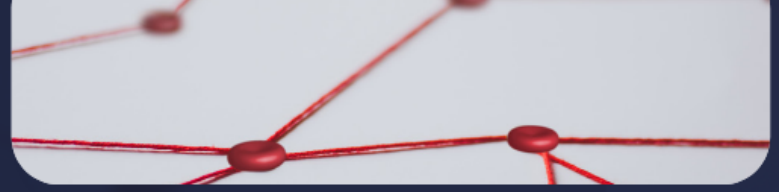


Patient with Rapidly Progressive Glomerulonephritis before deciding whether to undergo Therapeutic Apheresis

Aglaia Chalkia MD PhD

Consultant in Nephrology, General Hospital of Athens, Greece

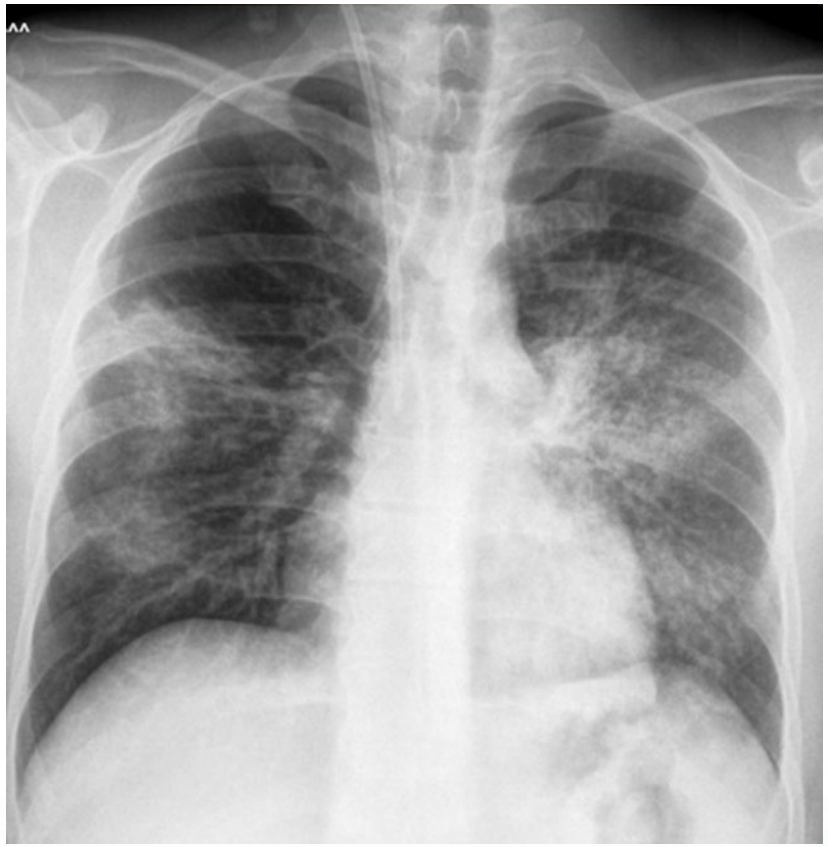
ERA Fellowship, Vasculitis and Lupus Research Group, University of Cambridge, UK

A 38- year-Old man

Presentation February 2022

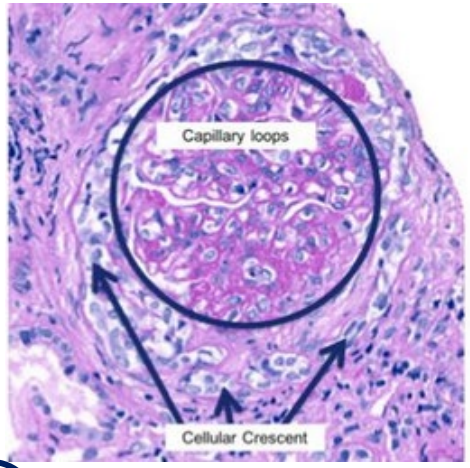
- Rapidly progressive GN
- Cre=5mg/dL (eGFR=14ml/min/1.75m2)
- Hematuria 9-12 RBC
- Proteinuria 870mg/24H
- CRP=45 g/dL

- Fever
- Cough/ dyspnea/ Haemoptysis



Rapidly progressive glomerulonephritis (RPGN)

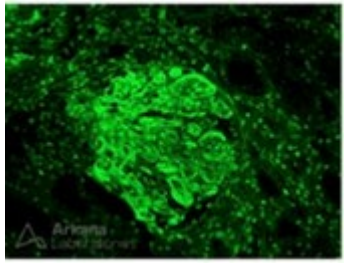
- Decline eGFR (days or months)
- Hematuria or/and proteinuria
- Crescents formations



Most common

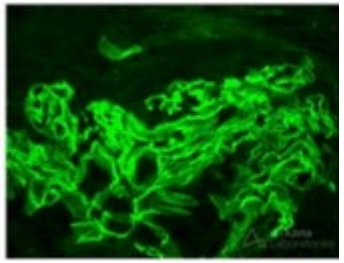
Immunocomplex

- Immune deposits in glomeruli
- IgA vasculitis, cryoglobulinemia



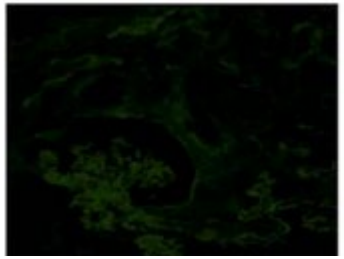
Anti-GBM disease

- Anti-glomerular basement membrane antibody
- Linear IgG IF



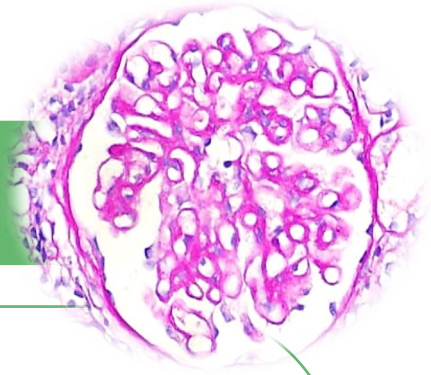
Pauci Immune

- Minimal immune deposits, (-) IF
- ANCA (+)



Jennette JC. Kidney Int. 2003

A 38- year-Old man

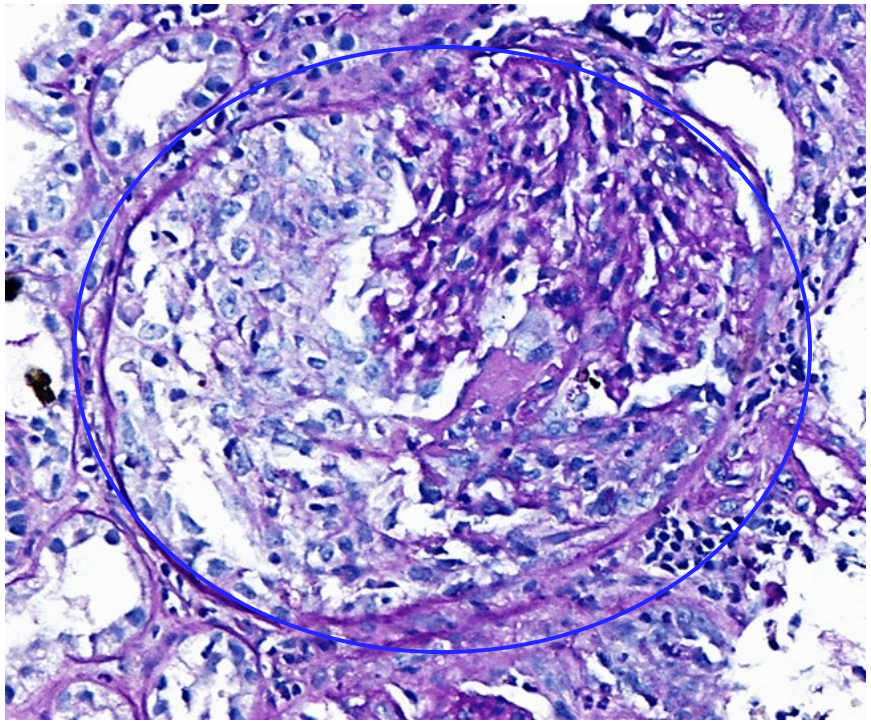


Kidney biopsy

- 13 glomeruli
- 30% global sclerosis
- 54% cellular crescents
- 12% normal glomeruli
- 30% interstitial fibrosis
- Immunofluorescence (-)

- AKRIS: High risk
- Berden: crescentic class

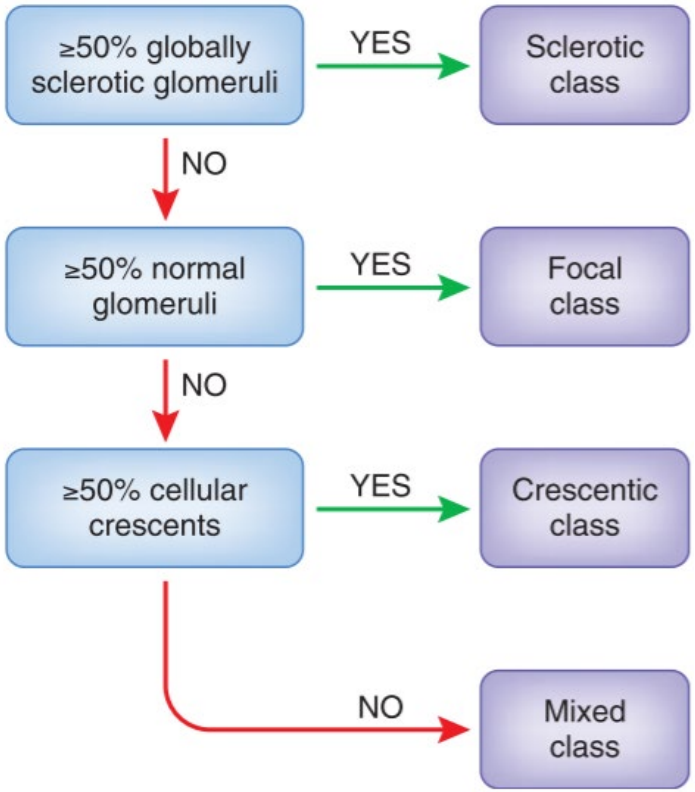
cellular crescent



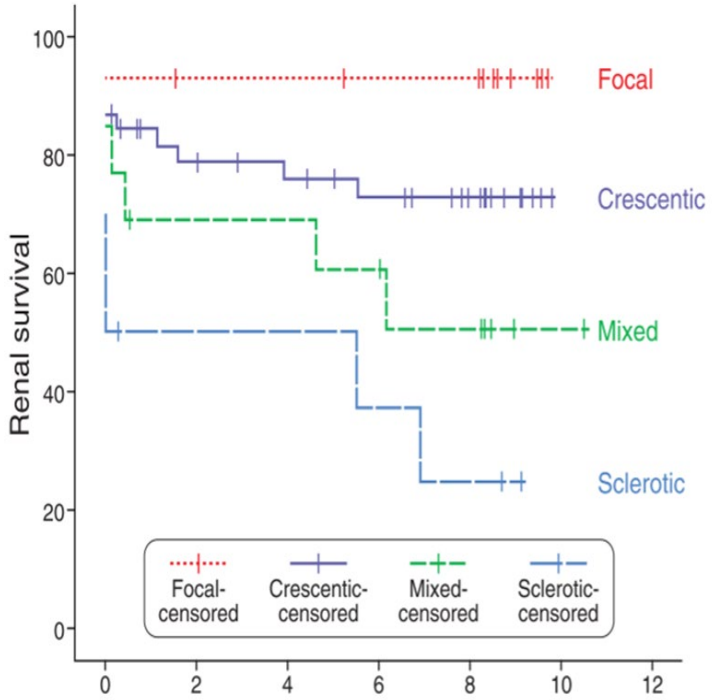
PR3-ANCA=80 IU/ml

Kidney Prognosis

Berden Classification



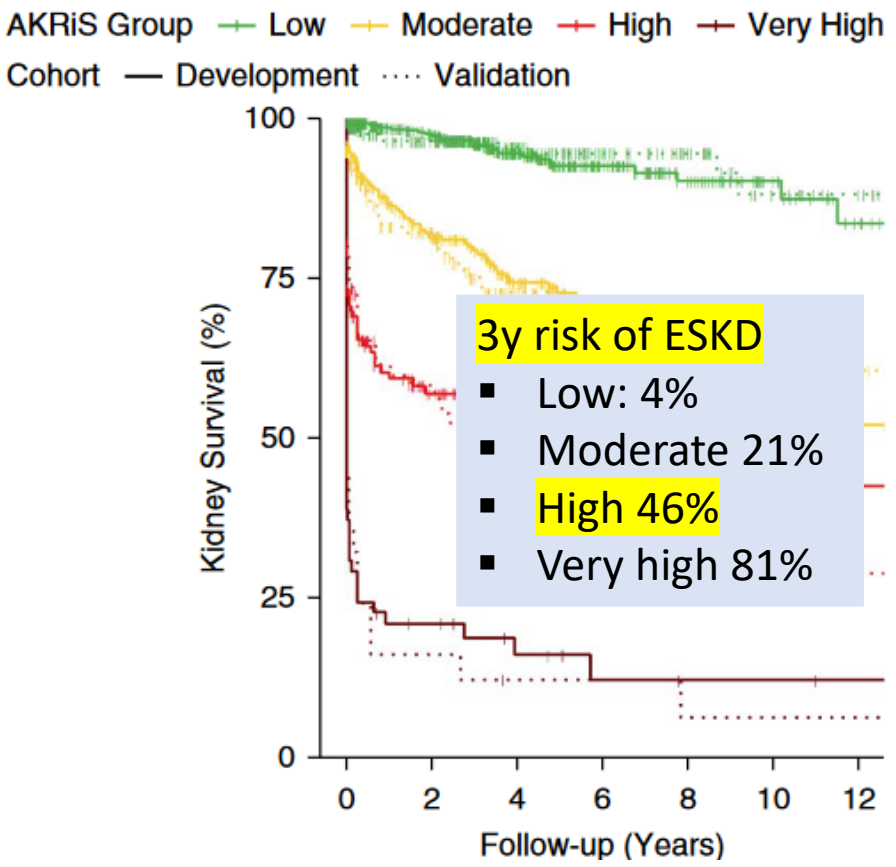
ESKD



1y risk of ESKD

- Focal: 7%
- Mixed: 31%
- Crescentic 16%
- Sclerotic 50%

AKRiS



3y risk of ESKD

- Low: 4%
- Moderate 21%
- High 46%
- Very high 81%

Berden A et al. JASN 2010

Bate S et al. JASN 2023

A 38- year-Old man

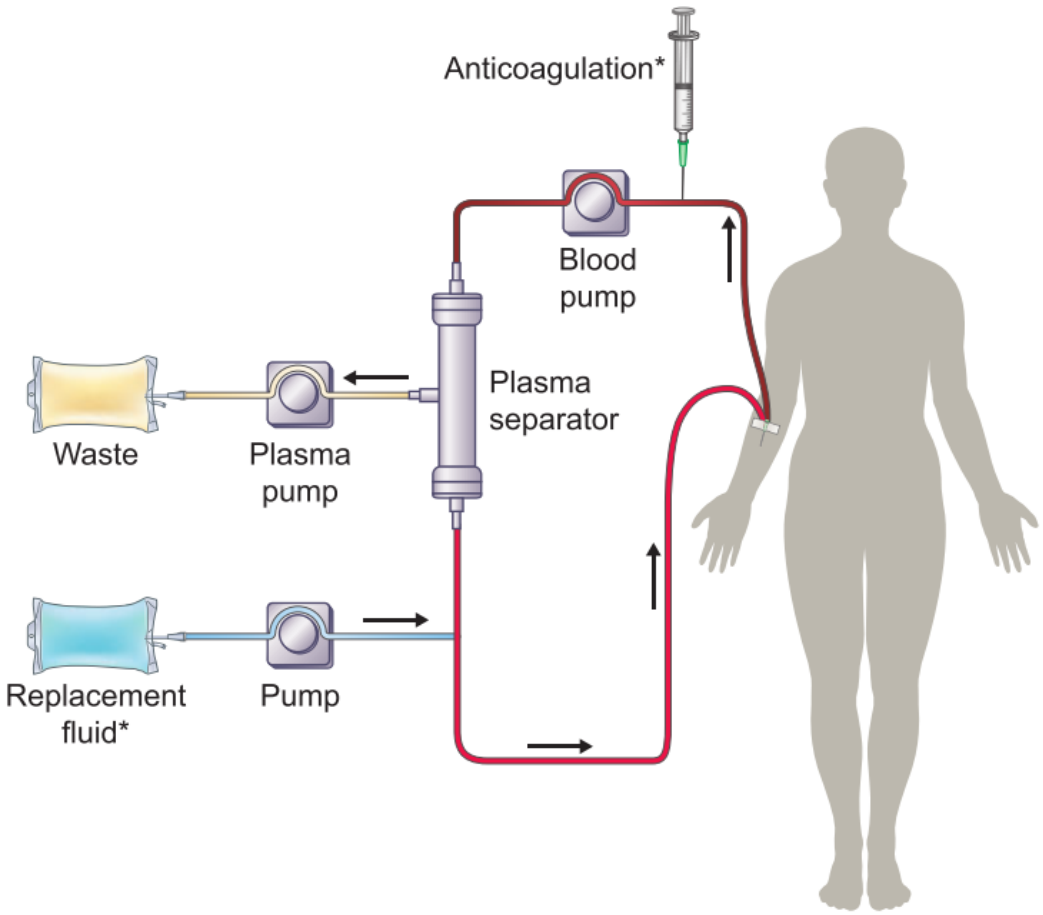
Treatment

- IV solumedrol 3gr
- Tb Medrol 64mg x1 reduced GCs regimen
  - IV CYC 2 doses
- RTX 1gr for 2 doses

‘’Combination’’
RITUXVAS regimen

Should we add PLEX?

Rationale of PLEX



***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)

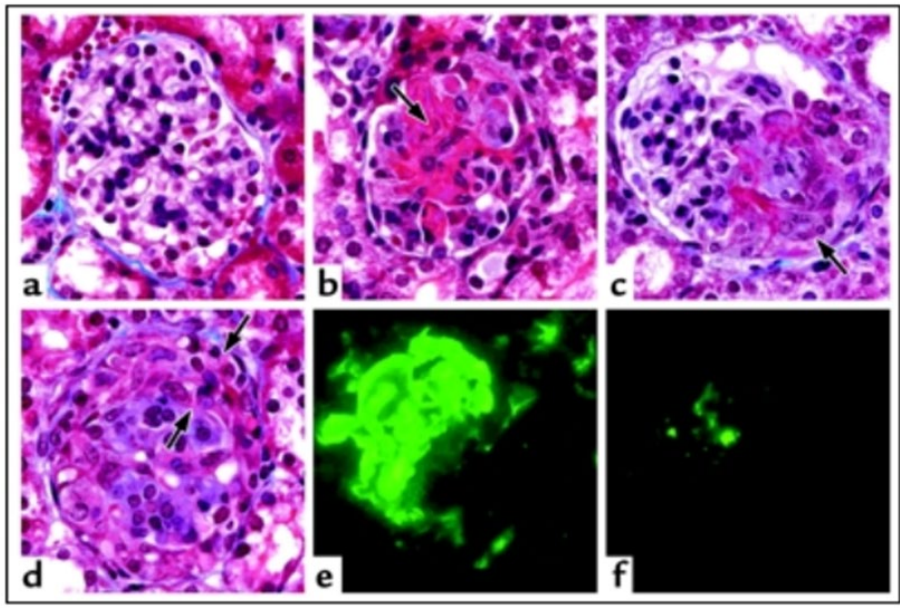
IL = interleukin
TNF = tumor necrosis factor
VEGF = vascular endothelial growth factor
ANCA = anti-neutrophil cytoplasmic antibody
PLEX = plasma exchange

Kronbichler A et al. NDT 2021

Rationale of PLEX

Removal of factors of pathogenic relevance:

- Cytokine, chemokine
- Coagulation factors
- Complement factors
- NETS-Neutrophil extracellular traps and neutrophil microparticles
- Antibodies (ANCA, anti-GBM)

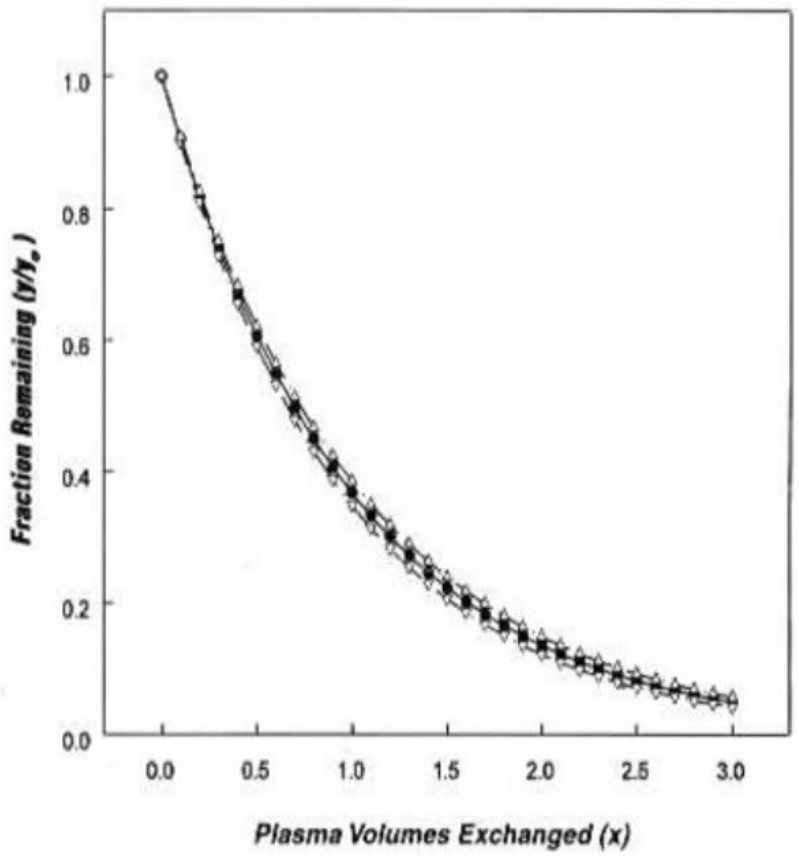


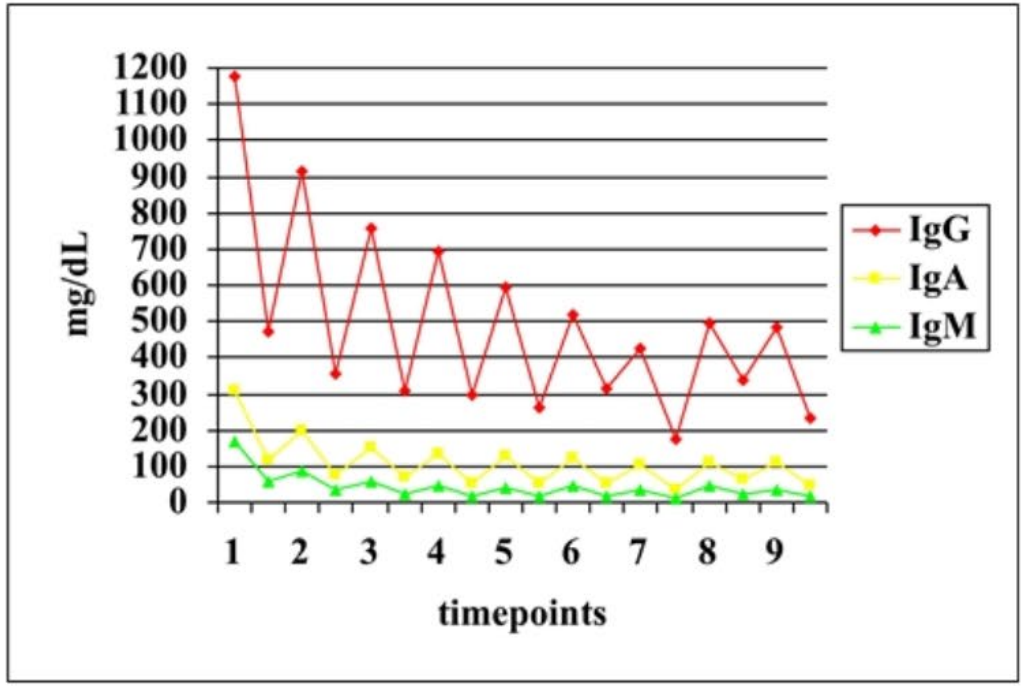
MPO-ANCA animal model

ANCAs are pathogenic
and rapid reduction of their levels
makes sense from a pathogenesis standpoint

Alba M. et al. Semin Respir Crit Care Med 2018

Therapeutic mechanism of PLEX





PLEX is capable of reducing antibodies by 60% per session with a recovery rate of 45% after 48h

Kidney International, Vol. 40 (1991), pp. 757–763

Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies

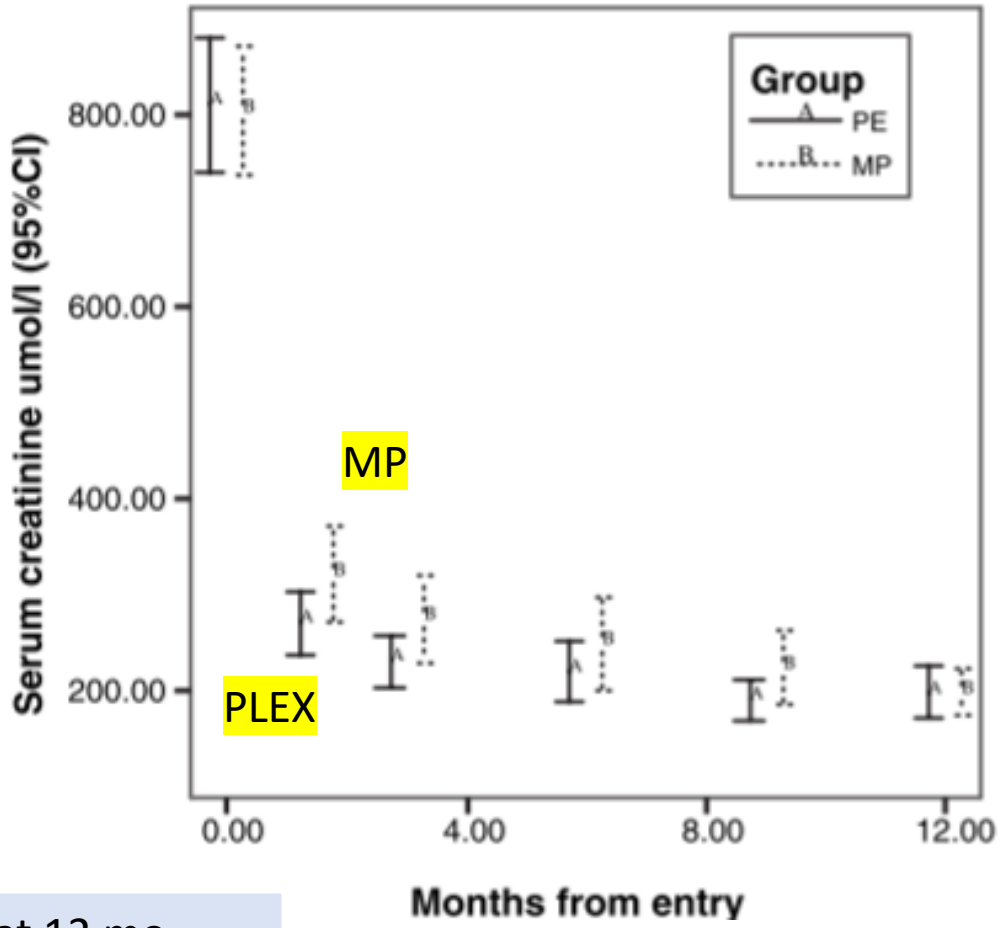
CHARLES D. PUSEY, ANDREW J. REES, DAVID J. EVANS, D. KEITH PETERS, and C. MARTIN LOCKWOOD

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

- N=48 10 of 11 Plasma exchange patients became haemodialysis independent versus 3 of 8 patients in the control group at 1st month
- Kidney histology was comparable
- Long-term effect maintenance (from 3 to 11 years)
- High mortality 36% (3 on PLEX vs 6 on control)

Short-effect of PLEX
MEPEX trial

- The MEPEX trial compared PLEX with IV MeP as adjuvants to cyclophosphamide and oral prednisolone in patients with a new diagnosis of AAV and a serum creatinine >500 mmol/l or requiring dialysis.
- N=137
- The primary outcome for MEPEX was renal recovery defined as a creatinine <500 mmol/l or dialysis independence within 12 months of randomization
- Comparable kidney histology



- ❑ PLEX ↓ 22% the risk for ESRD at 3mo and 24% at 12 mo compared to IV MeP
- ❑ No difference on mortality (26%) or adverse events (leukopenia or infections)

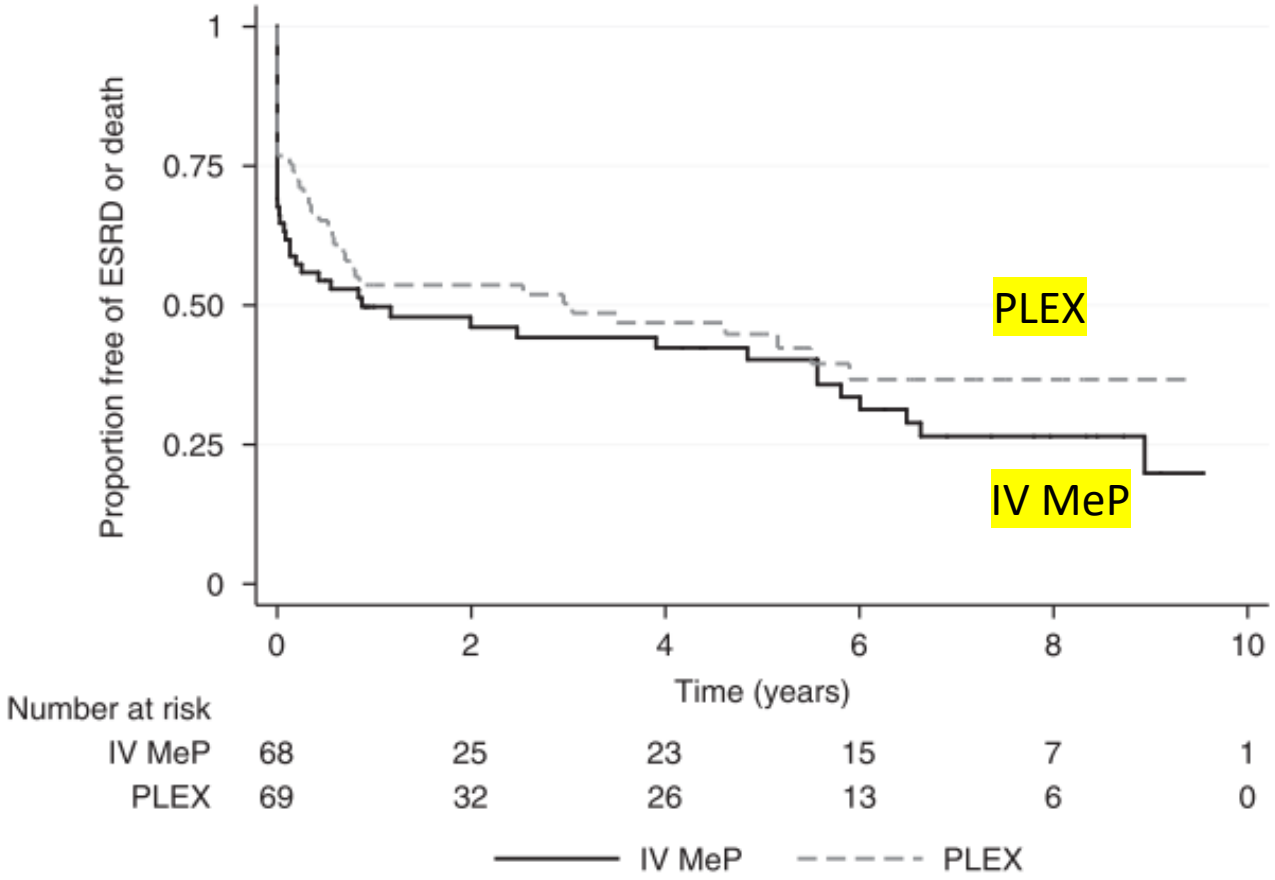
Jayne D et al. JASN 2007

Long-term effect of PLEX
MEPEX trial

- Median of 3.95 years
- N=122

- 41% ESKD (23 PLEX vs 33 IV MeP)
- 63% ESKD or death (40 PLEX vs 46 IV MeP)

No effect of PLEX on the composite end-point (HR, 0.81; 95% confidence interval (CI), 0.53–1.23; P=0.32) or on the all-cause death (HR, 1.08; 95% CI, 0.67–1.73; P=0.75)



Walsh M et al. Kidney Int 2013

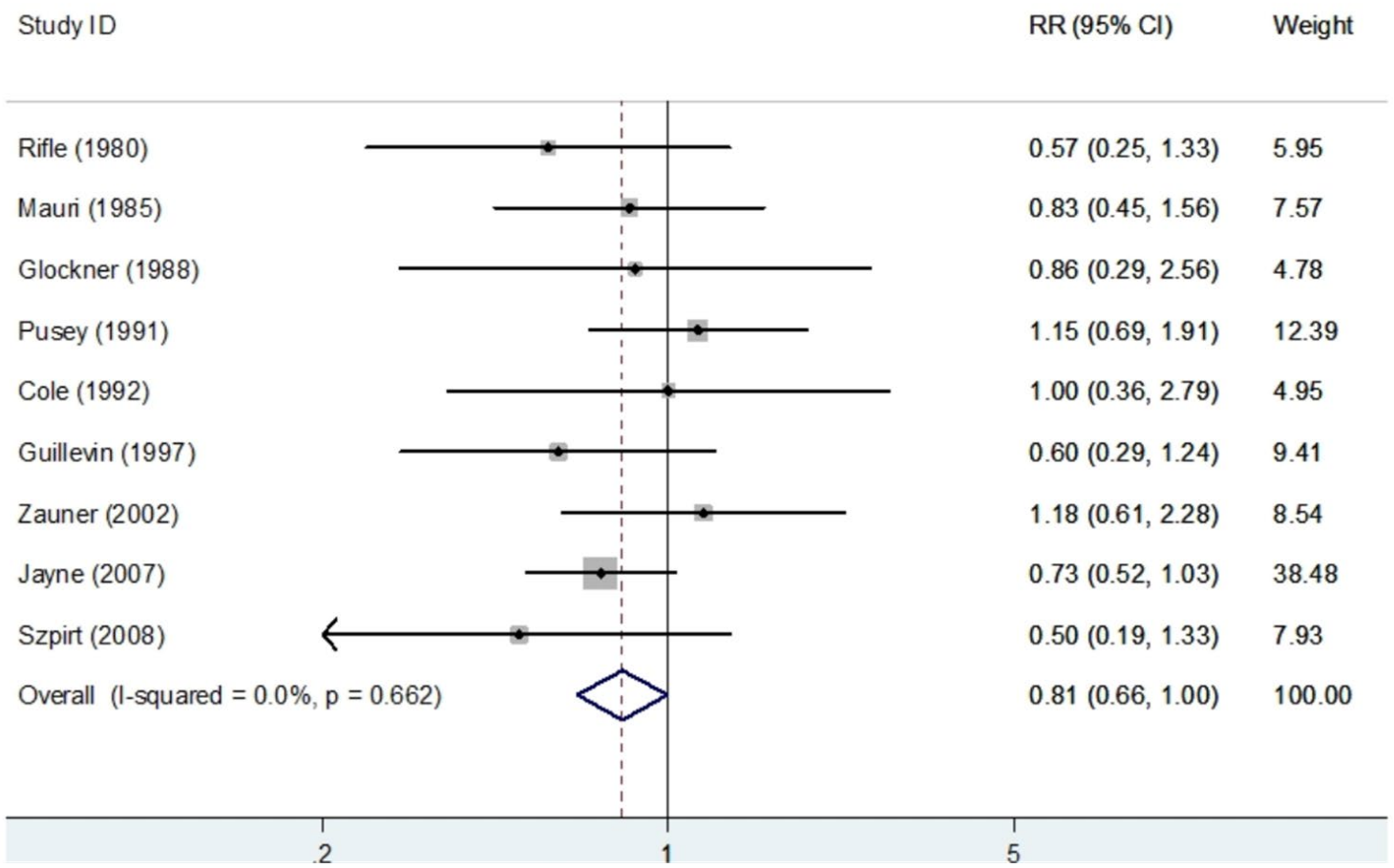
Effect of PLEX

9 trial (n=387 pts)

- statistically significant ↓ 20% RR of ESKD

- there are too

few patients randomized and sensitivity analyses were not sufficiently robust to reliably conclude that PLEX has at least a moderate reduction of the composite endpoint of ESRD or death



Walsh M et al. Am J Kidney Dis 2011

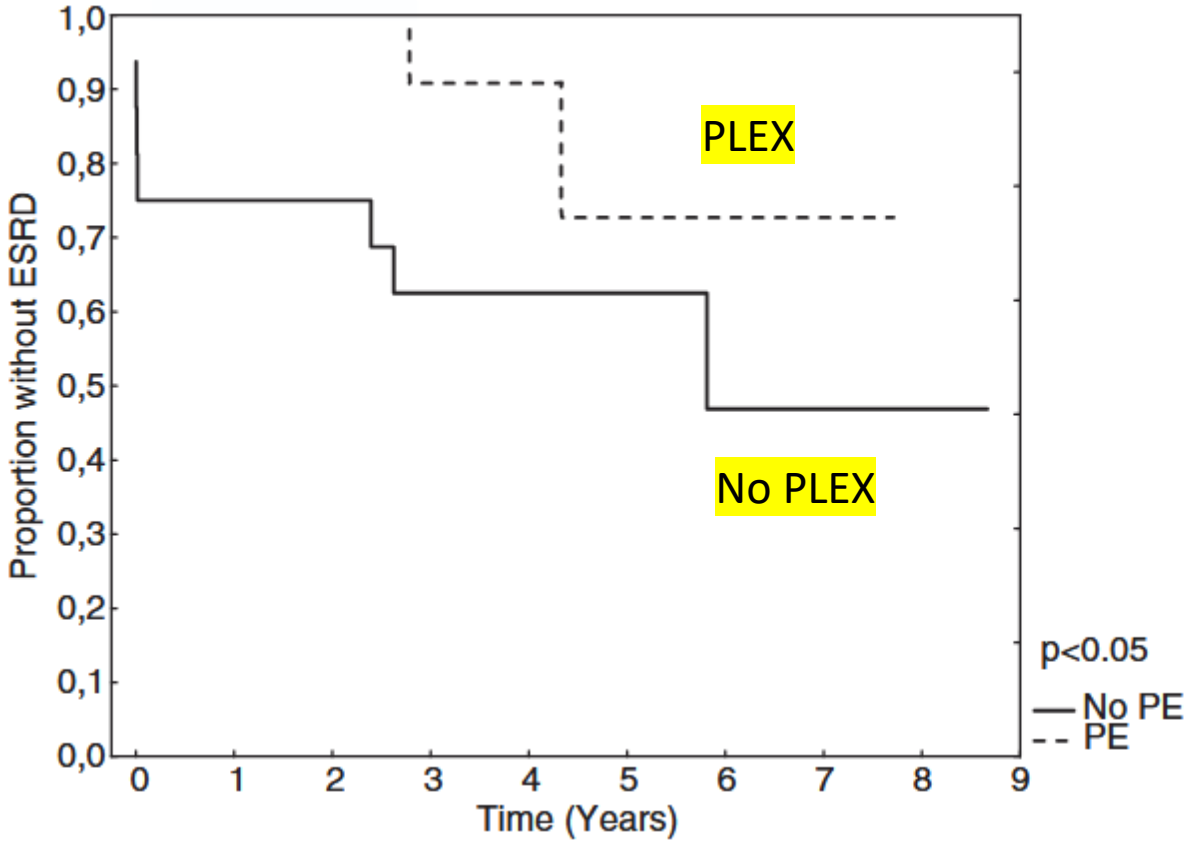
Extensive evidence of PLEX benefit in lower kidney function

- N=32 AAV

With or without PLEX

- Renal survival after 1, 3 and 12 months, and 5 years was significantly better in the PE groups.

- Multivariate analysis demonstrated that PE improved renal survival (P<0.01) at initial plasma creatinine levels >250 µmol/L (2.85 mg/dL).



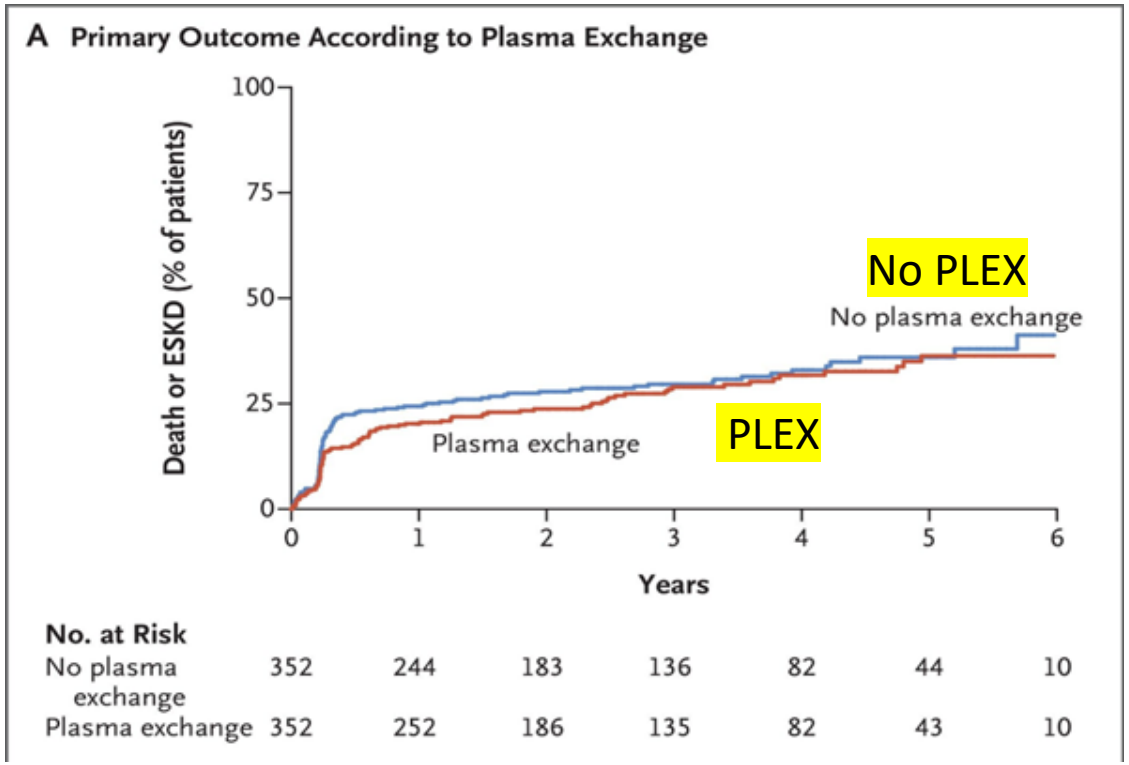
Szpirt V et al. NDT 2011

PEXIVAS trial

PEXIVAS
2-by-2 factorial design
1:1:1:1

N=704 AAV+ eGFR<50ml/min or DAH

PLEX+standard GCs, PLEX+reduced GCs, no PLEX+standard GCs, no PLEX+reduced GCs



- ❑ 100 (28.4%) PLEX vs 109 (30.9%) control
- ❑ 99 (14%) patients died and 137 (20%) developed ESKD, 3 year follow-up
- ❑ No benefit either death (HR 0.87) or ESKD (HR 0.81)

Walsh M et al. NEJM 2020

PEXIVAS trial

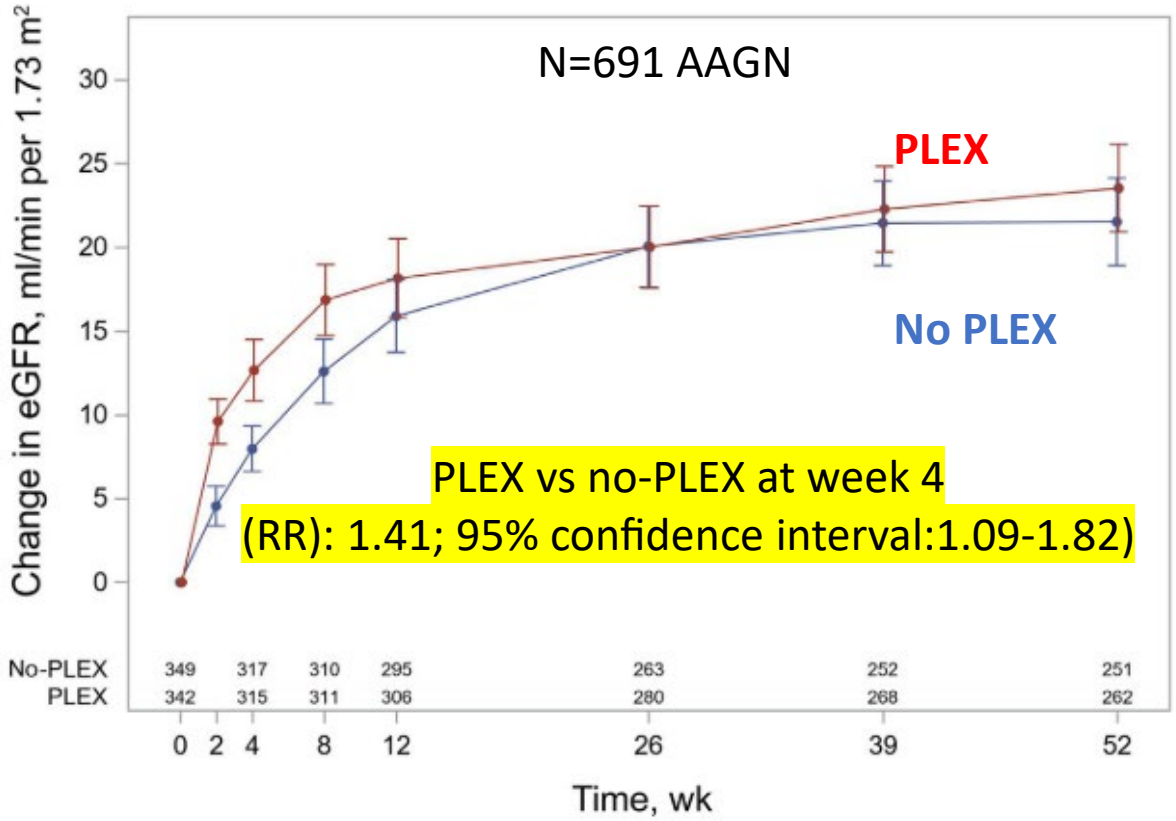
PEXIVAS
2-by-2 factorial design
1:1:1:1

N=704 AAV+ eGFR<50ml/min or DAH

PLEX+standard GCs, PLEX+reduced GCs, no PLEX+standard GCs, no PLEX+reduced GCs

Change in eGFR from baseline over the course of the 52-week in pts PLEX (red line) and no PLEX (blue line)
The mean change was higher in the PLEX group as compared to the no PLEX group at weeks 2, 4 and 8 (p<0.01)

Early renal recovery

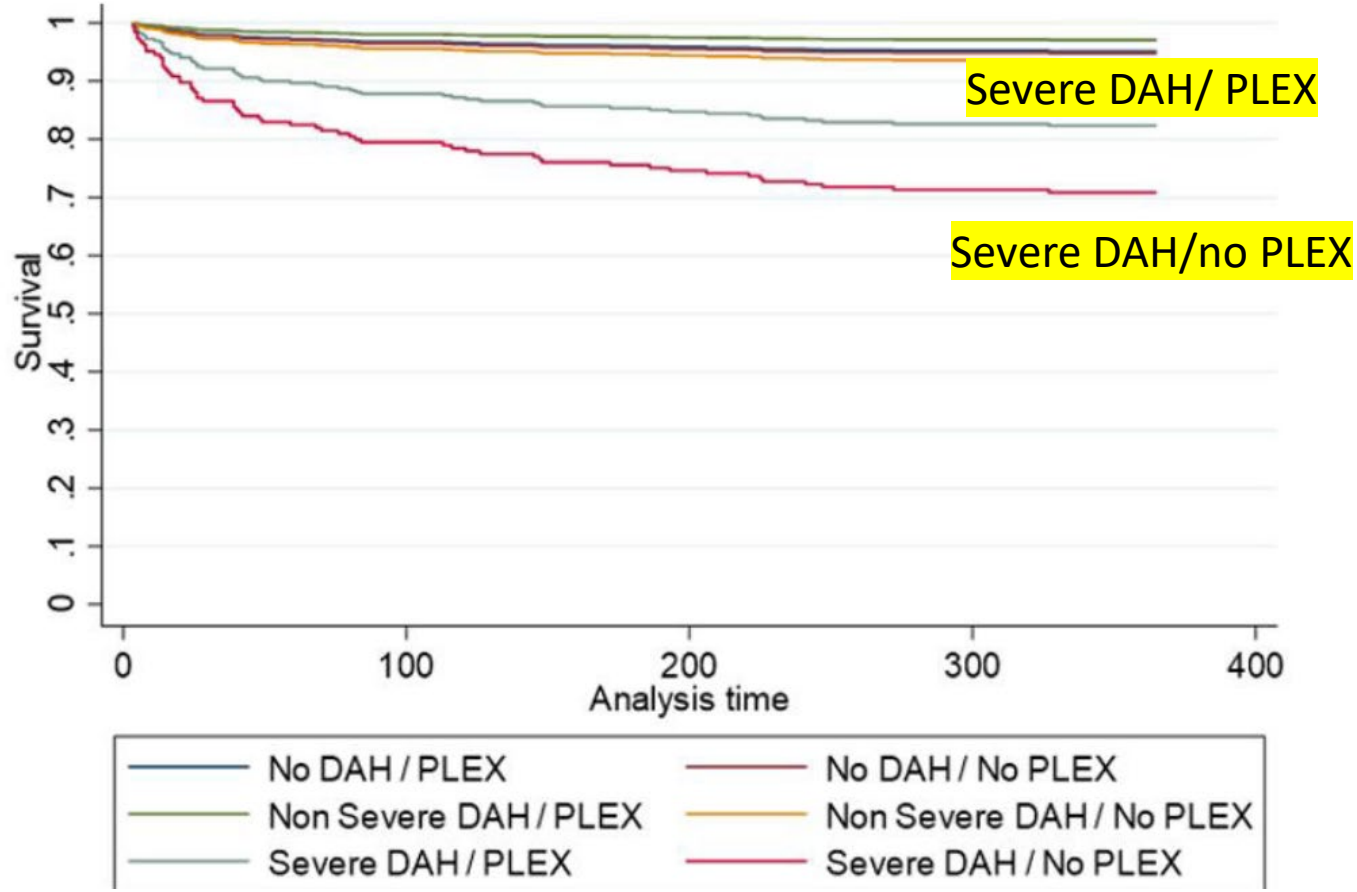


recovery of kidney function at week four→ ↓risk for ESKD week 52 (RR: 0.29: 0.16-0.52)

Odler B et al. Kidney Int 2024

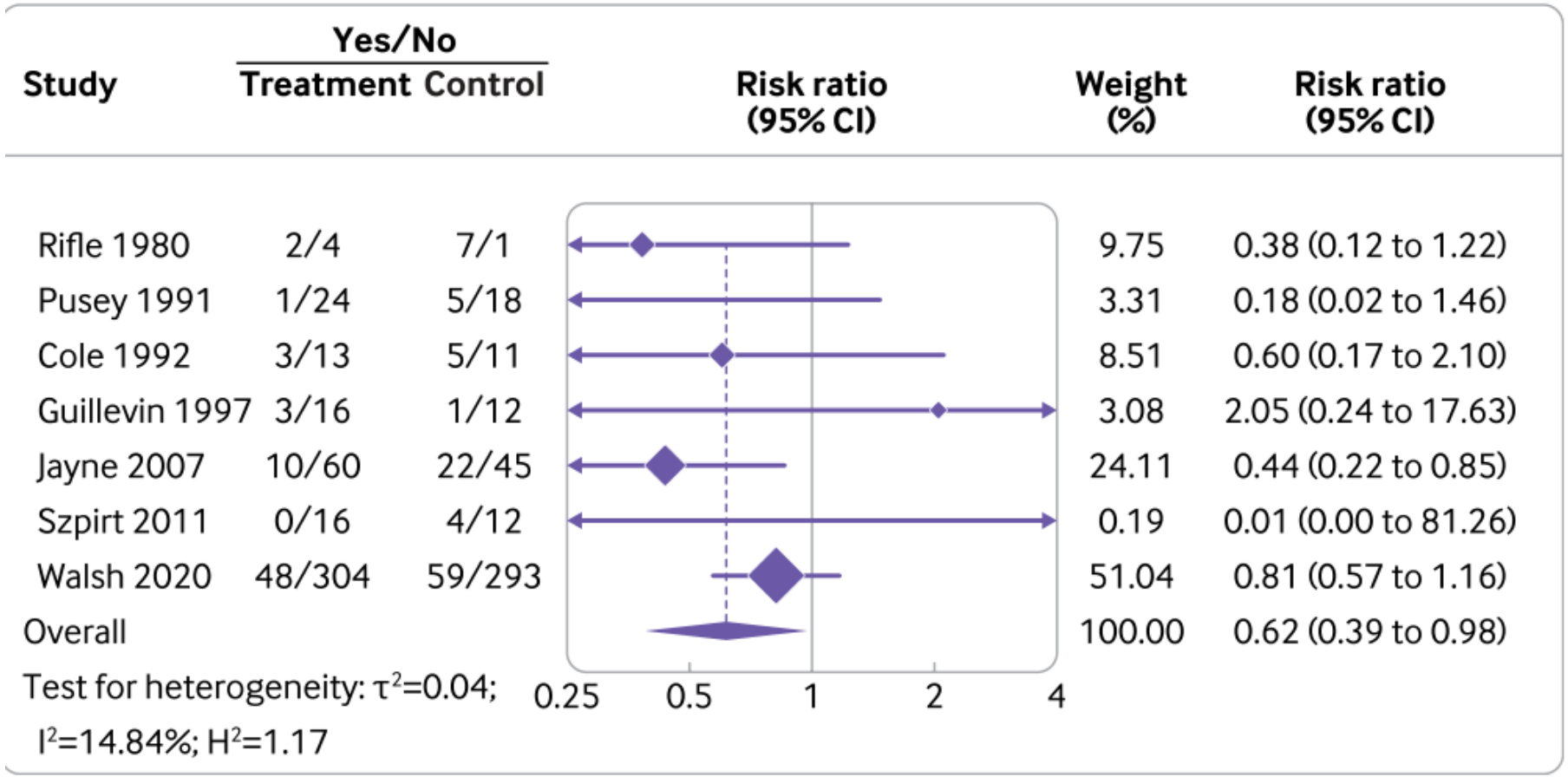
PEXIVAS Pulmonary Haemorrhage (n=191, 27%)

Figure 1: One year survival in PEXIVAS by plasma exchange (PLEX) and severity of diffuse alveolar hemorrhage (DAH), adjusted for age, sex, ANCA type, kidney function, and initial treatments



- Non-severe (non-hypoxic) n=130
  HR 0.43 (0.08-2.21)
- Severe (hypoxic) n=60
  HR 0.45 (0.24 -1.14)

Fussner L et al. Am J Respir Crit Care Med V 2024



9 trials/ 1060 patients

At 1 year Mortality RR 0.90 (0.64-1.27), ESKD RR 0.58 (0.38-0.89) Infection RR 1.27 (1.08-1.49)

Walsh M et al. BMJ 2022

Risk group for end stage kidney disease (ESKD)	LOW	Low to moderate	Moderate to high	High
Baseline serum creatinine level	≤ 200 µmol/L	>200-300 µmol/L	>300-500 µmol/L	> 500 µmol/L
Baseline risk of developing ESKD at 1 year	≤ 2.5%	>2.5-7.5%	>7.5-25.0%	>25.0%

Effect of PLEX on absolute risk	↓ ESKD	0.1%	2.1%	4.6%	16.0%
	↑ Infection	2.7%	4.9%	8.5%	13.5%

Walsh M et al. BMJ 2022

PLEX- Guidelines

Practice Point 9.3.1.9: Consider plasma exchange for patients with SCr >3.4 mg/dl (300 µmol/l) requiring dialysis or with rapidly increasing SCr, and in 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 vasculitis and anti-glomerular basement membrane (GBM).

~ 10% double positive

PLEX schedule

- 7 sessions
- 40-60ml/Kg replacement fluid

Rituximab removal from PLEX (3 sessions ↓ by 36%)
Maximize time from RTX infusion to next session

KDIGO 2023 **Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis**	Practice Point 9.3.1.9: Consider plasma exchange for patients with SCr >3.4 mg/dl (300 µmol/l) requiring dialysis or with rapidly increasing SCr, and in patients with diffuse alveolar haemorrhage who have hypoxemia. Practice Point 9.3.1.10. Add plasma exchange for patients with an overlap syndrome of ANCA vasculitis and anti-glomerular basement membrane (GBM)
EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update	Plasma exchange may be considered as part of therapy to induce remission in GPA or MPA for those with a serum creatinine >300 µmol/L due to active glomerulonephritis. Routine use of plasma exchange to treat alveolar haemorrhage in GPA and MPA is not recommended.
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 (2022)	Microscopic polyangiitis Granulomatosis with polyangiitis Eosinophilic granulomatosis with polyangiitis
2021 American College Rheumatology/ Vasculitis Foundation for the management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis	Recommendation: In patients with GPA/MPA with active glomerulonephritis, we conditionally recommend against the routine addition of plasma exchange to remission induction therapy. Recommendation: In patients with active, severe GPA/MPA with alveolar haemorrhage, we conditionally recommend against adding plasma exchange to remission induction therapies.

Chalkia A, Petras D. Transfusion and Apheresis Science 63 (2024)

Should Histology Influence Treatment?

Clinical and Histologic Determinants of Renal Outcome in ANCA-Associated Vasculitis: A Prospective Analysis of 100 Patients with Severe Renal Involvement

Robert A.F. de Lind van Wijngaarden,* Herbert A. Hauer,† Ron Wolterbeek,‡ David R.W. Jayne,§ Gill Gaskin,‖ Niels Rasmussen,¶ Laure-Hélène Noël,** Franco Ferrario,†† Rüdiger Waldherr,‡‡ E. Christiaan Hagen,§§ Jan A. Bruijn,* and Ingeborg M. Bajema;* for the European Vasculitis Study Group (EUVAS)

No

PLEX had benefit on kidney function recovery on all histology classes

A 38- year-Old man

Treatment

- IV solumedrol 3gr
- Tb Medrol 64mg x1

reduced GCs regimen

- IV CYC 2 doses
- RTX 1gr for 2 doses

Should we add PLEX?

YES

- **↑ risk of ESKD**

  ↑ creatinine

  crescentic class

  high risk
- **↓ risk of infections**

  young age

  no comorbidities

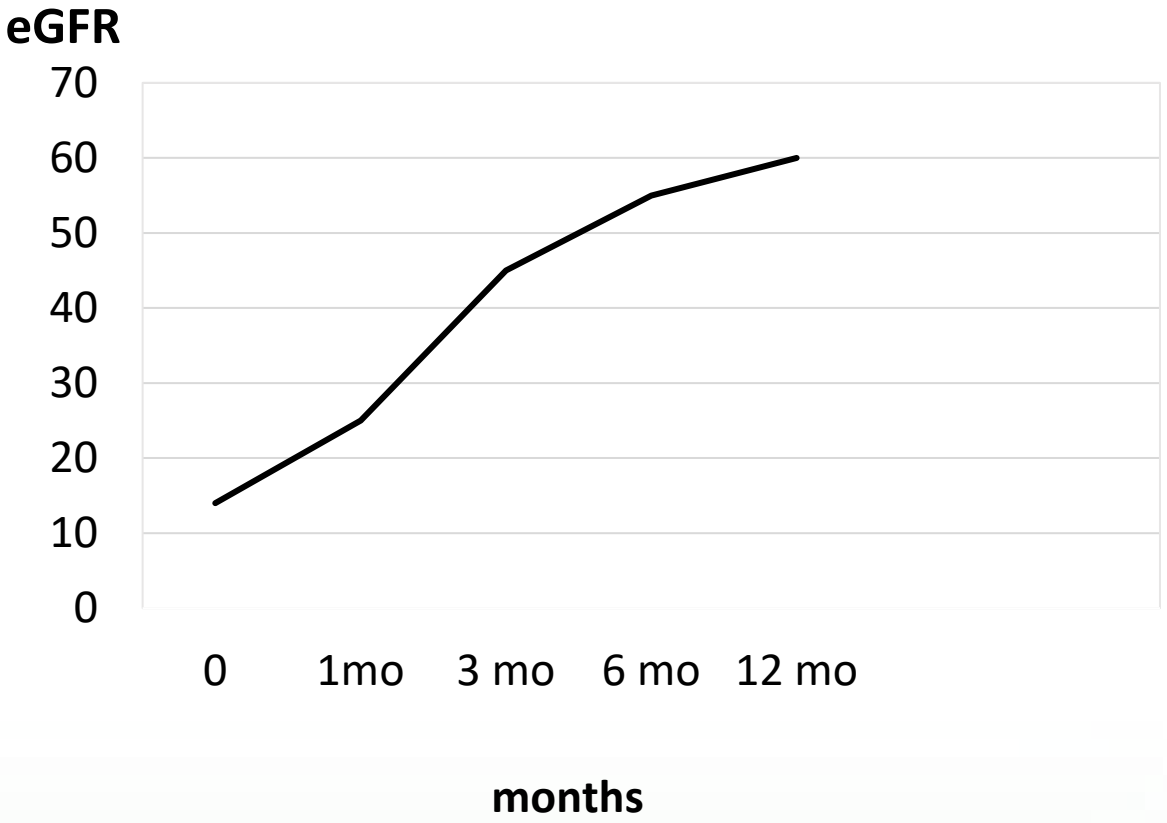
A 38- year-Old man

Treatment

- IV solumedrol 3gr
- Tb Medrol 64mg x1 reduced GCs regimen
  - IV CYC 2 doses
- RTX 1gr for 2 doses

Should we add PLEX?

YES



Conclusions

- The use of plasma exchange (PLEX) for the treatment of patients with RPGN (AAV) has been a matter of debate

- There is benefit of PLEX in selected cases of RPGN for renal recovery

- PLEX may increase the risk of infections