Strategies for Desensitization

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BC Nephrology Day October 8th 2010

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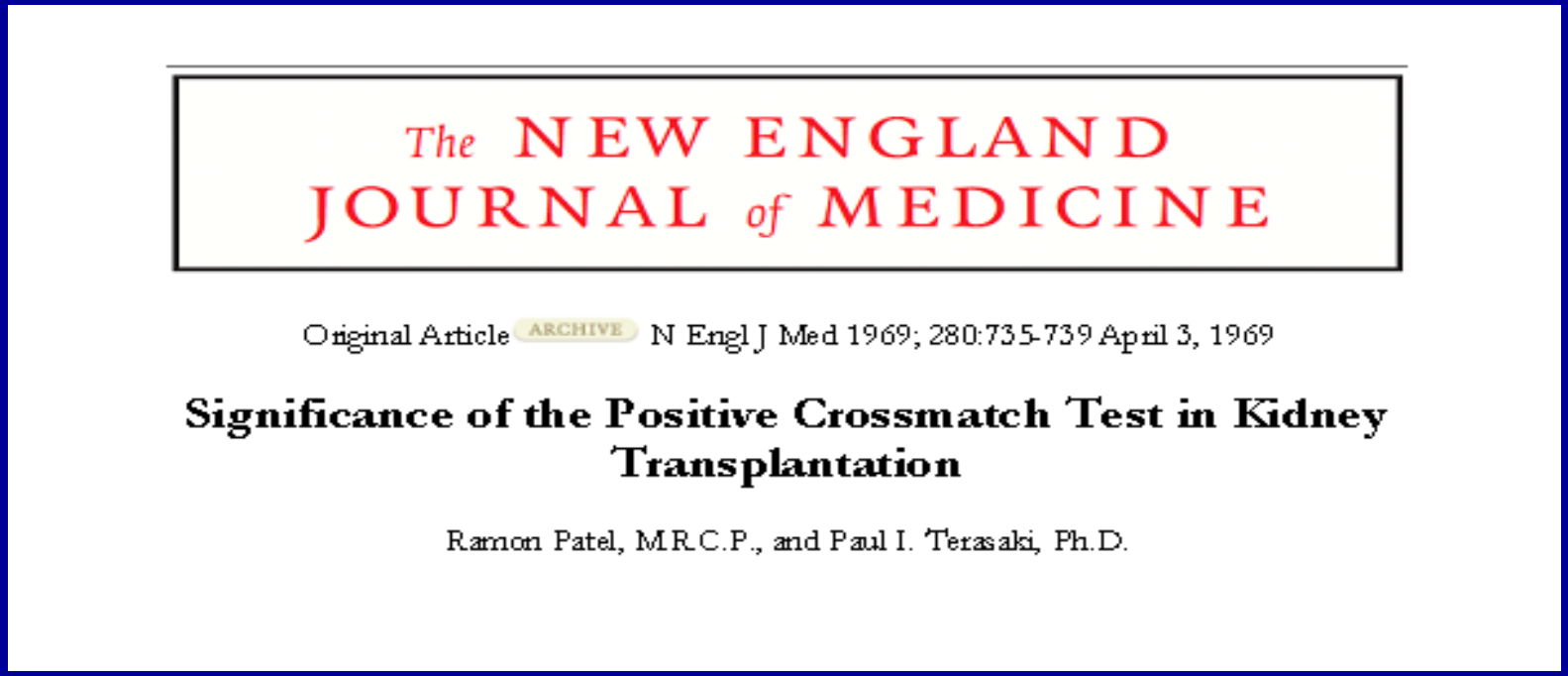


The NEW ENGLAND JOURNAL of MEDICINE

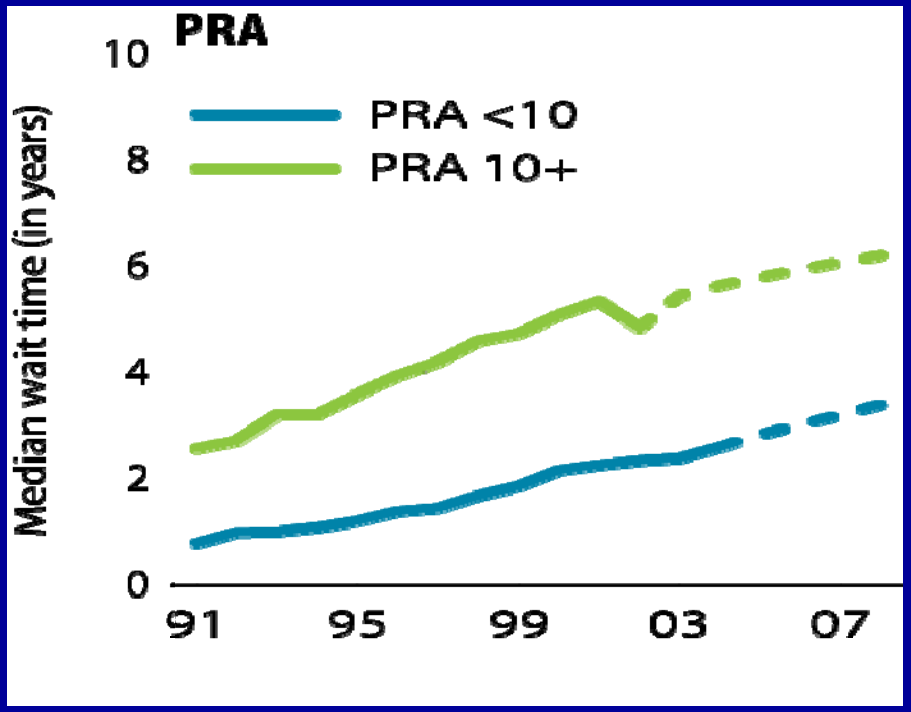
Original Article ARCHIVE N Engl J Med 1969; 280:735-739 April 3, 1969

Significance of the Positive Crossmatch Test in Kidney Transplantation

Ramon Patel, M.R.C.P., and Paul I. Terasaki, Ph.D.

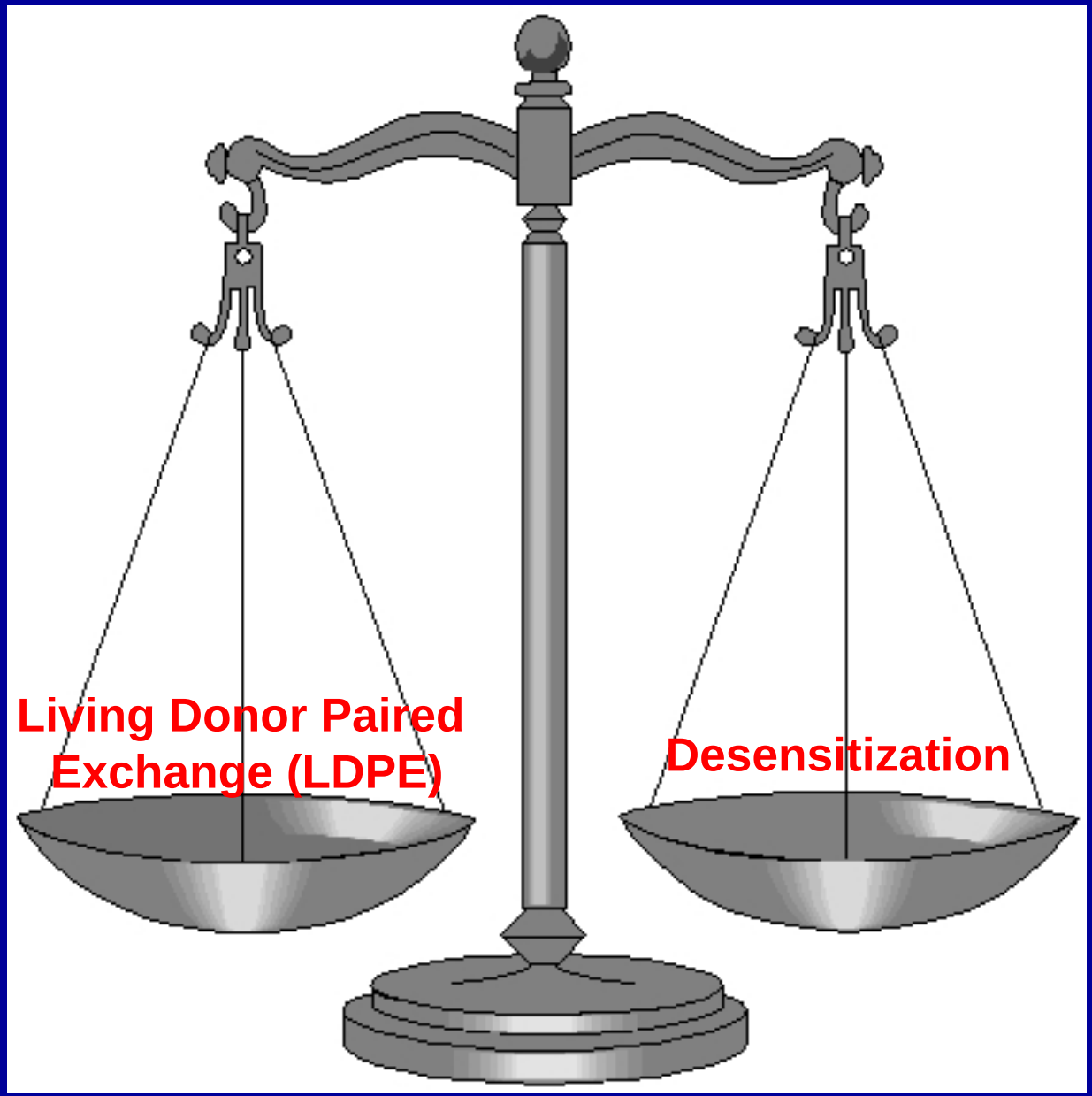
- Pre-transplant crossmatch (CMX) with donor lymphocytes has been standard of practice
- Positive CDC CXM → contraindication to transplant
- Modifications to CXM → increased transplant success rates but relegated increased number of patients to longer waiting times

Sensitization Increases Median Waiting Time



- In U.S. 30% of patients on waiting list are sensitized (transfusion, pregnancy, transplant)
- 6.5% of highly sensitized patients (PRA >80%) receive a transplant per year

US Renal Data System Annual Data Report 2008
OPTN. Scientific Registry of Transplant Patients


Living Donor Paired Exchange (LDPE)
Desensitization

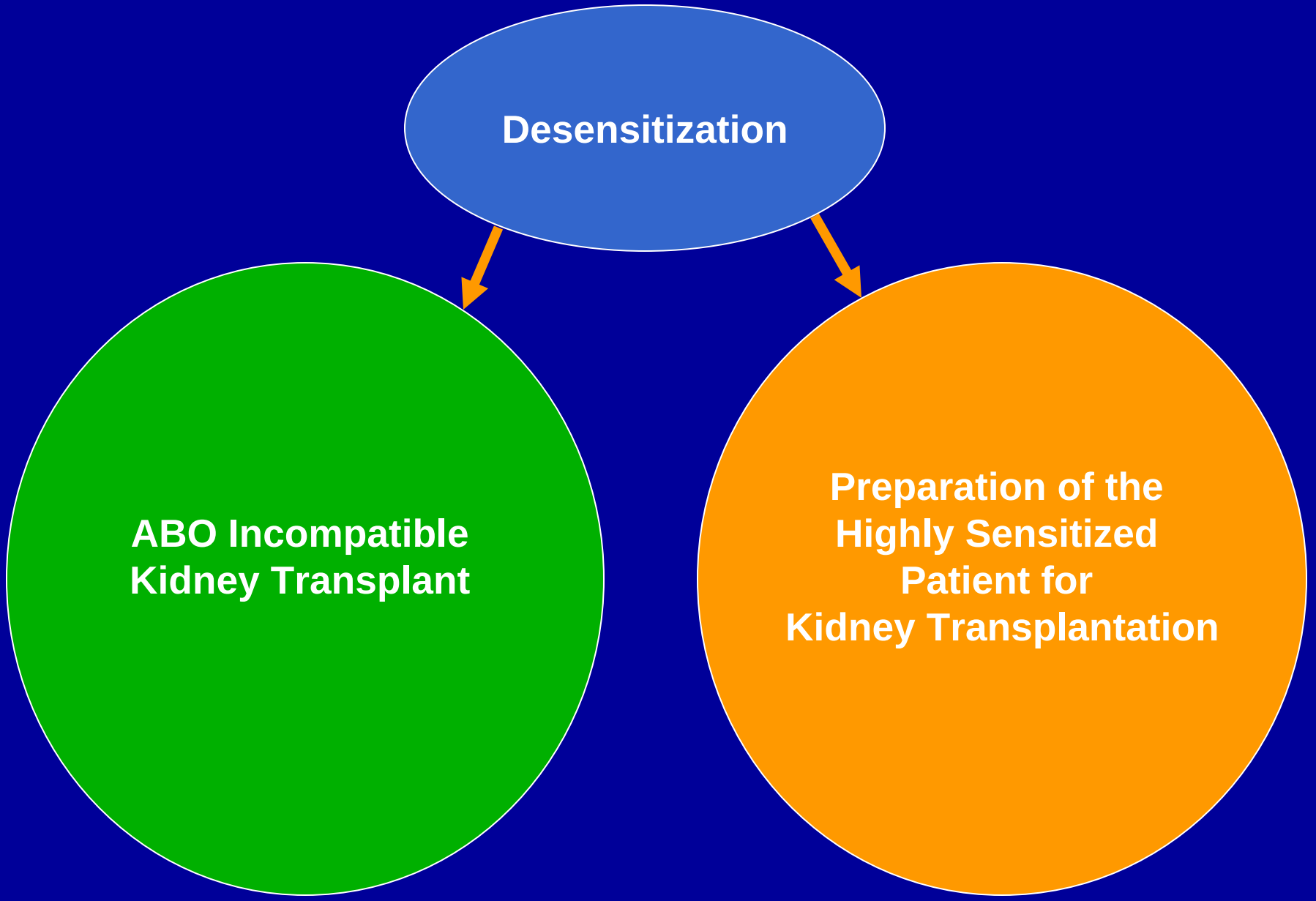
Donor Specific Antibody

Panel Reactive Antigen

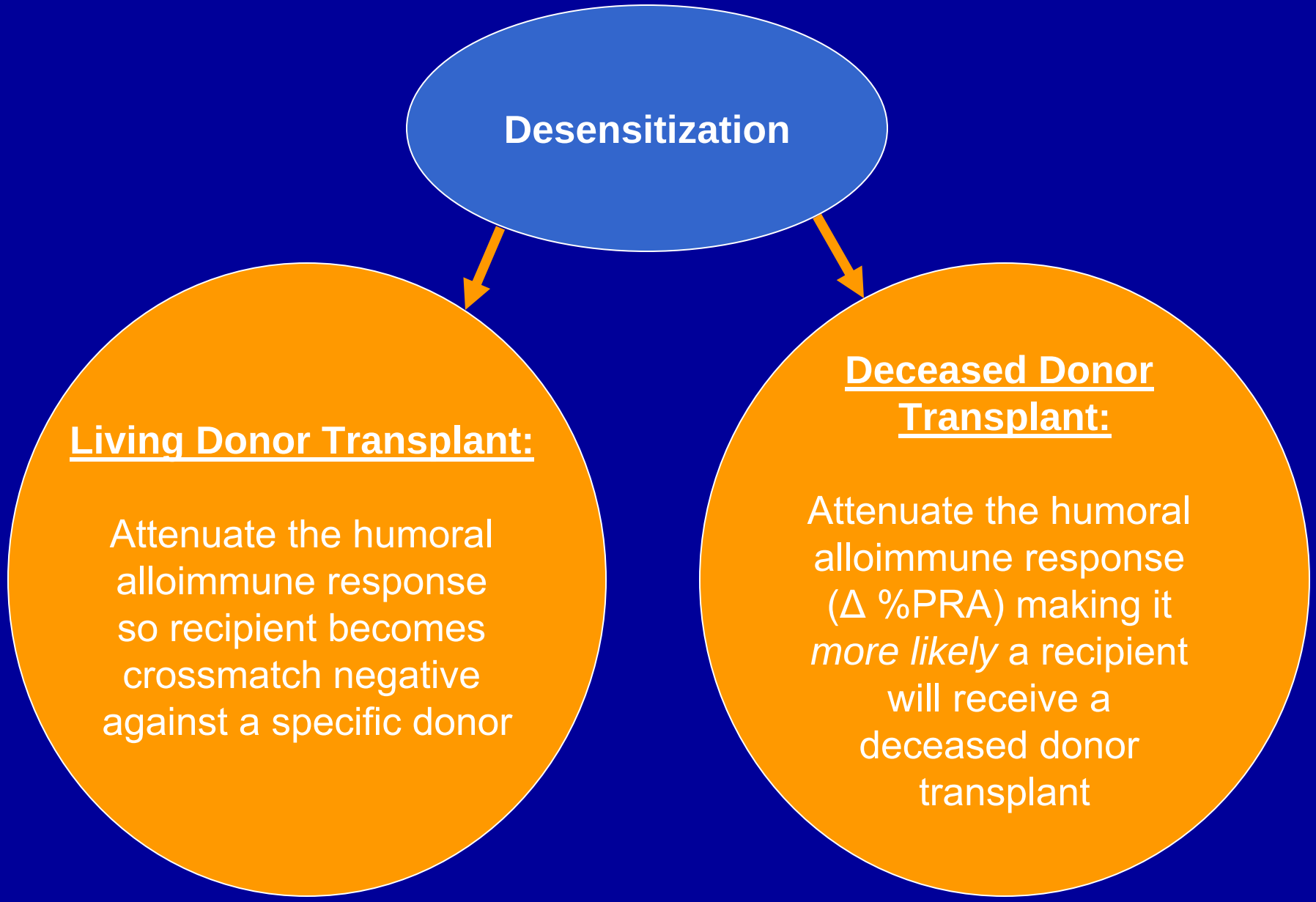
Low DSA **Low PRA** **O Donor** Easy for LDPE and Desensitization	**High DSA** **Low PRA** Difficult for Desensitization
Low DSA **High PRA** LDPE → Desensitization	**High DSA** **High PRA** **AB Donor** Difficult for LDPE and Desensitization (LDPE + Desensit)

Adapted from Segev et al TTS 2010

Definitions

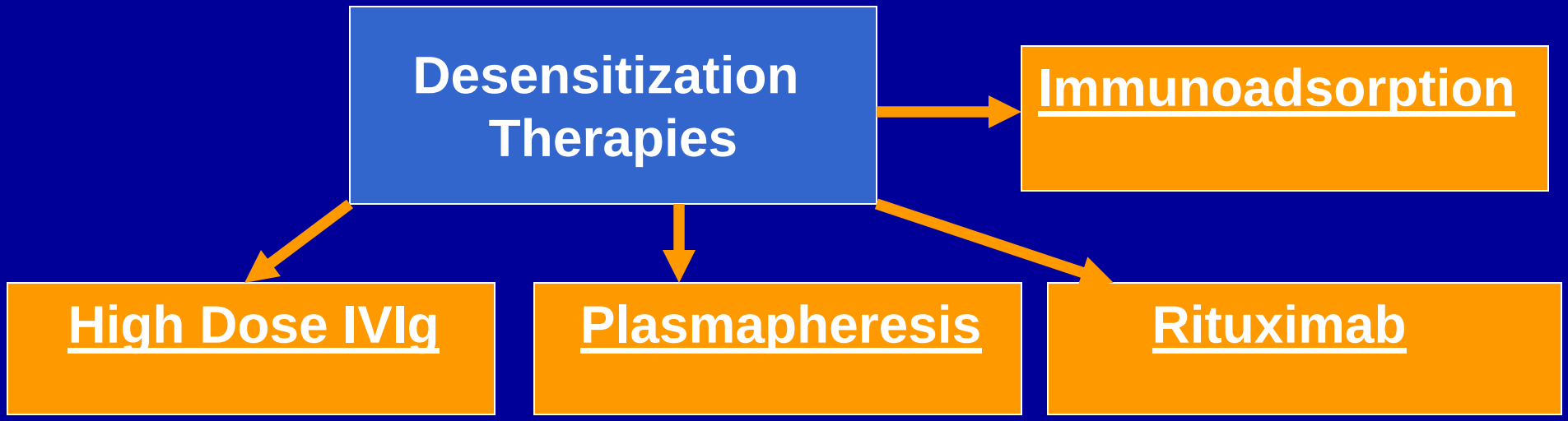


Definitions

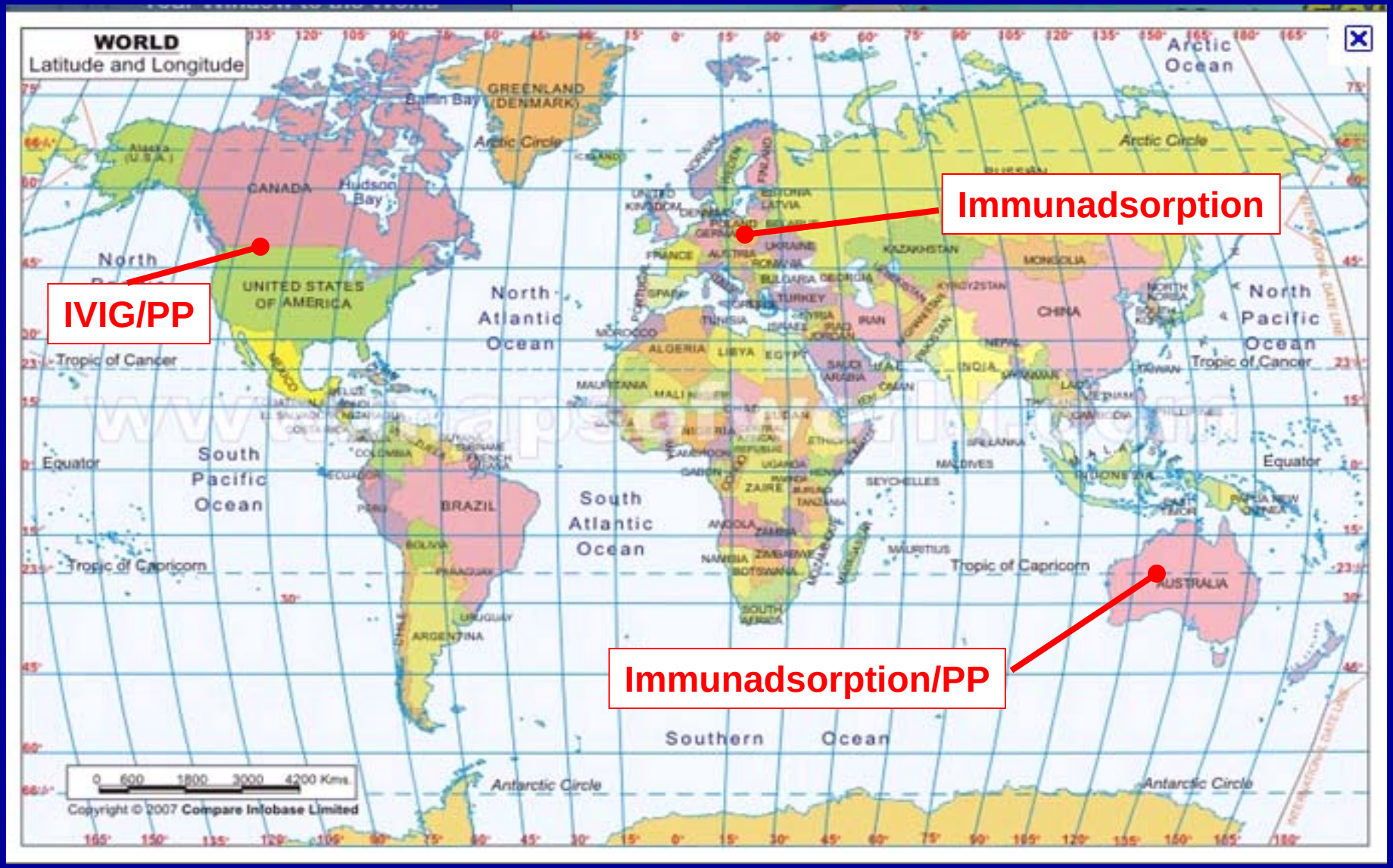


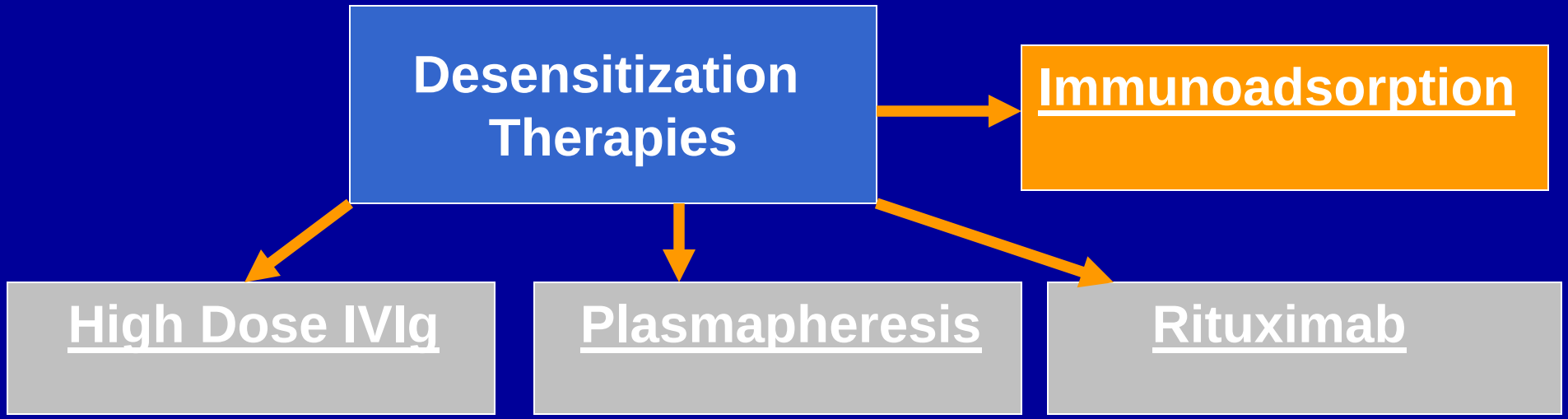
General Approach to Desensitization

1. Remove or neutralize anti- IgG
2. Prevent formation of new anti- IgG before transplantation
3. Transplant when crossmatch (CMX) is negative
4. Prevent formation of new anti- IgG after transplantation
5. Rapidly diagnose and reverse acute AMR if it occurs

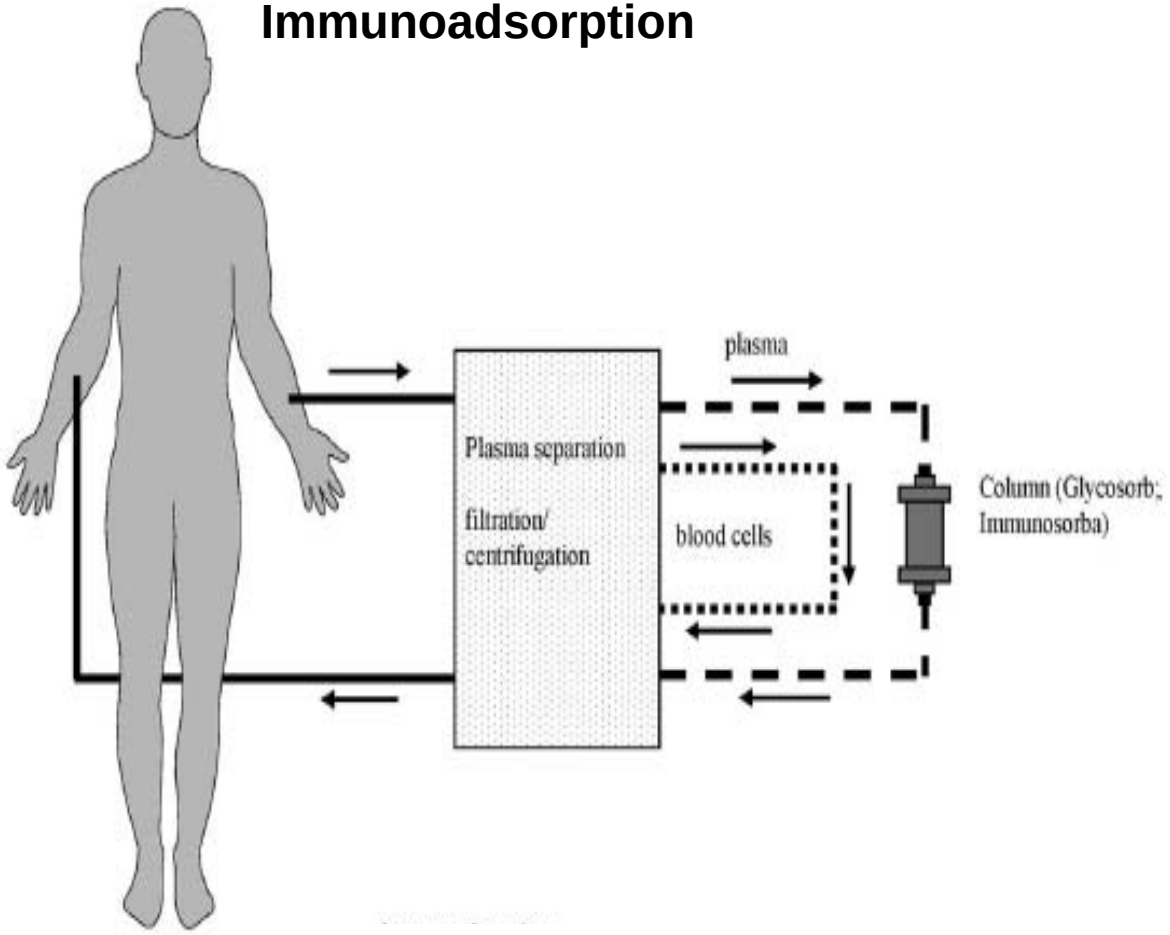

Desensitization Therapies
Immunoadsorption
High Dose IVIg
Plasmapheresis
Rituximab

Desensitization worldwide




Desensitization Therapies
Immunoadsorption
High Dose IVIg
Plasmapheresis
Rituximab

Immunoadsorption



Plasma is separated from whole blood by filtration or centrifugation. The plasma is then processed through an immunoadsorbent column and re-infused to the patient. There are no volume losses and thus no need for replacement fluids.

Advantage of Protein A Column over Plasmapheresis: it only removes IgG

Tyden G. Transplant 2007, 84(s12): s27

Immunoadsorption (IA): Highly Sensitized

- **1996**: Kings College London[1]
  - CXM + → - with IA pre transplant but 70% AR and 53% graft survival at last follow up

- **1990-2003**: Vienna group[2]
  - 40 highly sensitized patients → IA pre and post deceased donor Tx + pre ATG x 10-14d
  - 73% 3-y survival graft survival; 20% cellular AR; 33% humoral AR

[1]Higgins RM. Lancet 1996; 348:1208
[2]Lorenz M. Transplantation 2005; 79:696

Common Desensitization Protocols in US

Desensitization Therapies

Immunoadsorption

High Dose IVIg

- Pooled from multiple donors
- Blocks Fc receptors on mononuclear phagocytes
- Anti-idiotypic effects
- Inhibits CD19 expression on activated B cells
- Inhibits complement
- Inhibits alloreactive T cells

Plasmapheresis

- Plasma separated from whole blood by filtration/centrifugation and discarded
- Replacement of plasma with 5% albumin + isotonic saline/FFP
- Removes anti-HLA antibodies
- Immediately followed by low-dose IVIg

Rituximab

- Chimeric murine/human monoclonal Ab against CD20 Ag on surface of B cells
- Not expressed on plasma cells
- Prevents formation of new alloantibody-producing plasma cells
- Inhibits B-cell driven Ag presentation and costimulation of T cells

Plasma exchange

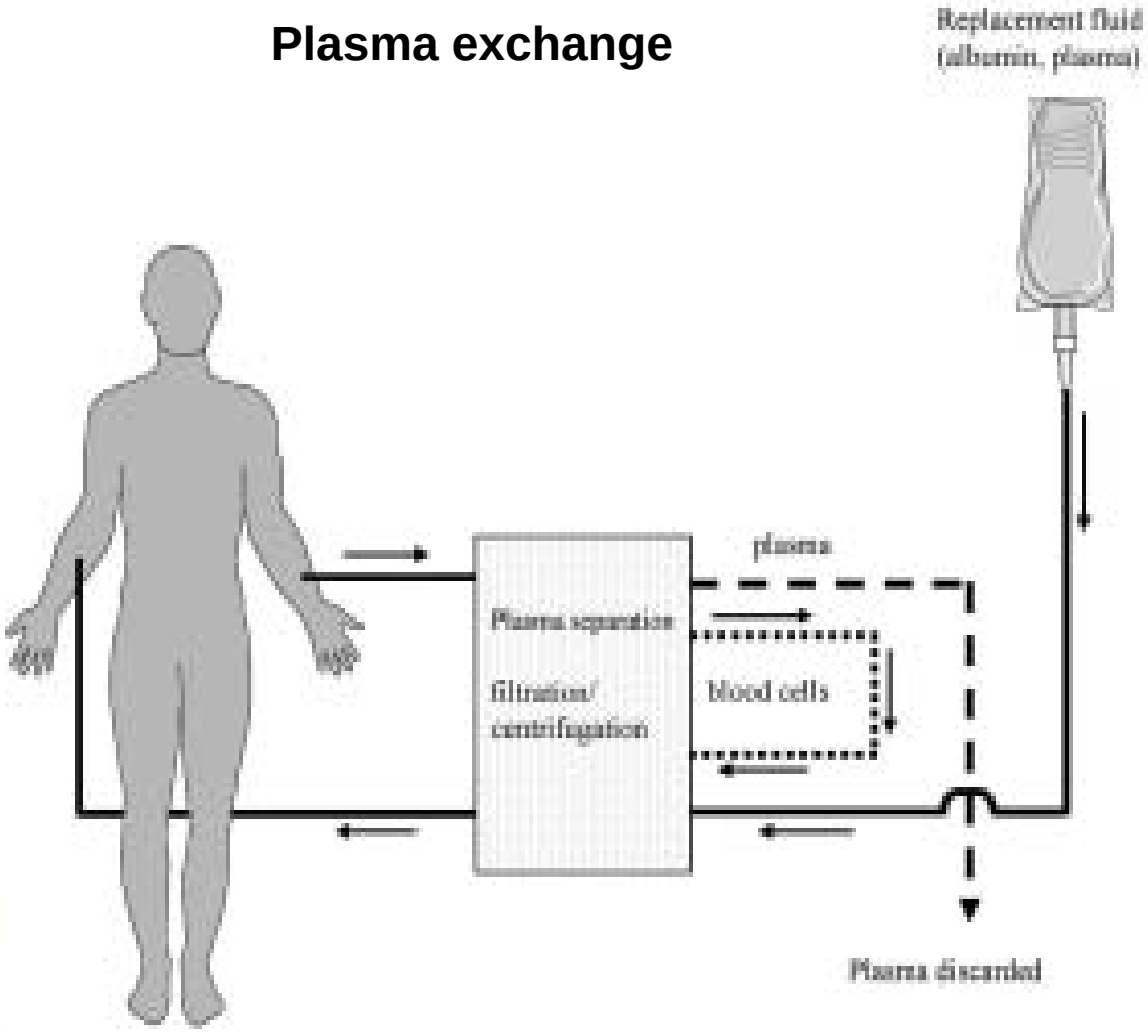


FIGURE 1. Plasma exchange. Plasma is separated from whole blood by filtration or centrifugation and then discarded. The whole plasma volume is replaced by Ringer's solution and albumin and/or fresh-frozen plasma.

Tyden G. Transplant 2007, 84(s12): s27

Double-filtration plasma exchange

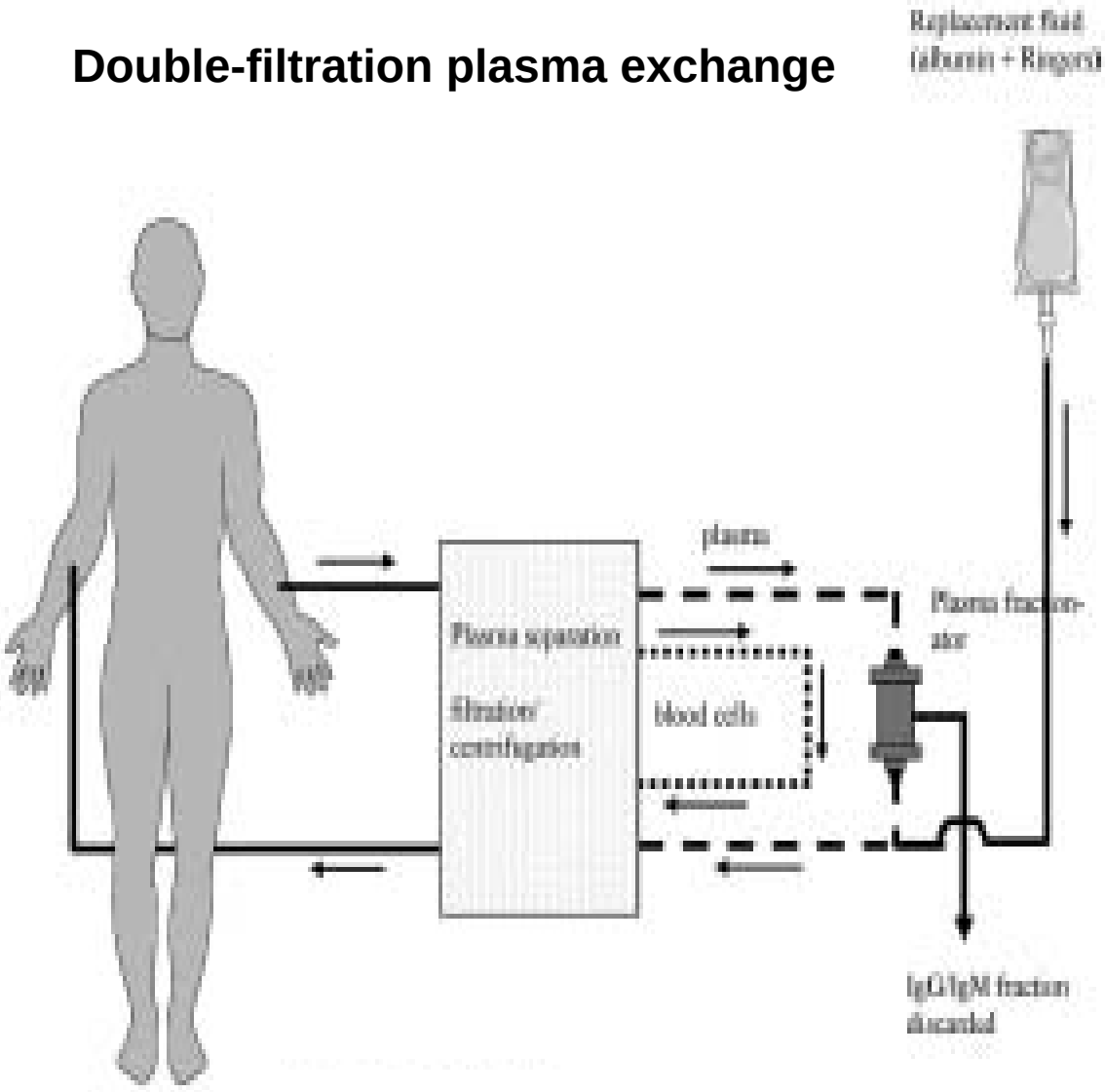
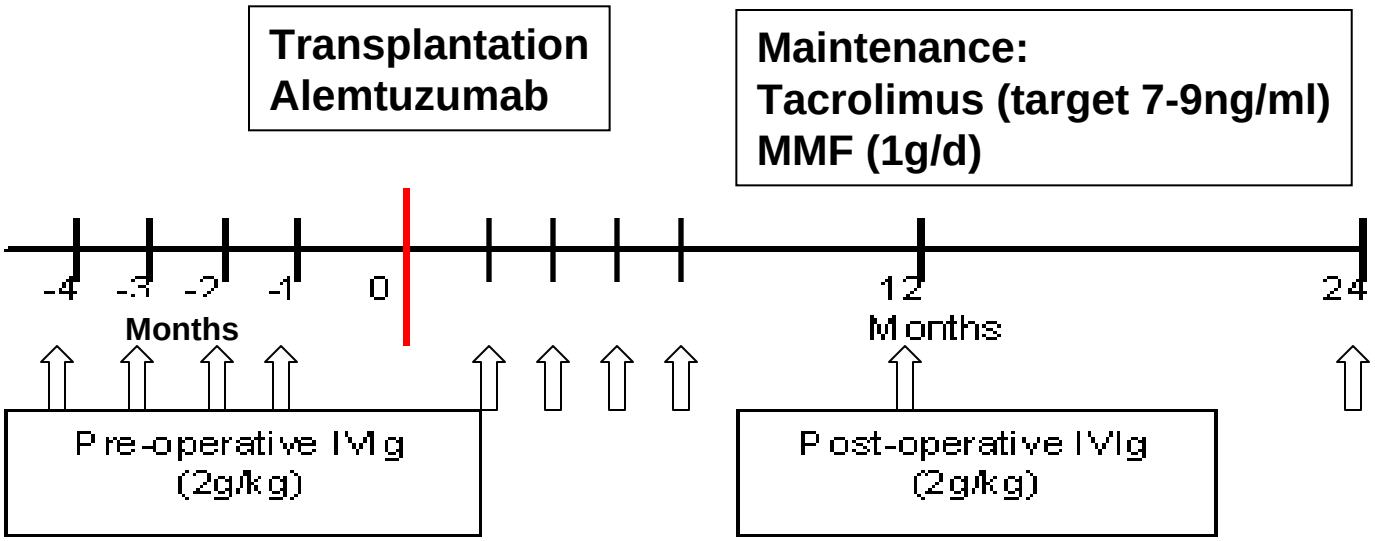


FIGURE 2. Double-filtration plasmapheresis. Plasma is separated from whole blood by filtration. The plasma is then passed through a second filter where substances with molecular weights of 170,000 (IgG) and 1,000,000 (IgM) are filtered out and discarded. Only the volume of the discarded immunoglobulin fraction is replaced by Ringer's solution and albumin.

Tyden G. Transplant 2007, 84(s12): s27

NIH IG02 Study
IVIg is superior to placebo in reducing anti-HLA Ab levels and improving transplantation rates in the highly sensitized

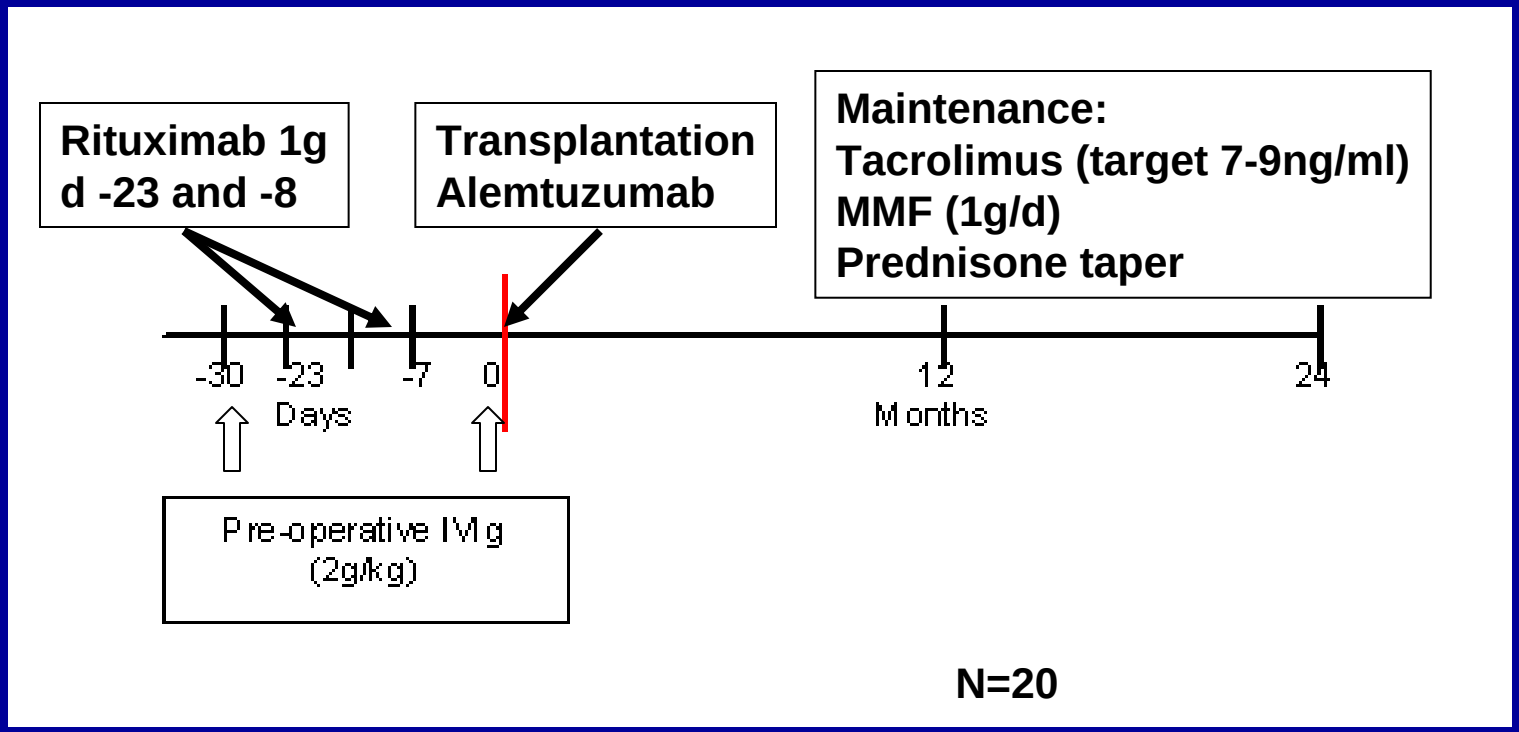


IVIg total dose not >180g

- 35% of IVIg v 17% placebo → transplant
- AR 9/17 IVIg; 1/10 placebo

Jordan SC. JASN 2004, 15:3256

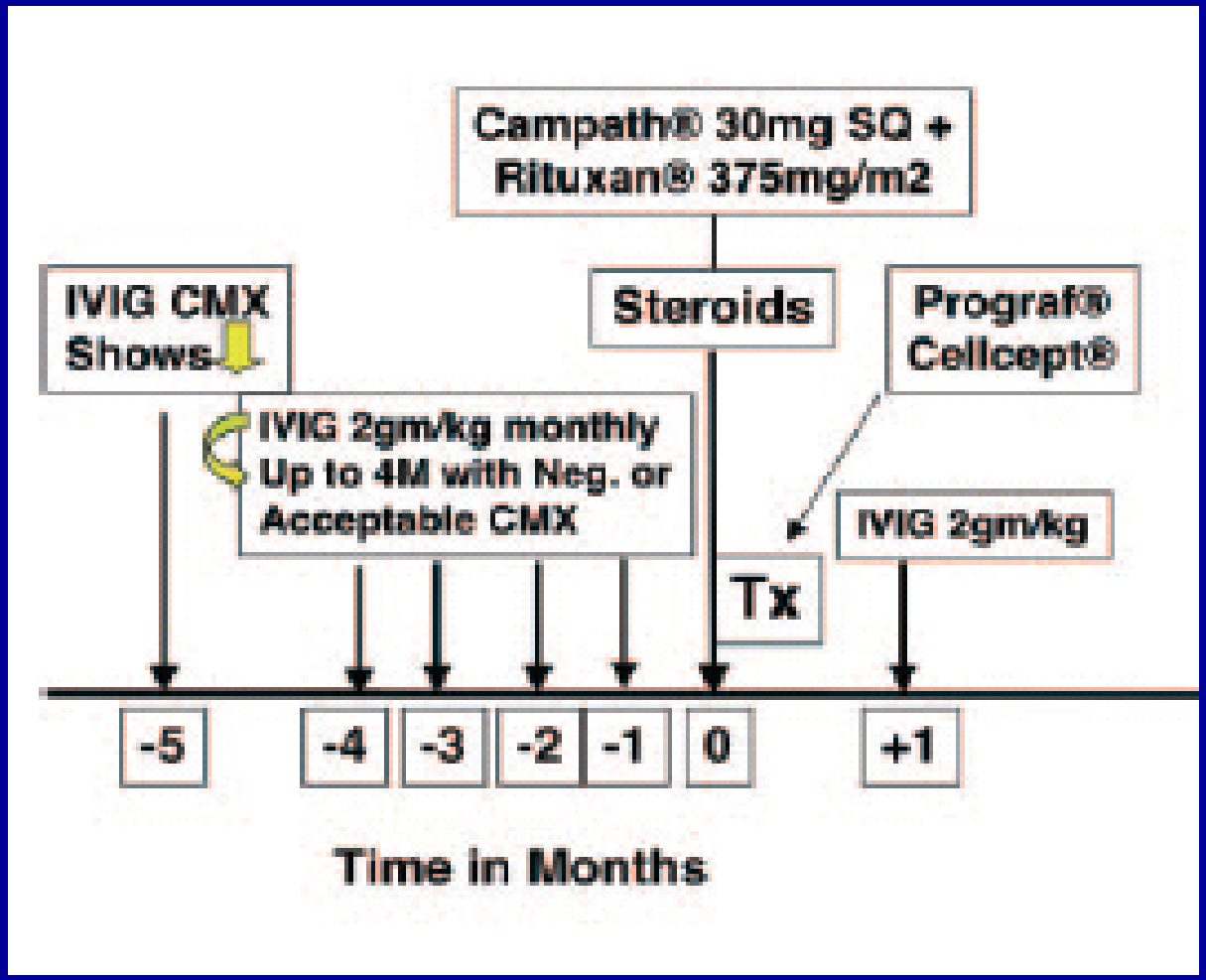
Combining Rituximab and High Dose IVIg Reduces the Total Dose of IVIg



- PRA ↓ to 44% ± 30% (from 77% ± 19%)
- 16/20 transplanted; mean time to transplant = 5±6m
- AR = 50% (31% AMR); patient and graft survival at 1y = 100 and 97%

Vo AA, Jordan SC NEJM 2008, 359:242

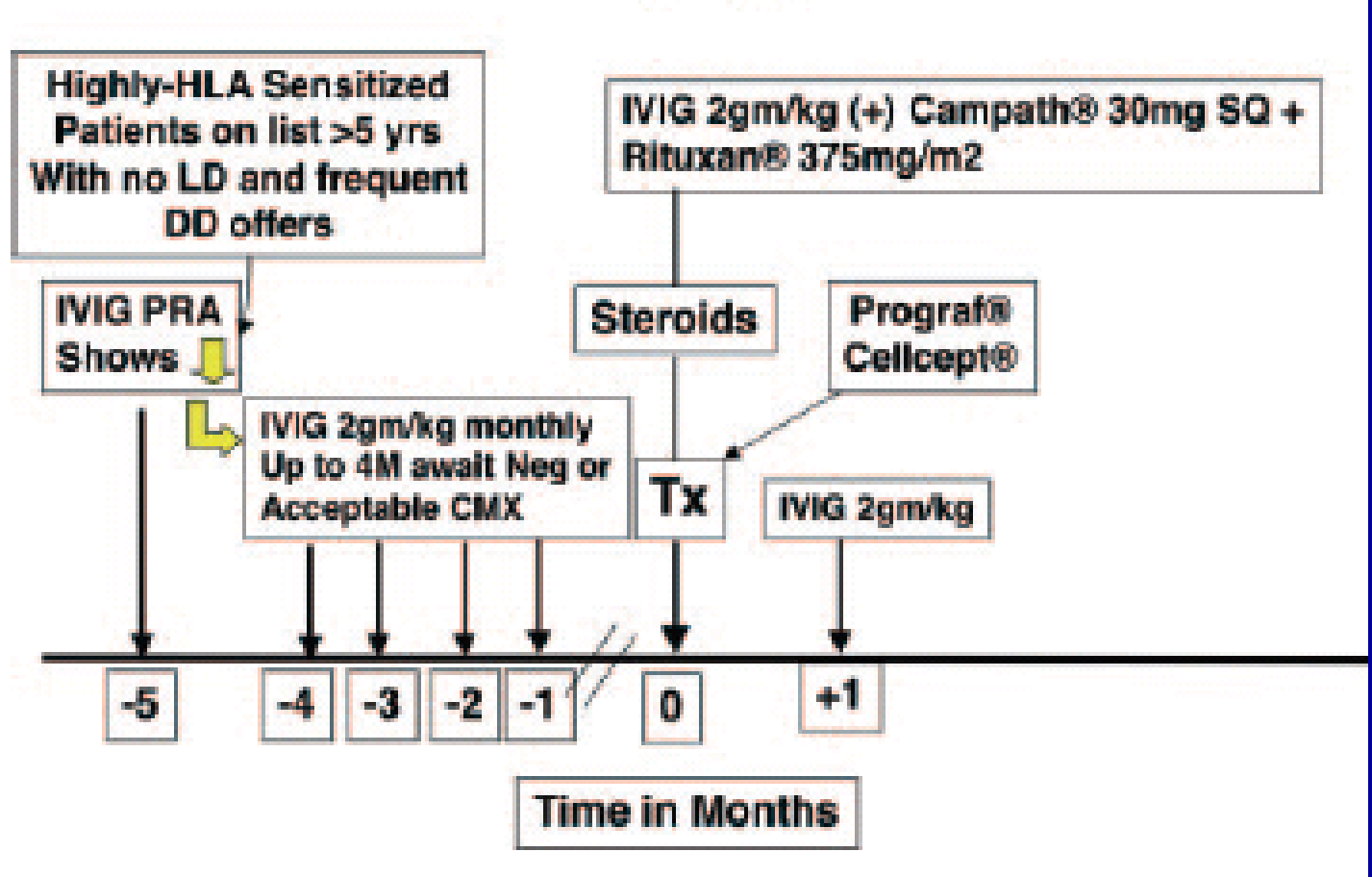
Cedar-Sinai Protocol Using High Dose IVIg : Positive CMX Living Donor Desensitization



IVIg total dose not >140g

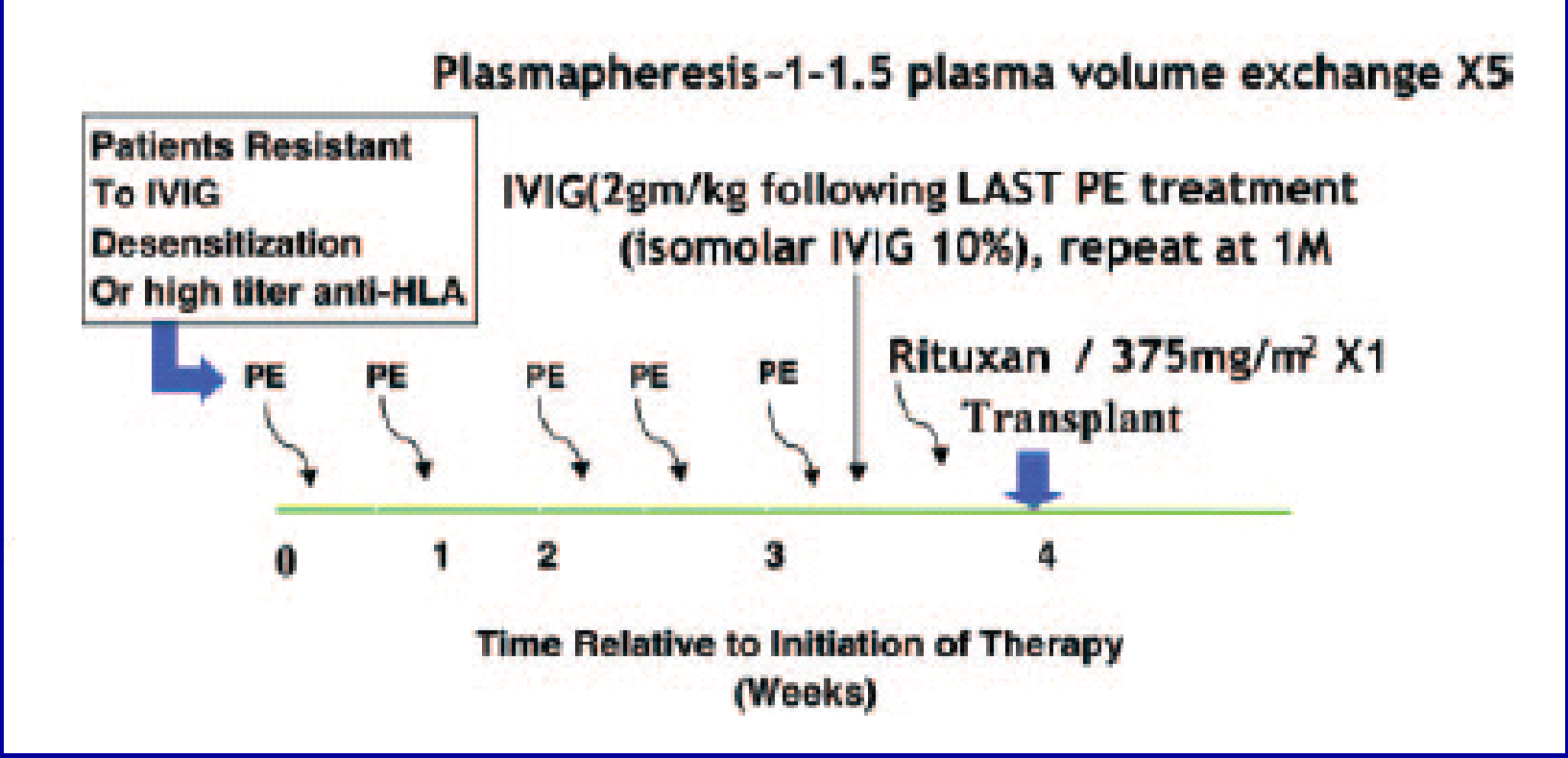
Jordan SC. CJASN 2006, 1:421

Cedar-Sinai Protocol Using High Dose IVIg : Positive CMX Deceased Donor Desensitization



Jordan SC. CJASN 2006, 1:421

Cedar-Sinai Protocol Using High Dose IVIg + Rituximab in Highly Sensitized Patients Resistant to IVIg



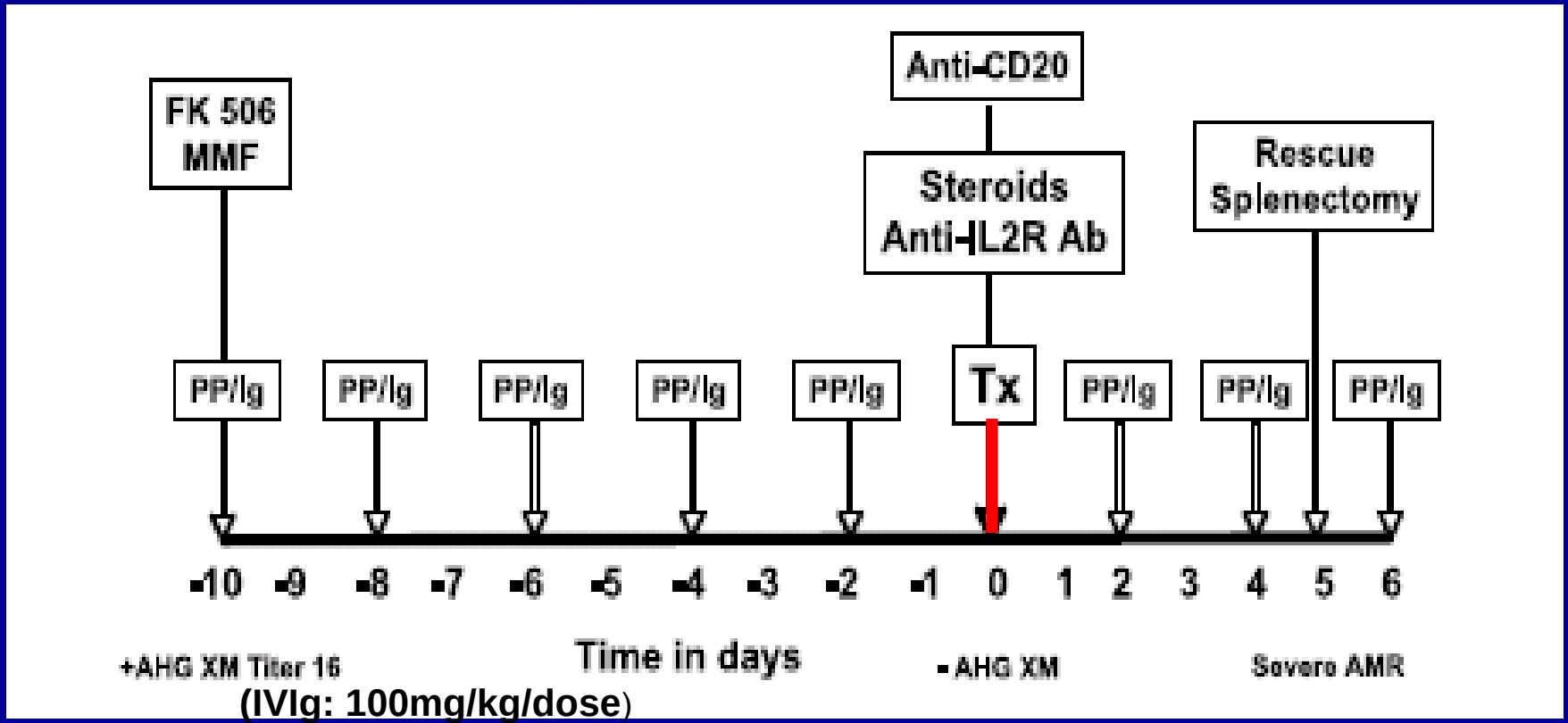
If CMX is negative or acceptable T cell
(flow CMX <250 channel shifts) → Transplantation

IVIg + Rituximab: Rejection and survival

- July 2006 - February 2009: 76 HLA-sensitized (HS) patients received KTX after desensitization using:
  - IVIG 2 g/kg (days 1 and 30)
  - Rituximab (1 g, day 15)
- 76 HS CMX+ treated patients (31 LD/45 DD) → TX
- Significant ↓ in T-cell flow CMXs from pretreatment to time of transplant.
- Time on wait list for DD recipients was ↓ from 95±6 months to 4.2±4.5months after treatment.
- 37% → acute rejection (29% C4d+/8% C4d-).
- Patient and graft survival at 24 months = 95% and 84%.

Vo AA, Jordan SC. Transplant 2010, 89:1095

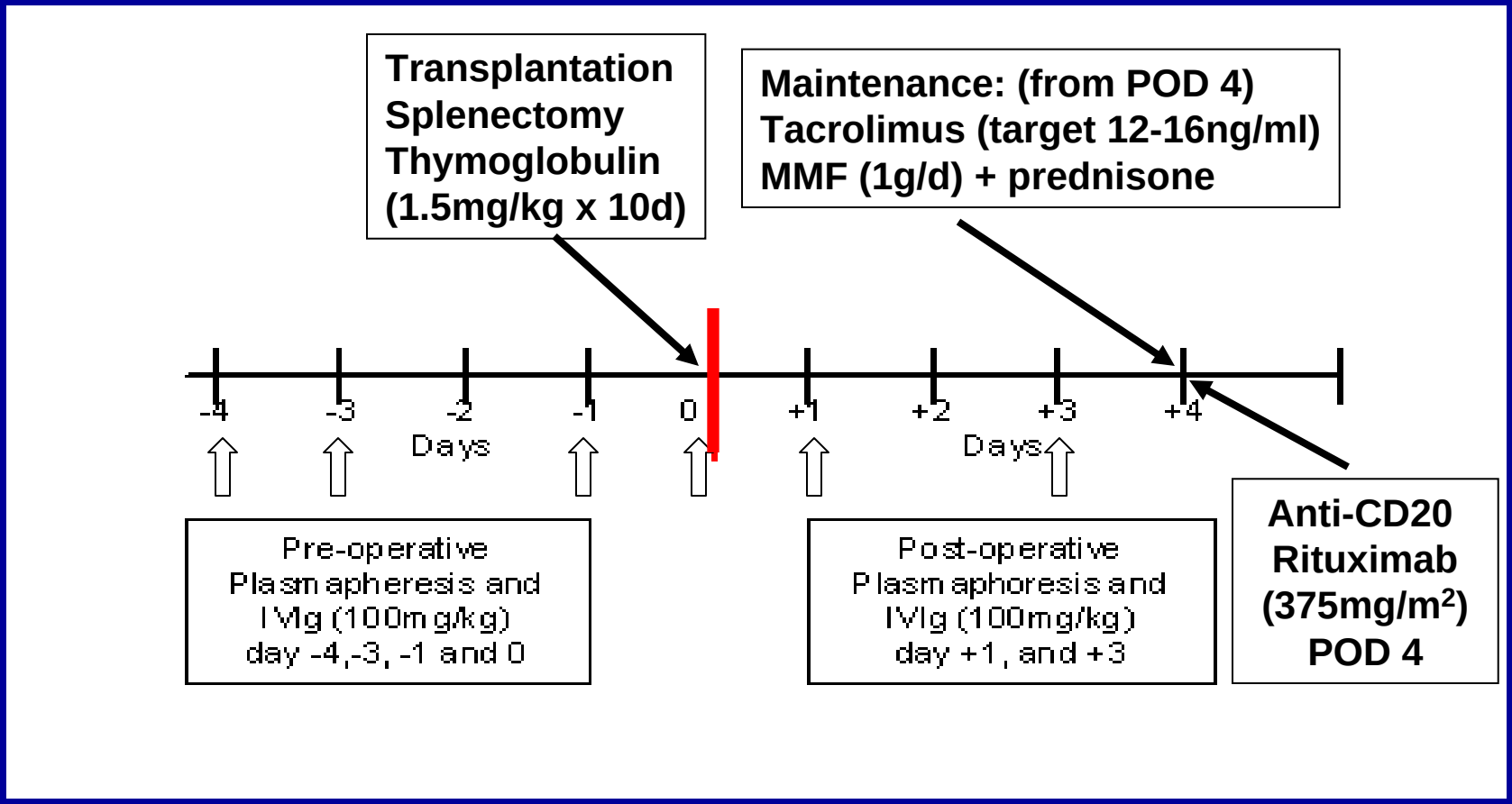
Johns Hopkins Protocol: CXM +



- If recipient begins with a positive AHG CDC crossmatch (+AHG XM) titer of 16.
- Average decrement of one dilution per PP/IVIg. 5 treatments → -AHG XM.
- In selective high-risk cases anti-CD20 given night before transplant.
- Induction includes an anti-IL2 blockade and high-dose steroids.
- Several posttransplant PP/IVIg treatments are performed by protocol.
- About 5% of +XM patients require rescue splenectomy for severe AMR.

Montgomery RA Am J Transplant 2010; 10:449

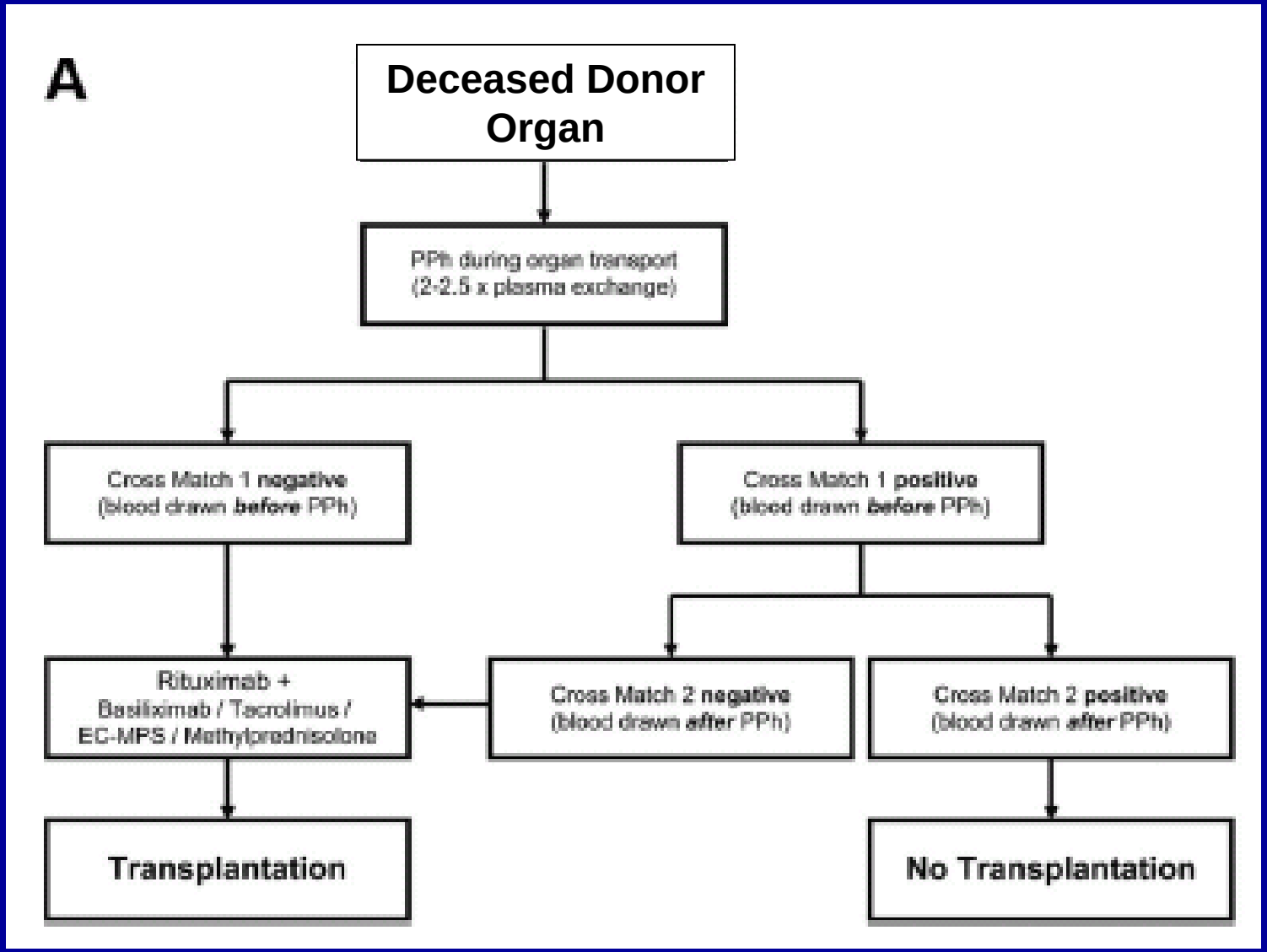
Mayo Clinic Protocol



- N=14 + CXM to living donor
- AMR 29% but all reversible

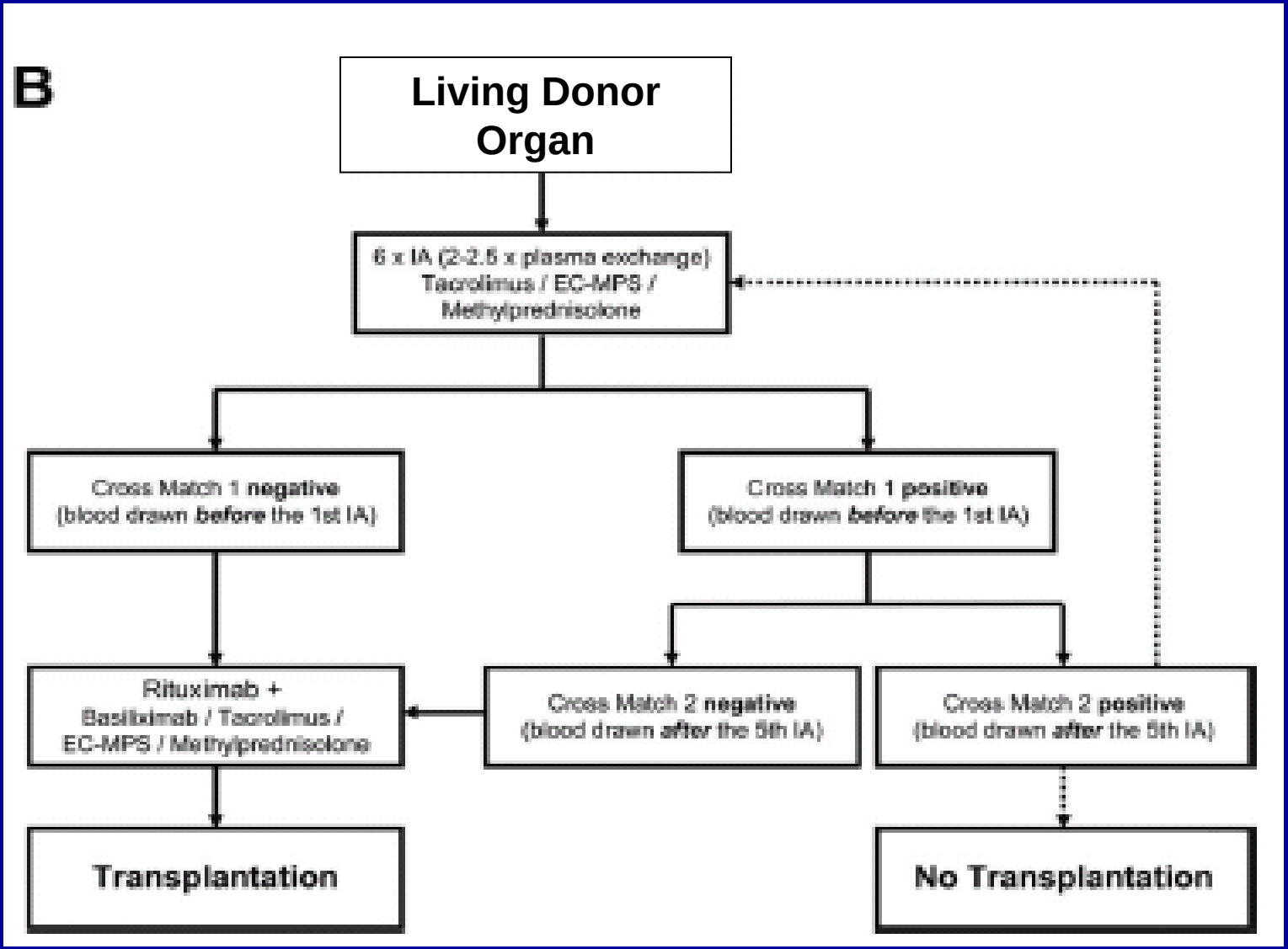
Gloor JM. AmJTransplant 2003, 3:1017

Eurotransplant Algorithm Highly Sensitized



Morath C Transplant 2010, 90:645

Eurotransplant Algorithm: Highly Sensitized



Morath C Transplant 2010, 90:645

High-Dose IVIg vs. PP + CMV-Ig

High-Dose IVIg

Advantages:

- Less expensive
- Success in living and deceased donor transplant
- Easy and safe (dialysis)
- Long-lasting desensitization in most cases

High-Dose IVIg

Disadvantages:

- Non- and incomplete responders (approx 10%)
- May interferes with DSA assays
- Antibody removal slower vs. PP + CMV-Ig
- Some IVIg products have toxicity (sucrose, saline)
- Fever, chills, H/A, anaphylaxis, thrombosis, nephrotoxicity (use isotonic)

High-Dose IVIg vs. PP + CMV-Ig

PP + CMV-Ig

Advantages:

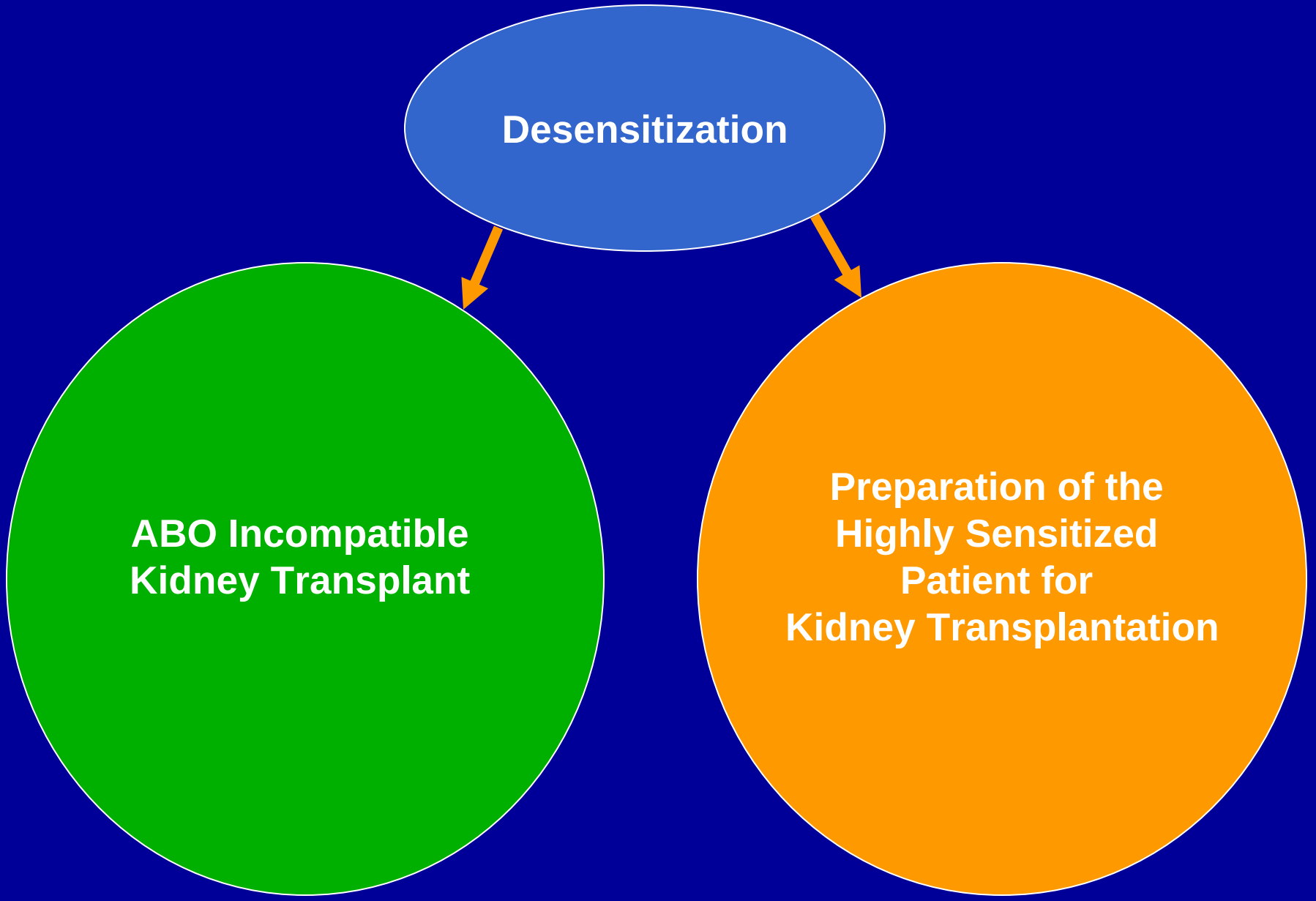
- Highly effective
- Few non-responders
- DSA easy to follow
- Kinetics of DSA removal predictable
- Also removes anti-ABO-A or anti-ABO-B antibodies allowing potential transplantation across 2 incompatible barriers

PP + CMV-Ig

Disadvantages:

- Expensive
- Labor intensive
- Not useful if no living donor
- DSA can return post transplant
- Transplant must follow treatment or possible rebound
- Depletion of clotting factors, hypocalcemia, fever, chills

Definitions



Johns Hopkins Protocol: ABO incompatible

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

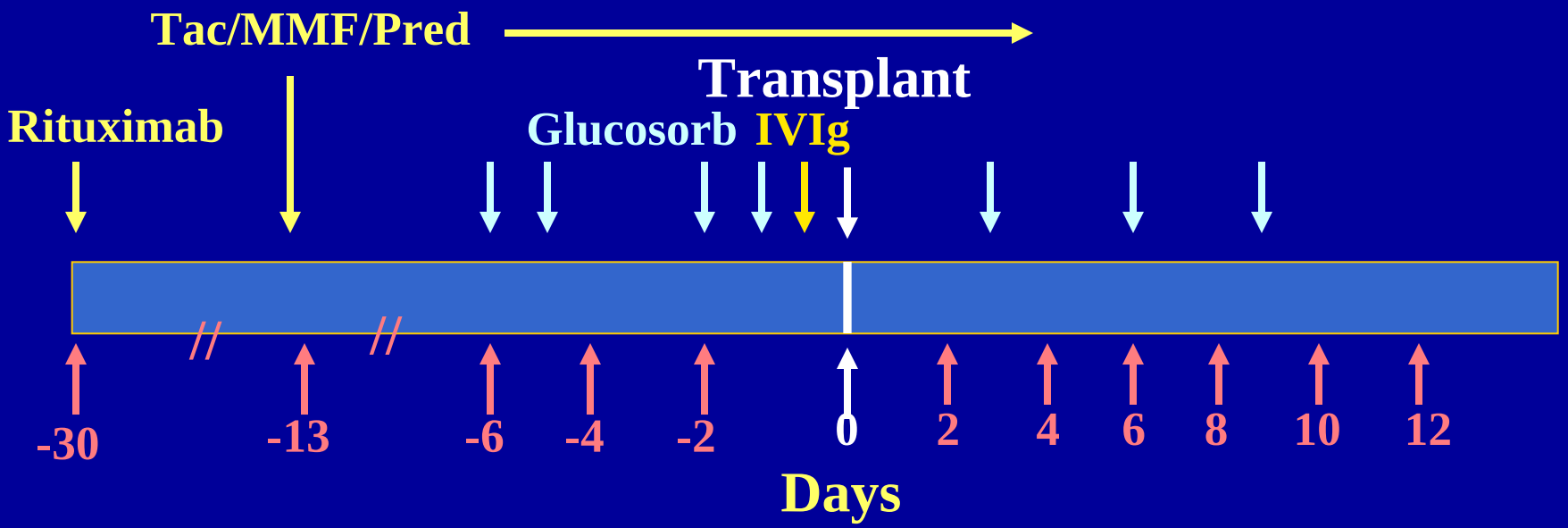
Starting isoagglutinin AHG titer	Pretransplant PP/IVIG treatments	Posttransplant PP/IVIG treatments
<16	2	2
16–32	3	2–3
64	4	3
128	5–6	4
256	7–8	4
512	9–10	5
>512	>10	6

PP, plasmapheresis; AHG, anti-human globulin.

- **Pre-op:** Alt day PP (COBE Spectra centrifuge-driven cell separator) → CMVIg (100mg/kg) and FK506 + MMF at time of 1st PP/CMVIg as per table
- Goal AHG titer ≤ 16 at time of Tx
- **Peri-op:** Steroids and daclizumab, hold FK506 am of surgery
- **Post-op:** FK506/MMF/steroids (wean to 20mg/d at d/c)
- Alt day PP/CMVIg as per table if titers fail to fall
- Protocol bx at 1, 3, 6, 12 months; 15%→ AHR; survival = other LRD Tx

Montgomery RA Transplantation 2009; 87(8):1246

Swedish Protocol: ABO Incompatible

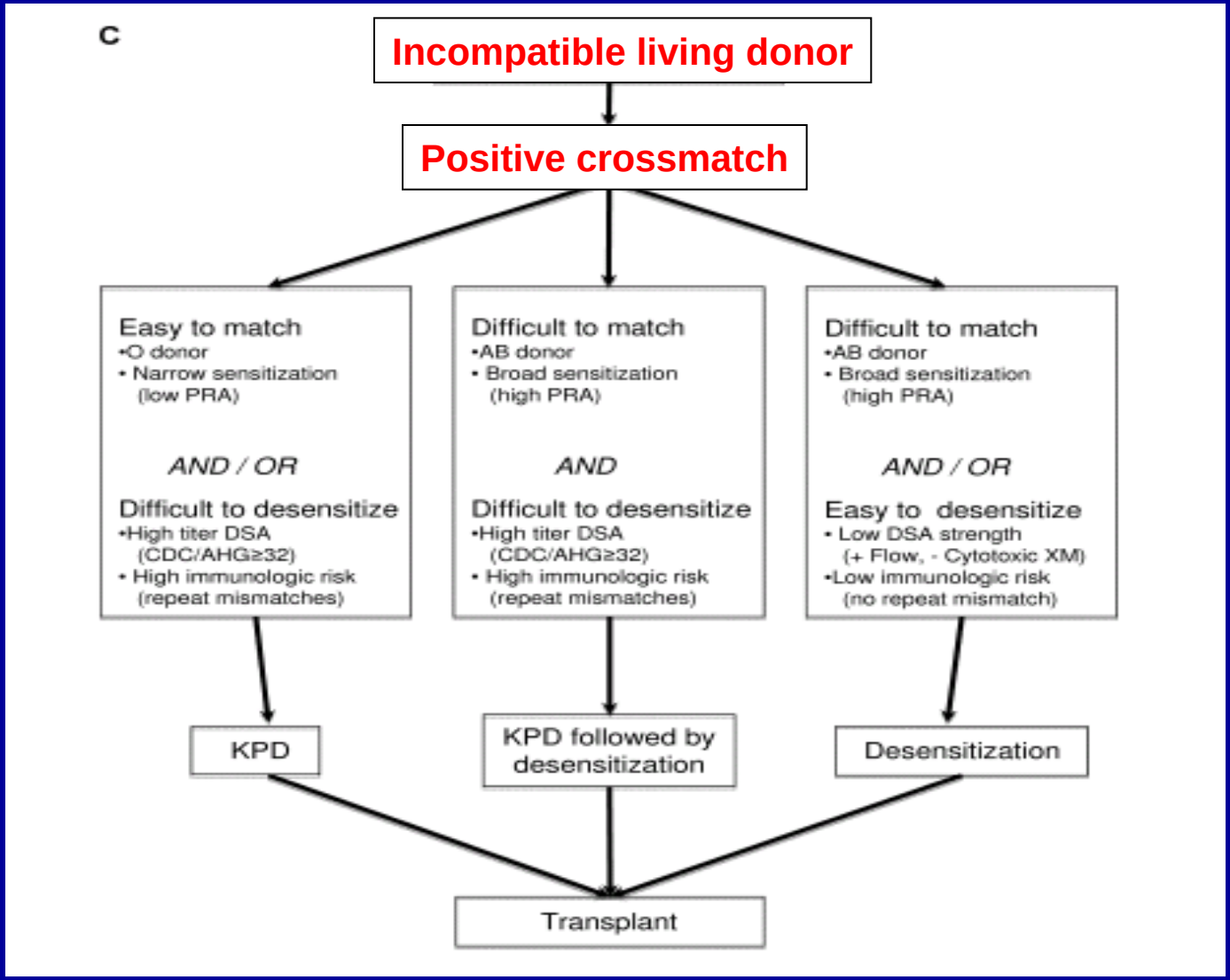


- **Pre-op:** Rituximab (375mg/m2) d-30; Tac/MMF/Pred d-14
- Glucosorb IA d-6, -5, -2, -1 to target IgG titer <1:8 (if target titer not achieved 4 more IA over 1 w pre-op or IVIg (0.5g/kg) after last IA)
- **Post-op:** Glucosorb IA d 3, 6 and 9 with additional IA if titers >1:16

- Restricted to patients with titers <1:128
- 3-y outcomes equivalent to LRD; no ↑ AR

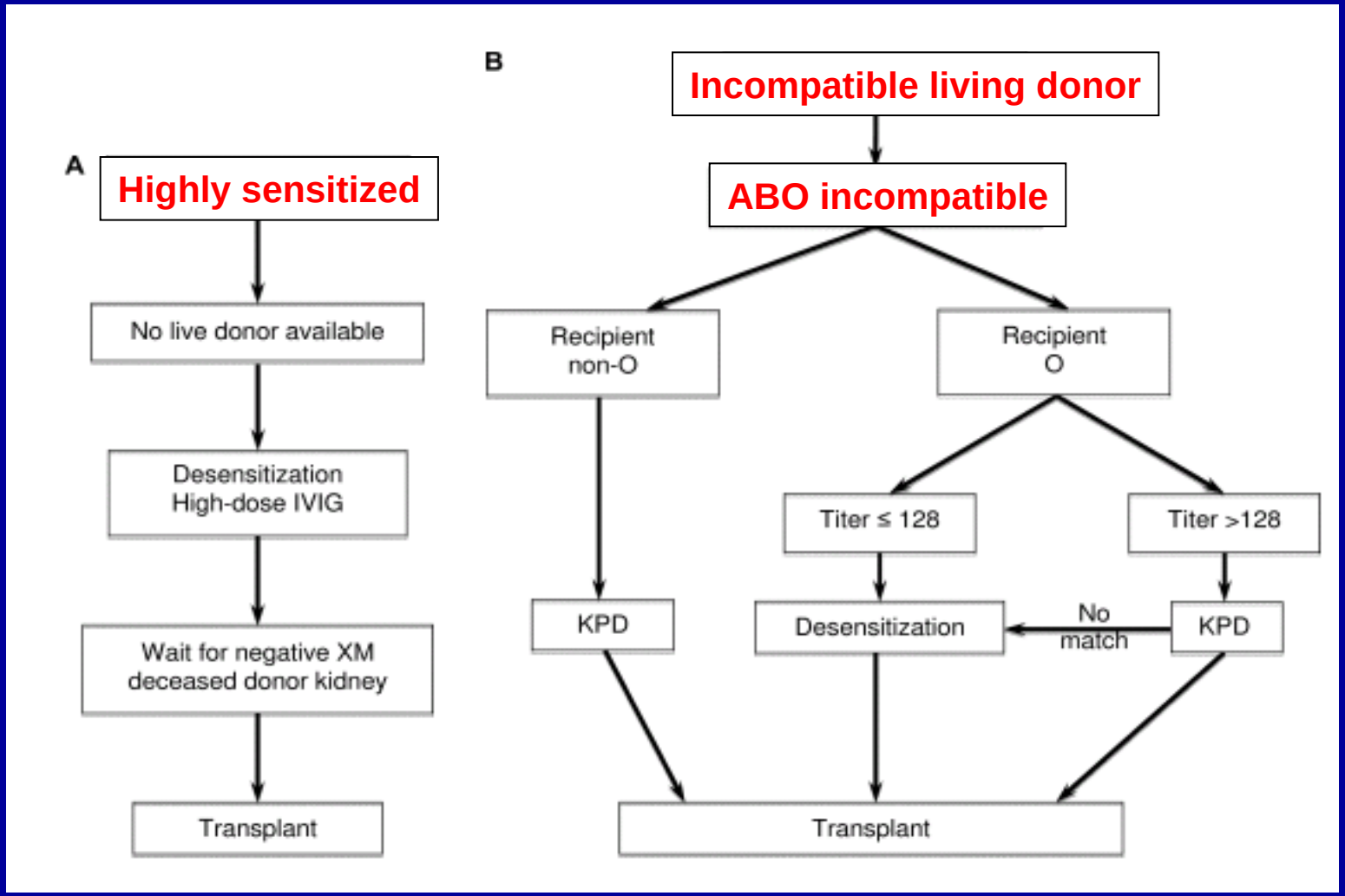
Genberg H Transplant 2008; 85:1745

Desensitization versus LDPE



Montgomery RA Am J Transplant 2010; 10:449

Desensitization versus LDPE



Montgomery RA Am J Transplant 2010; 10:449

Summary and Conclusion

- High dose IVIg, although slower to remove Abs, is an effective desensitization modality for both living and deceased donor transplantation.
- Combined PP + IVIg is highly effective for both HLA and ABO incompatibility but is expensive, time consuming and is not useful unless a transplant is imminent.
- Both protocols have favorable results in reducing transplant waiting time for highly sensitized ESRD patients
- For highly sensitized patients with a living donor: should try LDPE first and if fails then resort to desensitization. For highly sensitized patients with no donor → National Highly Sensitized Registry.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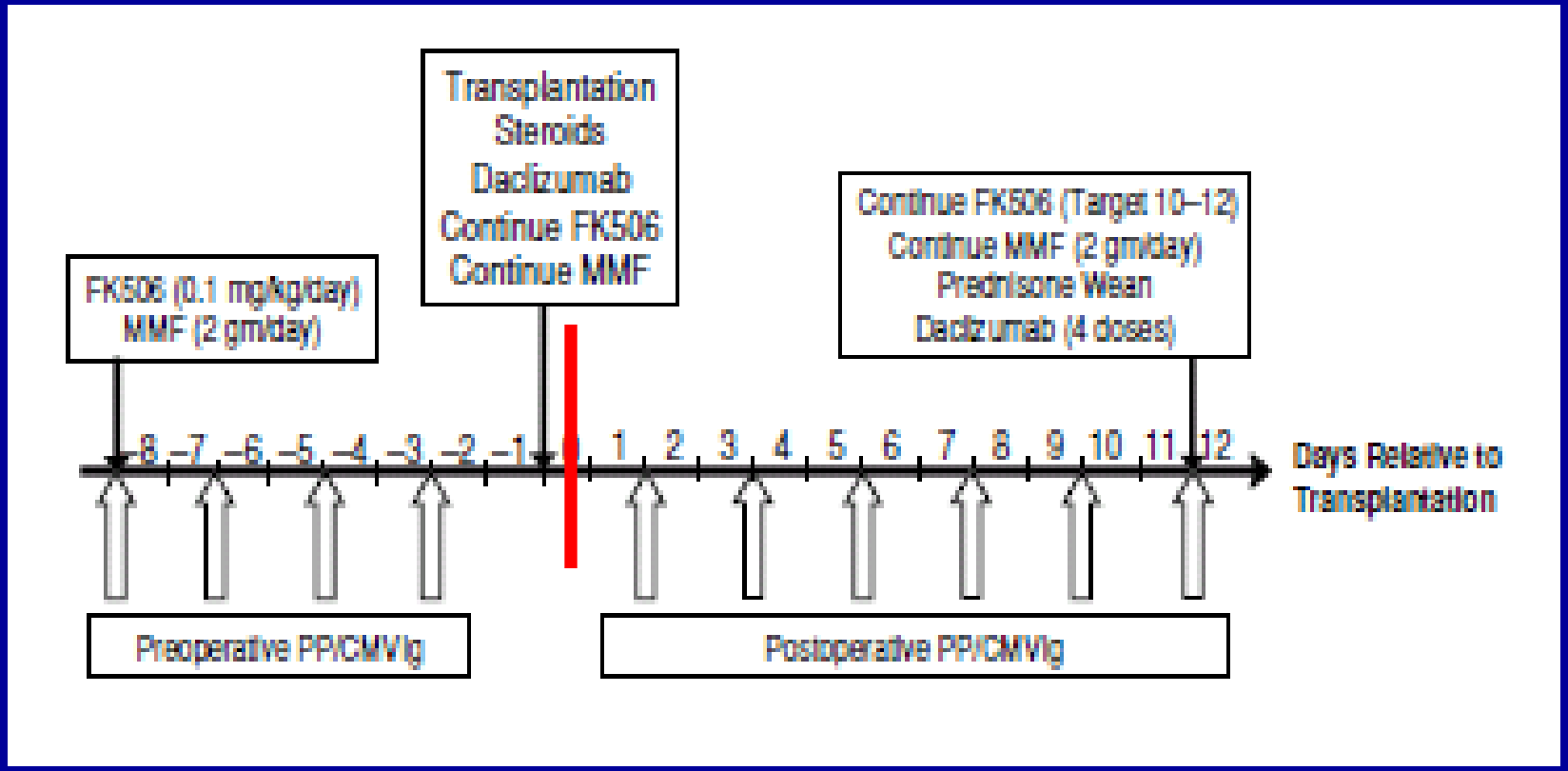
Johns Hopkins Protocol



Original Protocol: Montgomery RA. Transplantation 2000, 70(6):887

- Splenectomy at transplantation in high risk or ABOi patients
- Superseded by antiCD20 (375mg/kg) night pre-transplant

Segev DL AmJTransplant 2005, 5:2570

New Protocol: neither Abstract # 1319 ATC, Boston 2009