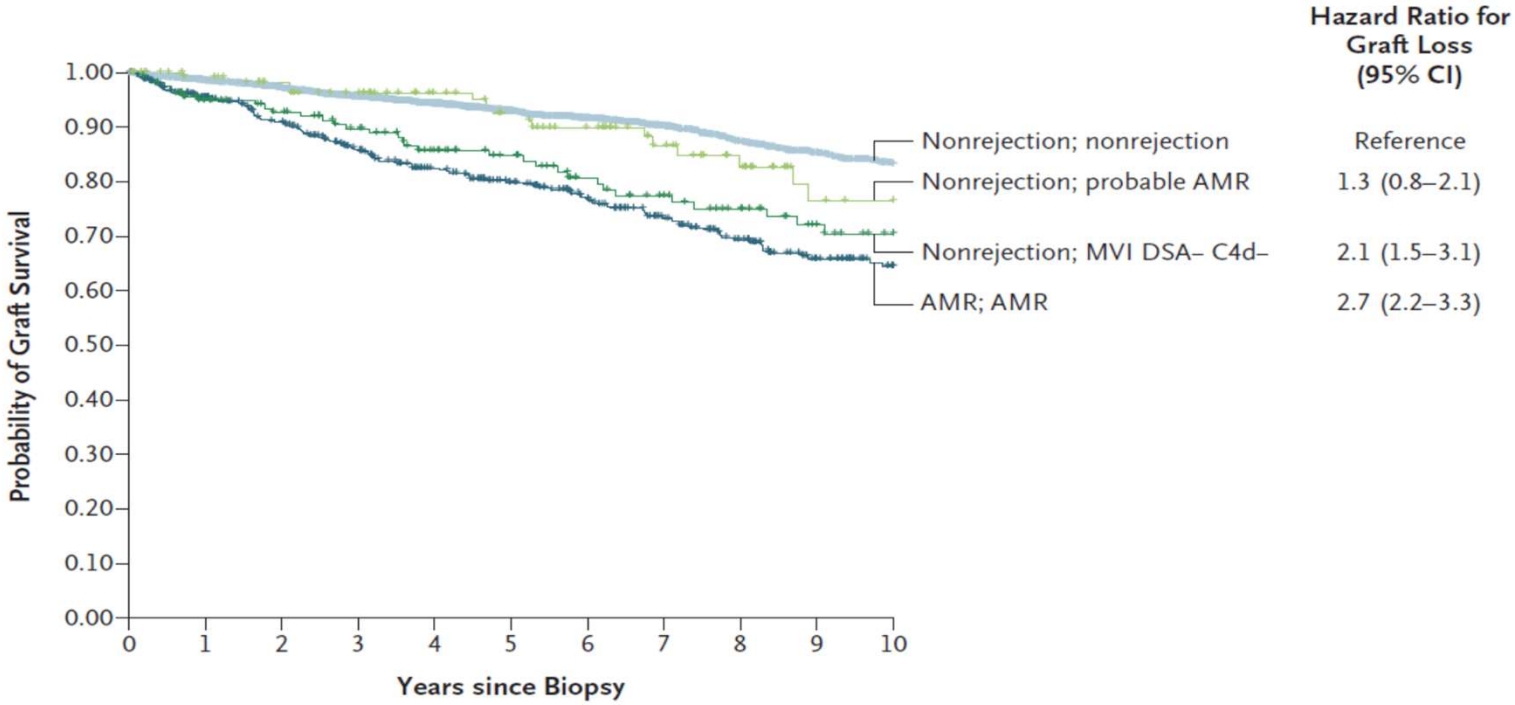
CORSO SIN LOMBARDIA

AFERESI: UNA RISORSA TERAPEUTICA STRATEGICA E MULTIDISCIPLINARE

Utilizzo della plasmaferesi nel rigetto umorale acuto di trapianto di rene

Alberto Menegotto
Milano, 18 settembre 2026

Figure 2. Risk Stratification of Kidney-Allograft Survival According to Microvascular Inflammation–Related Diagnoses..



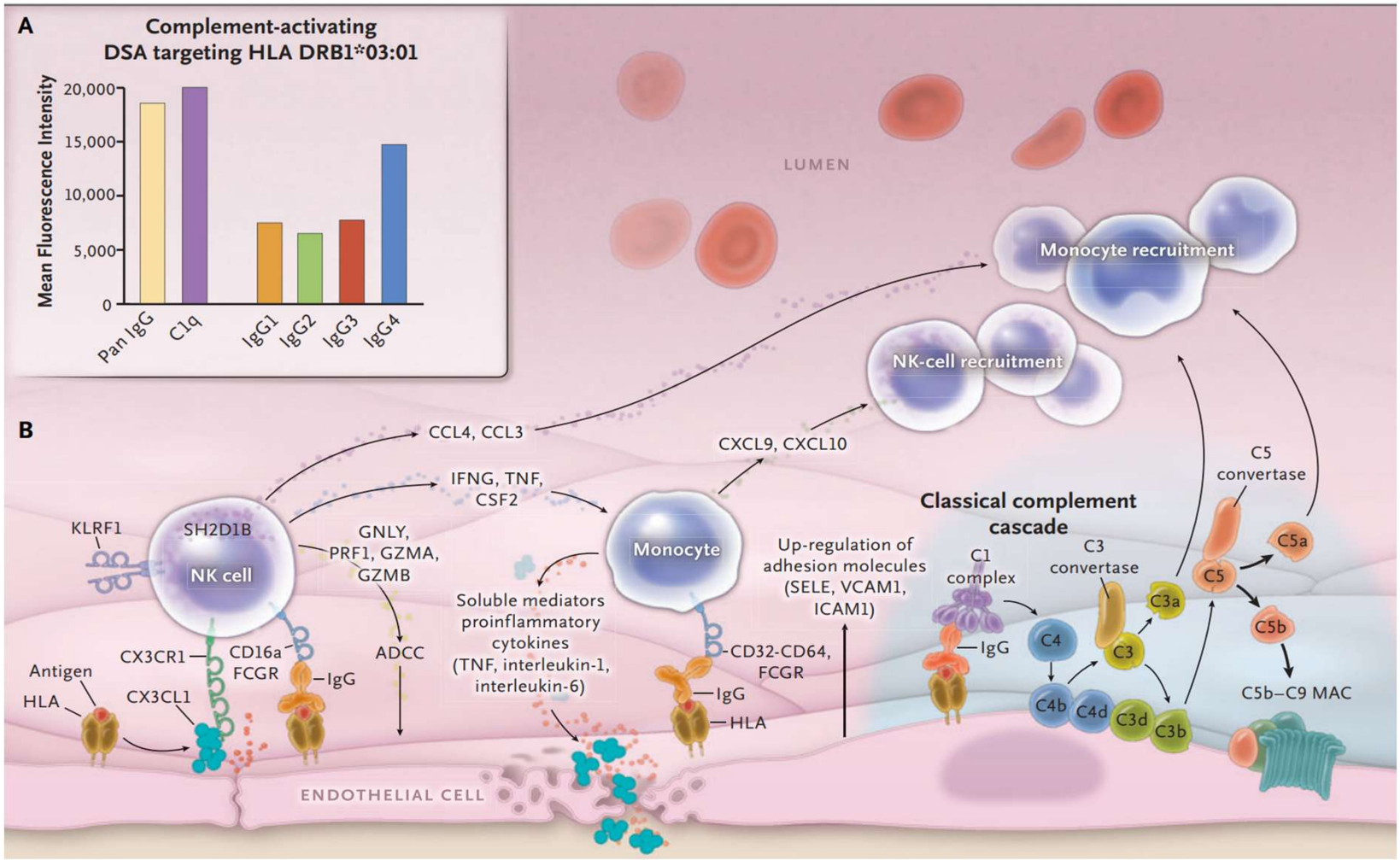
No. at Risk

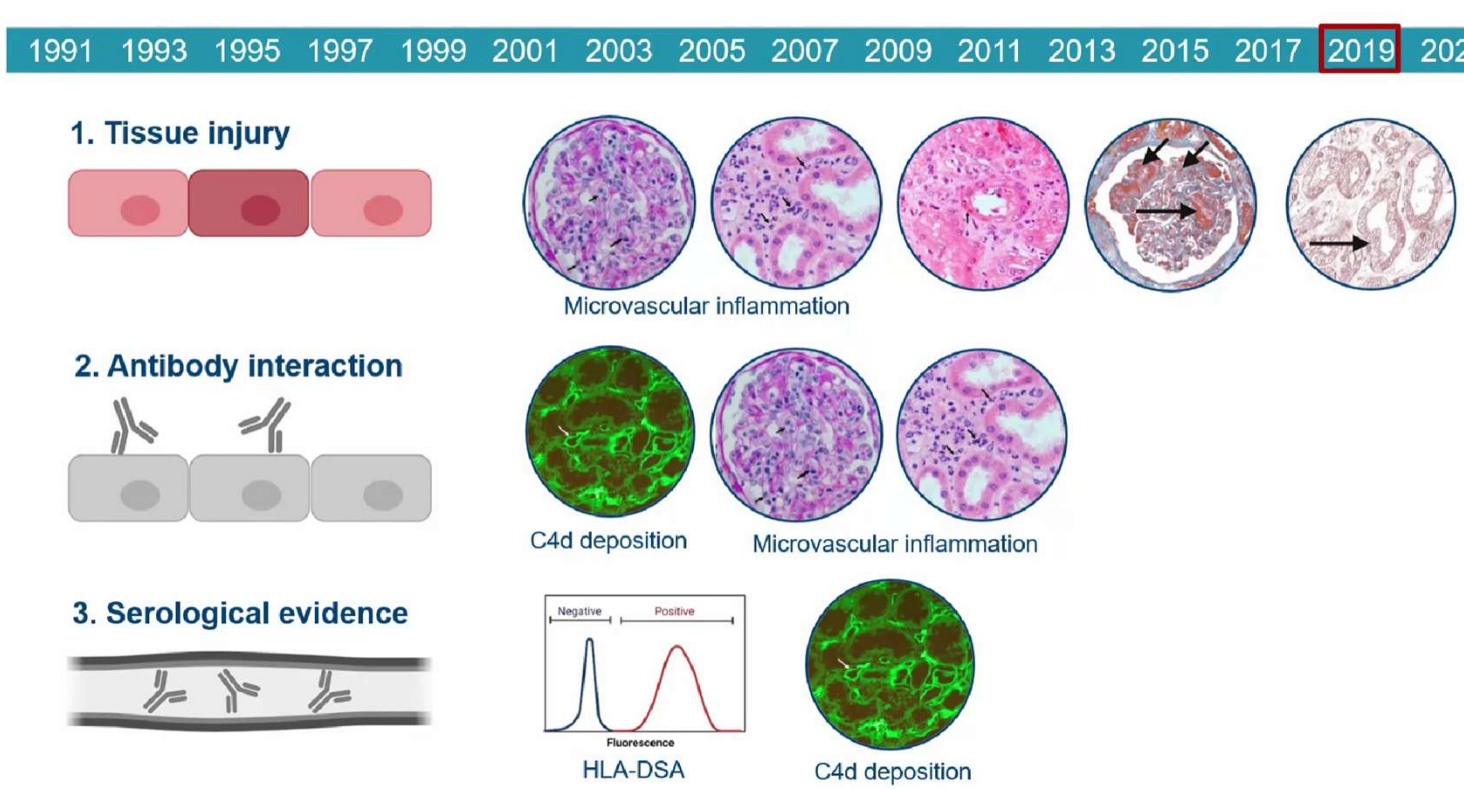
Nonrejection; nonrejection	3604	3167	2893	2537	2145	1762	1466	1243	999	829	676
Nonrejection; probable AMR	122	110	101	93	80	72	63	50	39	25	23
Nonrejection; MVI DSA–C4d–	159	139	128	116	99	88	74	66	57	45	38
AMR; AMR	489	423	380	331	292	256	222	185	150	116	94

Table 1. Comparison of the dominant characteristics of classes 1 and 2 donor-specific antibodies (6–10,25–30)

	Class 1 Donor-Specific Antibodies	Class 2 Donor-Specific Antibodies
HLA		
Antigens	A, B, and C	DR, DQ, and DP
Epitopes location	α-chain	α- and β-chains
Expression	All nucleated cells	Antigen-presenting cells
Preformed donor-specific antibodies		
Important	Very	Less
Positive crossmatch	T cells	B cells
Transplant decision	No transplant	Permissible
***De novo* donor-specific antibodies**		
Detection	Sooner	Later
IgG subclasses	IgG1, IgG3	IgG2, IgG4
Complement binding	Strong	Weak/no
Frequency	Fewer	Common, especially DQ
Antibody-mediated rejection		
Phenotypes	Acute	Chronic, subclinical
Presentation	Early	Later
Graft dysfunction	Rapidly	Slowly
C4d deposit	Positive	Negative
Treatment	More responsive	Less responsive
Graft loss	Early	Later

Zhang, Clin J Am Soc Nephrol 13: 182–192, January, 2018


A
Complement-activating
DSA targeting HLA DRB1*03:01
Mean Fluorescence Intensity
20,000
15,000
10,000
5,000
0
Pan IgG
C1q
IgG1
IgG2
IgG3
IgG4
B
LUMEN
Monocyte recruitment
NK-cell recruitment
CCL4, CCL3
IFNG, TNF, CSF2
CXCL9, CXCL10
KLRF1
SH2D1B
NK cell
GNLY, PRF1, GZMA, GZMB
Monocyte
Up-regulation of adhesion molecules (SELE, VCAM1, ICAM1)
Classical complement cascade
C1 complex
C3 convertase
C5 convertase
C5a
C5
C5b
C5b–C9 MAC
C3a
C4
C3
C4b
C4d
C3d
C3b
IgG
Antigen
HLA
CX3CR1
CX3CL1
CD16a FCGR
IgG
ADCC
Soluble mediators proinflammatory cytokines (TNF, interleukin-1, interleukin-6)
CD32-CD64, FCGR
IgG
HLA
ENDOTHELIAL CELL


1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011 2013 2015 2017 2019 2022
1. Tissue injury
Microvascular inflammation
2. Antibody interaction
C4d deposition
Microvascular inflammation
3. Serological evidence
Negative
Positive
Fluorescence
HLA-DSA
C4d deposition

Caso clinico

- donna, 46 anni
- Malattia renale cronica con rene sx grinzo e rene destro multicistico (familiarità +, analisi genetica negativa)
- Dialisi peritoneale dal 04/24
- ipertensione arteriosa
- non trasfusioni
- 1 figlia, 1 aborto

- In data 23/04/2026 trapianto di rene singolo da donatore deceduto DBD
- MM 4/6
- PRA classe I 80%, classe II 5%
- Ricerca Ig anti HLA rivolti contro il donatore al trapianto (DSA): negativa
- XM negativo (CDC)

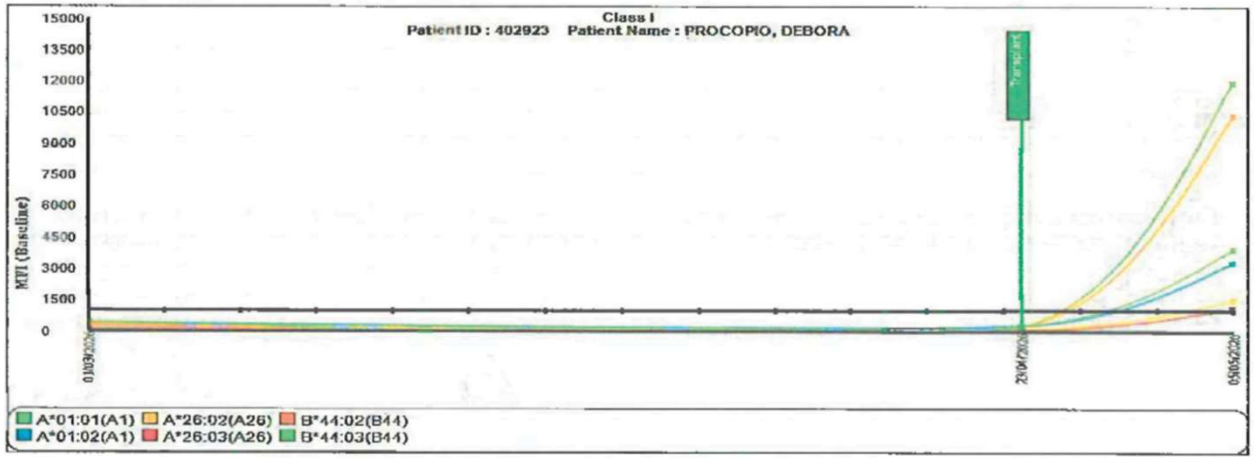
- Protocollo terapeutico in paziente iperimmune:

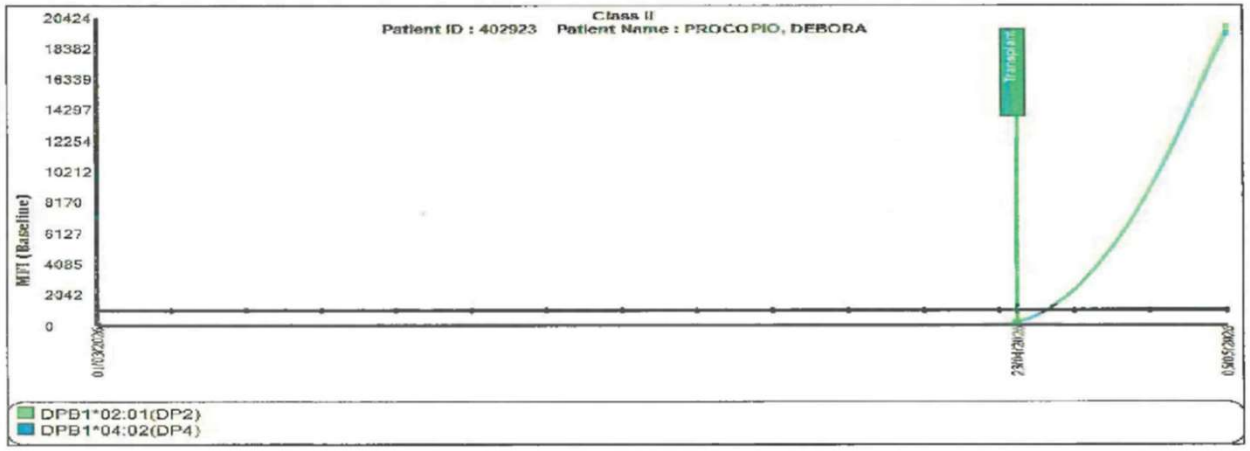
Thymoglobuline 5 mg/Kg, metilprednisolone, micofenolato mofetile, tacrolimus, Immunoglobuline umane 2g/Kg

- Ripresa funzionale renale immediata, non necessità di dialisi nel post intervento

- In data 30/04 (7 gg post operatoria): creat 1,4 mg/dL
- In data 01/05 (8 gg post operatoria): creat 2,5 mg/dL

- Nel sospetto di rigetto acuto di trapianto:
  - Somministrato metilprednisolone 500 mg x 5
  - Nuova ricerca Ig anti HLA (05/05/26)
  - Biopsia renale (05/05/26)





Conclusioni: rispetto al controllo precedente, nel siero del 05/05/2026, si rileva la presenza dei seguenti DSA: A1= 3584 MFI, A26=1263 MFI, B44=11111 MFI, DP2=19042 MFI, DP4=19857 MFI.

Biopsia renale (05/05/26)

Agobiopsia di corticale renale comprendente 12 glomeruli, di cui 1 ialino.
Membrane lievemente-moderatamente ispessite.
Lieve e segmentale ispessimento di matrice e cellularità mesangiale, con dubbia focale mesangiolisi.
Presenza di occasionali linfociti T nei capillari dei flocculi.
Fibrosi e fibroedema interstiziale diffusi, di intensità lieve-moderata, associati a denso infiltrato linfomonocitario interstiziale (CD3+, CD68+), in assenza di significativo interessamento intratubulare/intraglomerulare.
Sofferenza tubulare di grado moderato-severo, caratterizzata da epiteli vacuolizzati con aree diffuse di ipotrofia e note di necrosi.
Capillari peritubulari ectasici, caratterizzati da elementi infiammatori intraluminali (CD3+, CD68+).
Positiva la colorazione immunoistochimica per C3d (+++) e C4d (++) nei capillari peritubulari e glomerulari.
Vasi di grosso/medio calibro assenti.

C: rigetto umorale acuto attivo. C4d +

- A fronte della diagnosi di rigetto umorale attivo con DSA circolanti, la paziente è stata trattata con:

- 5 sedute di plasmaferesi (12-14-15-18-20/05)

Spectra Optia Apheresis System, continuous-flow centrifugal device

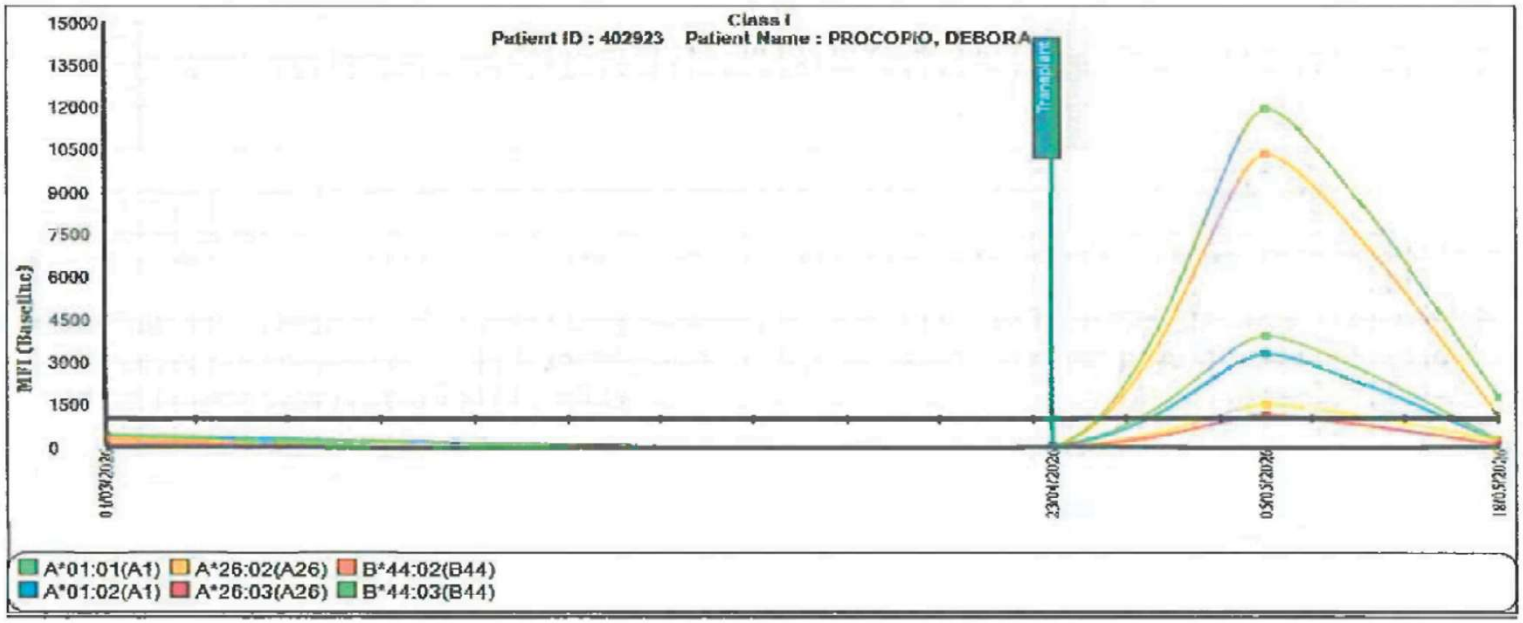
Sostituzione di 2500 cc di plasma (1 volume plasmatico) con albumina 5% 2500 cc

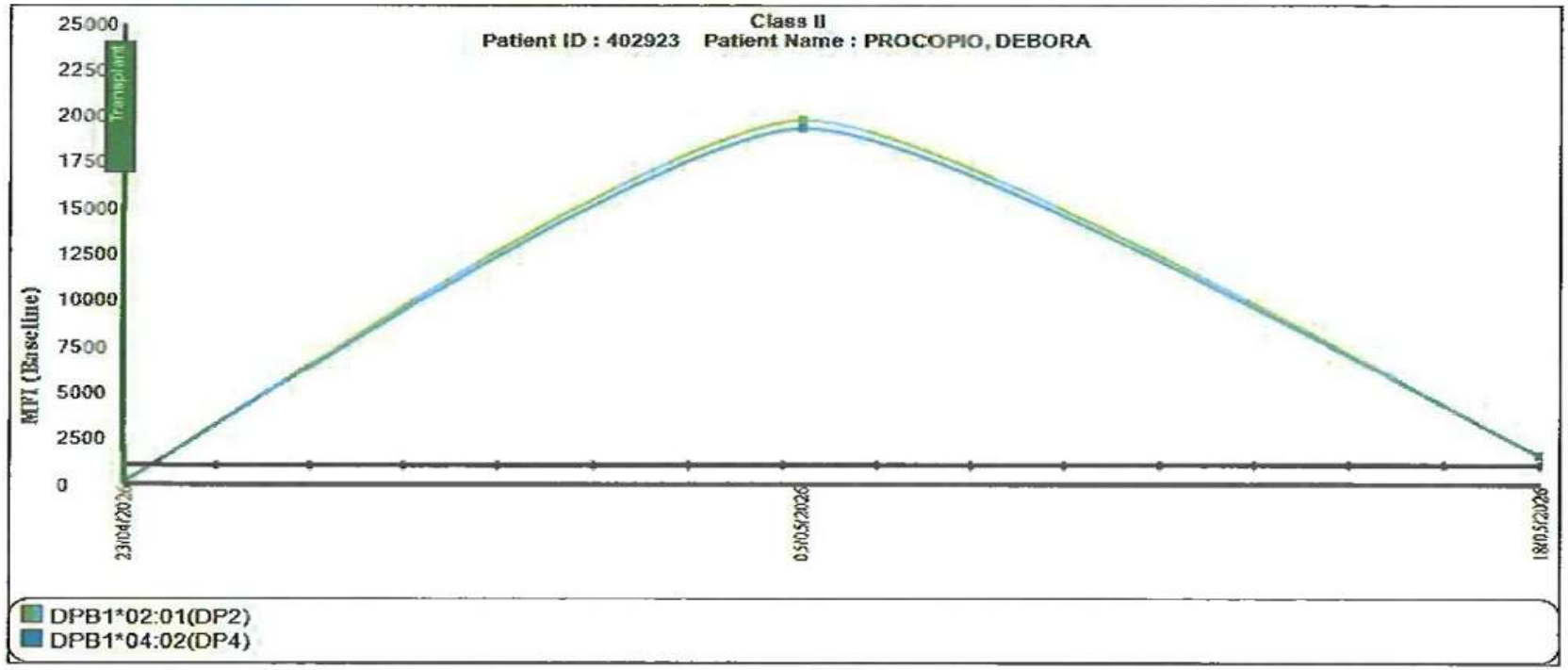
Somministrazione ACD (Anticoagulant Citrate Dextrose Solution) 49 mL

Calcio gluconato 1 g in infusione continua per profilassi ipocalcemia ACD indotta

- Rituximab 500 mg in data 20/05

Milano, 21/05/2026





Classe II

Conclusioni: rispetto al controllo precedente, nel siero del 18/05/2026, i valori di MFI per i DSA: B44 e DP4 diminuiscono, si conferma la negativizzazione del DSA: DP2.

- In dimissione (28 gg post Tx): creat 1,33 mg/dL, urea 39 mg/dL.
- Terapia: Tacrolimus 4,5 mg/die, MMF 1 g x 2, Metilprednisolone 8 mg.

- Ultimo controllo 09/26:

creat 1.39 mg/dL, Uprot 0,3 g/die, DSA sotto soglia

The primary goal of treating ABMR is:

- **to reduce the titer of existing pathogenic donor-specific antibodies (DSAs)**
- to eradicate the clonal population of B cells or plasma cells that is responsible for their production
- to prevent complement activation and reduce endothelial injury
- to optimize the immunosuppression
- to maintain medication adherence

→ **to preserve graft function**

Schinstock C.A., *Transplantation* 2020;104: 911–922

Böhmig et al, *Nephrol Dial Transpl.* 2025; 40:1615

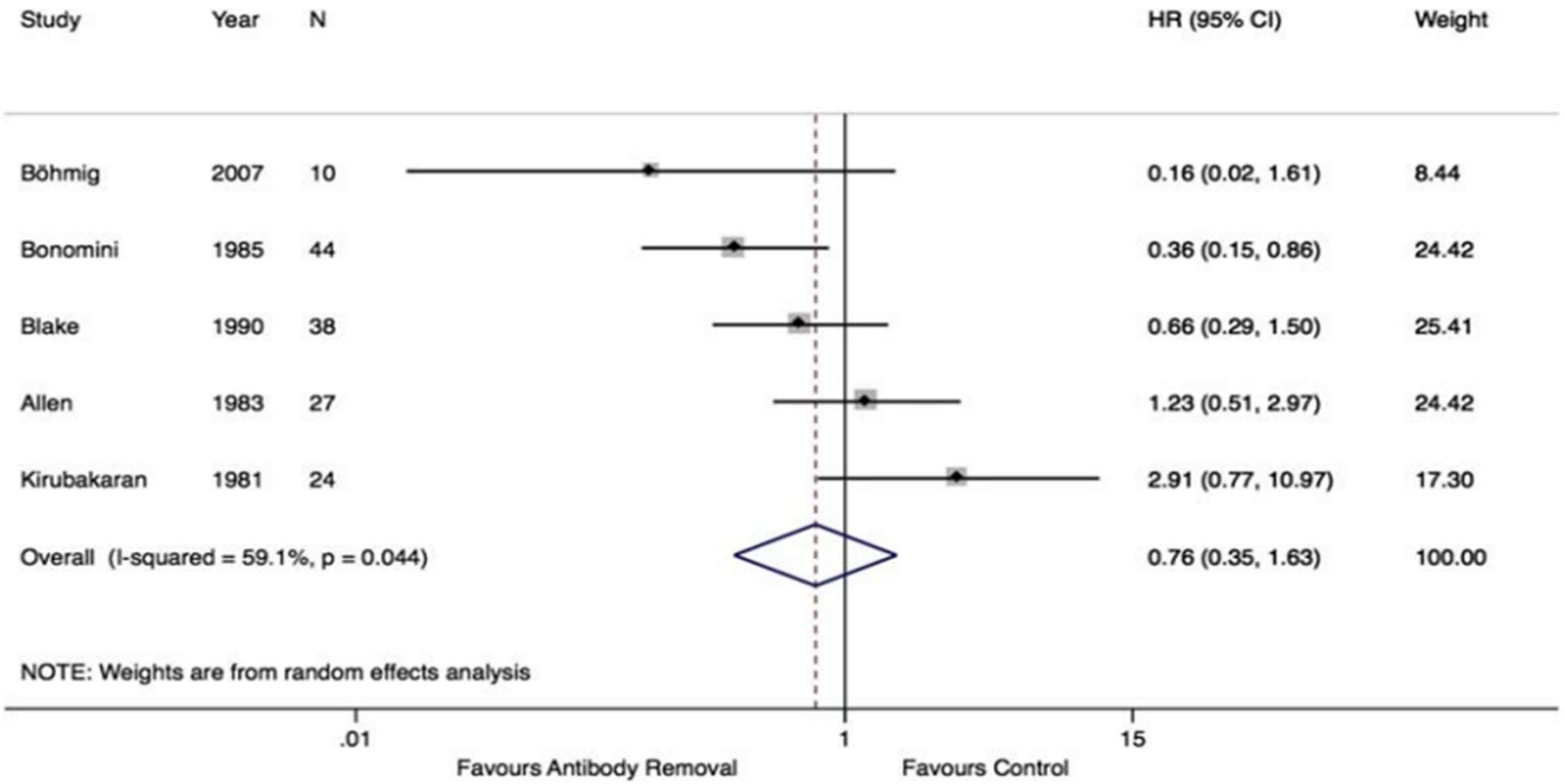
Recommended Treatment for Antibody-mediated Rejection After Kidney Transplantation: The 2019 Expert Consensus From the Transplantion Society Working Group

Consensus treatment recommendations based on available evidence and expert opinion

Timing	DSA	Histology (Banff 2017)	Standard of care[a]	Consider adjunctive therapies
Early[a] Acute (<30 days posttransplant)	Preexisting DSA (or nonimmunologically naive)	Active AMR	Plasmapheresis (daily or alternative day × 6 based on DSA titer) (1C)[b] IVIG 100 mg/kg after each plasmapheresis treatment or IVIG 2 g/kg at end of plasmapheresis treatments (1C) Corticosteroids (EO)	Complement inhibitors (2B) Rituximab 375 mg/m^2 (2B) Splenectomy (3C)
Late (>30 days posttransplant)	Preexisting DSA	Active AMR	Plasmapheresis (daily or alternative day × 4–6 based on DSA titer) (2C)[b] IVIG 100 mg/kg after each plasmapheresis treatment or IVIG 2 g/kg at end of plasmapheresis treatments (2C) Corticosteroids (EO)	Rituximab 375 mg/m^2 (2B)
		Chronic AMR	Optimize baseline immunosuppression (eg, add steroids if on a steroid-free regimen) (1C)	IVIG (3C)
	De novo DSA	Active AMR	Optimize baseline immunosuppression (eg, add steroids if on a steroid-free regimen) (1C) Evaluate and manage nonadherence	Plasmapheresis and IVIG (3C) Rituximab (3C)
		Chronic AMR		IVIG (3C)

[a]For all cases, treatment of concomitant T-cell–mediated rejection (≥borderline) and optimizing immunosuppression is recommended. Optimizing immunosuppression includes the use of tacrolimus with goal trough of >5 and use of maintenance steroid equivalent to prednisone 5 mg daily.
[b]Fresh-frozen plasma to be used for replacement fluid for plasmapheresis if a biopsy was performed within 24–48 h. The codes for grades of evidence have been taken from KDIGO.[54,56]
AMR, antibody-mediated rejection; DSA, donor-specific antibody; EO, expert opinion; IVIG, intravenous immune globulins; KDIGO, Kidney Disease: Improving Global Outcomes.

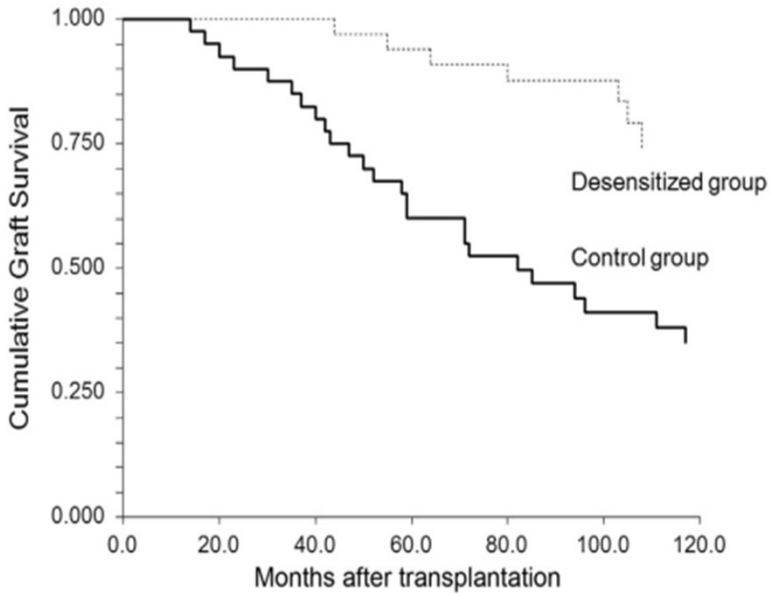
Individual and pooled estimates of the effect of antibody removal compared to control on graft survival

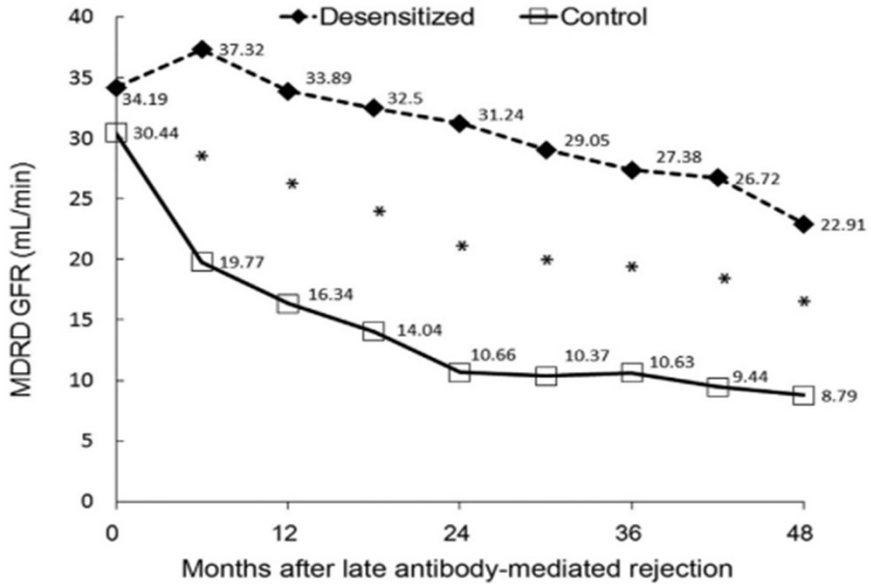


Antibody removal consists of plasmapheresis or column immunoadsorption.

Wan et al, Transplantation ■ April 2018 ■ Volume 102 ■ Number 4

Repeated cycles of high-dose intravenous immunoglobulin and plasmapheresis for treatment of late antibody-mediated rejection of renal transplants





CY Lee et al, J Formos Med Assoc. 2016; 115:845–852

Comparison of Combination Plasmapheresis/IVIg/ Anti-CD20 Versus High-Dose IVIg in the Treatment of Antibody-Mediated Rejection

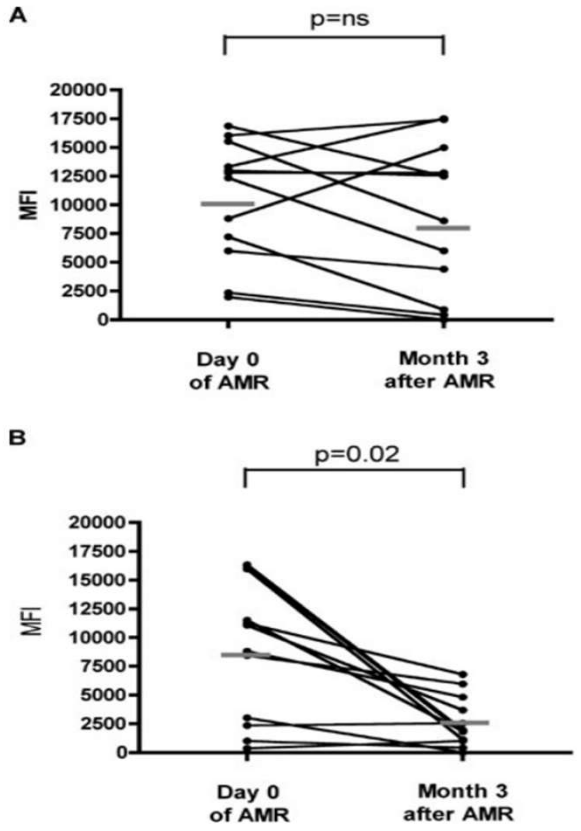
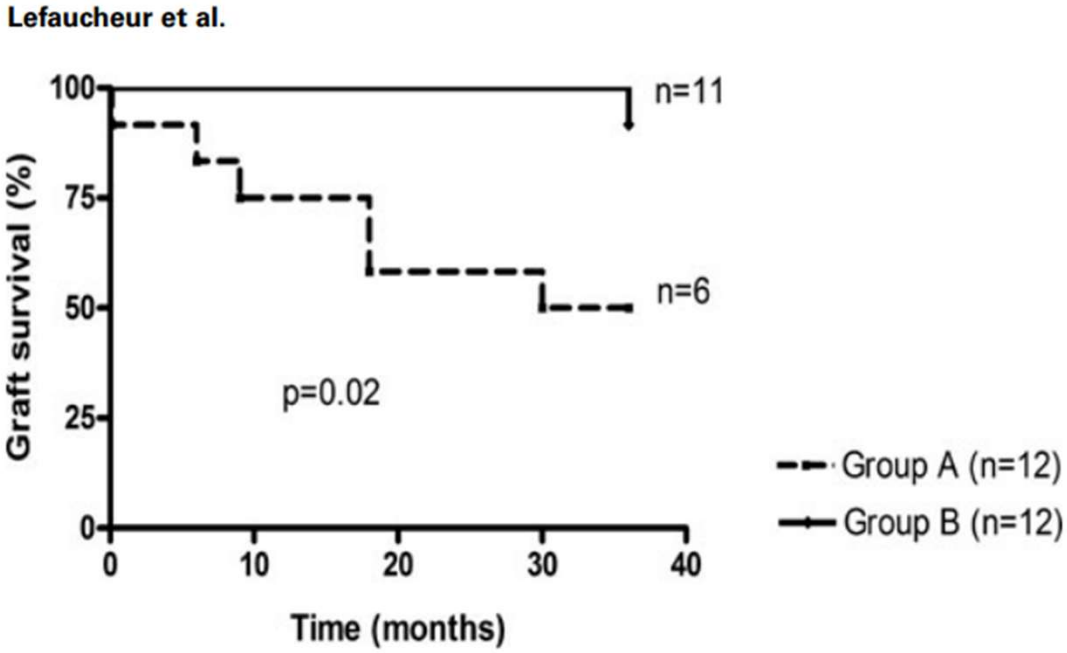


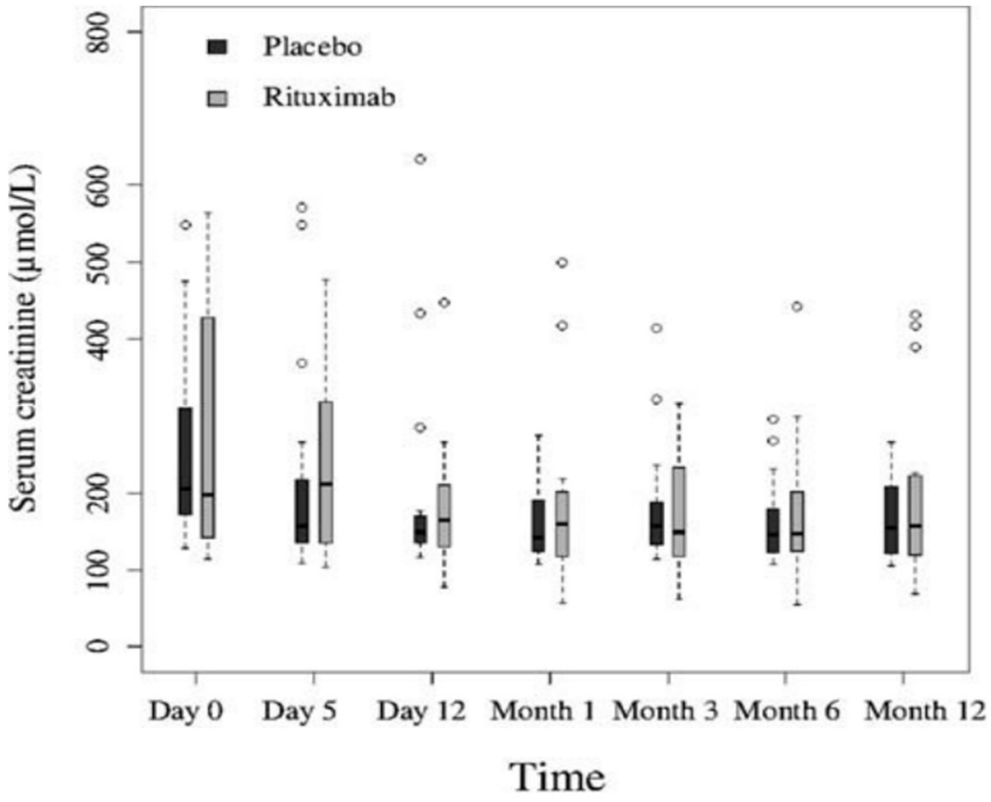
Figure 1: Variations in DSA MFImax between day 0 and 3 months post-AMR. (A) in group A (IVIg) and (B) in group B (PP/IVIg/anti-CD20).



(A) group A. AMR patients treated by IVIg protocol (B) group B. AMR patients treated by PP/IVIg/anti-CD20 protocol.

Lefaucheur et al, American Journal of Transplantation 2009; 9: 1099

RITUX ERAH, a Multicenter Double-blind Randomized Placebo-controlled Trial



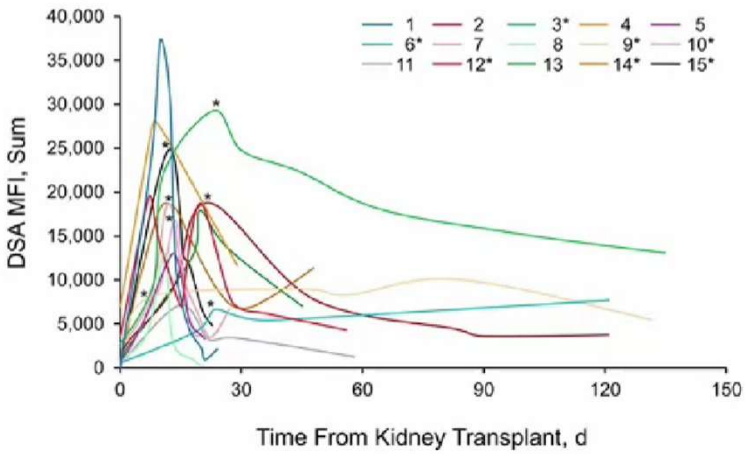
- **38 patients with biopsy proven AMR**
- **To receive rituximab (375 mg/m2) or placebo at day 5**
- **All patients received PE, IVIg, and CS.**
- **The primary endpoint was a composite of graft loss or no improvement in renal function at day 12.**

Sautenet , Transplantation ■ February 2016 ■ Volume 100 ■ Number 2

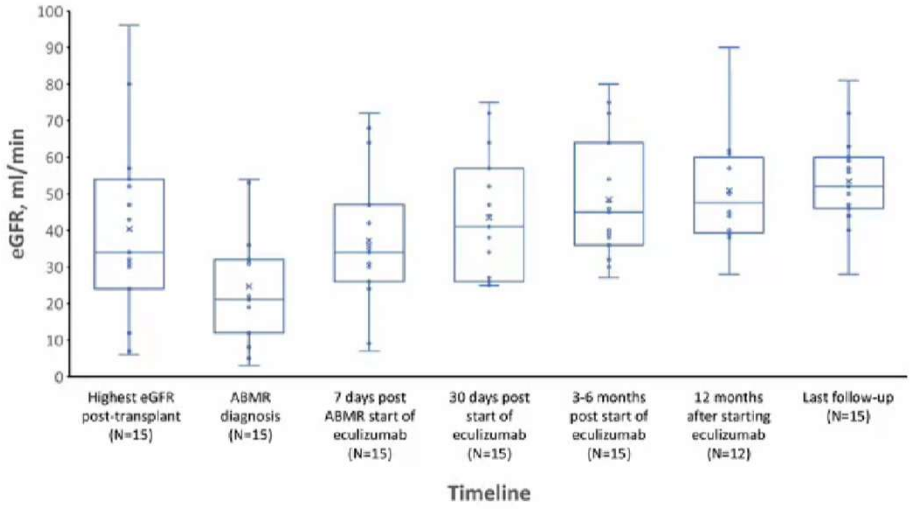
Eculizumab ± plasmapheresis for early AMR

	Value
Posttransplant day, median (IQR)	10 (7–11)
Serum creatinine at onset of AMR, median (IQR), mg/dL	2.4 (1.8–4.4)
eGFR at onset of AMR, median (IQR), mL/min	21 (12–32)
Doses of eculizumab, median (IQR), n	5 (2–10)
Plasmapheresis, n (%)	12 (80.0)
Sessions of plasmapheresis, median (IQR), n	7 (3–10)
Splenectomy, n (%)	1 (6.7)

AMR, antibody-mediated rejection; eGFR, estimated glomerular filtration rate; IQR, interquartile range.



Case series - 15 patients

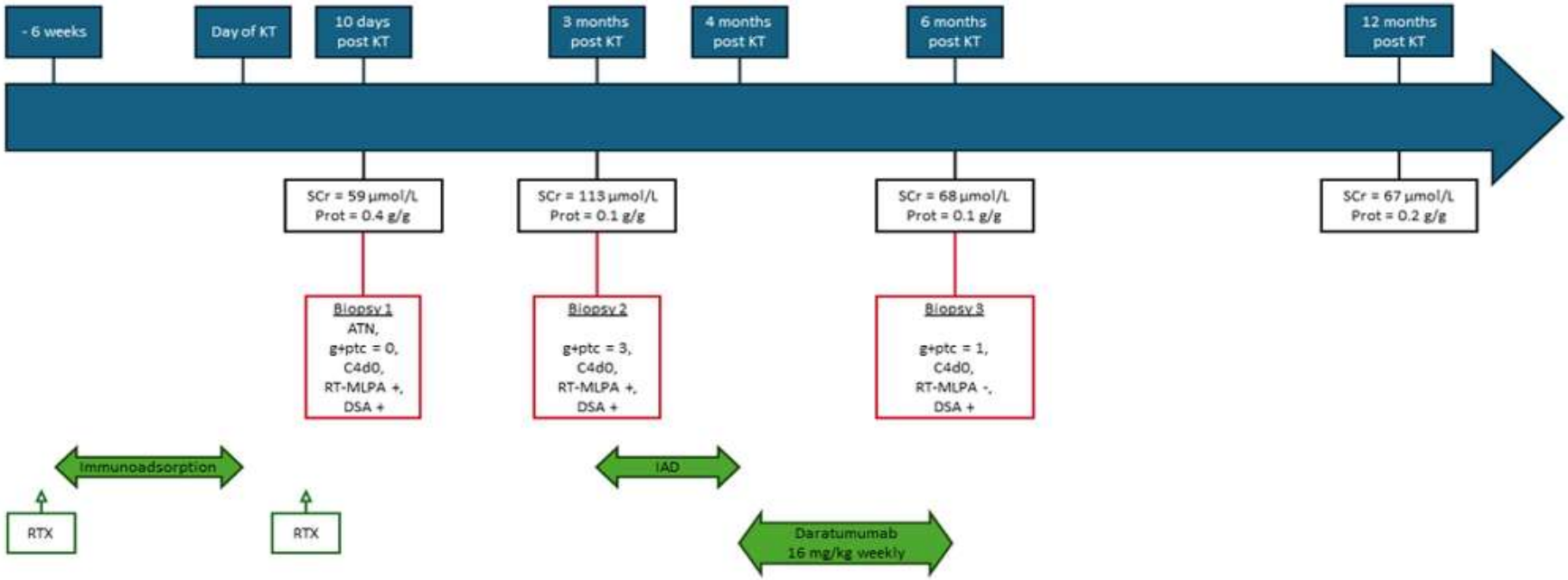


Tan et al., *Transplantation*. 2019; 103(11):2397

Prompt eculizumab treatment as primary therapy is safe and effective for early active AMR after kidney transplant

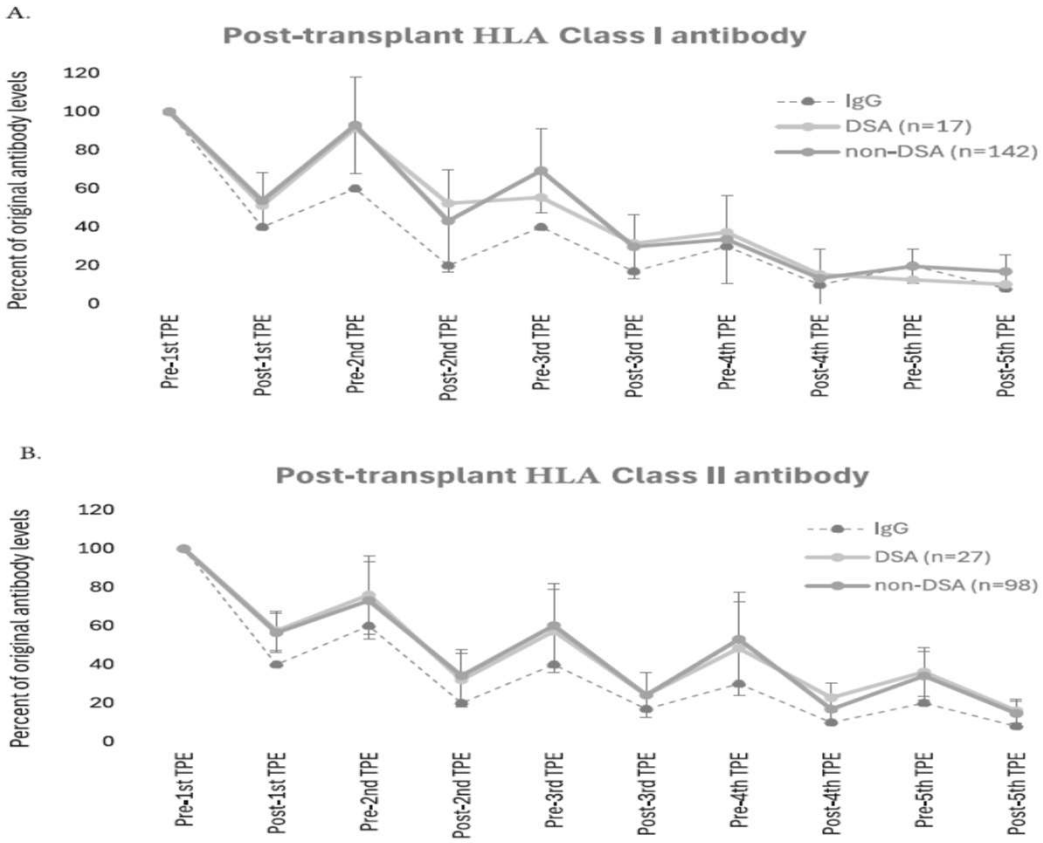
Daratumumab for antibody-mediated rejection: Is it time to target the real culprit?

Tristan de Nattes [1,*], Rangolie Kaveri [2], Fabienne Farce [2], Arnaud François [3], Dominique Guerrot [4], Mélanie Hanoy [5], Charlotte Laurent [5], Sophie Candon [6], Dominique Bertrand [5]



American Journal of Transplantation 23 (2023) 1990–1994

Figure 4. Antibody reduction in response to TPE in patients with AMR. Both DSA and non-DSA levels were evaluated for class I (A) and class II (B) antibodies. DD, deceased donor; DSA, donor-specific antibody; LD, living donor; TPE, therapeutic plasma exchange.



Standard TPE treatment consisted of 5 procedures of 1–plasma volume exchange with 5% albumin replacement scheduled every other day, followed by 100 mg/kg sucrose-free IVIG and 1000 mg/kg after the last TPE.

After 5 TPE sessions scheduled every other day:
Class I Ab levels were reduced by 85-90%
Class II Ab levels were reduce by 75-80%

Anti HLA are removed by TPE similarly to total IgG

Vantair N et al American Journal of Transplantation 25 (2025) 1491–1501

Plasma volume treated with double filtration plasmapheresis and outcomes of acute antibody-mediated rejection in kidney transplant recipients: A retrospective cohort study

Noppakun K et al. Ther Apher Dial. 2021;25:341–349.

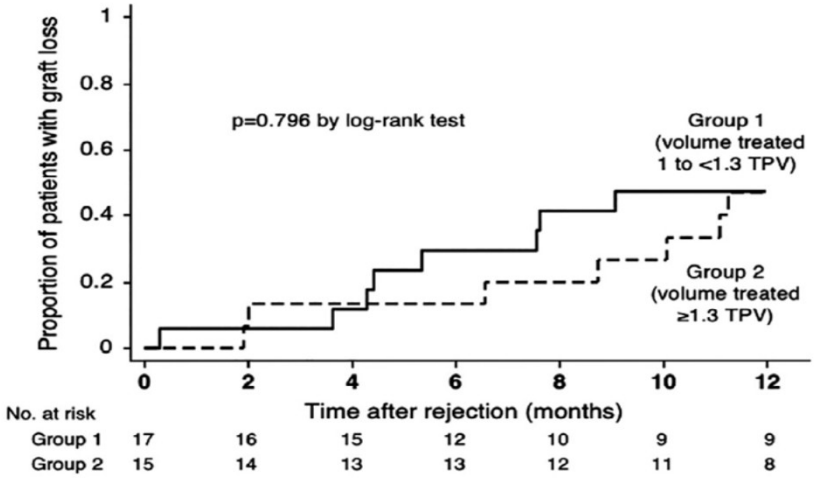


FIGURE 2 Cumulative incidence of graft loss during 1 year. TPV, total plasma volume

- retrospective cohort study
- association between the plasma volume treated by double filtration plasmapheresis and allograft outcomes for the treatment of acute antibody-mediated rejection in kidney transplant recipients.
- group 1 (pts 17), plasma volume treated between 1 and <1.3 total plasma volume
- group 2 (pts 15), plasma volume treated ≥1.3 total plasma volume.
- Therapy: MP 500 mg x 3, FK 5-20 ng7Ml; MMF 2g/die, IvIg 100 mg/Kg
- Primary outcome (≥50% reduction of serum creatinine)

Primary outcome occurred in 41% of group 1 and 40% of group.
Graft loss at 1 year did not differ between the two groups.
Infection tendency seemed to be higher in group 2 (40% vs 18%, P = .243).

A Comparison of Methods of Plasmapheresis for the Treatment of Late Antibody Mediated Rejection in Kidney Transplant Recipients

Caliskan Y, Mirioglu S, Dirim AB, et al. | *Ther Apher Dial*. 2023

Study Population

69 patients with late AMR (antibody-mediated rejection)

Chronic AMR

55.1% of patients

Acute AMR

42.0% of patients

TCMR

11.6% of patients

Treatment Arms

All arms received **IVIg 2 g/kg + Rituximab 375 mg/m²** in 75.4% of cases

PE

Plasma Exchange
n = 30

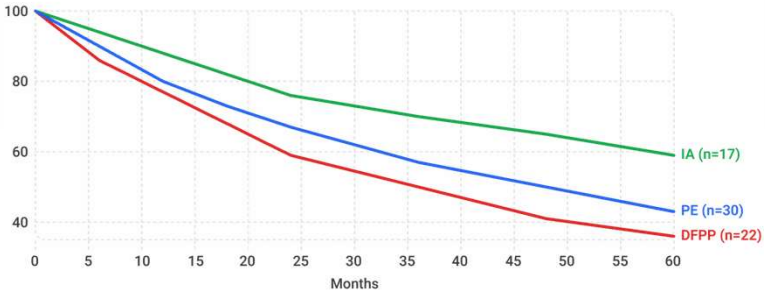
DFPP

Double Filtration Plasmapheresis
n = 22

IA

Immunoadsorption
n = 17

Kaplan-Meier — Death-Censored Graft Survival by Treatment Group



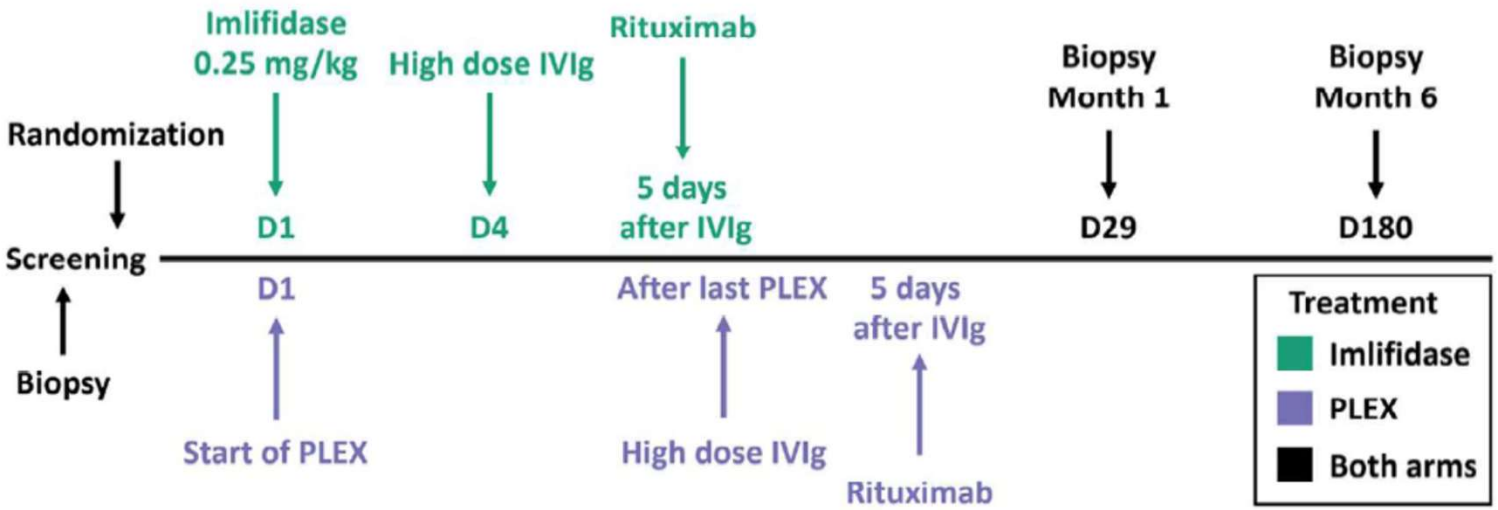
Graft survival (%) over 60 months follow-up. PE = Plasma Exchange; DFPP = Double Filtration Plasmapheresis; IA = Immunoadsorption.

A Randomized Trial Comparing Imlifidase to Plasmapheresis in Kidney Transplant Recipients With Antibody-Mediated Rejection

Fabian Halleck[1,2] | Georg A. Böhmig[3] | Lionel Couzi[4,5] | Lionel Rostaing[6] | Gunilla Einecke[7,8] | Carmen Lefaucheur[9] | Christophe Legendre[10,11] | Robert Montgomery[12] | Peter Hughes[13,14] | Anil Chandraker[15] | Kate Wyburn[16] | Phil Halloran[17] | Angela Q. Maldonado[18] | Kristoffer Sjöholm[18] | Anna Runström[18] | Paola Lefèvre[18] | Jan Tollemar[18] | Stanley Jordan[19]

- 6-month
- randomized, open-label, multicenter trial
- 14 transplant centers
- 30 patients randomized to either imlifidase or PLEX treatment.
- Primary endpoint: reduction in DSA level during the 5 days following the start of treatment.

Trial schedule, colors according to legend



Sampling for DSA, creatinine, pharmacodynamics and pharmacokinetics throughout the study

Clinical Transplantation, 2024; 38:e15383

A Randomized Trial Comparing Imlifidase to Plasmapheresis in Kidney Transplant Recipients With Antibody-Mediated Rejection

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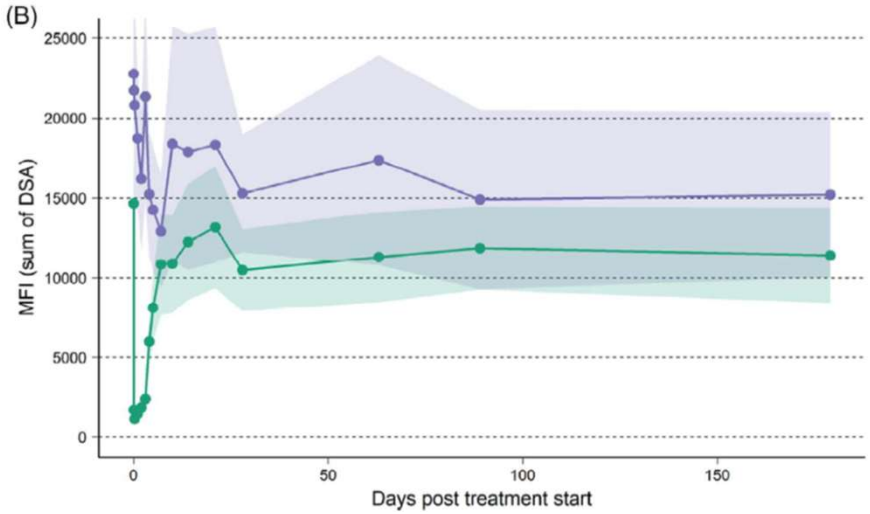
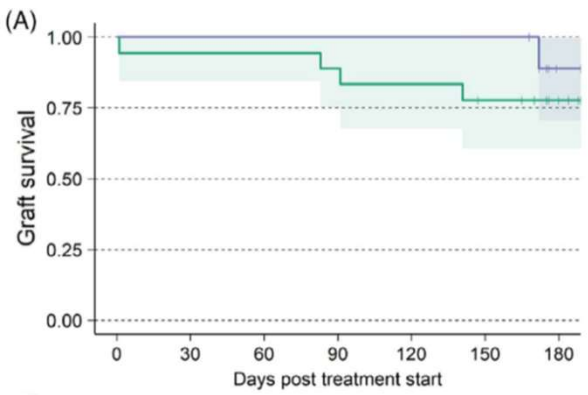
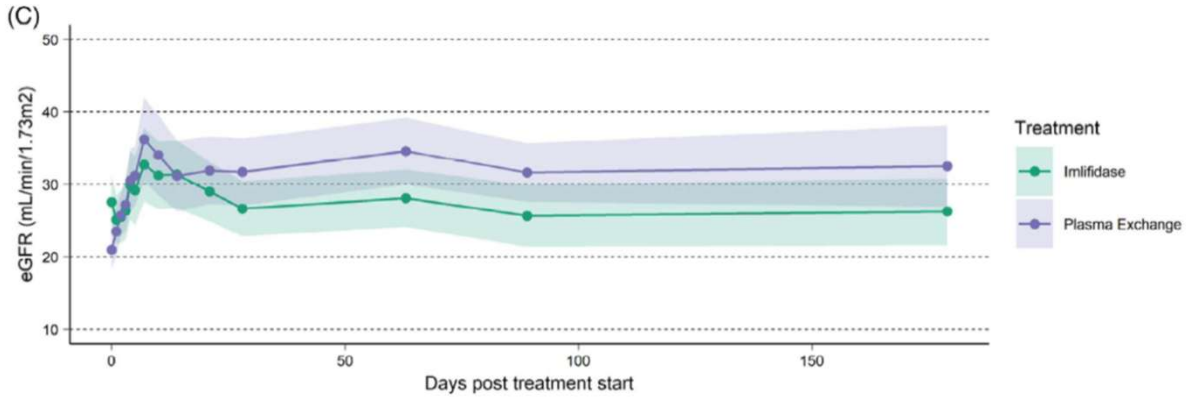
Clinical Transplantation, 2024; 38:e15383







Immunosuppressive therapy during therapeutic plasma exchange

Therapy	Relationship with PLEX	Practical timing
Eculizumab	Markedly removed by PLEX	**Immediately after PLEX**
Eculizumab – supplemental dose	Required after PLEX	**600 mg within 60 min after each PLEX** if the most recent scheduled dose was ≥600 mg
Rituximab	Significantly removed by PLEX	Give **after PLEX whenever possible**
Rituximab → subsequent PLEX	Important drug loss if PLEX is performed too early	**Preferably ≥72 h after rituximab**
IVIG	Significantly removed by PLEX	**After PLEX**, preferably after the final session
Tacrolimus	Limited removal	No specific timing requirement
Cyclosporine	Limited removal	No specific timing requirement
Mycophenolate mofetil	Some removal possible	Preferably **after PLEX** when feasible
Corticosteroids	Limited clinically relevan oval	Can generally be administered independently

Despite the lack of robust evidence from large randomized controlled trials, PLEX remains a cornerstone of the treatment of acute ABMR, supported by strong biological rationale, extensive clinical experience, observational data, and expert consensus.

PLEX is a part of the treatment of antibody-mediated rejection, which relies on a combination of therapeutic interventions.

The earlier the antibody-mediated injury, the greater the theoretical benefit of antibody removal.

The efficacy of plasma exchange in late acute and chronic antibody-mediated rejection remains unproven.

Immunosuppressive drugs should be administered at the appropriate time during plasma exchange to minimize their removal.