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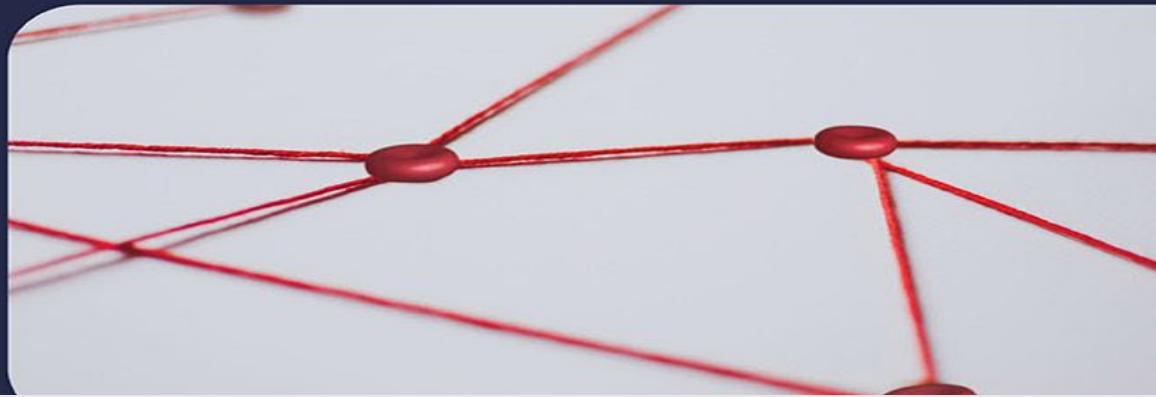
ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ

10th Hellenic Haemapheresis Association Conference



Therapeutic apheresis in renal transplantation

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NKUA Medical School , Laiko Hospital, Greece

Journal of Clinical Apheresis: Volume 3, Issue 1

Special Issue: Clinical Applications

Pages: fmi, i-VI, 1-92

1986

→ Rejection in Kidney transplantation

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Ninth Special Issue

L Connelly-Smith et al. J Clin Apher. ***2023****;38:77–278*

Therapeutic apheresis (TA) and kidney transplantation

Disease/condition	Indication	Procedure	Category	Grade
Transplantation, kidney, ABO compatible	Antibody-mediated rejection	TPE/IA	I	1B
	Desensitization/prophylaxis, living donor	TPE/IA	I	1B
Transplantation, kidney, ABO incompatible	Desensitization, living donor	TPE/IA	I	1B
	Antibody mediated rejection	TPE/IA	II	1B
Focal segmental glomerulosclerosis	Recurrent in kidney transplant	TPE/IA	I	1B

L Connelly-Smith et al. J Clin Apher. ***2023****;38:77–278*

Therapeutic apheresis techniques performed in the setting of kidney transplantation

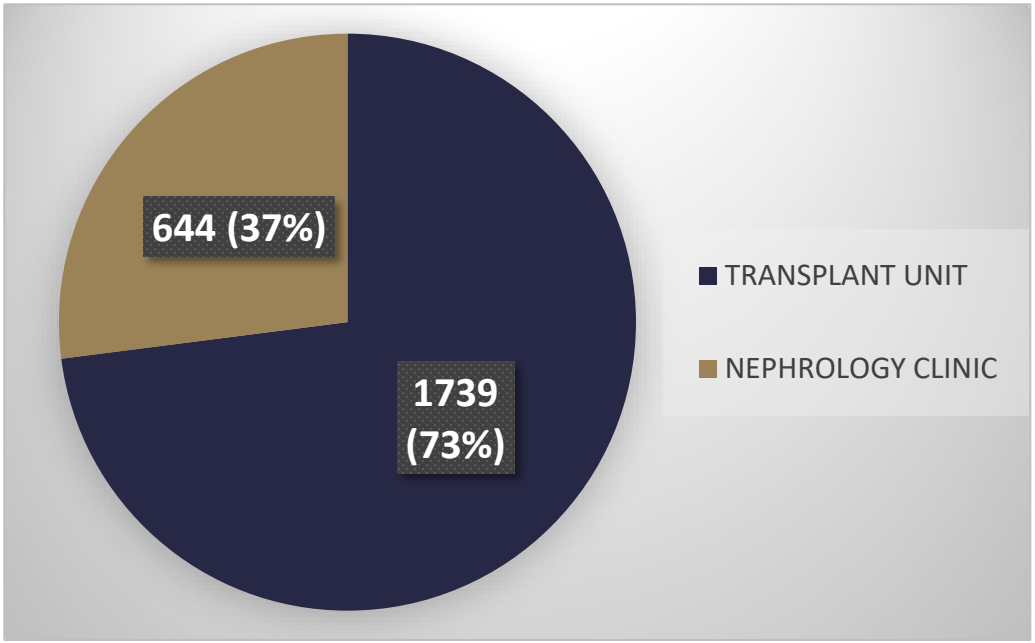
Therapeutic plasma exchange (TPE/PLEX)

(depending on the machine type)

- ***Membrane plasmapheresis (mTPE)***
- Centrifugal plasmapheresis (cTPE)

Kes et al. Transfusion 2016;56;3065–3072

Therapeutic apheresis (mTPE) in the Clinic of Nephrology and Renal Transplantation of Laiko Hospital (2015-2024)

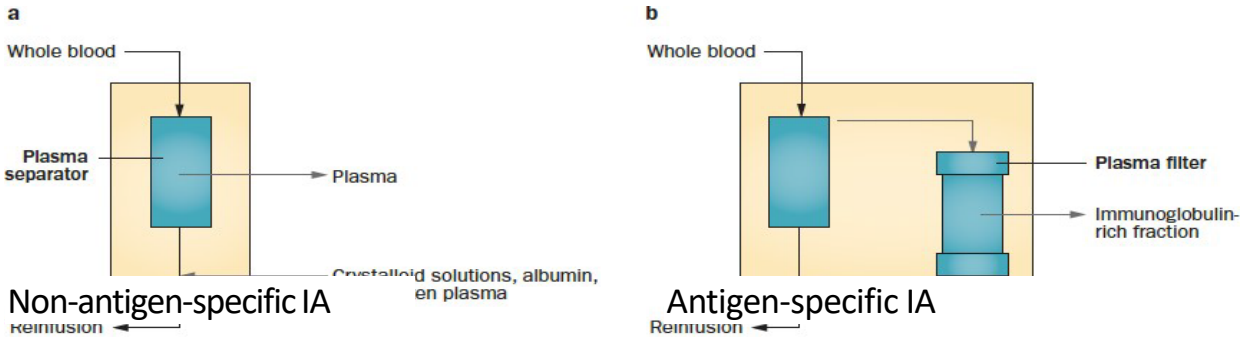


From 2015 to 2024,
a total of 2.383 TA sessions were performed, of which 1.739 (73%) were for transplantation

mTPE techniques performed in the setting of kidney transplantation

Plasma exchange

Double-filtration plasmapheresis

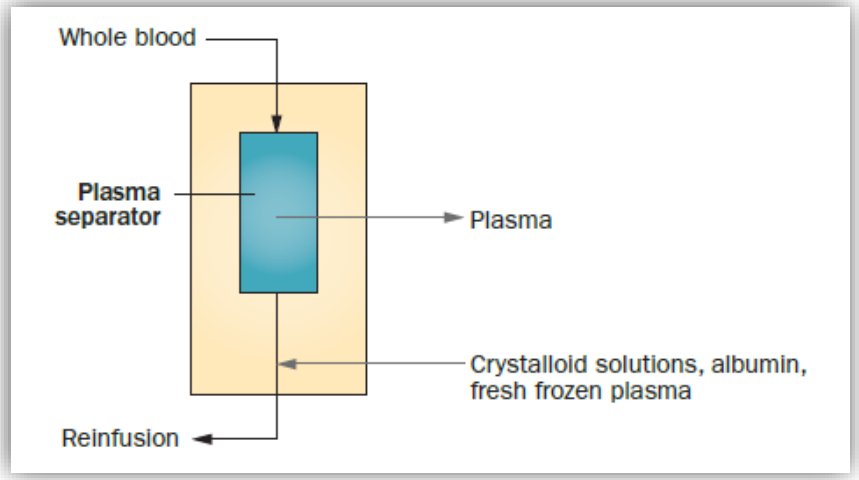


Non-antigen-specific IA

Antigen-specific IA

Böhmig G et al. Nat Rev. Nephrol. 2015;11(12):732-47

Plasma exchange (PLEX)



Advantages

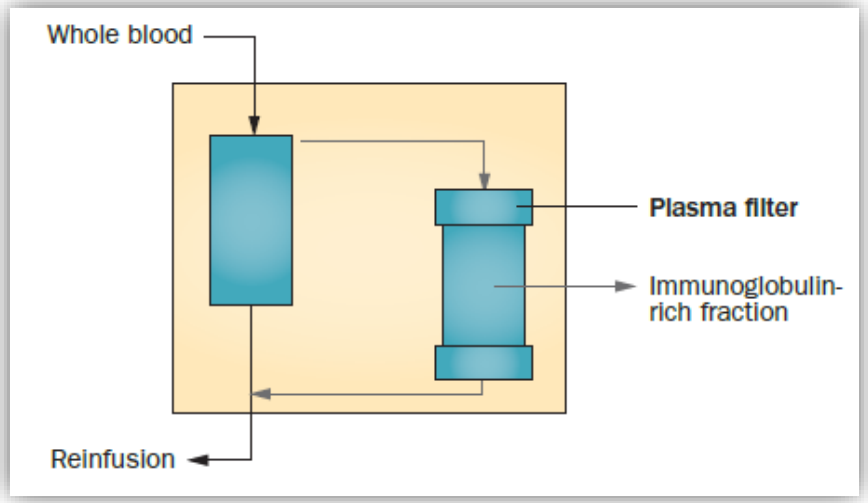
- Low cost
- Simultaneous removal of different Abs (anti-ABO , anti-HLA),cytokines, inflammatory mediators

Disadvantages

- Elimination of essential plasma components as albumin and coagulation factors
- Allergic and infections risks associated with the use of replacement solutions

Böhmig G et al. Nat Rev. Nephrol. 2015;11(12):732-47

Double-filtration plasmapheresis (DFPP)



Advantages

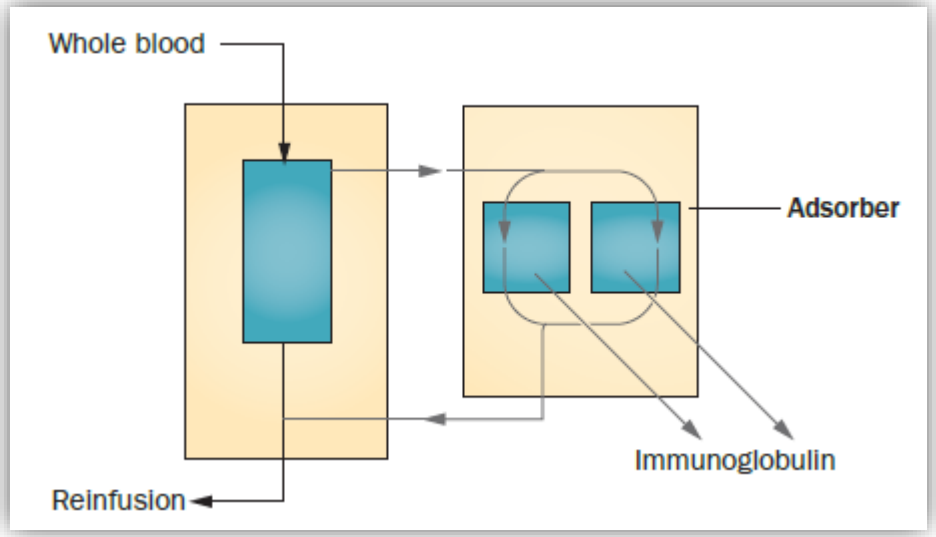
- Less substitution fluid
- Very low risk of allergic reactions and infections

Disadvantages

- Not effective removal of low-molecular weight Ig and substances smaller than albumin

Altobelli C et al. Kidney Blood Press Res 2023;48:66–78

Non-antigen-specific Immunoadsorption (IA)



Advantages

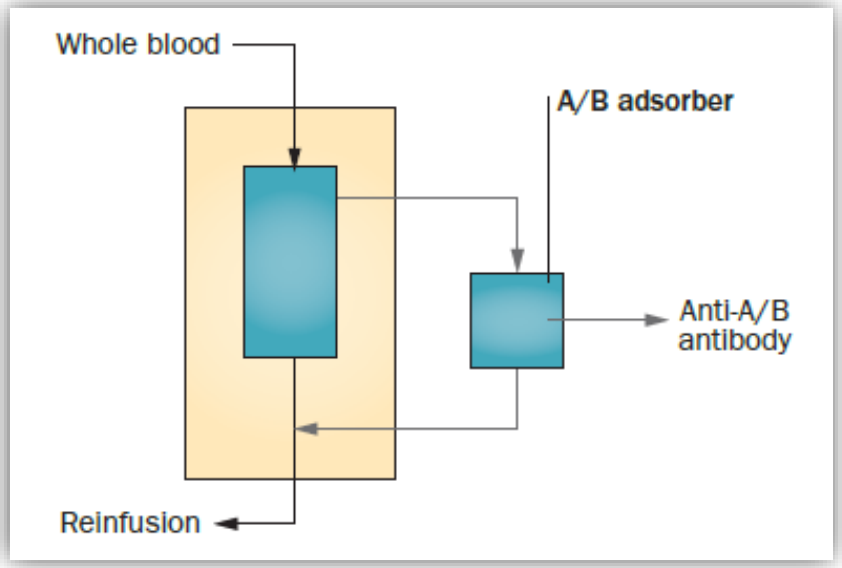
- Lower risk of contamination and allergic reactions
- Reusable
- Cost-effective
- Elimination of potentially harmful anti-HLA alloantibodies

Disadvantages

- Limited capacity to reduce levels of IgM antibodies

Böhmig G et al. Nat Rev. Nephrol. 2015;11(12):732-47

Antigen-specific Immunoadsorption (IA)



Advantages

- No need for replacement fluid
- No coagulation disorders, no nonspecific protein adsorption, no activation of coagulation factors
- Treatment of large amount of PV

Disadvantages

- High cost

Böhmig G et al. Nat Rev. Nephrol. 2015;11(12):732-47

Clinical indications for therapeutic apheresis in kidney transplantation

Pre-transplant

Desensitization in ABO-incompatible kidney transplantation

Desensitization in kidney transplant recipients with preformed HLA-antibodies

Post-transplant

Antibody-mediated rejection

Recurrence of primary FSGS

De novo TMA

Complement-mediated aHUS

Recurrent ANCA-associated vasculitis

Recurrent and de novo anti-GBM disease

Antiphospholipid syndrome and systemic lupus erythematosus

C.Melexopoulou, V.Filiopoulos, S.Marinaki. Transfus Apher Sci. 2024 Feb;63(1):103844

Pre-transplant PLEX

Approximately 1/3 of patients with a potential living donor are excluded from transplantation due to blood group incompatibility and/or a positive crossmatch

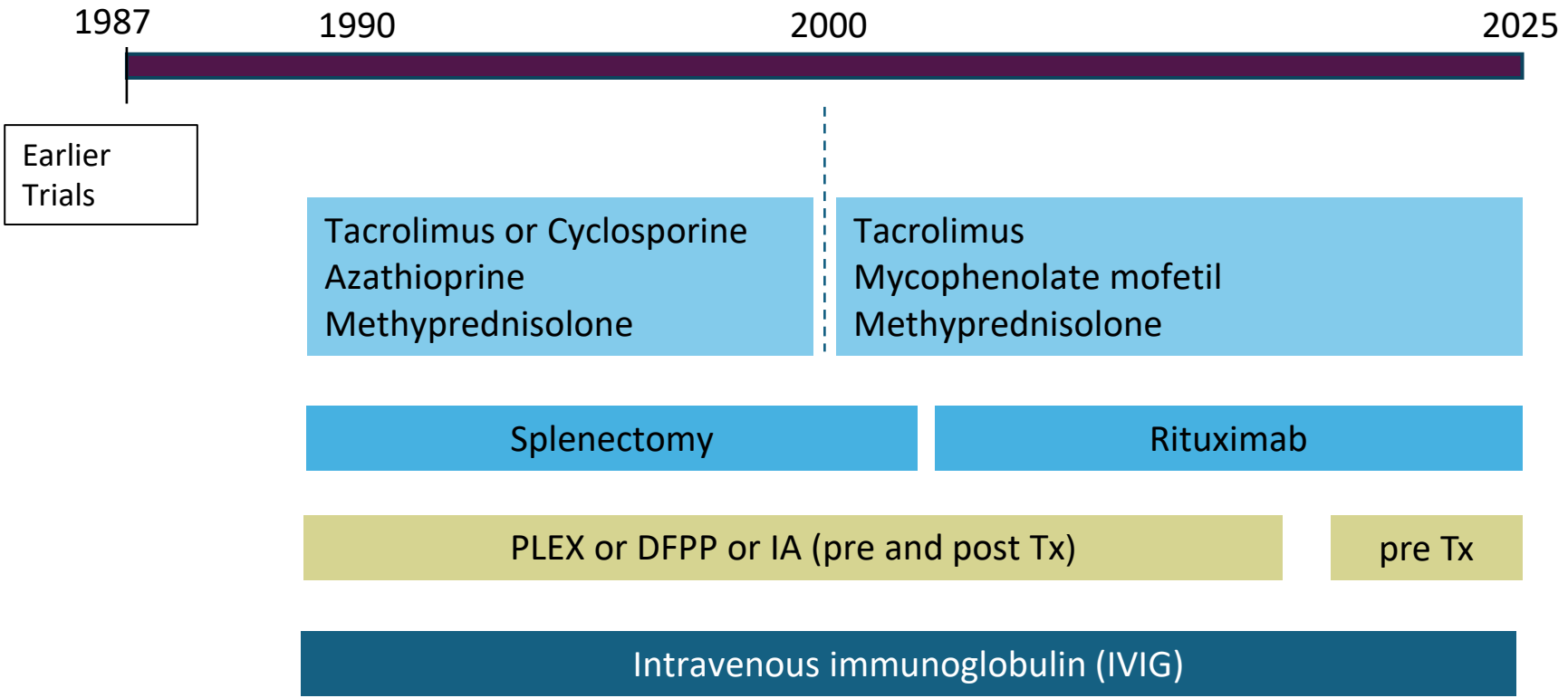
JAMA 2015;293:1883-1890

…….but desensitization protocols have successfully overcome barriers in incompatible kidney transplantation

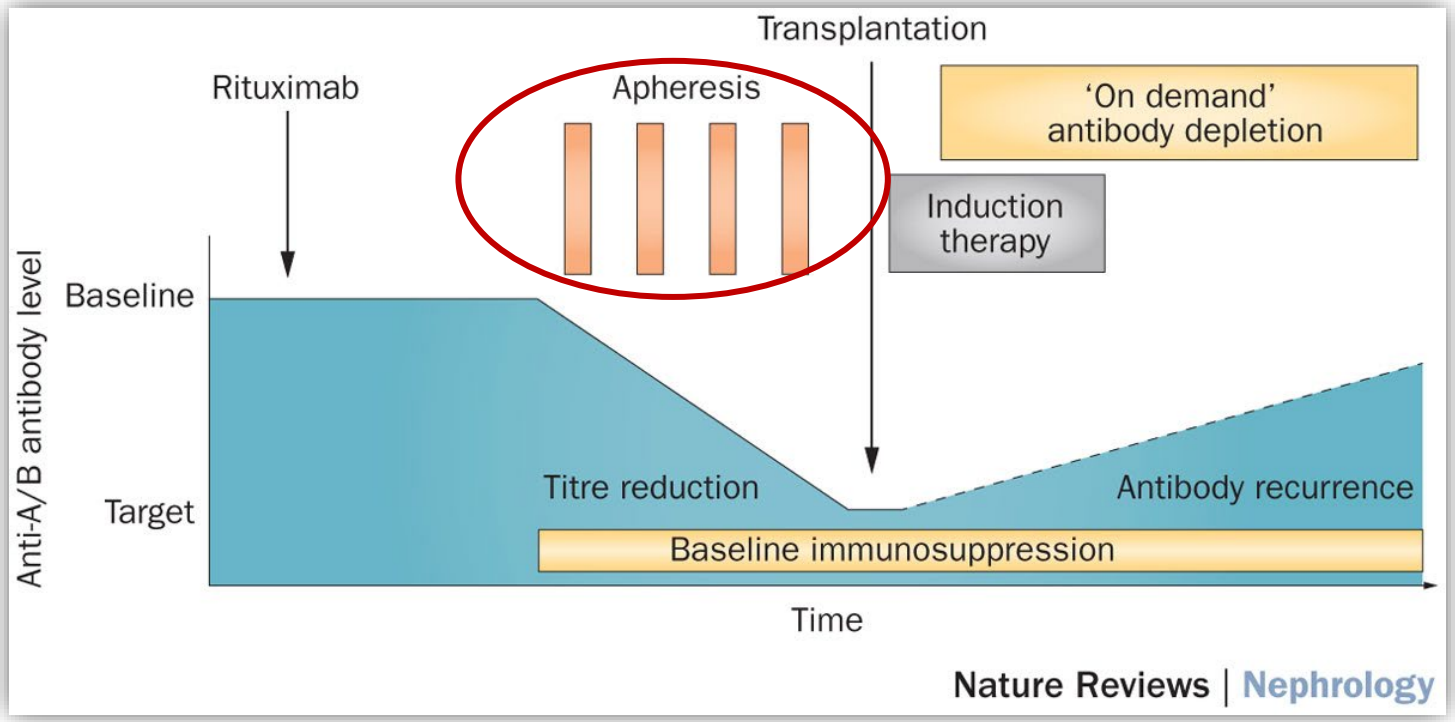
ABO-incompatible kidney transplantation

Blood group mismatch
is no longer a barrier

Clinical protocols for ABO-incompatible KT: evolution over time



Key elements of recipient desensitization in ABO-incompatible KT



Böhmig, G. A. et al. (2015) Nat. Rev. Nephrol. doi:10.1038/nrneph.2015.144

- ***Desensitization protocol***
- ***Apheresis technique***
- ***Anti-ABO Ab titer measurement***
- ***Anti-ABO Ab threshold for Tx***
- ***Monitoring after Tx***

Desensitization protocol

Administration of intravenous immunoglobulin (IVIG) in plasmapheresis-based protocols

- Administration of low-dose IVIG after each treatment session
- IA-based protocols limit IVIG use to a single infusion

Potential disadvantage

The available preparations contain ABO antibodies
→ transient unwanted rise in Ab titres

Apheresis technique

Plasmapheresis

Elimination of essential plasma components (albumin/coagulation factors)
limitation of volumes of plasma that can be processed
frequent necessitation of plasma substitution

DFPP

Losses of macromolecular coagulation factors (fibrinogen/factor XIII)
↑risk of bleeding complications.

Non-antigen-specific Immunoadsorption

Nonspecific elimination of immunoglobulins

Advantage

Elimination of core-chain-specific anti-A/B antibodies and HLA antibodies

Disadvantage

Limited capacity to reduce levels of IgM anti-A/B antibodies

The use of semiselective IA as a sole strategy could carry immunological risks. In some patients additional plasmapheresis sessions are required to sufficiently reduce antibody titres

ABO-specific immunoadsorption

Advantages

- Highly efficient elimination of ABO antibodies without major losses of essential plasma components.
- ABO-specific IA also reduces levels of distinct complement components, which could contribute to treatment efficiency.

Disadvantages

- Might not be suitable for the elimination of core-chain-specific antibodies
  lack of efficiency in a small subset of patients.

- ABO-specific adsorbers are approved for single use only, which substantially increases treatment costs

Anti-A/B antibody titer measurement

Haemagglutination

High level of assay variability between laboratories

Flow cytometry and surface plasmon resonance

Alternative techniques for anti-A/B antibody measurement
Not widely applicable in the clinical setting

Anti-ABO Ab threshold for Tx

- Optimal anti-A/B antibody titers have not been defined, but generally range between ≤ 1:8 and ≤ 1:32 at the day of transplantation

Monitoring after Tx

The value of post-transplantation antibody monitoring is less clear and remains controversial.

Serial monitoring of antibody titres

A major element of successful desensitization protocols is serial pretransplantation anti-A/B antibody monitoring before and during desensitization to guide the intensity of recipient preconditioning.

Individualized desensitization protocol

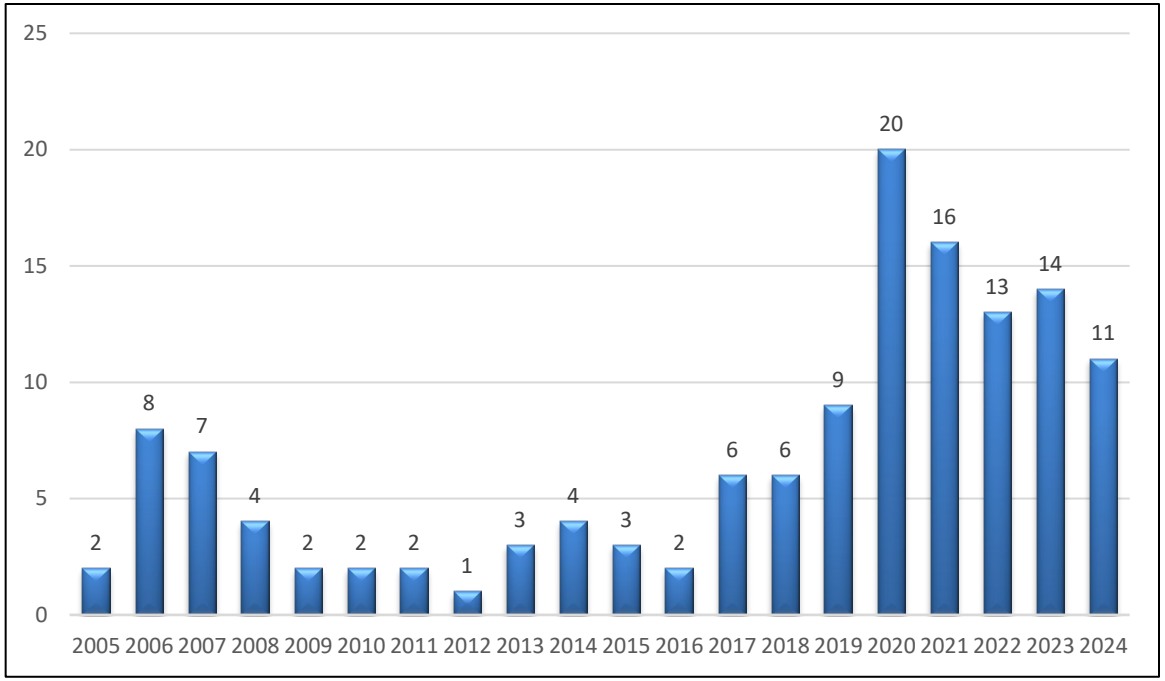
“Titred approach”
Various components of the desensitization scheme are adjusted according to initial antibody levels

- Apheresis treatment introduced only in patients with baseline titres of ≤1:8
- DFPP in those with titres between 1:16 and 1:64
- Antigen-specific IA in those with titres above 1:64

Antigen-specific IA was used in the latter group because these patients require the highest number of sessions of Ab removal and DFPP is associated with a higher bleeding risk

The number of apheresis sessions was guided by the course of titres
IVIG administration was completely omitted and rituximab was not applied in patients with titres <1:16

ABO-incompatible KT in Laiko General Hospital



>150 ABOi KT from 2005

ORIGINAL ARTICLE

Observational Study

Excellent long term patient and renal allograft survival after ABO-incompatible kidney transplantation: Experience of one center

Christina Melexopoulou, Smaragdi Marinaki, George Liapis, Chrysanthi Skalioti, Maria Gavalaki, George Zavos, John N Boletis

World J Transplant 2015 December 24; 5(4): 329-337

Patient and graft- survival at 8 years

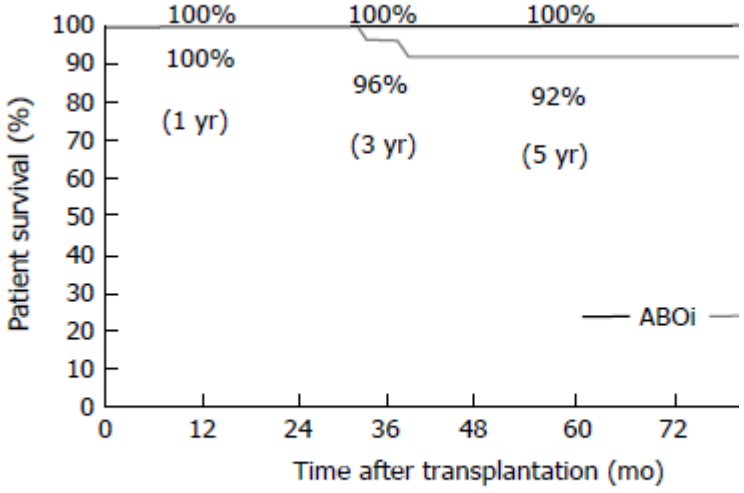


Figure 1 Patient survival (Kaplan-Meier).

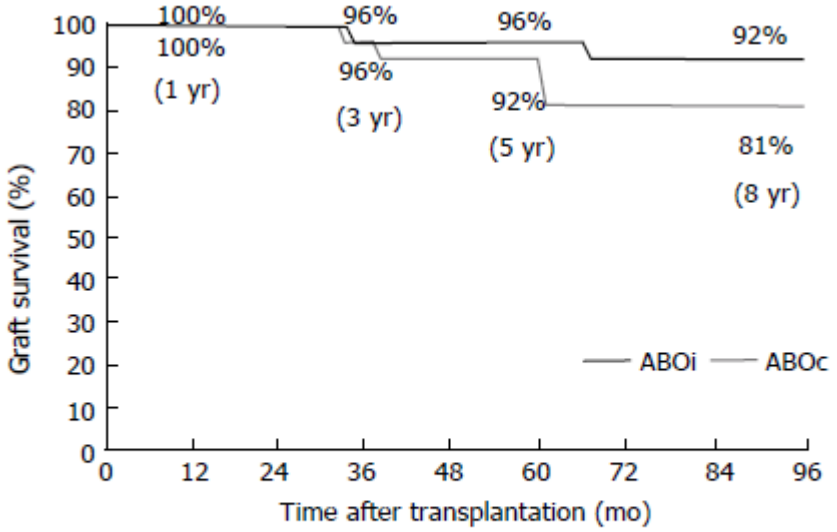
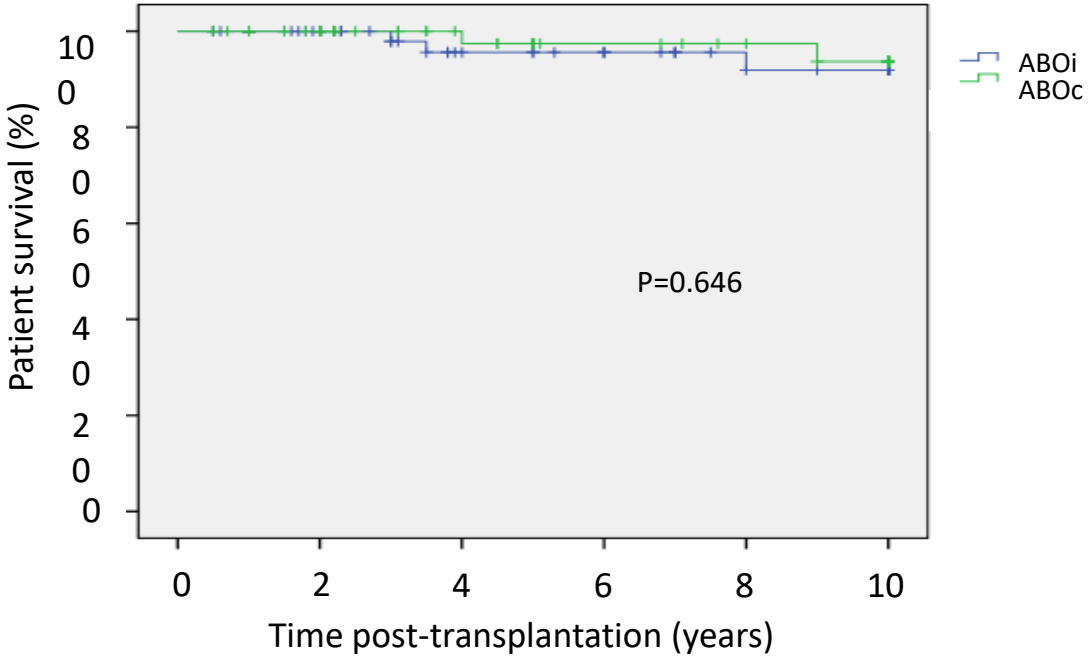


Figure 2 Graft survival (Kaplan-Meier).

n=30 ABOi pts vs 30 ABOc controls

Patient- survival at 10 years

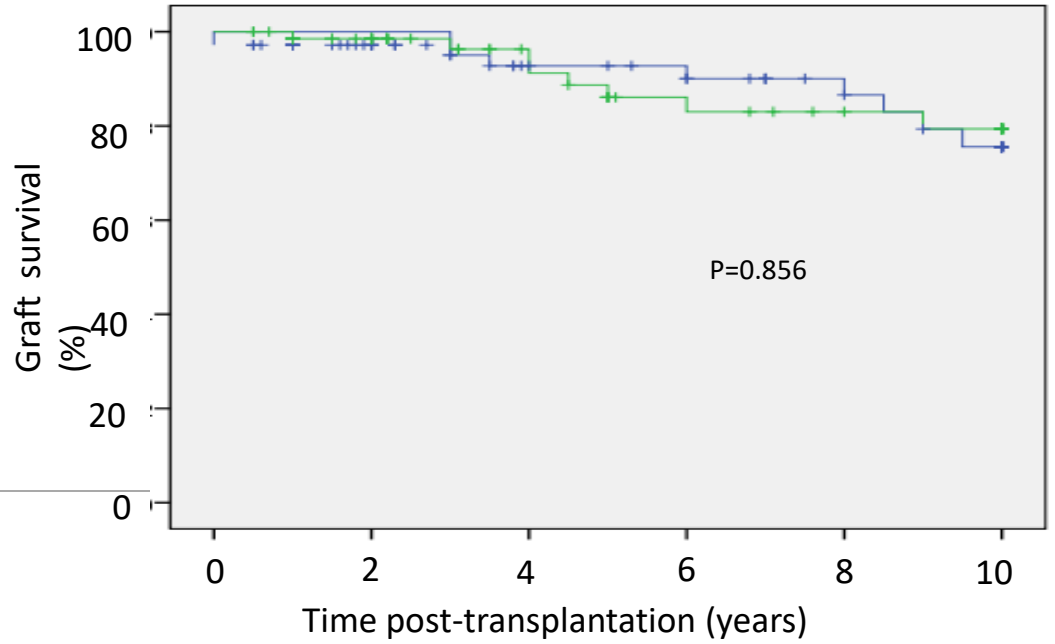


10 year survival
- 91.9% ABOi
- 93.7% ABOc

n=70 ABOi pts vs 70 ABOc controls

Unpublished data

Graft survival at 10 years



10 year survival
- 75.6% ABOi
- 79.4% ABOc

n=70 ABOi pts vs 70 ABOc controls

Unpublished data

Clinical outcomes after ABO-incompatible renal transplantation: a systematic review and meta-analysis

Florian G Scurt, Lara Ewert, Peter R Mertens, Hermann Haller, Bernhard M W Schmidt, Christos Chatzikyrkou

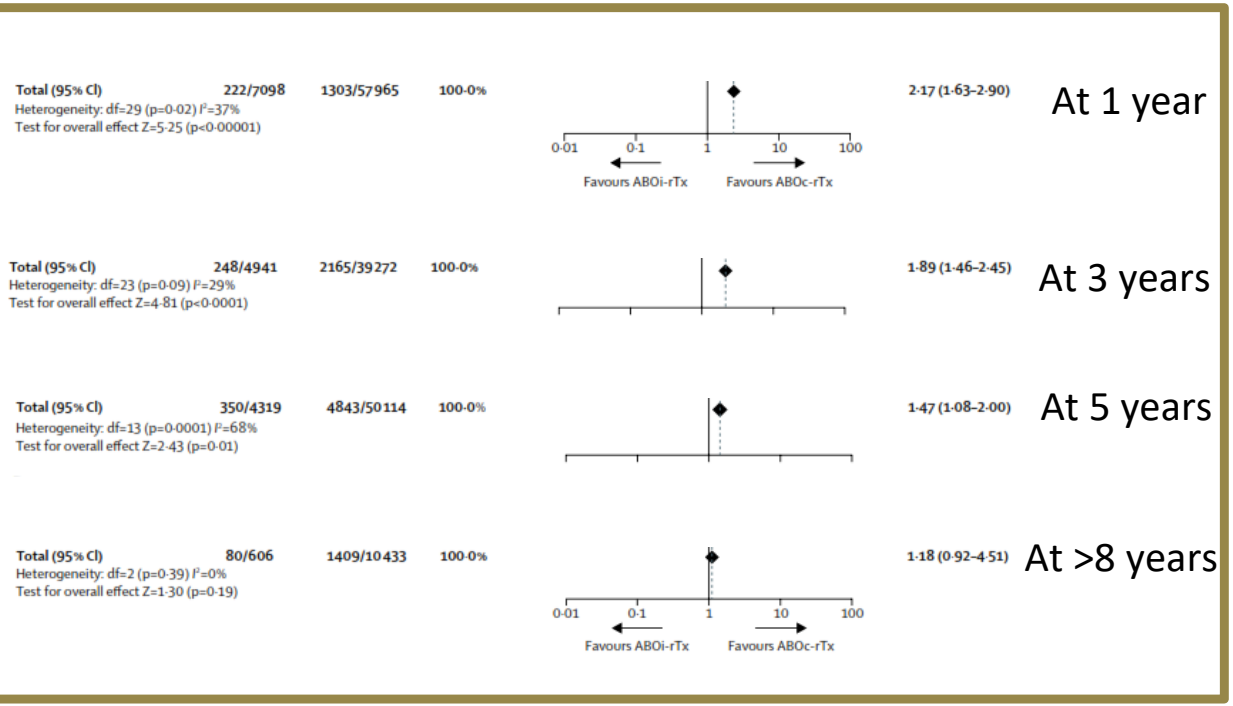
1264 studies screened
40 studies including 49 patient groups were identified

65 063 patients :eligible for analysis
7098 pts had undergone ABOi-rTx

Compared with ABOc-rTx, ABOi-rTx
Significantly higher 1-year mortality (OR 2·17, p<0·0001)
3- year mortality (OR 1·89, p<0·0001)

Lancet. 2019 May 18;393(10185):2059-2072

Clinical outcomes after ABO-incompatible renal transplantation



All-cause mortality after ABOi-rTx versus ABOc-rTX

Excess mortality and loss of kidney grafts was found compared with ABOc-rTx within the first 3 years after transplantation. Only long-term outcomes after 5 years yielded equivalent survival rates and organ function.

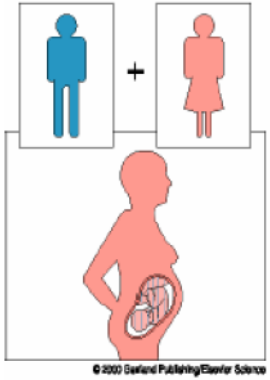
Lancet. 2019 May 18;393(10185):2059-2072

Kidney transplantation with preformed HLA-antibodies

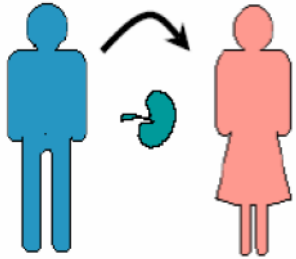
Major Barrier to successful Transplantation…

Presence of Donor Specific Antibodies (DSA)

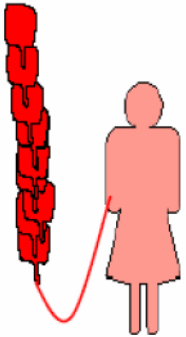
- 30% of patients on the transplant waiting list are sensitized



Pregnancies



Prior Tx



Transfusions

J. Scornik et al. BMC Nephrology 2013
A. Amir et al. Blood 2010

Desensitization

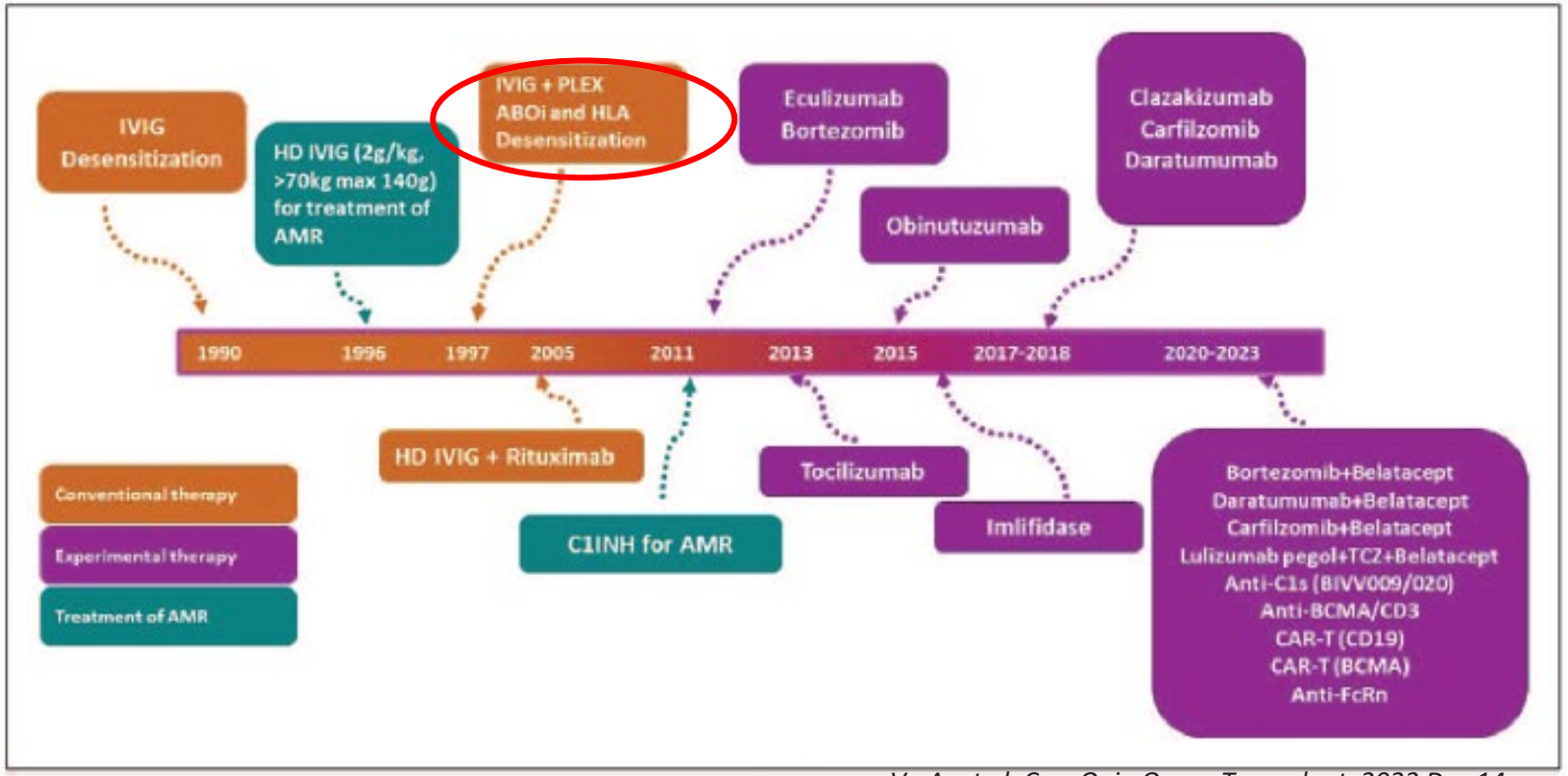
Managing highly sensitized renal transplant candidates in the era of kidney paired donation and the new kidney allocation system: Is there still a role for desensitization?

Carrie A. Schinstock[1,2] | Byron H. Smith[3] | Robert A. Montgomery[4] | Stanley C. Jordan[5] | Andrew J. Bentall[1,2] | Martin Mai[6] | Hasan A. Khamash[7] | Mark D. Stegall[2,8]

Despite the increase in HS transplantation rates after the implementation of prioritization systems and the development of KPD programs, a significant proportion of these patients **may remain on the waiting list for a long time** or **never find a compatible transplant**

Schinstock CA et al. Clin Transplant. 2019;33(12):e13751

Evolution of desensitization protocols



Vo A, et al. Curr Opin Organ Transplant. 2023 Dec 14

- The molecular weight of HLA IgG is approximately 150 kDa with 40% intravascular distribution

➡ Efficient removal with PLEX

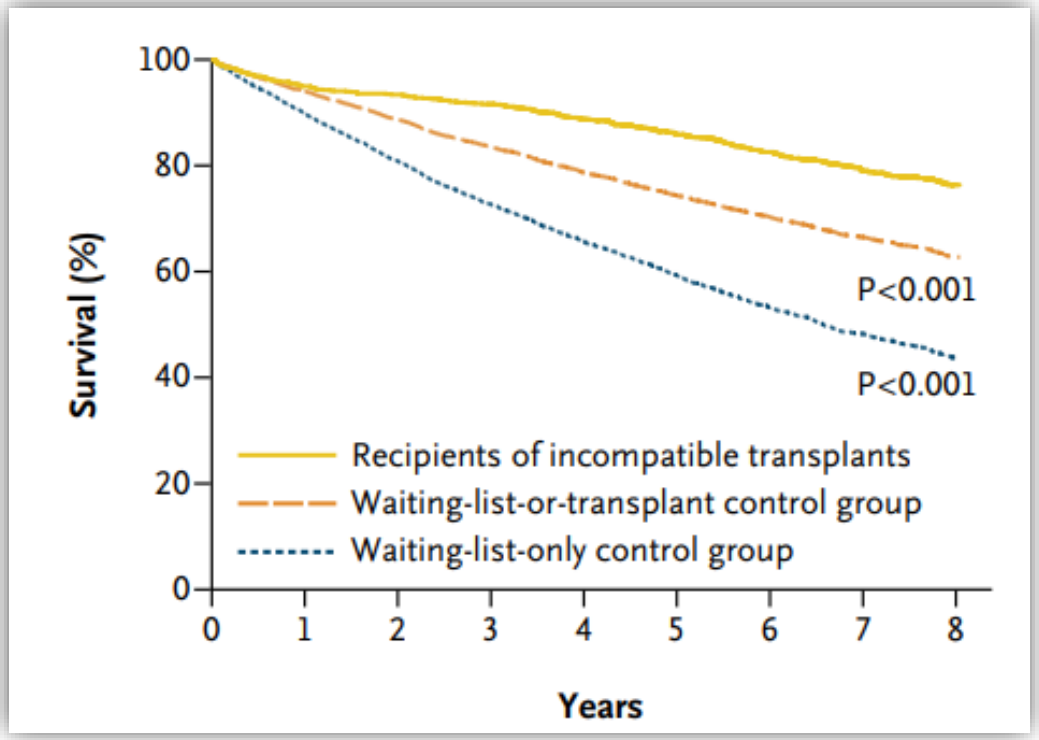
A. Kaplan J Clin Apher 2013;28(1):3-10

HLA desensitization and therapeutic apheresis

- No removal technique (PE, DFPP, IA) is superior
- Typically 3–5 sessions before transplantation and 0-3 afterwards in an every-other-day schedule
- Administration of IVIG 100–150 mg/kg after each session
- Number of sessions: depends on the antibody titer

Orandi BJ. N Engl J Med 2016;375(3):288-9

Clinical outcomes after HLA-incompatible KT



- Multicenter study, 22 centers
- 1025 patients with DSAs, KT from a living donor after desensitization
- 8 years of follow-up

Significant survival benefit at 1,3,5,8, years post-KT

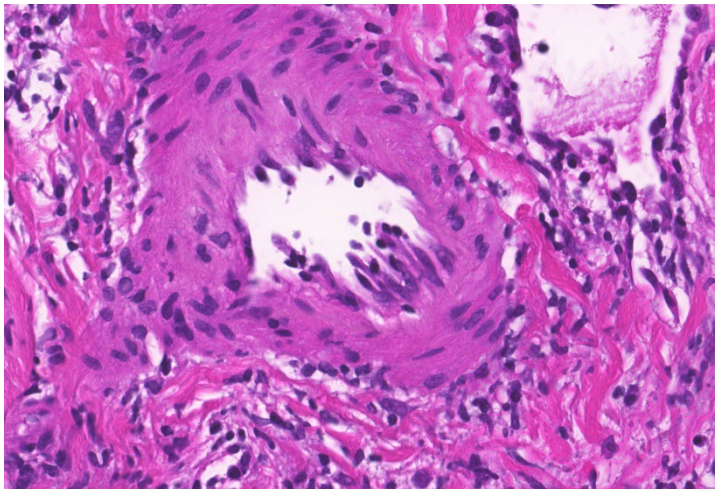
Orandi BJ. N Engl J Med 2016;375(3):288-9

Post-transplant

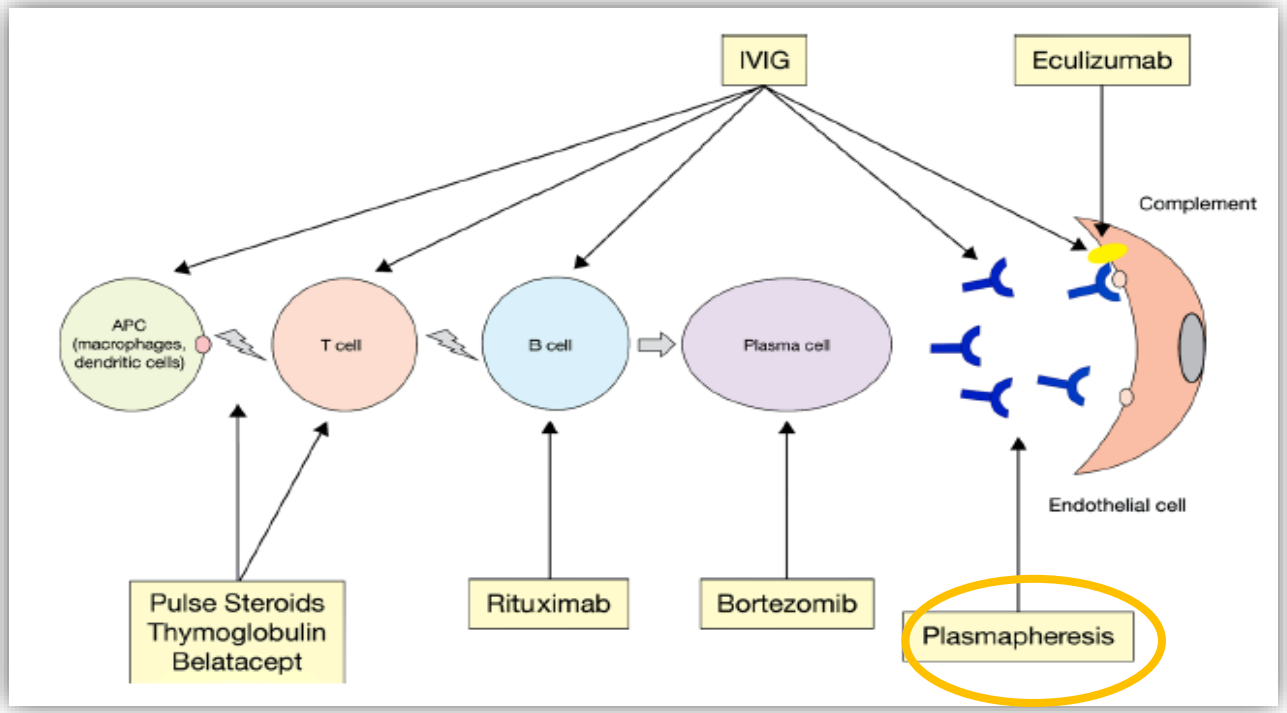
Antibody-mediated rejection (ABMR)

- 5% in compatible KT
- **50% in incompatible KT**

Anti-HLA Abs, non-HLA Abs, anti-ABO



Therapeutic modalities for ABMR



American Journal of Transplantation 2014; 14: 255–271

Antibody-mediated rejection and therapeutic apheresis

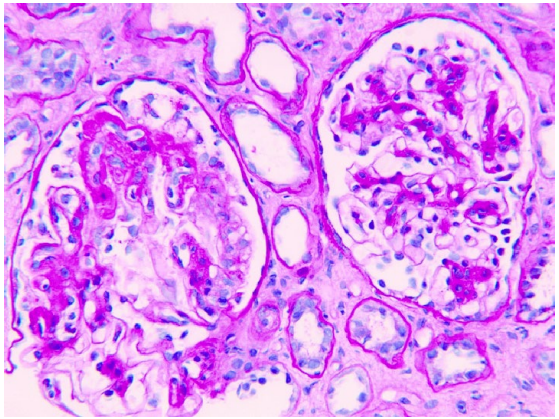
The most commonly used technique in ABMR is plasma exchange

- **Volume per session:** 1–1.5 plasma volumes
- **Frequency:** Daily or every other day, usually for six sessions
- **Administration of IVIG after each session** (100–150 mg/kg) and **500 mg/kg at the end of all sessions**
  (total dose: **1–2 g/kg**)

Check DSAs after last PLEX

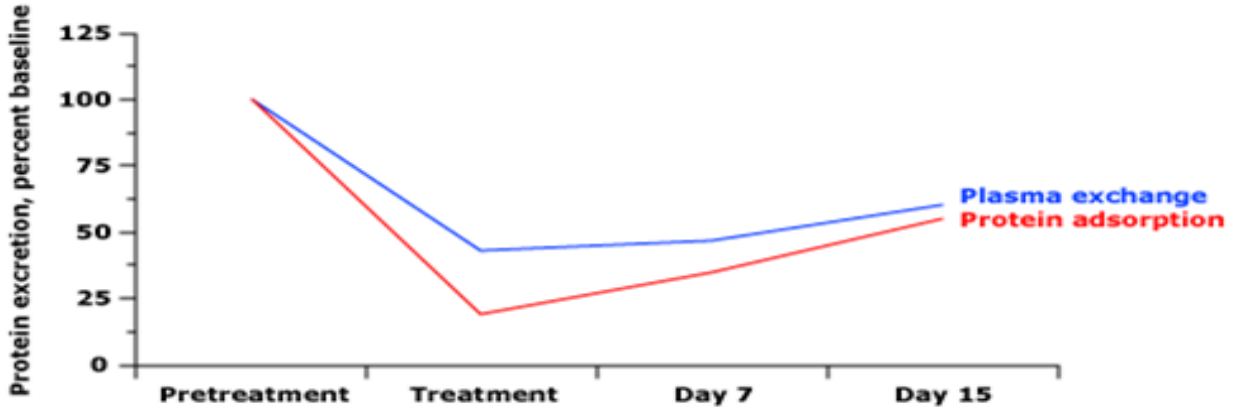
Recurrent focal segmental glomerulosclerosis (FSGS)

- FSGS may recur with a risk of 20% to 50% for first transplants, reaching 80% to 100% in repeated transplants



- Recurrence can happen within a few hours to 2 years post-transplant
- Believed to be due to a circulating permeability factor

Graph showing effect on protein excretion of removal of a circulating factor in recurrent focal and segmental glomerulosclerosis



N Engl J Med. 1994 Jan 6;330(1):7-14

Permeability factors:anti-nephrin Abs

Discovery of Autoantibodies Targeting Nephrin in Minimal Change Disease Supports a Novel Autoimmune Etiology

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Two independent patient cohorts
(Bx proven MCD + Active NS)

Nephrotic Syndrome Study Network — Patients at our institutions

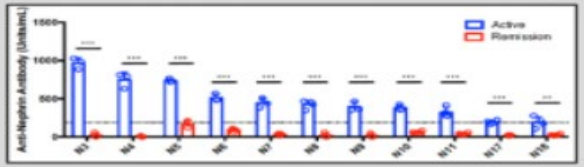
ELISA for anti-nephrin antibodies (both cohorts)

Immunofluorescence evaluation of renal biopsies for punctate IgG (our cohort)

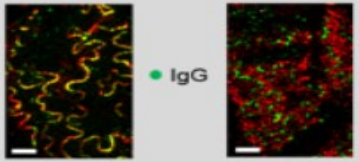
Comparison of circulating nephrin autoantibodies pre and post treatment response (both cohorts)

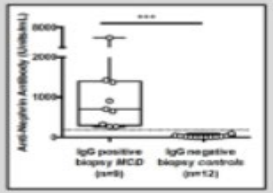
Circulating nephrin autoantibodies are present in almost 1/3 of patients with MCD in the NEPTUNE cohort and correlate with disease activity

29%
(18/62)



Nephrin autoantibodies are detectable both in serum and renal biopsies of patients with MCD





Nephrin is the target of circulating autoantibodies in a subset of patients with minimal change disease

doi: 10.1681/ASN.2021060794

A multi-institutional study found a possible role of anti-nephrin antibodies in post-transplant focal segmental glomerulosclerosis recurrence

22 Japanese pediatric kidney transplant recipients with recurrent FSGS after transplantation

- **14** cases with a **primary FSGS/ 8 patients with a genetic FSGS**.
  11/14 (**78.6%)** had **recurrent FSGS** and had
  circulating **anti-nephrin antibodies** (median **899 U/ml)**.

- Responders to therapy had a significant decrease in antibody levels, while non-responders had persistently high titers.

- Patients with genetic forms of FSGS had a median anti-nephrin antibody level of 113 U/ml

Shirai Y et al. KI 2024 Mar;105(3):608-17

Recurrent FSGS and therapeutic apheresis

Plasmapheresis or immunoadsorption initiated immediately upon relapse

- **Volume per session:** 1–1.5 plasma volumes
- **Replacement fluid:** Albumin
- **Typically:** 3 daily sessions followed by 3 sessions per week
- **Monitoring:** With proteinuria measurements

Recurrent FSGS and therapeutic apheresis

- Lipoprotein apheresis (LA) removes lipoprotein(a) [Lp(a)] and sometimes LDL cholesterol from the blood

- LA is used as a second-line treatment in recurrent FSGS, based on the idea that nephrotic hyperlipidemia creates a lipotoxic environment that impairs podocyte function.

  - Usually 2 times per week for 3 weeks followed by 6 weekly treatments

Raina Front Pediatr 2019;7:454 *Shah et al. Pediatr Nephrol 2019;34(11):2343*

Thrombotic microangiopathy (TMA)

•**Drug-related TMA**

Occurs in ~1% of patients on calcineurin inhibitors (CNIs)

→ Management: **dose reduction, discontinuation, or switch of CNI** and/or **plasmapheresis** *(Category III, Grade 2B)*

•**Complement-mediated TMA (aHUS)**

First-line treatment: **Eculizumab**

If unavailable → **plasmapheresis**

Exception

In cases with **anti-CFH antibodies**, plasmapheresis is a **Category I** indication

Therapeutic apheresis has significantly contributed to the progress of kidney transplantation, improving outcomes both before and after the procedure

- **Before transplantation**

It has enabled transplantations that were once considered impossible, such as transplants across immunologic barriers

- **After transplantation**

Apheresis contributes to the protection and long-term survival of the graft, especially in cases of rejection