Quale ruolo delle tecniche di aferesi nelle vasculiti ANCA associate e nella malattia anti-GBM?

Chiara Salviani
UO Nefrologia e Dialisi
ASST Spedali Civili Brescia

C’era una volta…

- Uomo di 53 anni
- Creatinina ed esame urine nella norma in corso di ricovero ad Agosto 2014

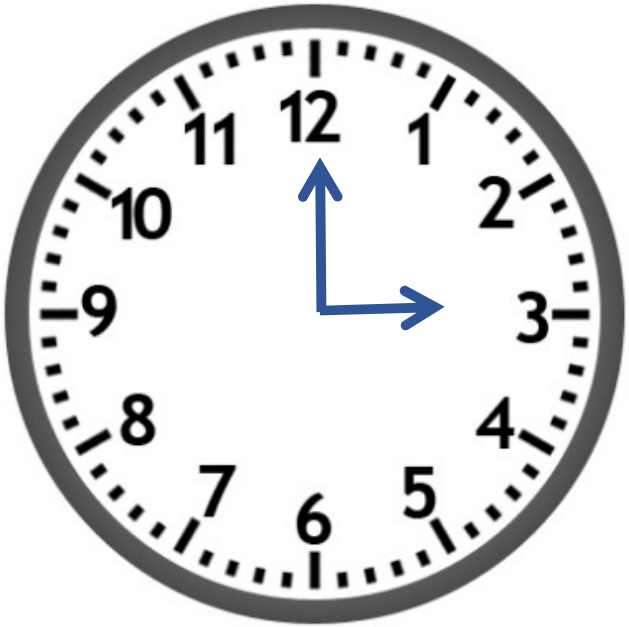
- Da Dicembre 2016 astenia ingravescente
- Da Gennaio 2017 ripetuti episodi di emoftoe

- 01/02/2017
  - Esami di laboratorio: anemia (Hb 9.2 g/dl); proteinuria 100 mg/dl e Hb +3
  - Rx torace: “sfumato addensamento parenchimale nel lobo inferiore sin”

- Inizia antibiotico-terapia, senza beneficio

C'era una volta…

13/02/2017



Ore 15:00 - Arrivo in PS

- Esami di laboratorio: Hb 6.3 g/dl, creatinina 11.9 mg/dl, sedimento nefritico
- Rx torace: "impegno interstizio-alveolare bilaterale, più esteso a sinistra, con relativo risparmio del campo superiore, e a destra confinato al campo inferiore"
- pO2 in aa 89 mmHg

C’era una volta…

13/02/2017

Ore 16:00
Ricovero in Pneumologia

Orientamento diagnostico di sindrome pneumo-renale

C'era una volta...

13/02/2017

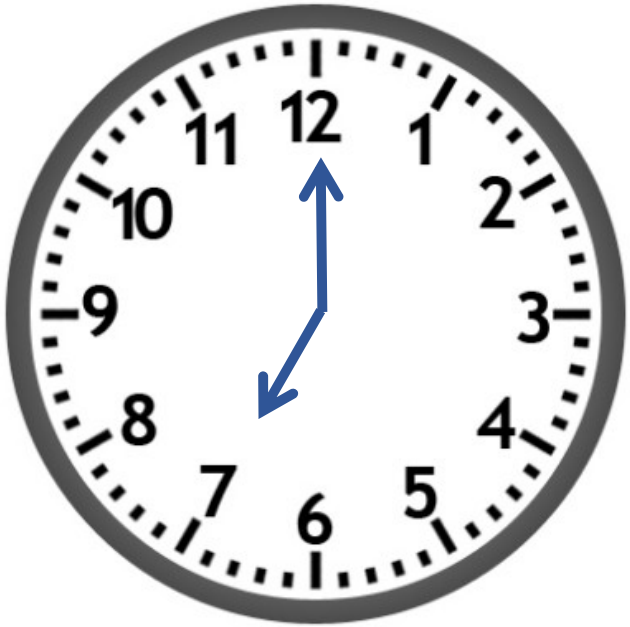
Ore 16:00
Ricovero in Pneumologia

Orientamento diagnostico di sindrome pneumo-renale

Ore 17:00
Trasferimento in Nefrologia

C’era una volta…

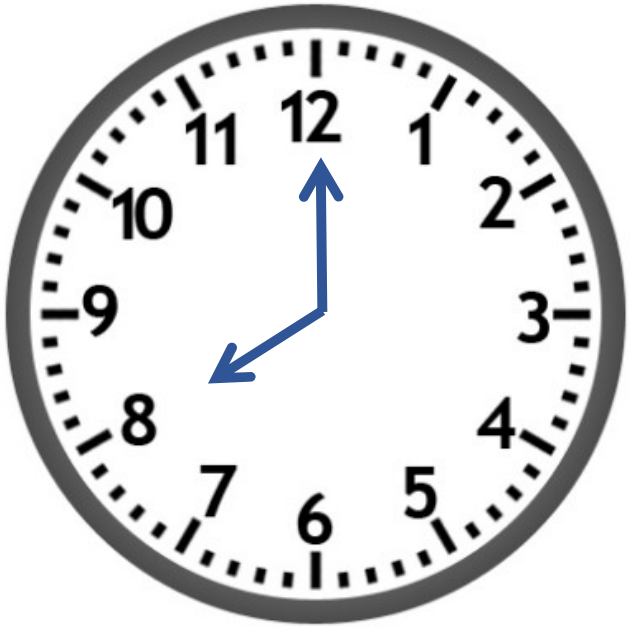
13/02/2017



Ore 19:00
TC torace:
“quadro compatibile con
emorragia endoalveolare”

C'era una volta…

13/02/2017



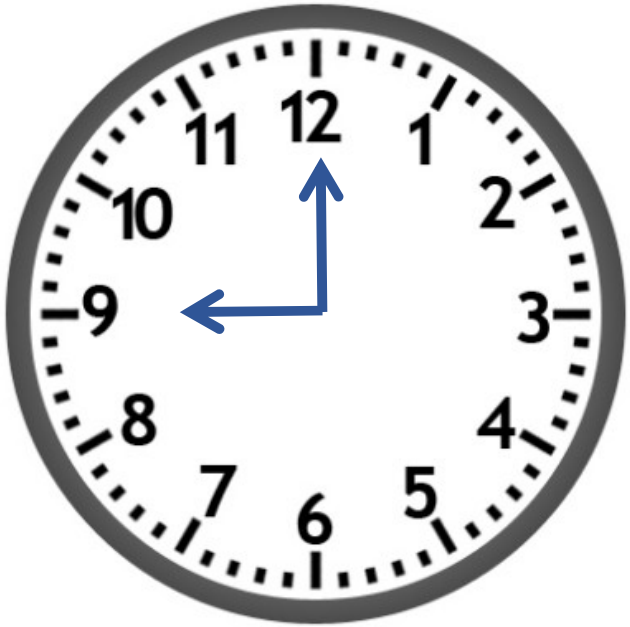
Ore 19:00
TC torace:
"quadro compatibile con **emorragia endoalveolare**"

Ore 20:00
Risultati ANCA

anti–MPO 120.8 RU/ml (vn <20)
anti-PR3 <2 RU/ml (vn <20)
anti GBM 0.1 <2 RU/ml (vn <20)

C'era una volta…

13/02/2017



Ore 19:00
TC torace:
"quadro compatibile con
emorragia endoalveolare"

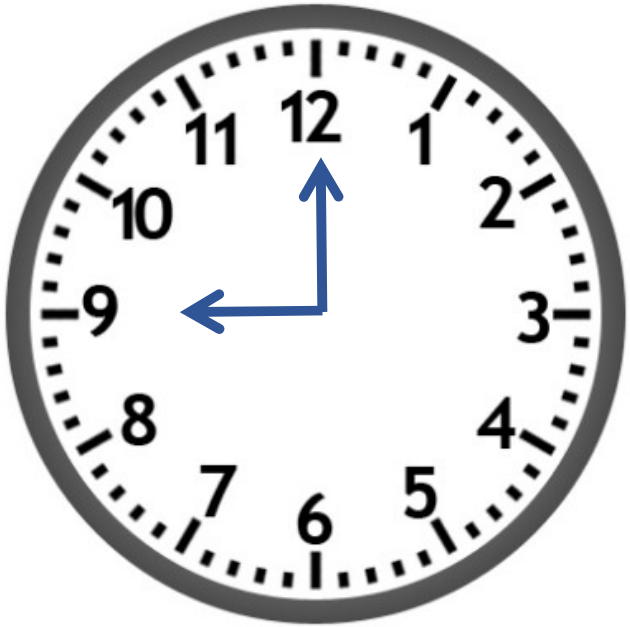
Ore 20:00
Risultati ANCA

anti–MPO 120.8 RU/ml (vn <20)
anti-PR3 <2 RU/ml (vn <20)
anti GBM 0.1 <2 RU/ml (vn <20)

Ore 21:00
1° bolo di steroide da 500 mg

C’era una volta…

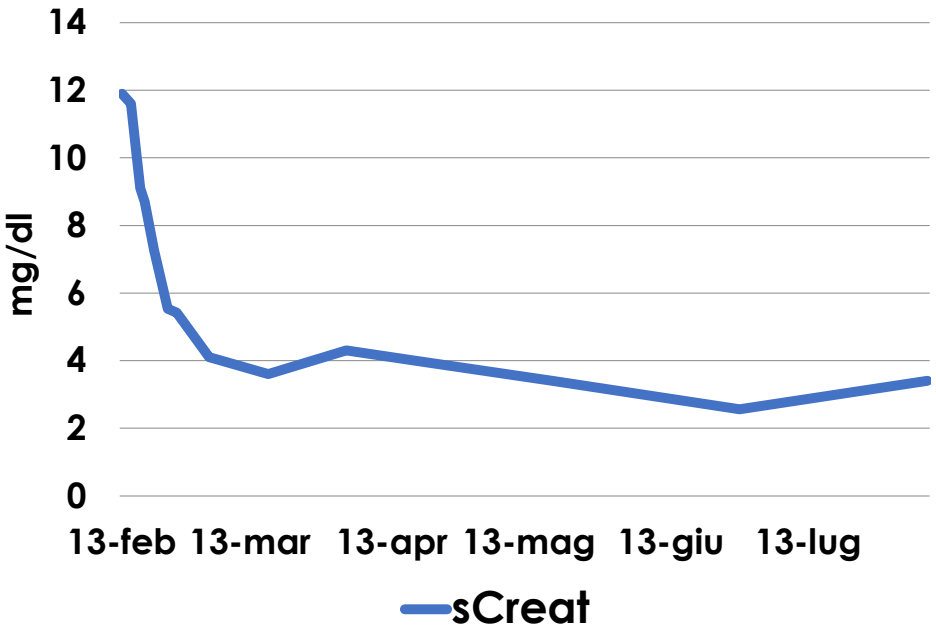
14/02/2017

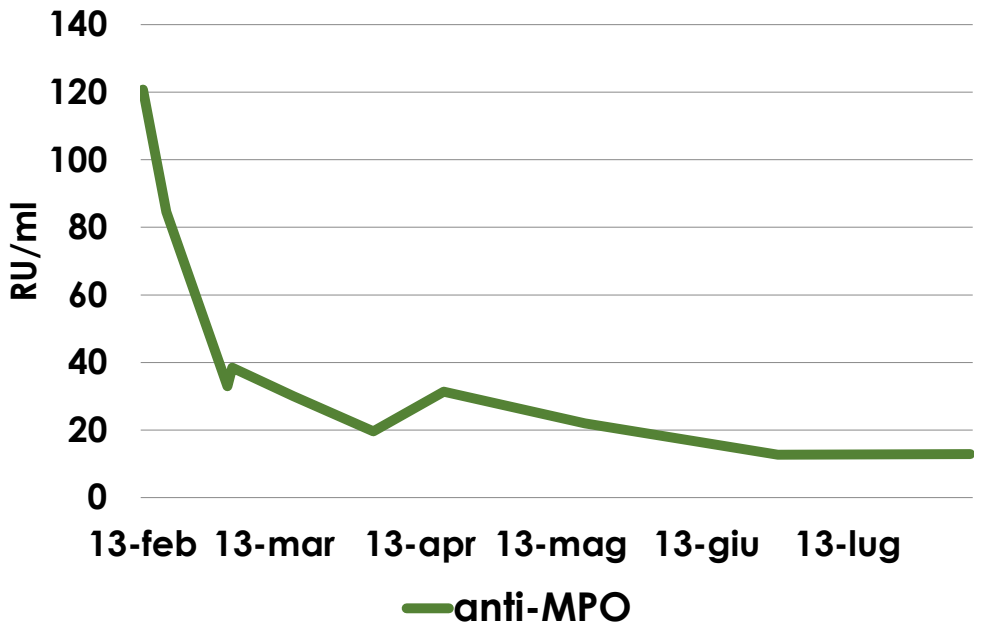


Ore 09:00
1° Plasma-exchange
2° e 3° in data 15 e 16/02,
4°, 5° e 6° in data 20-22-24/02

17/02/2017
1° di 4 dosi settimanali di Rituximab
(375 mg/m^2)

Andamento della funzione renale e del titolo degli ANCA





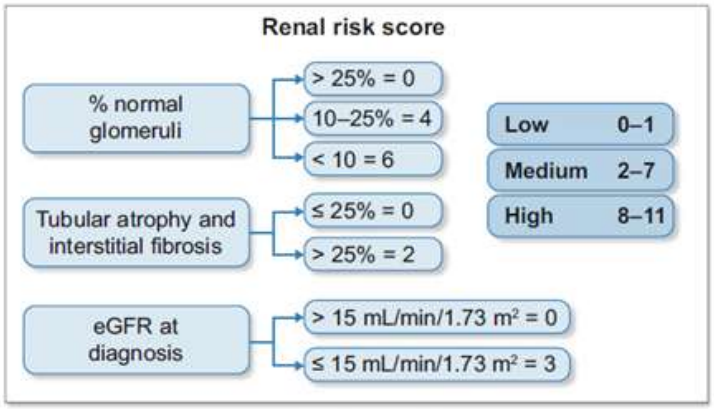
Ultimi esami (25/08/2026): creatinina 2.9 mg/dl eGFR 21.6 ml/min, esame urine negativo
ANCA 65 RU/ml, linfociti B assenti

Obiettivi della terapia delle AAV

Removing Antibody and Preserving Glomeruli in ANCA Small-Vessel Vasculitis

Sofia Lionaki and Ronald J. Falk
UNC Kidney Center, University of North Carolina, Chapel Hill, Chapel Hill, North Carolina

Best performance in predicting long-term kidney and patient survival



Focality of the glomerular lesions in AAV

It is possible that many segments of glomeruli or whole glomeruli may be spared from the disease, thereby allowing for long-term preservation of kidney function.

Lionaki S and Falk RJ. J Am Soc Nephrol 2007; 18: 1987–1989
Brix SR et al. Kidney Int. 2018; 94(6):1177-1188

Perché considerare la PEX per il trattamento dei pazienti affetti da vasculiti ANCA-associate?

Esigenza di controllare in modo rapido ed efficace le manifestazioni cliniche più gravi

Insufficienza renale

↓

ESKD

↓

Impatto sulla sopravvivenza a lungo termine e la qualità di vita

Emorragia endoalveolare diffusa

↓

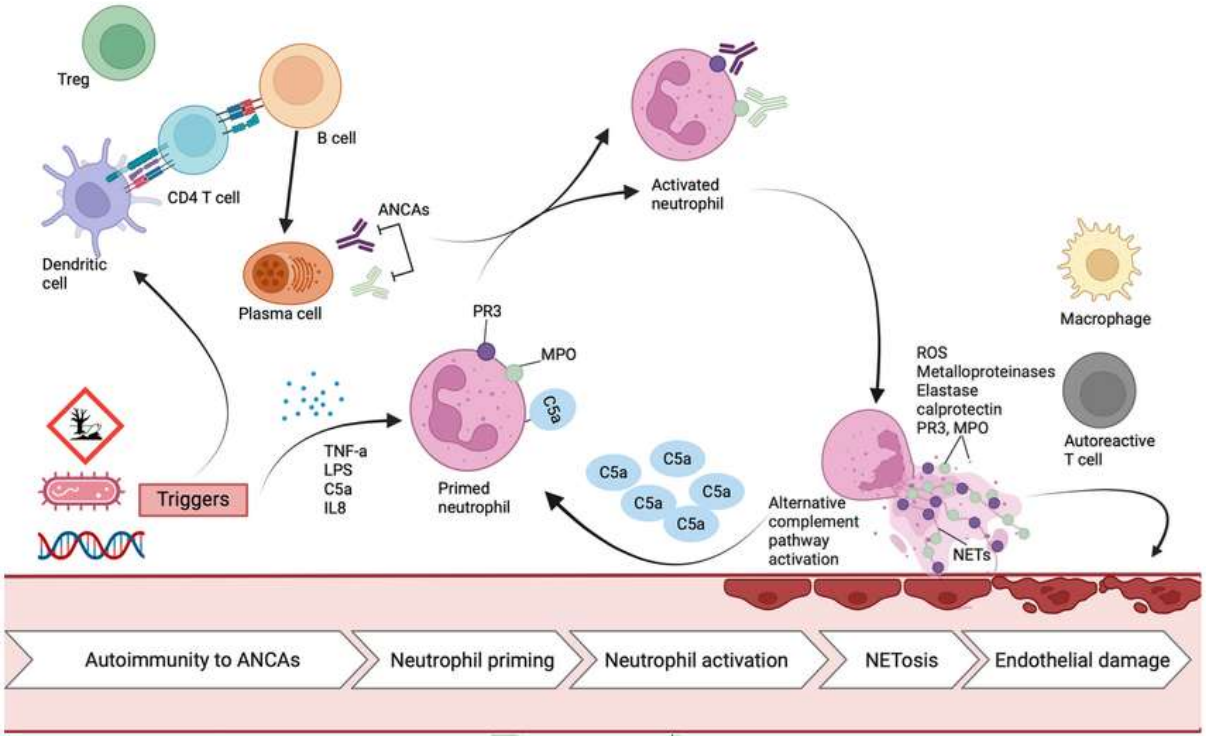
Insufficienza respiratoria

↓

Impatto sulla sopravvivenza nel breve termine

Perché considerare la PEX per il trattamento dei pazienti affetti da vasculiti ANCA-associate?

Ruolo patogenetico degli ANCA



Aqeel F et al. Curr Rheumatol Rep. 2024;26(8):290-301

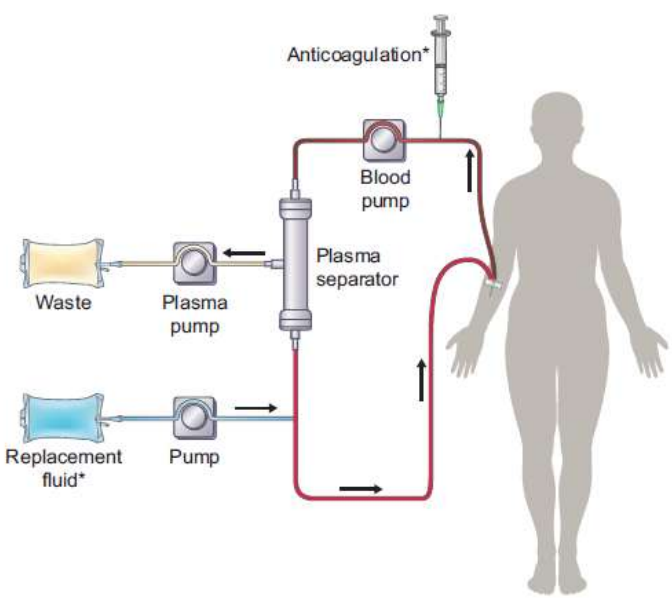
Effetti terapeutici della PEX nelle AAV

La plasmaferesi **rimuove**

- ANCA
- Fattori del complemento
- Fattori della coagulazione
- Citochine

RAPIDAMENTE

…mentre attendiamo che la terapia immunosoppressiva inibisca la risposta infiammatoria e prevenga un'ulteriore produzione degli ANCA



***Anticoagulation:**
- Heparin or citrate

***Replacement fluid:**
- Human serum albumin (3–5%, depending on local availability); may be combined with crystalloid (e.g. saline)
- Patients with active bleeding may receive supplemental (fresh frozen) plasma to replace clotting factors according to local practice

Seven plasma exchanges of 60 mL/kg are performed within 14 days or randomization

Serologic changes:
- ANCA level reduction > 70% (3–5 PLEX)
- ↓C_3a, C_5a, sC5b9
- C-reactive protein (↓64%, 1 session)
- IL-8 (↓34%), TNF-α (↓52%), VEGF (↓24%) (4–5 sessions)

IL = interleukin
TNF = tumor necrosis factor
VEGF = vascular endothelial growth factor
ANCA = anti-neutrophil cytoplasmic antibody
PLEX = plasma exchange

Kronbichler A et al. Nephrol Dial Transplant 2021; 36: 227-231

Possibili effetti avversi della PEX nelle AAV

Legati all'**accesso vascolare**:
- Ematomi
- Trombosi
- Infezioni

Nel paziente con **AAV severa**:
- Sanguinamento (polmonare se DAH, biopsia renale recente)
- Ipervolemia (pz oligoanurici)
- Rischio infettivo

Legati alla **procedura**:
- Anemia
- Ipotensione, dispnea, dolore toracico
- Trombocitopenia

Legati al **liquido di sostituzione**:
- Reazioni anafilattoidi (plasma)
- Coagulopatia (albumina)
- Infezioni (ipogammaglobulinemia)
- Alterazioni elettrolitiche: ipoK (albumina), ipoCa, IpoMg e alcalosi metabolica (plasma)

Cervantes CE et al. Am J Kidney Dise 2023; 81: 475-492

MEPEX trial

137 patients

28 European hospitals

03/1995-10/2002

Severe renal vasculitis

Serum creatinine >5.8 mg/dl

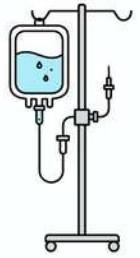
Biopsy proven pauci-immune ANCA-associated glomerulonephritis

All patients

Oral cyclophosphamide for 6 months

+

Oral prednisolone tapered over 12 months



Steroid group
1 g/d IV MP for 3 days

N = 67

PLEX group
7 sessions within14 days

N = 70

Exclusion criteria: Patients on dialysis from >2 weeks
Life-threatening nonrenal manifestations of vasculitis, including **alveolar hemorrhage** requiring mechanical ventilation<24h of admission

Jayne D et al. J Am Soc Nephrol 2007; 18: 2180–2188

MEPEX trial: baseline clinical features

Clinical and Laboratory Features at Entry	Intravenous Methylprednisolone (n = 67)	Plasma Exchange (n = 70)	Total (n = 137)	P
Age (yr; median [range])	66 (27 to 81)	67 (28 to 79)	66 (27 to 81)	0.93
Female gender (n [%])	24 (36)	29 (41)	53 (38.7)	0.50
Wegener's granulomatosis/microscopic polyangiitis (n [%])	24/43 (35.8/64.2 8)	18/52 (25.7/74.3)	42/95 (30.7/69.3)	0.20
Nonoliguric/dialysis requiring (n [%])	19/48 (28.4/71.6)	23/47 (32.9/67.1)	42/95 (30.7/69.3)	0.57
PR3-ANCA (n [%])	31 (46.3)	26 (37.1)	57 (42.6)	0.35
MPO-ANCA (n [%])	31 (46.3)	40 (57.1)	71 (51.9)	
ANCA negative (n [%])	3 (4.5)	4 (5.7)	7 (5.3)	
BVAS	21 (12 to 41)	21 (12 to 39)	21 (12 to 41)	0.69
Vasculitis Damage Index (median [range])	0 (0 to 4)	0 (0 to 7)	0 (0 to 7)	0.86
Creatinine (μmol/L; median [range])	718 (498 to 1566)	754 (500 to 1669)	735 (498 to 1669)	0.96
C-reactive protein (mg/L; median [range])	108 (2 to 264)	76 (7 to 281)	93 (2 to 281)	0.23
Erythrocyte sedimentation rate (mm/h; median [range])	84 (2 to 150)	94 (20 to 140)	89 (2 to 150)	0.34

[a]ANCA, autoantibodies to neutrophil cytoplasmic antigens; BVAS, Birmingham Vasculitis Activity Score; MPO, myeloperoxidase; PR3, proteinase 3.

Jayne D et al. J Am Soc Nephrol 2007; 18: 2180–2188

MEPEX trial: baseline histology

Table 2. Baseline histologic characteristics[a]

Histologic Lesion	Intravenous Methylprednisolone (n = 49)	Plasma Exchange (n = 51)	Total Group (n = 100)
Glomerular			
% normal glomeruli	13.6 ± 18.2	12.1 ± 12.1	12.8 ± 15.3
% fibrinoid necrosis	28.9 ± 25.3	22.2 ± 24.9	25.5 ± 25.2
% crescents	59.2 ± 28.6	53.0 ± 28.9	56.0 ± 28.8
segmental	23.1 ± 23.4	28.9 ± 31.3	25.9 ± 27.3
circumferential	76.9 ± 44.3	71.1 ± 54.3	74.1 ± 49.5
cellular	90.4 ± 49.1	90.8 ± 57.2	90.6 ± 53.0
fibrous	9.6 ± 12.6	9.2 ± 18.0	9.4 ± 15.3
% global sclerosis	24.6 ± 26.9	28.2 ± 24.6	26.4 ± 25.7
Tubulointerstitial and vascular			
interstitial edema (0/1)	0.5 ± 0.5	0.5 ± 0.5	0.5 ± 0.5
interstitial infiltrates (0/1/2/3)	1.8 ± 0.7	1.8 ± 0.6	1.8 ± 0.7
neutrophilic (0/1/2)	0.7 ± 0.4	0.7 ± 0.5	0.7 ± 0.5
mononuclear cell (0/1/2)	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4
eosinophilic (0/1/2)	0.4 ± 0.5	0.3 ± 0.5	0.4 ± 0.5
interstitial fibrosis (0/1/2)	1.2 ± 0.6	1.3 ± 0.6	1.2 ± 0.6
tubular casts (0/1)	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3
tubular necrosis (0/1)	0.8 ± 0.4	0.8 ± 0.4	0.8 ± 0.4
tubular atrophy (0/1/2)	1.1 ± 0.5	1.2 ± 0.6	1.1 ± 0.6
intraepithelial infiltrates (0/1)	0.8 ± 0.4	0.8 ± 0.4	0.8 ± 0.4
arteriosclerosis (0/1)	0.8 ± 0.4	0.7 ± 0.4	0.8 ± 0.4

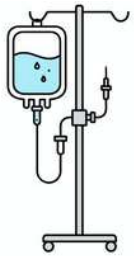
[a]The average distribution of the most characteristic glomerular, tubulointerstitial, and vascular lesions from 100 renal biopsies are described according to treatment group. This represents 75% of the 137 patients who were randomly assigned in this study. Glomerular lesions are expressed as a mean percentage ± SD of the total number of glomeruli per patient. All crescents were scored as either segmental or circumferential and as either cellular or fibrous, expressed as a percentage ± SD of the total number of crescents. Tubulointerstitial and vascular lesions were scored either in a dichotomous or in a semiquantitative manner. The numbers after every lesion indicate the possible scoring values.

Jayne D et al. J Am Soc Nephrol 2007; 18: 2180–2188

MEPEX trial: results

PRIMARY OUTCOME

Renal recovery (dialysis independence) at 3 months



Steroid group

33/67 (49%)

VS

PLEX group

48/70 (69%)

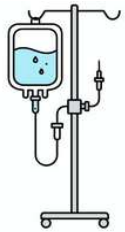
95% confidence interval for the difference 18 to 35%; *P*= 0.02

The **risk reduction for ESRD at 12 months** (43% for methylprednisolone *versus* 19% for plasma exchange) was **24%** (95% CI 6.1 to 41).

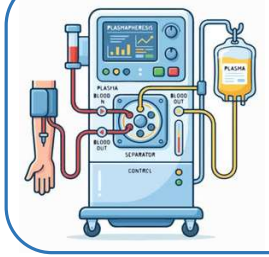
Jayne D et al. J Am Soc Nephrol 2007; 18: 2180–2188

MEPEX trial: results

SECONDARY OUTCOMES



Steroid group



PLEX group

Patient survival at 1 year	**51/67 (76%)**	**VS**	**51/70 (73%)** → **P = NS**
Severe adverse event rates	**32/67 (48%)**	**VS**	**35/70 (50%)** → **P = NS**

Jayne D et al. J Am Soc Nephrol 2007; 18: 2180–2188

MEPEX trial: long-term follow-up

Median follow up: 3.95 years

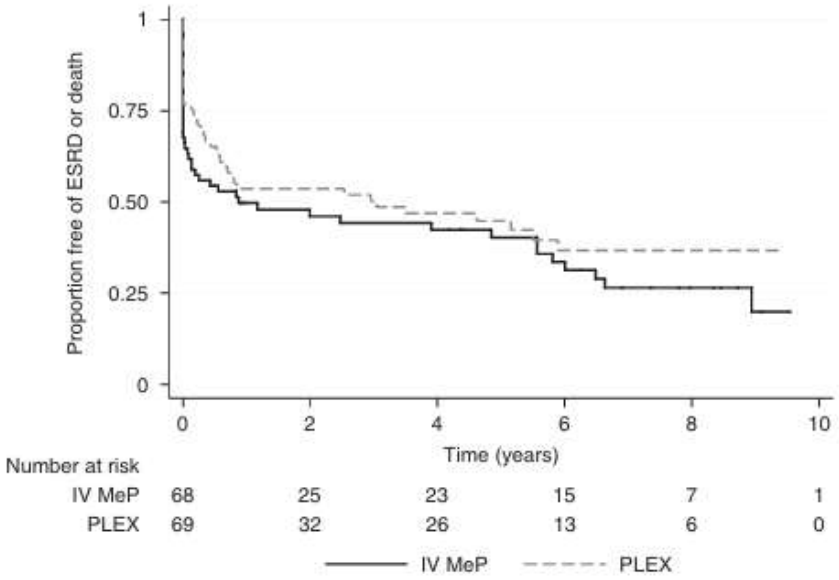


Figure 2 | Kaplan–Meier curve of composite outcome.
Kaplan–Meier curve of the composite outcome of end-stage renal disease (ESRD) or death according to randomization to treatment with intravenous methylprednisolone (IV MeP) or plasma exchange (PLEX).

Table 3 | Long-term primary and secondary outcomes by treatment group

Outcome	IV MeP, $n = 68$ (%)	PLEX, $n = 69$ (%)	HR (95% CI)	*P*-value
Death or ESRD	46 (68)	40 (58)	0.81 (0.53–1.23)	0.32
Death	35 (51)	35 (51)	1.08 (0.67–1.73)	0.75
ESRD[a]	33 (49)	23 (33)	0.64 (0.40–1.05)	0.08
Relapse[a]	16 (21)	10 (14)	0.56 (0.26–1.21)	0.14

Abbreviations: ESRD, end-stage renal disease; HR, hazard ratio; IV MeP, intravenous methylprednisolone; PLEX, plasma exchange group.
[a]Subhazard ratio presented.
P-value based on Cox regression or competing risk regression model.

Walsh M et al. Kidney Int 2013; 84:397–402.

Negli ultimi decenni…

Evoluzione terapie immunosoppressive
Miglioramento delle terapie di supporto
Maggiore precocità della diagnosi

Miglioramento della prognosi delle AAV

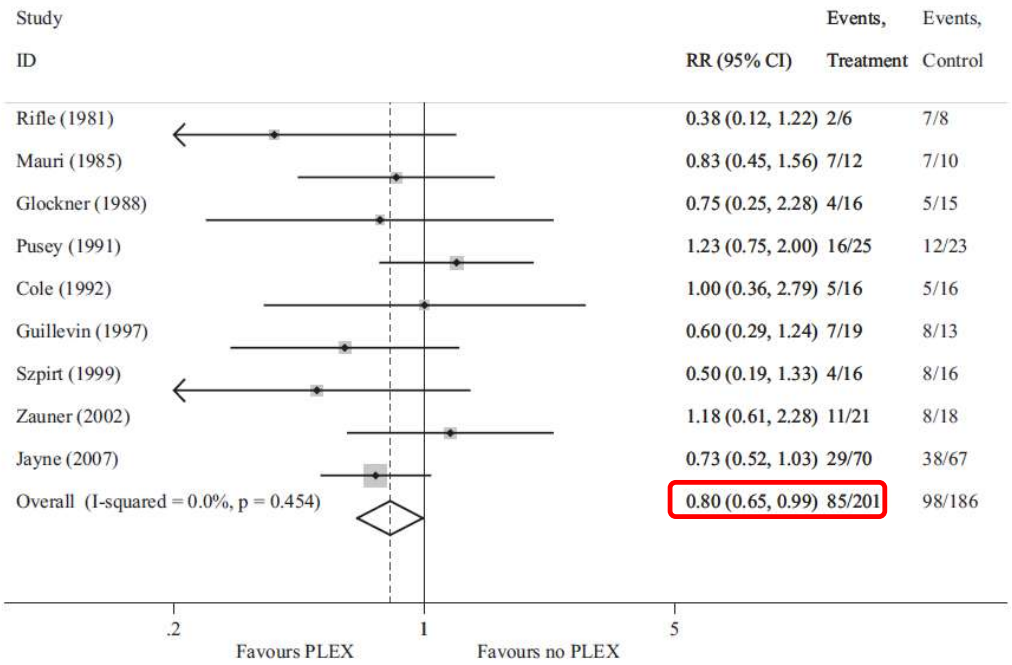
INCIDENZA DI ESKD: 20%
MORTALITÀ PRECOCE PER DAH: 5-11%

…quali evidenze sulla PEX nelle AAV?

Alamo BS, et al. Nephrol Dial Transplant. 2024, 0: 1-11
Cartin Ceba R et al. Arthritis Rheumatol. 2016;68(6):1467-76

Plasma Exchange for Renal Vasculitis and Idiopathic Rapidly Progressive Glomerulonephritis: A Meta-analysis

Michael Walsh, MD, MSc,[1,2] Fausta Catapano, MD, PhD,[2] Wladimir Szpirt, MD,[3] Kristian Thorlund, MSc,[1] Annette Bruchfeld, MD, PhD,[4] Loic Guillevin, MD,[5] Marion Haubitz, MD,[6] Peter A. Merkel, MD, MPH,[7] Chen Au Peh, MD, PhD,[8] Charles Pusey, DSc,[9] and David Jayne, MD[2]



Forest plot of effects of adjunctive PLEX
on the **composite end point** of **ESRD or death** in patients with AAV

In this meta-analysis of 9 trials including 387 patients, we could not show conclusive evidence that adjunctive plasma exchange decreases ESRD and death in patients with AAV. Despite statistically significant results suggesting a 20% RR reduction, too few patients are randomly assigned and sensitivity analyses were not sufficiently robust to reliably conclude that plasma exchange has at least a moderate decrease in the composite end point of ESRD or death. In addition, whether plasma exchange affects survival or only the development of ESRD is unclear.

Walsh M et al. Am J Kidney Dis. 2011; 57(4):566-574

PEXIVAS trial

704 patients

95 hospitals
in 16 countries

06/2010-09/2016

Kidney involvement and/or pulmonary involvement

eGFR<50
ml/min/1.73m^2
or diffuse alveolar hemorrhage

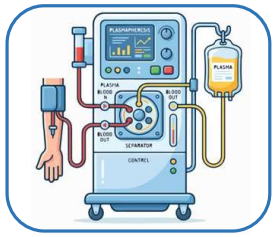
All patients

Induction therapy with rituximab or cyclophosphamide

+

daily iv methylprednisolone for 1 to 3 days, for a maximum cumulative dose of 1 to 3 g

PEX



7 treatments within 14 days after randomization

GC standard dose

GC reduced dose

NO PEX

GC standard dose

GC reduced dose

Walsh M et al, N Engl J Med 2020; 382:622-31

PEXIVAS trial: baseline characteristics

Table 1. Characteristics of the Patients at Baseline.*

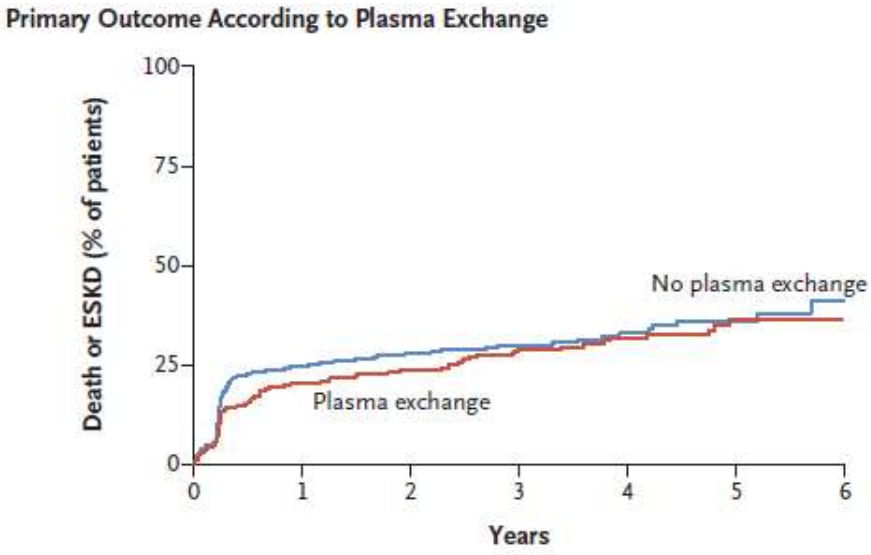
Characteristic	Plasma Exchange (N=352)	No Plasma Exchange (N=352)	Reduced-Dose Glucocorticoid Regimen (N=353)	Standard-Dose Glucocorticoid Regimen (N=351)
Age — yr	62.8±14.4	63.5±13.7	63.3±14.2	63.1±13.9
Female sex — no. (%)	149 (42.3)	158 (44.9)	156 (44.2)	151 (43.0)
History of vasculitis — no. (%)	35 (9.9)	28 (8.0)	34 (9.6)	29 (8.3)
ANCA subtype — no. (%)				
Proteinase 3	143 (40.6)	143 (40.6)	143 (40.5)	143 (40.7)
Myeloperoxidase	209 (59.4)	209 (59.4)	210 (59.5)	208 (59.3)
Median C-reactive protein level (IQR) — mg/liter	50.9 (13.8–122.8)	42.1 (14.0–97.2)	44.6 (13.0–117.0)	45.5 (14.0–98.0)
Median hemoglobin level (IQR) — g/liter	94 (83–105)	95 (85–105)	95 (84–105)	95 (84.5–105)
Kidney function				
Median serum creatinine level (IQR) — μmol/liter	327 (206–491)	336 (209–495)	320 (190–480)	335 (219–502)
Serum creatinine level ≥500 μmol/liter or undergoing dialysis — no. (%)	101 (28.7)	104 (29.5)	102 (28.9)	103 (29.3)
Undergoing dialysis — no. (%)	66 (18.8)	74 (21)	67 (19.0)	73 (20.8)
Severity of pulmonary hemorrhage — no. (%)				
No hemorrhage	257 (73.0)	256 (72.7)	257 (72.8)	256 (72.9)
Not severe	64 (18.2)	66 (18.8)	65 (18.4)	65 (18.5)
Severe†	31 (8.8)	30 (8.5)	31 (8.8)	30 (8.5)

Walsh M et al, N Engl J Med 2020; 382:622-31

PEXIVAS trial

PRIMARY COMPOSITE OUTCOME

Death from any cause or ESKD

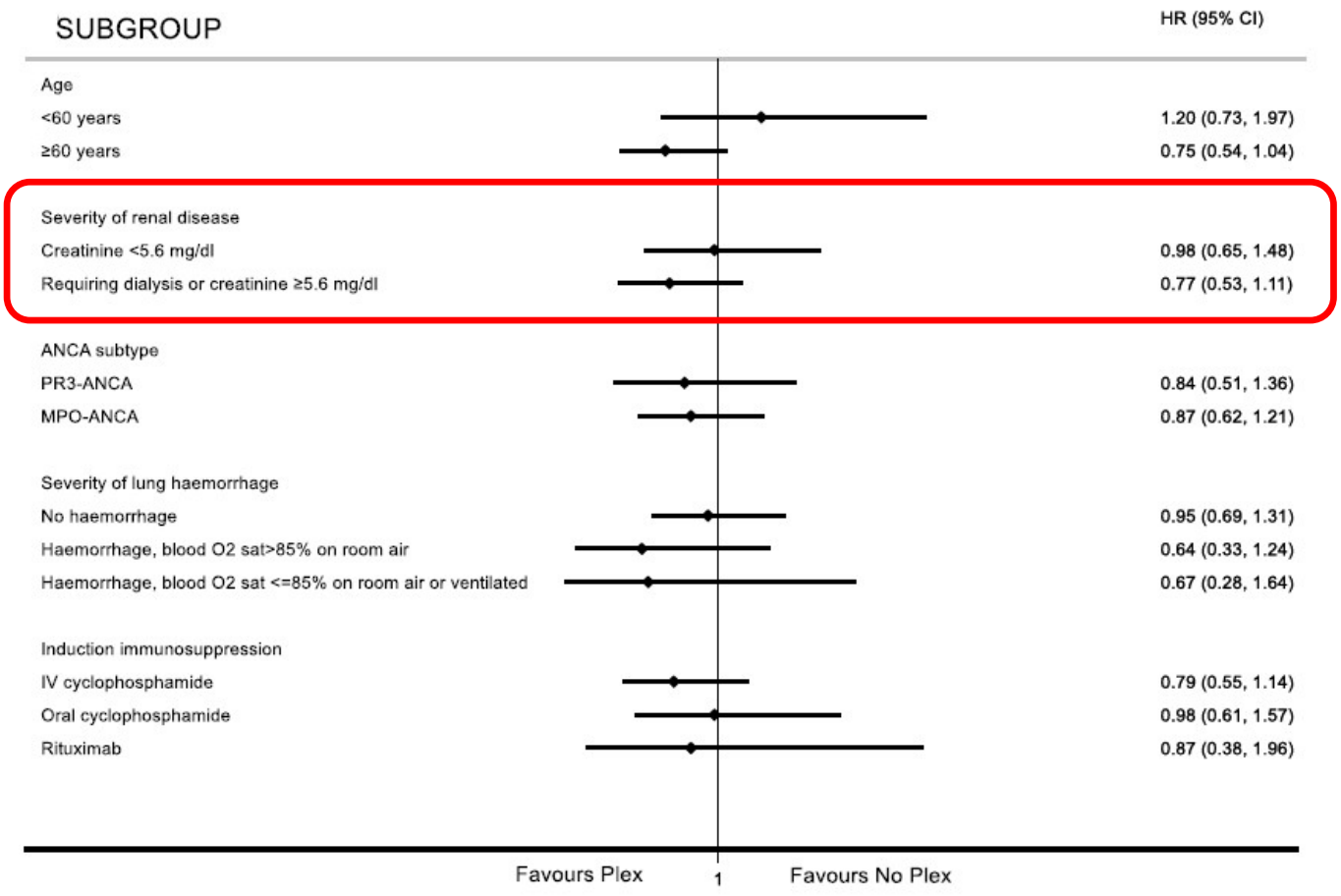


PEX group 28.4% vs control group 31.0%

(HR 0.86; 95% CI, 0.65 to 1.13; P = 0.27)

Walsh M et al, N Engl J Med 2020; 382:622-31

PEXIVAS trial: subgroup analysis

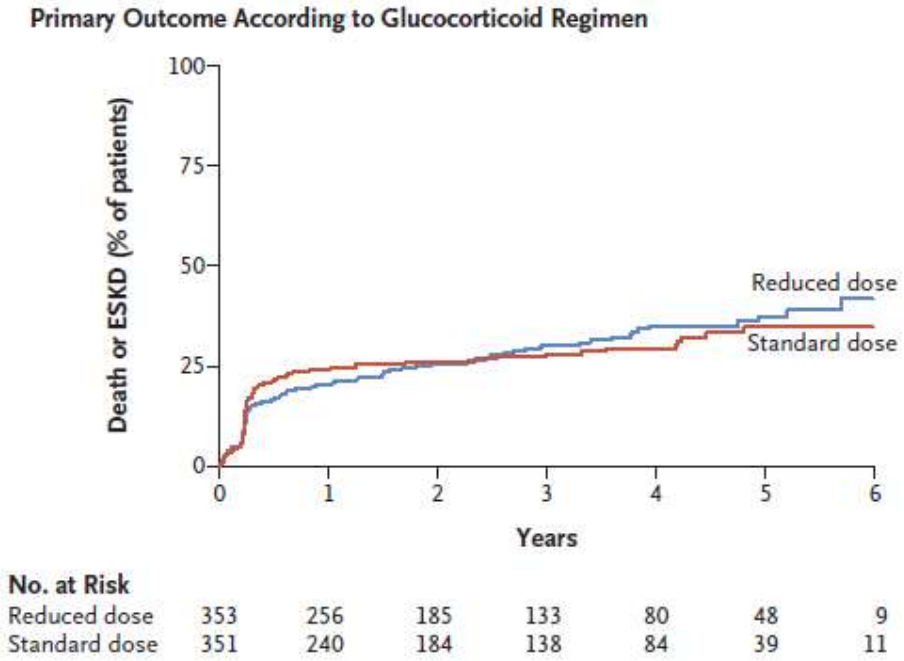


Walsh M et al, N Engl J Med 2020; 382:622-31

PEXIVAS trial

PRIMARY COMPOSITE OUTCOME

Death from any cause or ESKD



Noninferiority

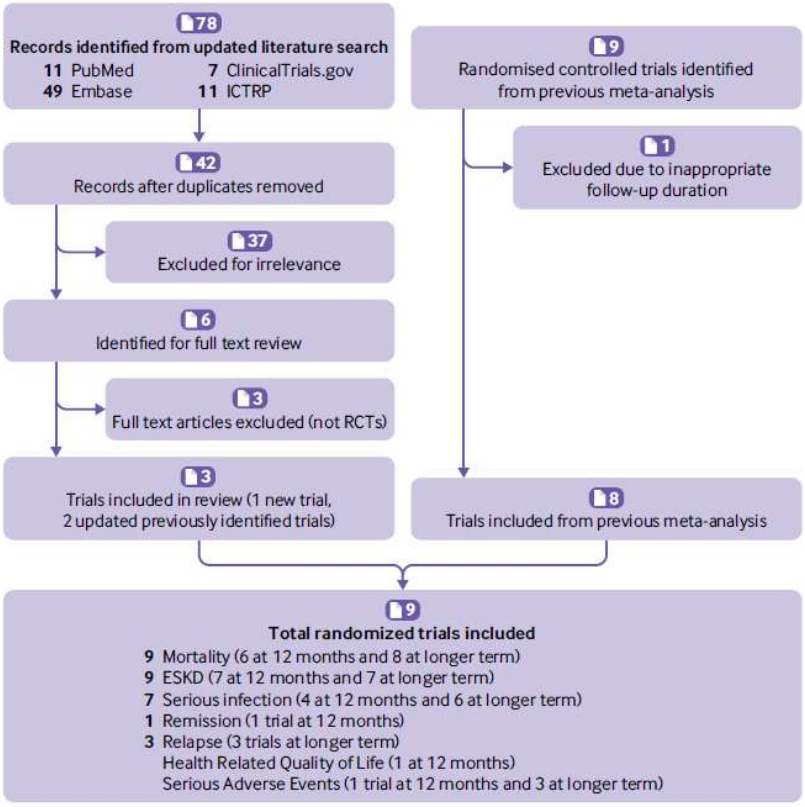
Reduced-dose group 27.9% vs 25.5% in standard-dose group

(absolute risk difference, 2.3 percentage points; 90% CI, −3.4 to 8.0)

Walsh M et al, N Engl J Med 2020; 382:622-31

The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis

Michael Walsh,[1,2,3] David Collister,[3,4] Linan Zeng,[2,5] Peter A Merkel,[6] Charles D Pusey,[7] Gordon Guyatt,[1,2] Chen Au Peh,[8,9] Wladimir Szpirt,[10] Toshiko Ito-Hara,[11,12] David R W Jayne,[13] on behalf of the Plasma exchange and glucocorticoid dosing for patients with ANCA-associated vasculitis BMJ Rapid Recommendations Group*



Nine trials including 1060 participants

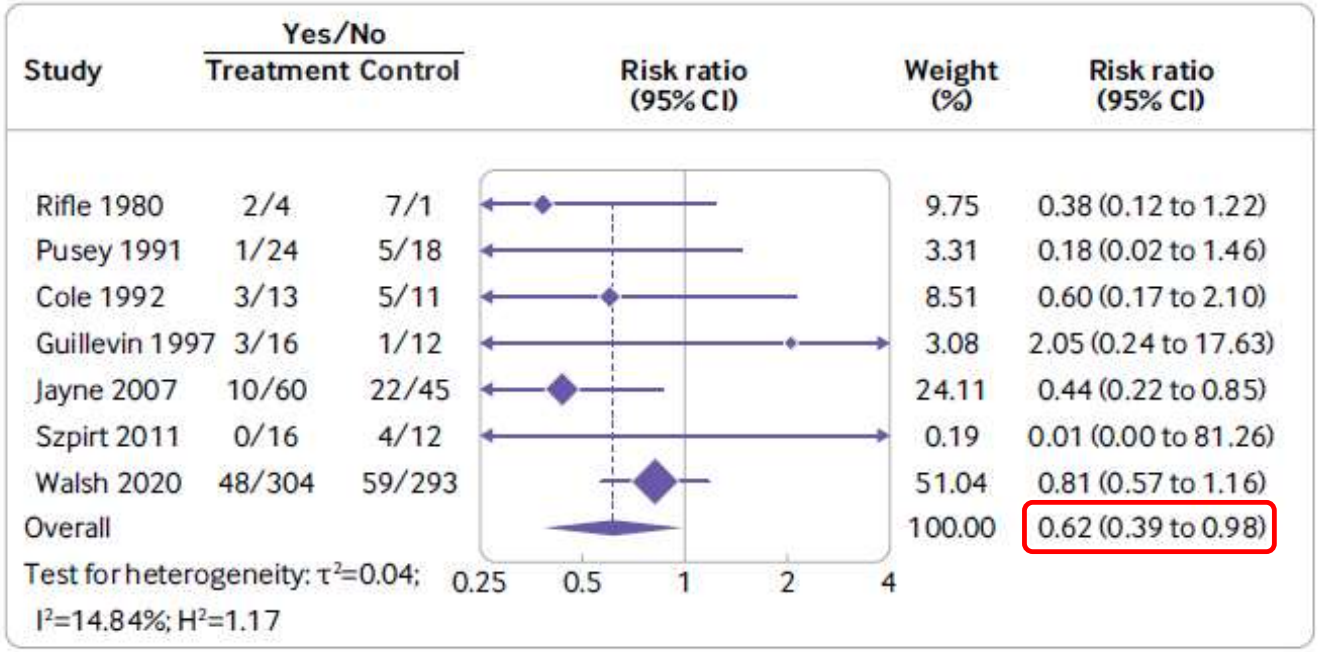
INTERPRETATION

For the treatment of AAV, plasma exchange has no important effect on mortality, reduces the 12 month risk of ESKD, but increases the risk of serious infections.

Walsh M et al. BMJ 2022; 376:e064604

Metanalysis

PEX reduces the risk of ESKD at 12 months

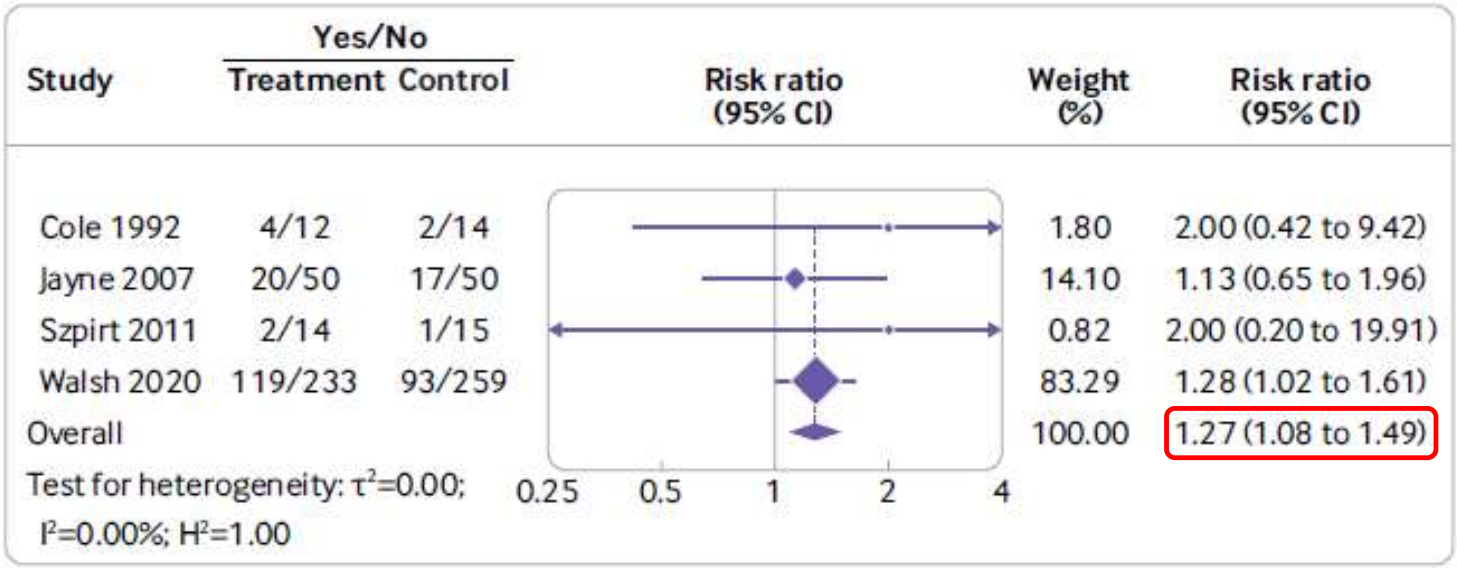


The absolute risk reduction in ESKD with PLEX was
0.1% in serum Cr <2.3 mg/dl
1.9% in sCr 2.3-3.4 mg/dl
4.2% in sCr 3.4-5.7 mg/dl
15.2% in sCr 5.7 mg/dL or on dialysis

Walsh M et al. BMJ 2022; 376:e064604

Metanalysis

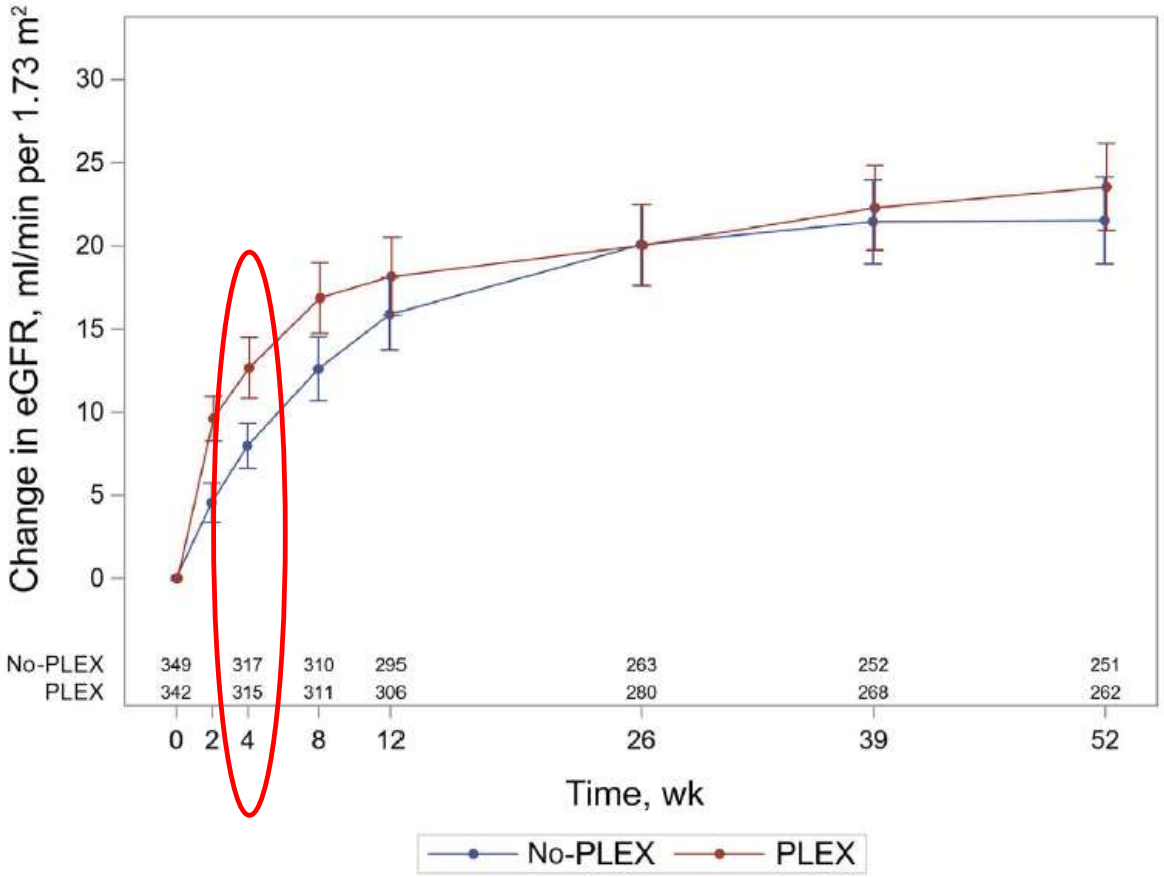
PEX increases the risk of serious infections within 12 months



Walsh M et al. BMJ 2022;376:e064604

Effect of PEX on early kidney function

***Post-hoc* analysis of PEXIVAS**

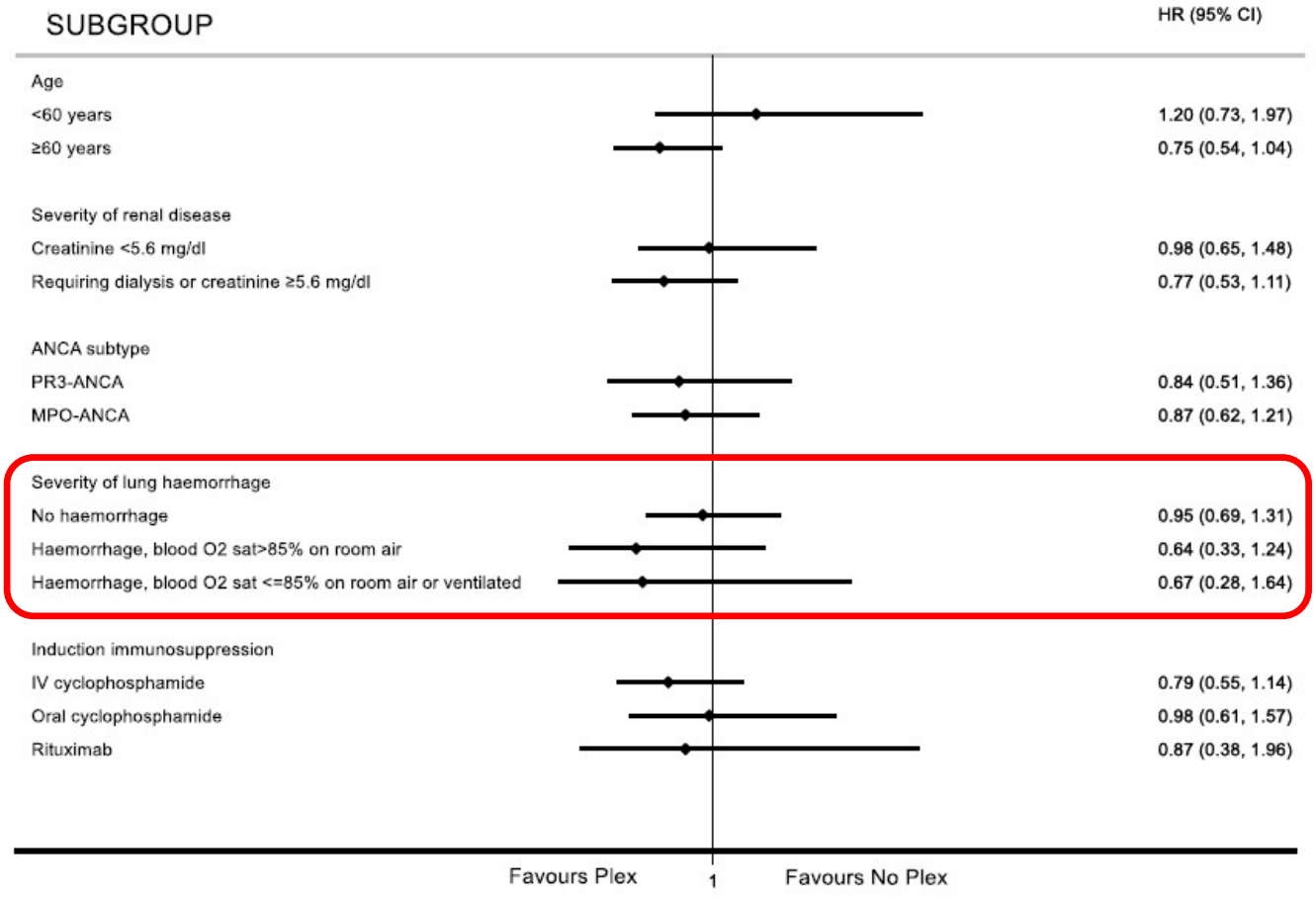


Increased eGFR or recovery of kidney function at week four

Lower risk for ESKD at week 52
(RR: 0.96: 0.95-0.97, and RR: 0.29: 0.16-0.52; respectively).

Odler B et al. Kidney Int 2025; 107, 558-576

DAH in PEXIVAS trial: subgroup analysis



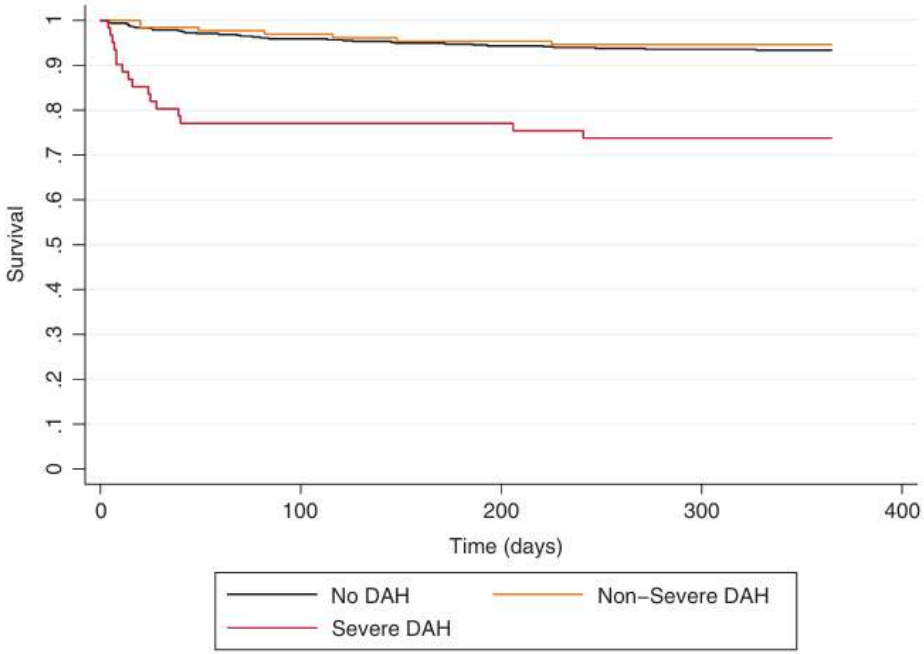
191/704 participants with DAH (27.1%) (61 severe, including 29 ventilated)

Underpowered study: **low number of events**

Walsh M et al, N Engl J Med 2020; 382:622-31

PEXIVAS trial: diffuse alveolar hemorrhage

Increased mortality for patients with severe DAH

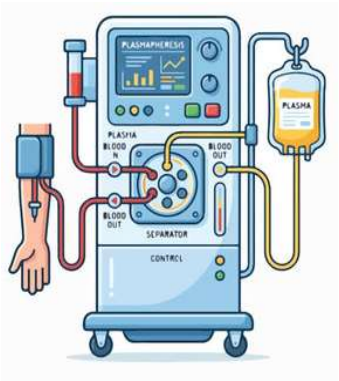


No effects of PEX

	Mortality at 3 months and 1 year	Ventilator-Free days	Rates of serious infection at one year
PLEX vs No PLEX	No difference	No difference	No difference
Standard vs Reduced Steroids	No difference	Reduced compared to standard steroids had fewer ventilator-free days Reduced (median 23, IQR 20-25) to Standard (median 26, IQR 25-28), p =0.009	No difference

Fussner L et al. Am J Respir Crit Care Med. 2024 May 1;209(9):1141-1151
Glassberg MK, Ali A, Gregorini G. Am J Respir Crit Care Med. 2024; 209(9):1062-1064

ACR Guidelines



Recommendation: In patients with GPA/MPA with active glomerulonephritis, we conditionally recommend *against* the routine addition of plasma exchange to remission induction therapy.

Plasma exchange should not be initiated in all patients with active glomerulonephritis but can be considered for patients at higher risk of progression to end-stage renal disease (ESRD) who accept a potential increased risk of infection.

Chung SA et al. Arthritis Rheumatol. 2021; 73(8):1366-1383.

American Society for Apheresis Guidelines

Two indications were changed when compared with the interim fact sheet: "vasculitis, ANCA associated, microscopic polyangiitis" and "Vasculitis, ANCA associated, granulomatosis with polyangiitis" (II→III for rapidly progressive glomerulonephritis and creatinine ≥5.7 mg/dL; I→III for diffuse alveolar hemorrhage). In this edition, the "Vasculitis, ANCA associated" indications are now separated by pathology (e.g., "Microscopic polyangiitis" and "Granulomatosis with polyangiitis"), and both are category III regardless of creatinine levels and the presence of diffuse alveolar hemorrhage.

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision-making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB/Ethics Committee approval is desirable if apheresis treatment is undertaken in these circumstances.

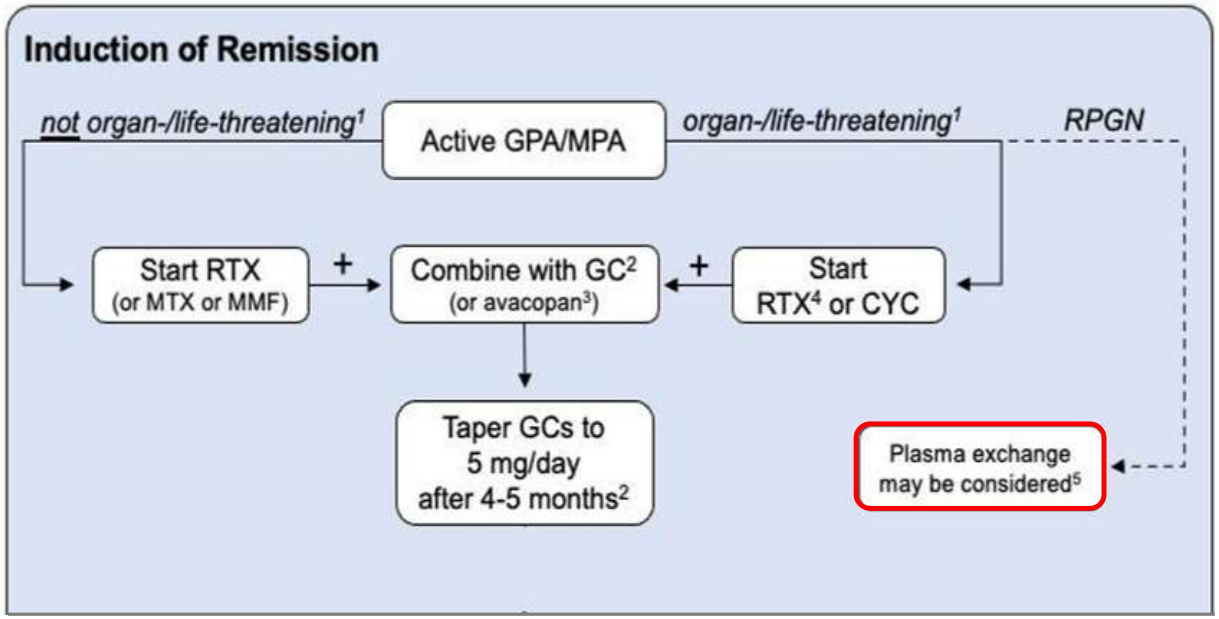
Abbreviation: IRB, Institutional Review Board.

Disease/condition	Indication	Procedure	Category	Grade
Vasculitis, ANCA associated	Microscopic polyangiitis	TPE	III	1B
	Granulomatosis with polyangiitis	TPE	III	1B
	Eosinophilic granulomatosis with polyangiitis	TPE	III	2C

Connelly-Smith L et al. J Clin Apher. 2023; 38(2):77-278.

eular | EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

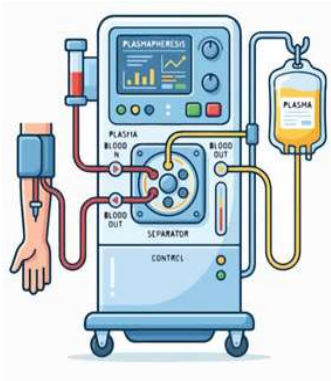
EULAR Guidelines



In selected patients with serum creatinine >300 µmol/L due to active glomerulonephritis, plasma exchange may be considered taken into account individual risk for end-stage kidney disease and patient preferences.

Hellmich B, et al. Ann Rheum Dis 2024;83:30–47

KDIGO Guidelines



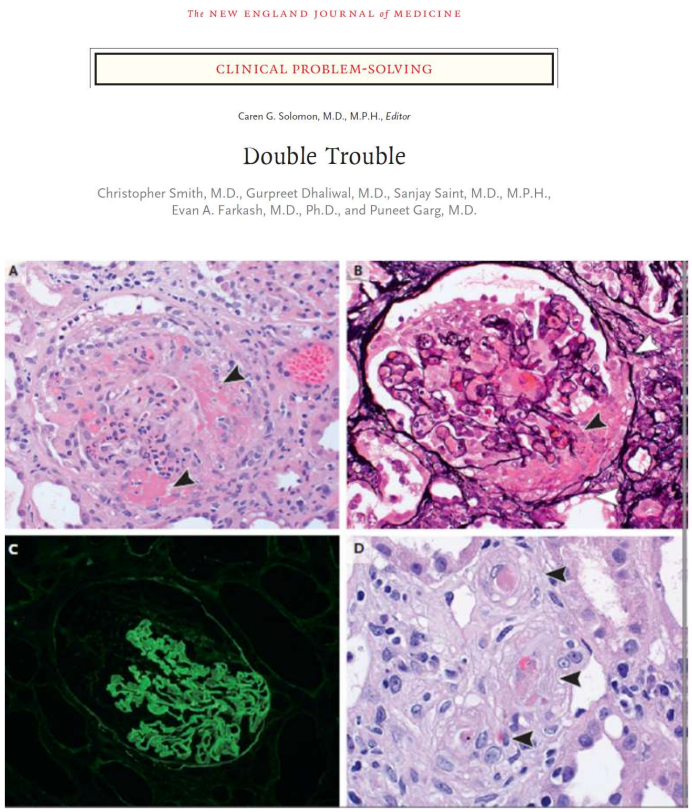
Practice Point 9.3.1.9: Consider plasma exchange for patients with SCr >3.4 mg/dl (>300 µmol/l), patients requiring dialysis or with rapidly increasing SCr, or patients with diffuse alveolar hemorrhage who have hypoxemia.

Practice Point 9.3.1.10: Add plasma exchange for patients with an overlap syndrome of ANCA-associated vasculitis and anti-glomerular basement membrane (GBM).

Kidney Disease: Improving Global Outcomes (KDIGO) ANCA Vasculitis Work Group. Kidney Int. 2024;105(3S):S71-S116

AAV and anti-GBM disease

- Large series of double positive in patients with AAV



	Double positive / Total AAV (%)
Zhao, 2007	61/652 (9%)
Jennette, 2003	25/179 (14%)
Jayne, 1990	20/266 (8%)
Hellmark, 1996	38/270 (14%)
Levy, 2004	38/954 (4%)
Rutgers, 2005	10/56 (18%)
McAdoo, 2017	37/605 (6%)

8% of AAV patients: **positive anti-GBM** antibodies

Smith C, et al. N Engl J Med. 2019;381(19):1854-1860

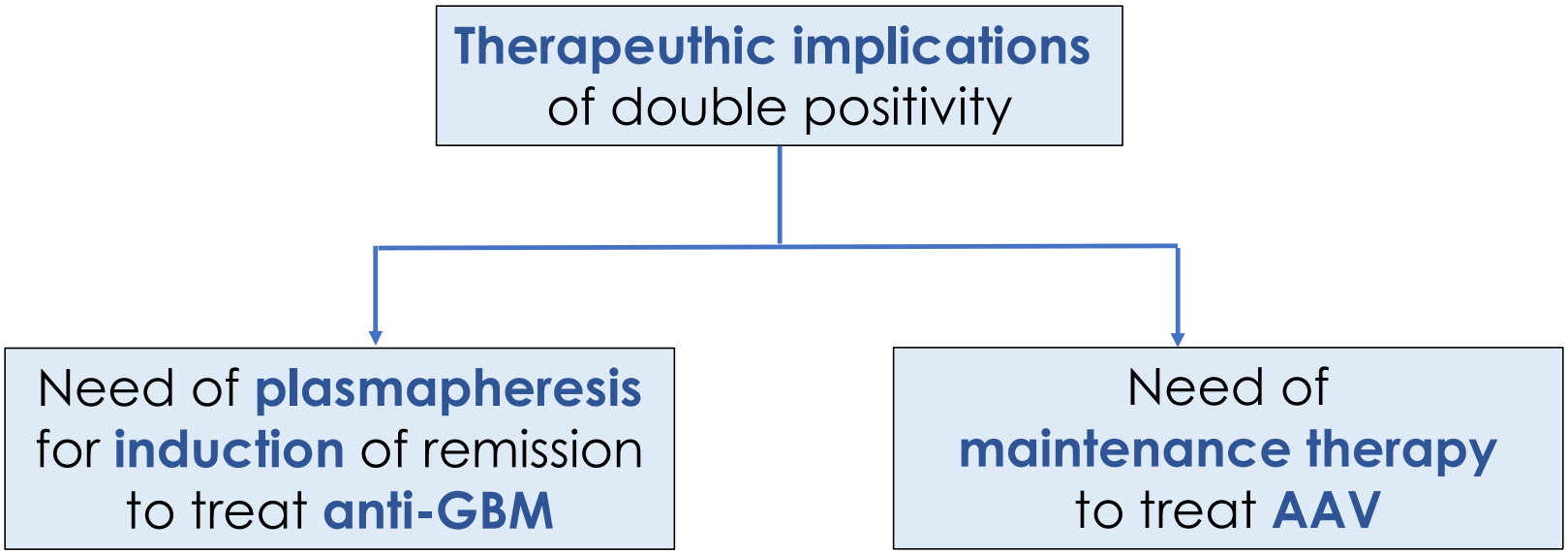
AAV and anti-GBM disease

- Large series of double positive in patients with anti-GBM antibodies

	Double positive / Total antiGBM (%)
Jayne, 1990	20/67 (30%)
Bosch, 1991	12/37 (33%)
Weber, 1992	7/23 (30%)
Short, 1995	34/160 (21%)
Westman, 1997	9/19 (47%)
Hellmark, 1997	38/100 (38%)
Denton, 2002	58/136 (43%)
Segelmark, 2003	29/79 (37%)
Cui, 2004	25/105 (24%)
Yang, 2005	11/23 (48%)
Rutgers, 2005	10/46 (22%)
Levy, 2005	38/121 (32%)
Yang, 2007	63/205 (31%)
Lindic, 2009	8/30 (27%)

32% of anti-GBM patients:
ANCA positive
(67% anti-MPO)

AAV and anti-GBM disease



PEX in anti-GBM disease: first report

IMMUNOSUPPRESSION AND PLASMA-EXCHANGE IN THE TREATMENT OF GOODPASTURE'S SYNDROME

C. M. LOCKWOOD, A. J. REES, T. A. PEARSON, D. J. EVANS, D. K. PETERS

Department of Medicine, Hammersmith Hospital, Royal Postgraduate Medical School, London W12 0HS

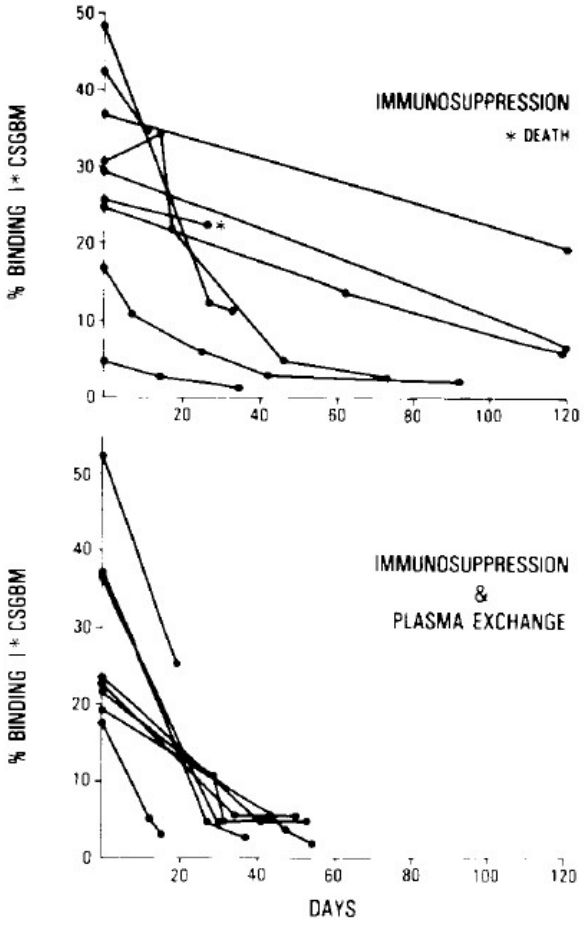
C. B. WILSON

Department of Immunopathology, Scripps Clinic and Research Foundation, La Jolla, California, U.S.A.

Summary Seven patients with Goodpasture's syndrome induced by anti-glomerular-basement-membrane (anti-G.B.M.) antibody were treated by a regimen of intensive plasma-exchange, cytotoxic drugs, and steroids. In the three patients retaining some renal function at presentation, this regimen led to suppression and eventual termination of antibody synthesis with improvement in renal function. In four patients, all anuric at presentation, antibody to G.B.M. persisted with variable reduction in the circulating levels. No return of renal function occurred in this group, all of whom had extensive changes on renal biopsy. Pulmonary hæmorrhage, life-threatening in one patient, was rapidly controlled in all five patients in whom it was a presenting feature. In addition to its effect on antibody levels, plasma-exchange, using volume-replacement with plasma-protein fraction (P.P.F.), resulted in substantial depletion of complement and fibrinogen, mediators possibly contributing to the antibody-induced injury.

Lockwood CM *et al. Lancet* 1976; 307:711–5

Anti-GBM antibodies removal by PEX



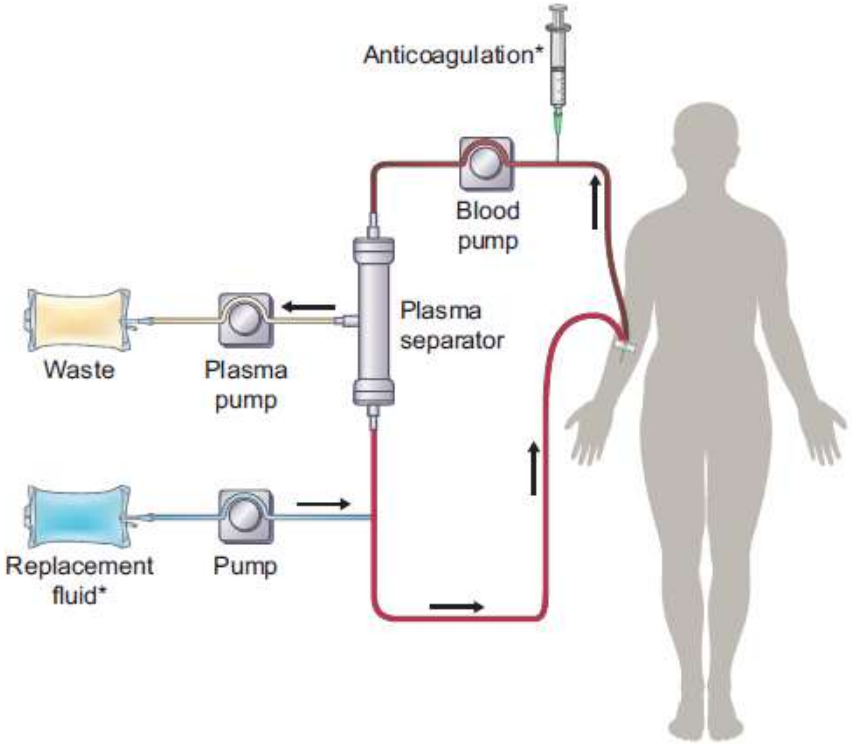
Therapy of Anti-Glomerular Basement Membrane Antibody Disease: Analysis of Prognostic Significance of Clinical, Pathologic and Treatment Factors

JOHN P. JOHNSON, M.D., JACK MOORE, JR., M.D., HOWARD A. AUSTIN, III, M.D., JAMES E. BALOW, M.D., TATIANA T. ANTONOVYCH, M.D., AND CURTIS B. WILSON, M.D.[1]

FIG. 1. Effect of therapy on anti-GBM antibody percent binding. Serial antibody determinations by RIA are plotted against time since initiation of therapy (see Methods). Individual curves were subjected to regression analysis and slopes compared by Group t analysis. Rate of disappearance of antibody (negative slope) was significantly greater for the plasma exchange group than for the immunosuppression alone group (0.78 ± 0.16 vs. 0.31 ± 0.11, $p < .05$).

Johnson JP et al. Medicine (Baltimore) 1985; 64 :219–27

PEX in anti-GBM disease



*Anticoagulation:
• Heparin or citrate

- **Daily 40-60 ml/Kg exchange for 5% human albumin solution**
- **Add fresh human plasma (300-600 ml) within 3 days of invasive procedure (e.g. kidney biopsy) or in patients with alveolar hemorrhage**
- **Continue until antibody levels are fully suppressed, typically 14 days**
- **Monitor antibody levels regularly during and after cessation of treatment; PEX may require reinstatement if antibody levels rebound**

- **Monitor and correct as required:**
  - Platelet count; aim >70×10^9 /L
  - Fibrinogen; aim >1 g/L
  - Haemoglobin, aim for >90 g/L
  - Corrected calcium; aim to keep in normal range
- **Access-related complications**
  - Infection
  - Venous thromboses

McAdoo S et al. Nephrol Dial Transplant. 2026, 41:42–54

PEX in anti-GBM disease

We recommend intensive treatment for anti-GBM glomerulonephritis when there is:

1) Clinically evident **alveolar haemorrhage** (regardless of renal function);

2) **Rapidly progressive glomerulonephritis** (RPGN) **without** immediate **dialysis** requirement;

3) **RPGN requiring dialysis, if**:

- < 100% glomerular crescents
- < 50% glomerulosclerosis
- Non-oliguric presentation
- Alternative biopsy findings to account for dialysis requirement (e.g. severe acute tubular injury)
- Recent dialysis initiation (e.g. < 72 h)
- Coexisting 'double-positive' ANCA disease

McAdoo S et al. Nephrol Dial Transplant. 2026, 41:42–54

PEX in anti-GBM disease

Rare cases of recovery despite adverse features, however, support **individualized treatment decisions:** a short trial of therapy may be reasonable, particularly in younger patients who may tolerate treatment with lower risk of adverse events, and this can be tapered if no renal recovery is evident within 2–4 weeks.

Short-term immunosuppression may also aid antibody clearance to facilitate earlier kidney transplantation.

McAdoo S et al. Nephrol Dial Transplant. 2026, 41:42–54

American Society for Apheresis Guidelines

Disease/condition	Indication	Procedure	Category	Grade
Anti-glomerular basement membrane disease	Diffuse alveolar hemorrhage	TPE	I	1C
	Dialysis-independence	TPE	I	1B
	Dialysis-dependence, no diffuse alveolar hemorrhage	TPE	III	2B

Technical notes

In the setting of DAH, plasma should be used for part or whole of the replacement fluid.

Volume treated: 1 to 1.5 TPV

Replacement fluid: Albumin; plasma when DAH present

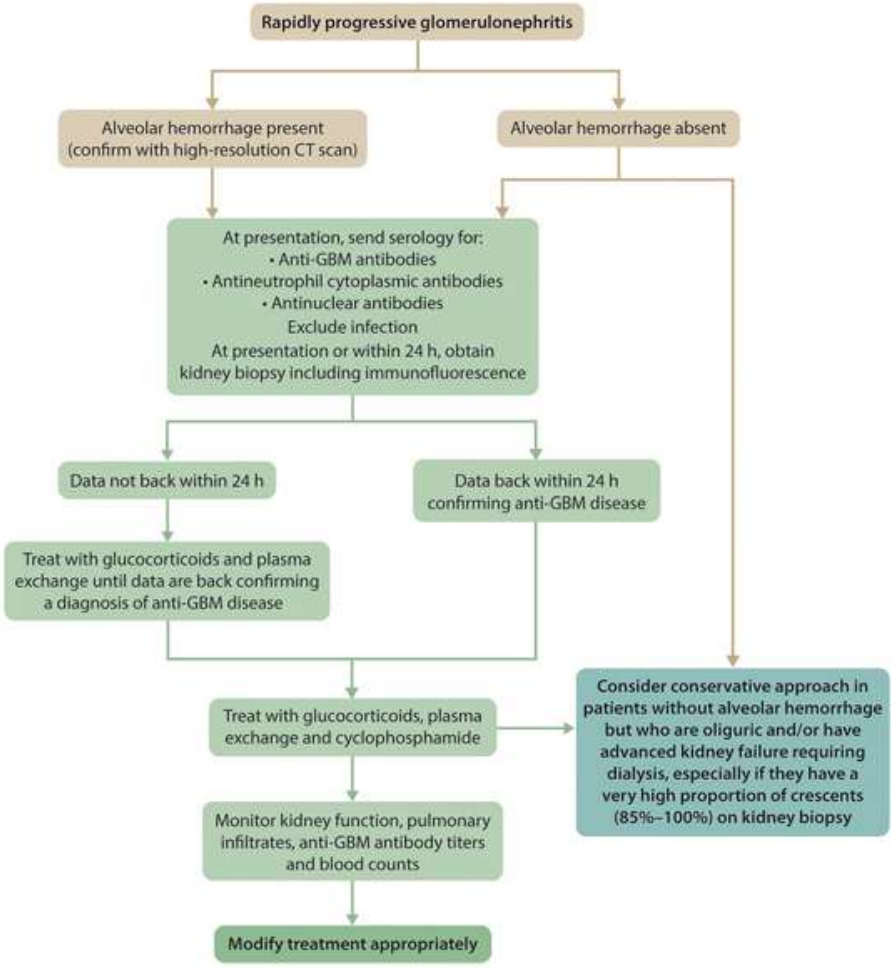
Frequency: Daily at initiation with subsequent reduction of frequency according to individual clinical course, up to 10 treatments might be necessary

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision-making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB/Ethics Committee approval is desirable if apheresis treatment is undertaken in these circumstances.

Abbreviation: IRB, Institutional Review Board.

Connelly-Smith L et al. J Clin Apher. 2023; 38(2):77-278.

KDIGO Guidelines



Recommendation 11.2.1: We recommend initiating immunosuppression with cyclophosphamide and glucocorticoids plus plasmapheresis in all patients with anti-GBM GN except those who are treated with dialysis at presentation, have 100% crescents or >50% global glomerulosclerosis in an adequate biopsy sample, and do not have pulmonary hemorrhage *(1C)*.

KDIGO Glomerular Diseases Work Group. Kidney Int. 2021 Oct;100(4S):S1-S276.

Conclusioni

Quale ruolo delle tecniche di aferesi nelle vasculiti ANCA associate e nella malattia anti-GBM?

Malattia anti-GBM: standard di cura imprescindibile, in particolare nei pazienti con emorragia endoalveolare diffusa e insufficienza renale rapidamente progressiva non in dialisi.

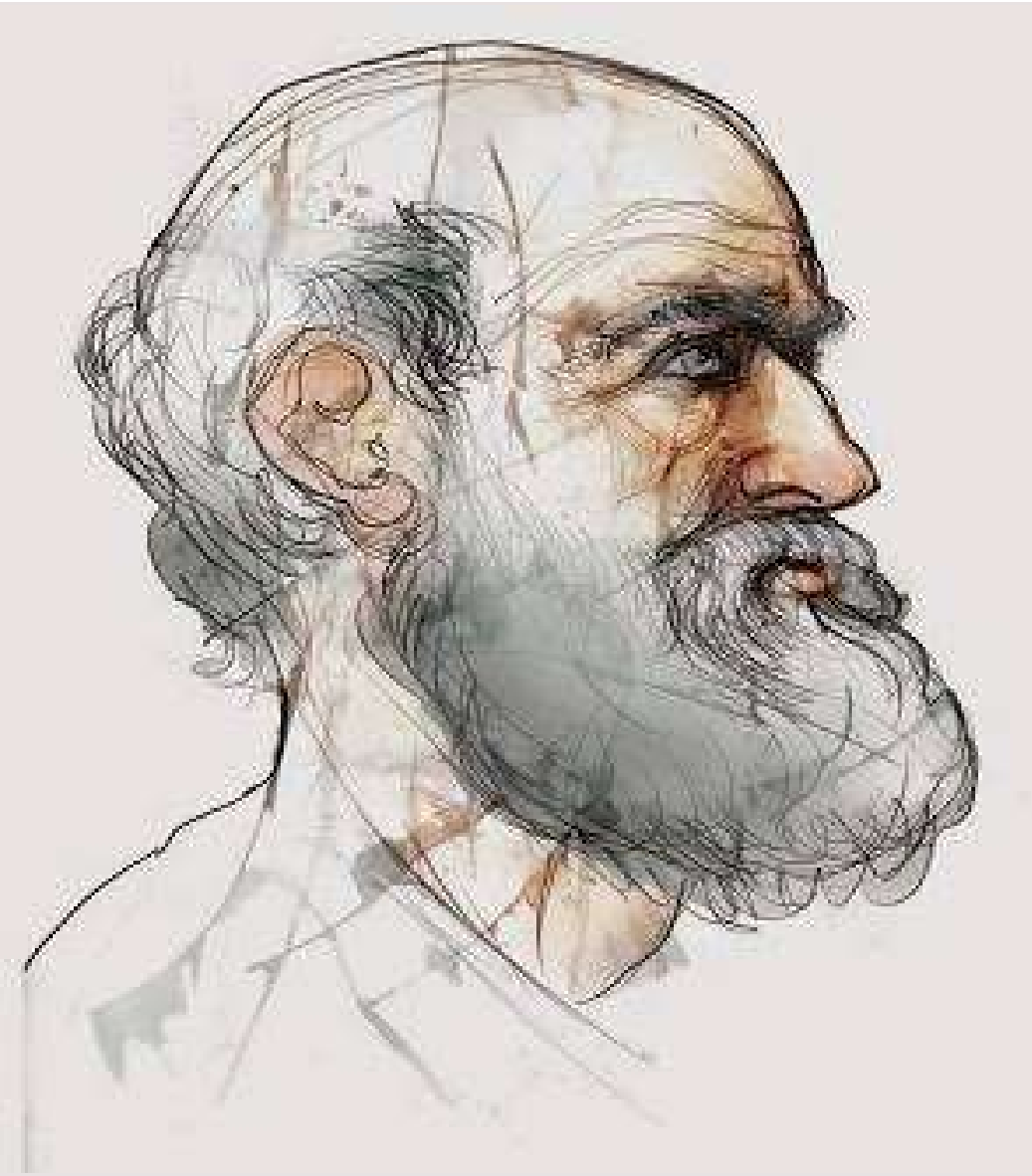
Doppi positivi: indicata nella terapia di induzione in aggiunta alla terapia immunosoppressiva standard; testare Sempre ANCA e anti-GBM nei pazienti con GNRP o sindrome pneumo-renale!

Vasculiti ANCA-associate: lo studio PEXIVAS ha ridimensionato l'uso routinario della PEX. Le linee guida internazionali più recenti raccomandano un **uso individualizzato e selettivo della PEX**, stratificando i pazienti in base al rischio renale basale, alla gravità dell'ipossiemia nell'emorragia alveolare.

Conclusioni

"While the sensation of wanting to 'do something' is common when caring for patients with organ- or life-threatening disease, it is not always right.
In the case of ANCA-associated vasculitis, PLEX may satiate the urge to do something more while awaiting the effects of the induction regimen, but we must thoughtfully apply evidence to our practice."

Specks U et al. Nephrol Dial Transplant 2021; 36: 231–236l



“Ci sono nei fatti due cose: scienza ed opinione; la prima genera conoscenza, la seconda ignoranza.”

“La guarigione è legata al tempo e a volte anche alle circostanze.”

“La vita è breve, l'arte vasta, l'occasione fuggevole, l'esperimento malcerto, il giudizio difficile.”

Ippocrate di Cos, V secolo a.C.

Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies

CHARLES D. PUSEY, ANDREW J. REES, DAVID J. EVANS, D. KEITH PETERS, and C. MARTIN LOCKWOOD

Departments of Medicine and Histopathology, Royal Postgraduate Medical School, Hammersmith Hospital, London, England, United Kingdom

Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. To determine whether plasma exchange was of additional benefit in patients treated with oral immunosuppressive drugs for focal necrotizing glomerulonephritis (without anti-GBM antibodies), we performed a randomized controlled trial with stratification for renal function on entry. Forty-eight cases were analyzed, 25 in the treatment group (plasma exchange, prednisolone, cyclophosphamide and azathioprine) and 23 in the control group (drug therapy only). There was no difference in outcome in patients presenting with serum creatinine < 500 μmol/liter ($N = 17$), or > 500 μmol/liter but not on dialysis ($N = 12$), all but one of whom had improved by four weeks. However, patients who were initially dialysis-dependent ($N = 19$) were more likely to have recovered renal function ($P = 0.041$) if treated with plasma exchange as well as drugs (10 of 11) rather than with drugs alone (3 of 8). Long-term follow-up showed that improvement in renal function was generally maintained. The results of this trial confirm that focal necrotizing glomerulonephritis related to systemic vasculitis responds well to immunosuppressive drugs when treatment is started early, and suggest that plasma exchange is of additional benefit in dialysis-dependent cases.

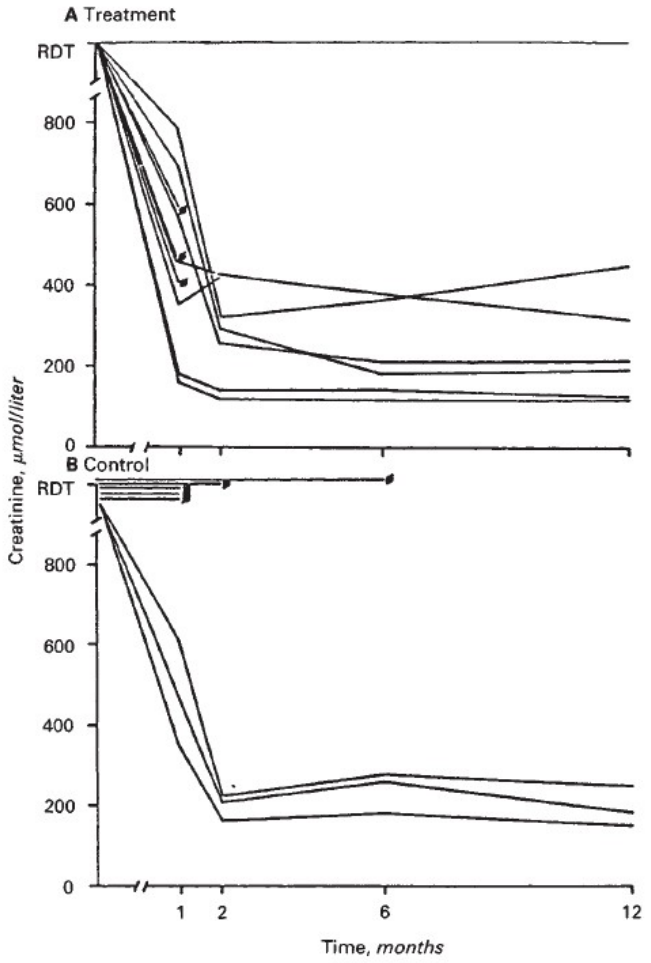
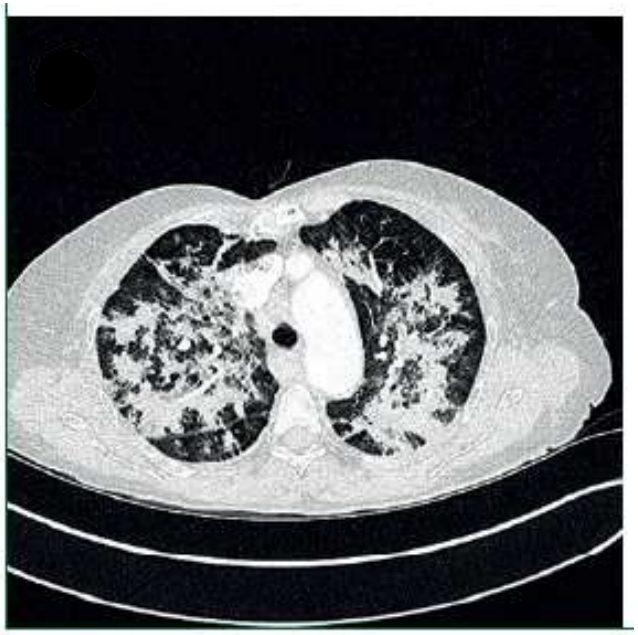


Fig. 3. *Serial serum creatinine in patients who were dialysis-dependent.* ø = died.

Pusey CD, et al. Kidney Int 1991; 40: 757–763

PEXIVAS trial: limitations



- **Definition of severe diffuse alveolar hemorrhage (DAH)**: sO2 ≤85% aa or need for mechanical ventilation.
- **Bronchoalveolar lavage not required** for diagnosis: possible confounding factors such as pulmonary oedema and infectious complications.
- **Selection bias** may have affected the relatively low recruitment of patients with **severe diffuse alveolar hemorrhage** in the trial since many physicians would hesitate not to use TPE in this population.
- Underpowered study: **low number of events**

Tsiakas S et al. J Clin Med. 2021; 10, 5154

KI REPORTS
KIReports.org
CLINICAL RESEARCH

Effect of Baseline Dialysis and Plasma Exchange on Renal Prognosis in Patients With Antineutrophil Cytoplasmic Autoantibody–Associated Vasculitis

- 394 patients included, 105 (26.6%) were on dialysis at baseline.
- Of these, 60 (57.1%) reached the composite end point compared with 29 patients (10.0%) who were not on RRT at baseline ($P < 0.001$).
- On multivariate analysis, age and sex were not associated with the composite outcome ($P = 0.945$ and $P = 0.154$, respectively); however, myeloperoxidase (MPO)-ANCA was (odds ratio [OR]: 3.60; 95% confidence interval [CI]: 1.79–7.60), as was a **high baseline histologic renal risk score** (OR: 1.29; 95% CI 1.17–1.44). The most strongly associated factor remained the need for dialysis at baseline (OR: 10.91; 95% CI: 5.52–22.70).
- **Of the 91 patients surviving after requiring dialysis at baseline, 45 were weaned from RRT (49.5%) at 1 year, and PLEX was independently associated with a reduced risk of the composite outcome (OR: 0.23, 95% CI: 0.05–0.80).**

Vignac M et a. Kidney Int Rep. 2025:10, 4199–4206

Anti GBM disease

- Given the direct pathogenicity of anti-GBM antibodies, their rapid removal with PEX is a central component of therapy. In Lockwood's seminal 1976 study, the use of PEX was associated with rapid removal of circulating autoantibodies, resolution of lung haemorrhage, and salvage of kidney function in patients who were not requiring dialysis at presentation [7].
- A subsequent small RCT likewise showed a more rapid fall in anti-GBM titres when PEX was added to immunosuppressive therapy, with a trend towards improved renal outcome (although groups were poorly matched based on histopathological severity) [8]. The early adoption of PEX was further supported by several observational studies that suggested improved renal and patient survival compared with historic cohorts treated with immunosuppression alone [9].
- More recent observational studies support the continued use of PEX in anti-GBM disease.
- A French multicentre study of 122 patients with severe disease (median creatinine 7 mg/dL; 78% pulmonary–renal syndrome; 68% dialysis-dependent) treated with PEX and immunosuppression reported 1-year survival of 87% [10]. In multivariable analysis, a higher number of exchanges improved survival [hazard ratio (HR) 0.87 per session; 95% confidence interval (CI) 0.77–0.98], with eight sessions predicting favourable outcomes (positive and negative predictive value 95% and 47%, respectively).
- A second French study of 119 patients (median age 54 years, median creatinine 7.2 mg/dL, 78% requiring dialysis) similarly showed excellent survival at 1 and 5 years (95% and 92%, respectively) [11]. PEX (used in > 80%) was associated with im-proved survival (HR 0.29; 95% CI 0.08–0.98).
- In a large Chinese cohort (*n* = 448, mean creatinine 9.2 mg/dL), 56% received PEX alongside glucocorticoids and cytotoxics [12]. Mortality fell dramatically over three decades (12-month mortality from 57.1% to 6.9%), paralleling greater use of PEX and earlier diagnosis. PEX was independently associated with reduced mortality (HR 0.30; 95% CI 0.16–0.95).
- Another retrospective study of 107 patients with anti- GBM disease treated in West China likewise found that treatment with PEX was independently associated with improved in-hospital outcomes [mortality and dialysis-dependency at discharge (HR 0.18; 95% CI 0.05–0.63)] and long-term survival [at 2 years (HR 0.15; 95% CI 0.04–0.55)] [13]. Notably, patients who initiated PEX early had better prognoses. The study also suggested that 5–10 PEX sessions might suffice for maximal risk reduction.
- Finally, a Japanese nationwide database study (*n* = 207) of patients with anti-GBM disease presenting with dialysis-dependent kidney failure, but without diffuse alveolar haemorrhage, found that the addition of PEX to glucocorticoid therapy was associated with a significant reduction in in-hospital mortality (10.7% versus 28.2%) [14]. This study underscores the potential benefit of PEX for survival, even in patients with severe renal disease.
- Although these retrospective studies have clear limitations, including variable use of concurrent immunosuppressants, lack of predictive histopathological data, and risk of confounding by indication, they consistently indicate that inclusion of PEX in the early treatment of anti-GBM is associated with improved outcomes. Both the American Society for Apheresis (Grade 1C–2B) and the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend inclusion of PEX in therapeutic regimens for anti- GBM disease [3 , 15]. Either centrifugal or plasma filtration methods can be used, as IgG is effectively cleared by both techniques. A recommended treatment schedule and practical considerations are summarized in Table 2 .

McAdoo S et al. Nephrol Dial Transplant. 2026, 41:42–54

Anti GBM disease

- Diffuse alveolar haemorrhage in anti-GBM disease may be life-threatening but is highly treatment responsive, with 90%–100% achieving remission with immunosuppression and plasmaphereis [9 , 24]. Therefore, treatment is always recommended when alveolar haemorrhage is present, regardless of the presence or severity of kidney disease.
- In patients with RPGN, dialysis status at treatment initiation is the most significant determinant of long-term kidney outcomes. Long-term follow-up of a large cohort (*n* = 71) treated consistently with PEX, cyclophosphamide and glucocorticoids found that in-dependent kidney function was maintained in most patients who did not require dialysis at presentation: renal survival at 1 and 5 years was 95% and 94%, respectively, with presenting creatinine < 500 µmol/L, and 82% and 50%, respectively, for creatinine > 500 µmol/L [9]. In dialysis-dependent patients, however, only 8% recovered independent kidney function at 1 year. Similarly low rates of recovery from dialysis-dependent kidney injury are consistently reported in more recent series [10 , 11 , 25 , 26], and optimistic rates of recovery approximate ∼17%–20% at best [27 , 28].
- The duration of dialysis requirement at the time treatment initiation may also be important. In our experience, patients requiring dialysis for > 7 days before initiation of immunosuppressive therapy very rarely recover independent kidney function, whereas those with a dialysis duration of < 72 h may still do so, particularly in the absence of adverse histological features (see below). We therefore recommend that the timing of dialysis initiation and its underlying indication (e.g. hyperkalaemia versus anuria) be carefully considered when evaluating the potential for renal recovery and when deciding whether to proceed with full immunosuppressive therapy.
- Several studies have sought to identify additional clinical or histopathological predictors of recovery. In the Levy series, no dialysis-dependent patient with 100% glomerular crescents recovered kidney function [9]. A larger multicentre biopsy study (*n* = 123) confirmed that dialysis-dependence, fewer normal glomeruli and greater interstitial infiltrate predict end-stage kidney disease (ESKD). No recovery was observed with 100% crescents or > 50% glomerulosclerosis [26]. A small UK study further identified oligoanuria as the strongest predictor of dialysis non-recovery [25].

McAdoo S et al. Nephrol Dial Transplant. 2026, 41:42–54

PEXIVAS trial

Previous trials have suggested a substantial benefit of plasma exchange in patients with severe kidney disease with respect to reducing the need for dialysis at 12 months.[7,17,18]

In contrast, our trial did not show large effects. Several factors may have contributed to the difference between our results and those of previous trials. Effect estimates in previous studies may have been confounded by the small number of events[19] or by systematic errors from bias resulting from unclear assignment methods.[7]

Alternatively, improvements in diagnosis, immunosuppression, and supportive care may have reduced the benefits of adjuvant plasma exchange in our trial.

Walsh M et al, N Engl J Med 2020;382:622-31.

Pathogenetic rationale for PEX in AAV

- **Anti-Neutrophilic Cytoplasmatic Antibodies (ANCA)** are mainly **IgG antibodies.**
- IgG **half-life: approximately 21 days**
- PEX: possibility of rapidly removing these pathogenic antibodies from the patients' plasma when added to the standard immunosuppressive regimen.
- **Both common techniques of TPE,** centrifugal apheresis and membrane plasma separation, **are effective in removing IgG molecules.**
- Due to extravascular distribution, **one day intervals between TPE sessions** are commonly applied in order to allow immunoglobulins to further redistribute into the vascular space; exceptions to this practice include emergency care circumstances where daily sessions are required, e.g., pulmonary hemorrhage.
- Besides antibody elimination, other putative beneficial mechanisms of action of TPE include the **removal of inflammatory mediators**, such as cytokines and complement components, and **the replenishment of plasma factors** via fresh frozen plasma infusion, such as factor H.

Tsiakas S et al. J. Clin. Med. 2021, 10, 5154

Pathogenetic rationale for PEX in AAV

- Considering the pathogenetic essence of ANCA, the removal of these antibodies may exert a beneficial effect on the disease.
- **Anti-Neutrophilic Cytoplasmatic Antibodies (ANCA)** are mainly **IgG antibodies.**
- Immunoglobulin G has **a half-life of approximately 21 days**; depletion of the serum IgG antibody levels solely by halting their production with immunosuppressive agents would require at least several weeks.
- TPE offers the possibility of rapidly removing these pathogenic antibodies from the patients' plasma when added to the standard immunosuppressive regimen.
- **Both common techniques of TPE, centrifugal apheresis and membrane plasma separation, are effective in removing IgG molecules.**
- Due to extravascular distribution, one day intervals between TPE sessions are commonly applied in order to allow immunoglobulins to further redistribute into the vascular space; exceptions to this practice include emergency care circumstances where daily sessions are required, e.g., pulmonary hemorrhage [27,28].
- Besides antibody elimination, other putative beneficial mechanisms of action of TPE include the **removal of inflammatory mediators**, such as cytokines and complement components, and **the replenishment of plasma factors** via fresh frozen plasma infusion, such as factor H [29].

Tsiakas S et al. J. Clin. Med. 2021; 10, 5154

MEPEX trial: long-term follow-up

Median follow up: 3.95 years

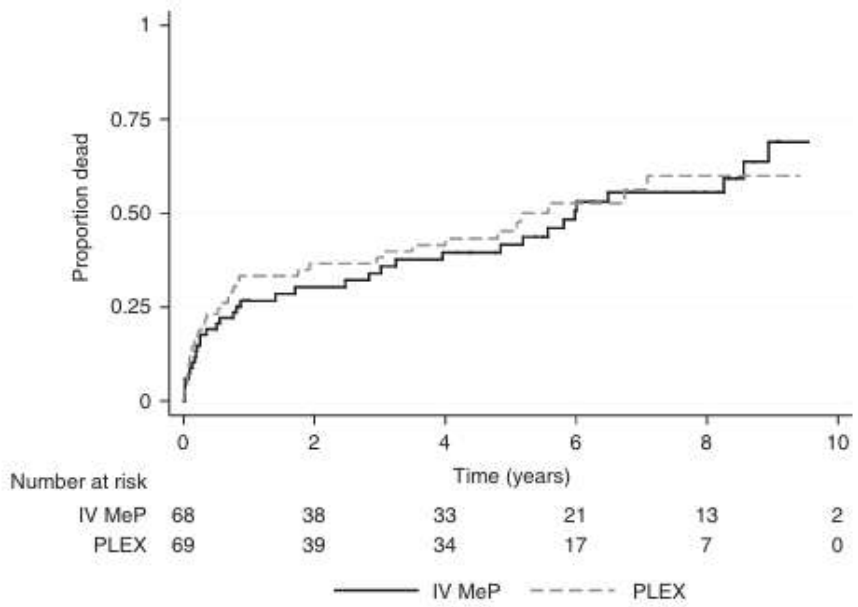


Figure 3 | Kaplan–Meier curve of deaths. Kaplan–Meier curve of deaths in patients with severe antineutrophil cytoplasm antibody–associated vasculitis randomized to intravenous methylprednisolone (IV MeP) or plasma exchange (PLEX).

Table 4 | Causes of death over the course of long-term follow-up

Primary cause of death, *n* (%)	IV MeP (*n* = 35)	PLEX (*n* = 35)
Vasculitis (%)	1 (2.9)	1 (2.9)
Pulmonary hemorrhage (%)	3 (8.6)	1 (2.9)
Infection (%)	9 (25.7)	15 (42.9)
Cardiovascular (%)	6 (17.1)	4 (11.4)
ESRD (%)	1 (2.9)	1 (2.9)
Cancer (%)	3 (8.6)	2 (5.7)
Other	12 (34.3%)	11 (31.4%)

Abbreviations: ESRD, end-stage renal disease; IV MeP, intravenous methylprednisolone; PLEX, plasma exchange.
There was no difference in the overall distribution of cause of death ($P = 0.80$).

Walsh M et al. Kidney Int 2013; 84:397–402.

PEXIVAS trial

SECONDARY OUTCOMES

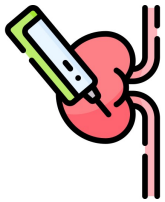
Table 3. Secondary Outcomes.*

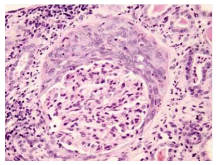
Secondary Outcome	Plasma Exchange vs. No Plasma Exchange	Reduced-Dose vs. Standard-Dose Glucocorticoid Regimen
	effect size (95% CI)	
Death from any cause	0.87 (0.58–1.29)	0.78 (0.53–1.17)
End-stage kidney disease	0.81 (0.57–1.13)	0.96 (0.68–1.34)
Sustained remission	1.01 (0.89–1.15)	1.04 (0.92–1.19)
Serious adverse events	1.21 (0.96–1.52)	0.95 (0.75–1.20)
Serious infections at 1 year	1.16 (0.87–1.56)	0.69 (0.52–0.93)

* The effect sizes for death from any cause and end-stage kidney disease are reported as hazard ratios, for sustained remission as relative risk, and for serious adverse events and serious infections at 1 year as incidence rate ratios. All analyses were performed in the intention-to-treat population.

Walsh M et al, N Engl J Med 2020; 382:622-31.

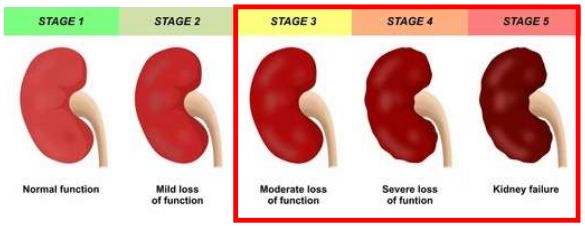
PEXIVAS trial: limitations





- **Kidney biopsy** not required at entry:
  no data about the degree of activity and the response to PEX.

- **Timing** for primary outcome:
  The **survival analysis** showed an **advantage**, albeit non-significant, of PEX in the **first year**: since TPE is a brief intervention of the induction therapy, improvement is anticipated in a short period of time after treatment. Other factors may influence the course of the disease in the long term.



- **Broad range of renal impairment** (eGFR <50 ml/min/1.73 m^2):
  previous clinical trials showed that PEX favors patients with severe active renal disease at presentation.

Tsiakas S et al. J. Clin. Med. 2021, 10, 5154