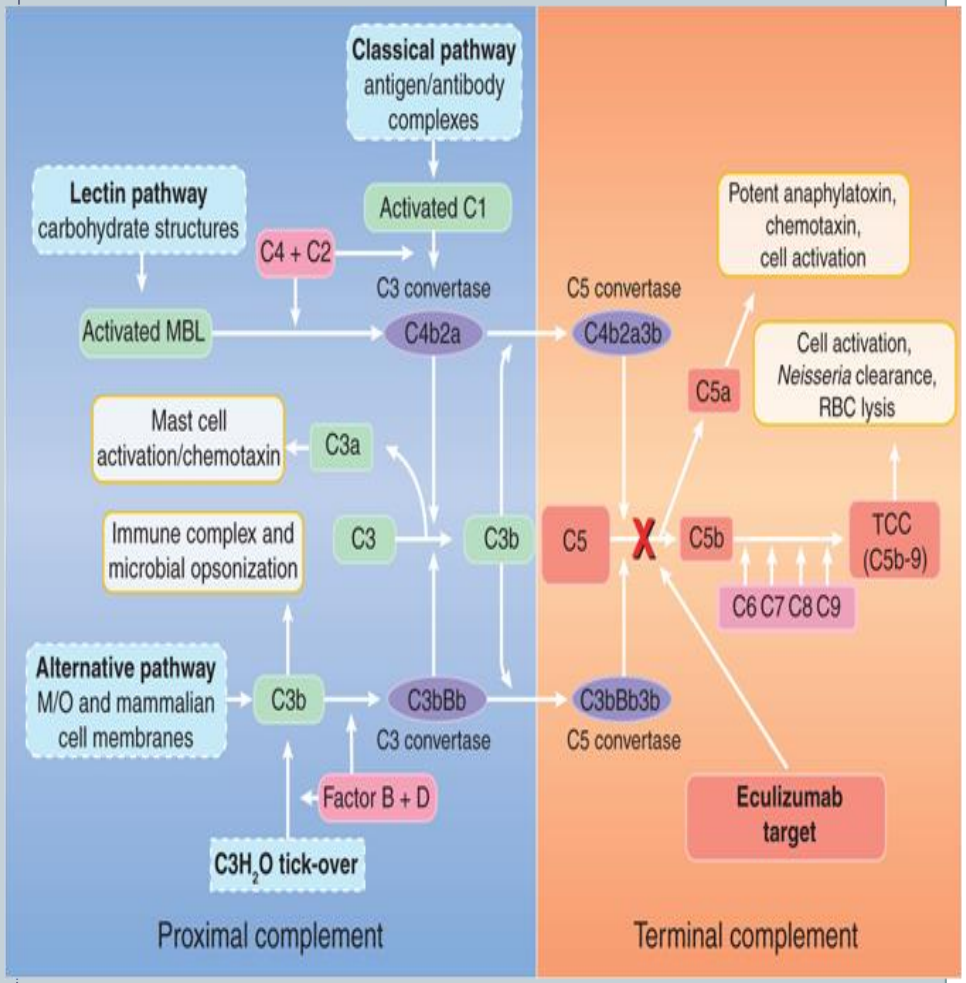
- Proteasome inhibitor
- Directly targets antibody production by plasma cells
- FDA approved for multiple myeloma
- Primarily used for ABMR
- Limited efficacy in desensitization protocols
- Side effects include thrombocytopenia and disabling neuropathy



Richardson et al. NEJM 2003; 348:2609

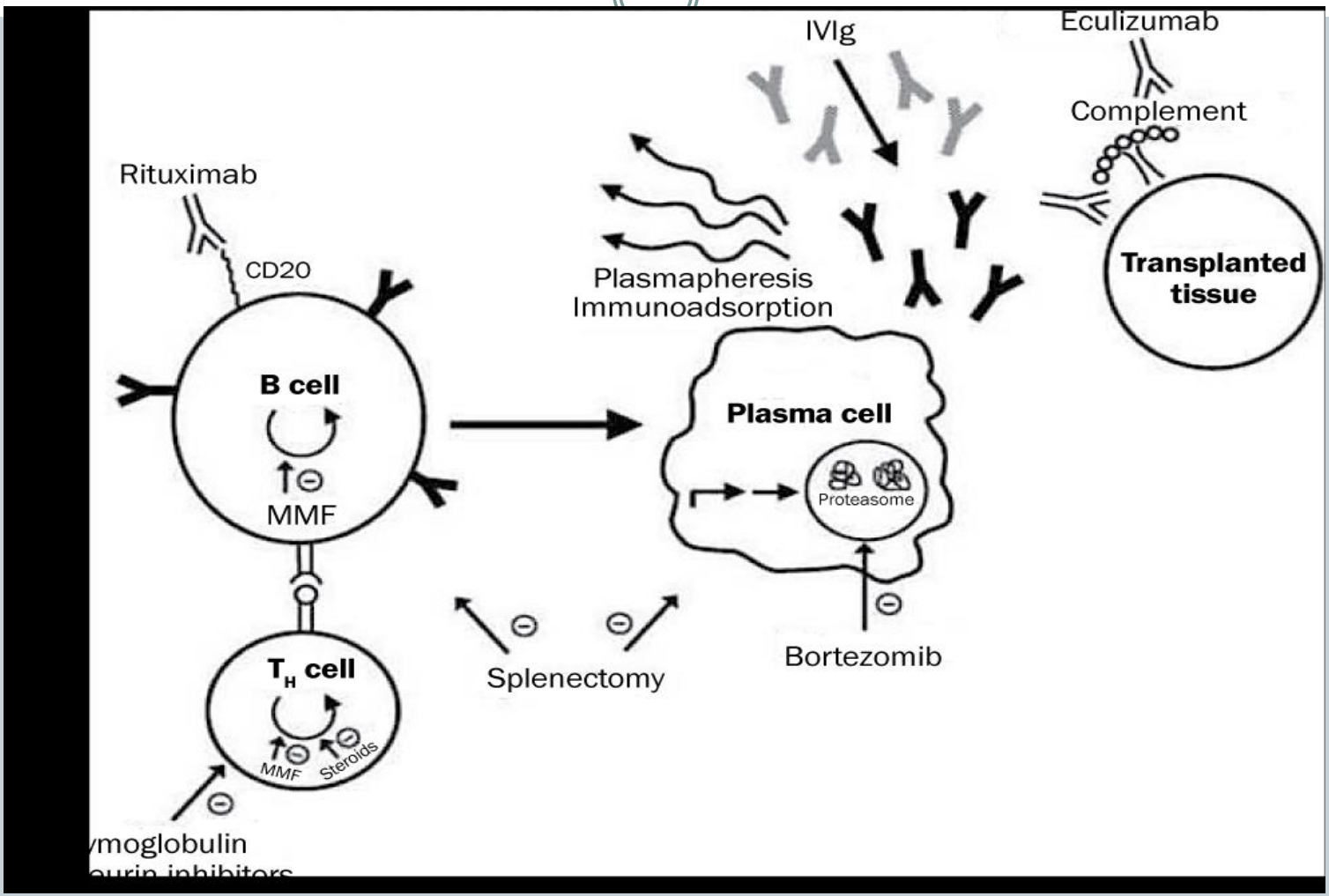
Eculizumab

- Genetically humanized monoclonal antibody
- Anti-C5
- Blocks the activation of terminal complement
- FDA approved for treatment of PNH
- Primarily used for ABMR
- Limited efficacy with desensitization (only short term decrease in AMBR)
- Increased risk of infections with encapsulated bacteria



Hillmen et al. NEJM 2006; 355:1233

Overview of Targets in Treating AMR



Levine MH, Abt PL. Treatment options and strategies for antibody mediated rejection after renal transplantation. Semin Immunol. 2012;24:136–142

Experimental Drugs

- IL-6R antagonist (tocilizumab)
- IL-6 one of the major cytokines involved in differentiation of B cells to IgG-secreting plasmablasts and finally to plasma cells
- IL-6 also:
  - stimulates Th17 cells that increase inflammation and allograft rejection
  - inhibits the generation of Treg cells
- Been used successfully as add on therapy for:
  - desensitization
  - chronic active ABMR

Experimental Drugs

- C1 esterase inhibitor – prevention and treatment of acute AMR
  - C1 esterase – serine protease that inactivates C1r and C1s
  - Multiple effects on classical and lectin complement pathways
  - Major effects on coagulation cascade and vascular permeability
- Small studies show improvement in rates of biopsy features of ABMR Transplant Glomerulopathy

Experimental Drugs

- The IgG-degrading enzyme derived from *Streptococcus pyogenes* (IdeS)
  - an endopeptidase, cleaves human IgG at the hinge region into $F(ab')_2$ and Fc fragments inhibiting complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity
- IdeS can completely eliminate donor-specific antibodies over a few hours to facilitate transplantation of a kidney from an otherwise HLA-incompatible donor
- risk for rebound of donor-specific antibodies that trigger acute antibody-mediated rejection
- innovative treatment alternative to current desensitization protocols
- possibly a better (rapid) desensitization option for those without a living donor option

Commonly used protocols

- Antibody Production blockade:
  - Rituximab (anti CD20)
- Antibody Removal:
  - Plasmapheresis (TPE) or immunoabsorption
  - TPE x 3 - 5 sessions should remove ~90% of antibody
- Antibody Inhibition:
  - IVIG

Ideally should recheck DSA MFI and CDC/FC Crossmatch prior to transplant

The Cost?

- Increased (initial) costs financially
- Greater risk of rejection (vs HLA compatible transplants)
- Greater risk of infection
- Possible greater risk of malignancy

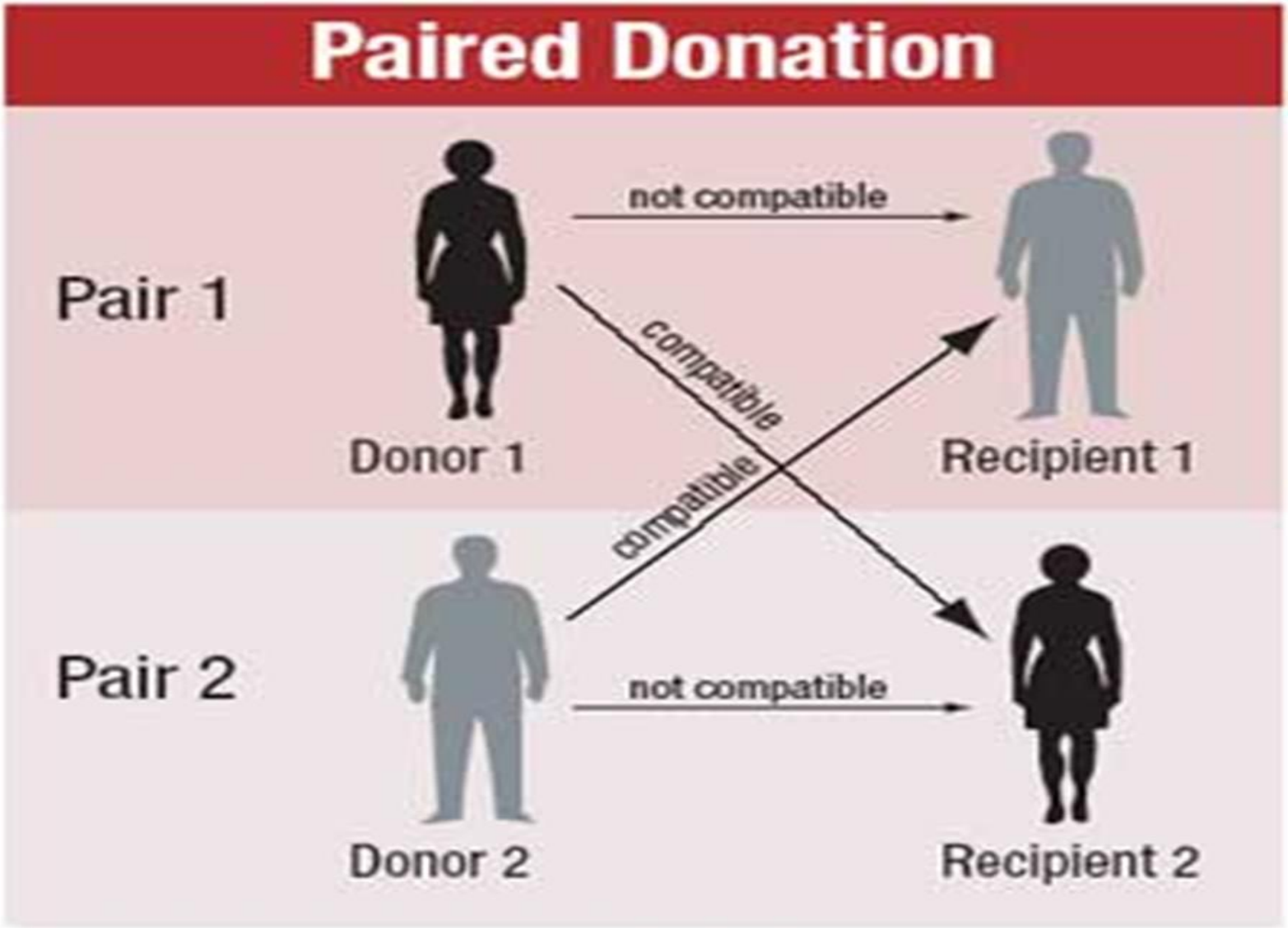
INFECTIOUS complications

- Compared with ABOc-rTX, ABOi-rTx was associated with a higher risk of:
  - Sepsis OR 2.14
  - CMV infection OR 1.27
  - BK Virus Infection 1.59
  - Pneumocystis Pneumonia 2.59
  - But not UTI OR 0.91
- Scurt et al. Lancet 2019, 393, pg 2059-72

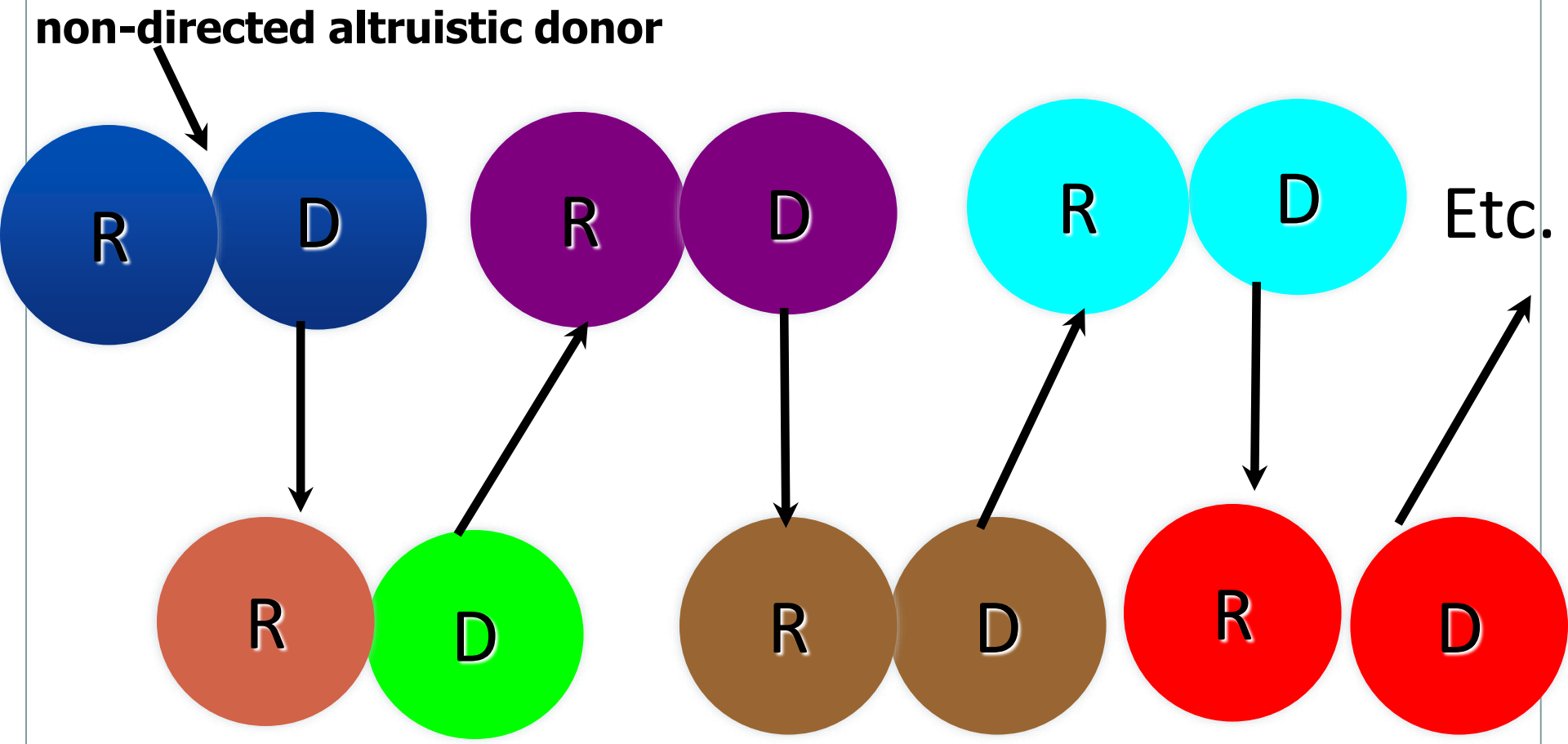
Alternative Strategies
Non-immunosuppressive

- Prioritizing Highly Sensitized Patients
- Paired Donation
- Domino Donation
- Altruistic Donation

Paired Kidney Exchange



Kidney Transplant Chains



Highly Sensitized Patients still disadvantaged

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ORIGINAL ARTICLE

Persistently low transplantation rate of ABO blood type O and highly sensitised patients despite alternative transplantation programs

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Thank you