Therapeutic Apheresis for Renal Disease
Strategies and Controversies
ISBP 2023

Andre A. Kaplan, MD, FACP, FASN
Emeritus Professor of Medicine
University of Connecticut Health Center
Farmington, CT

Plasmapheresis for antibody associated GN: Rationale:

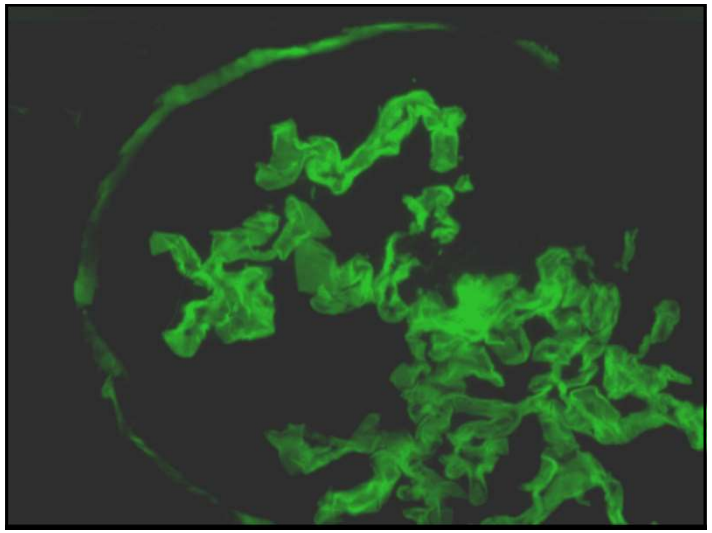
- IgG half life is 21 days: Even with complete cessation of production, there is a prolonged period with substantial amount of antibody still present
- Plasmapheresis is the most reliable and rapid means of lowering antibody levels

Apheresis for Renal Disease

- Primary Renal Disease
  - Goodpasture's disease
  - IgA nephritis/HSP
  - Pauci-immune RPGN
  - Focal segmental glomerulosclerosis
- Secondary Renal Disease
  - SLE
  - APA syndrome
  - Cryoglobulinemia
  - Multiple Myeloma
  - TTP/HUS
  - Transplantation

Apheresis for Renal Disease

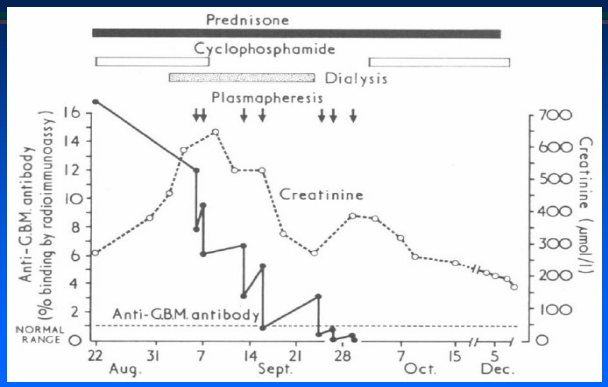
- Primary Renal Disease
  - Goodpasture's disease
  - IgA nephritis/HSP
  - Pauci-immune RPGN
  - Focal segmental glomerulosclerosis
- Secondary Renal Disease
  - SLE
  - APA syndrome
  - Cryoglobulinemia
  - Multiple Myeloma
  - TTP/HUS
  - Transplantation



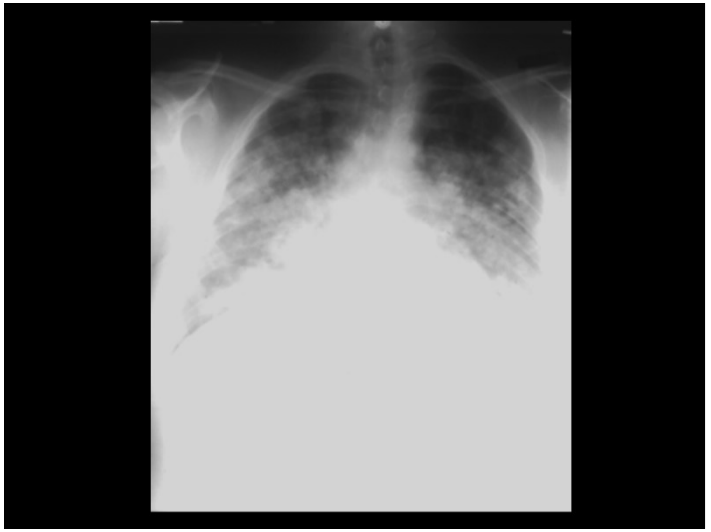
Anti-GBM Antibody and Goodpasture's Syndrome

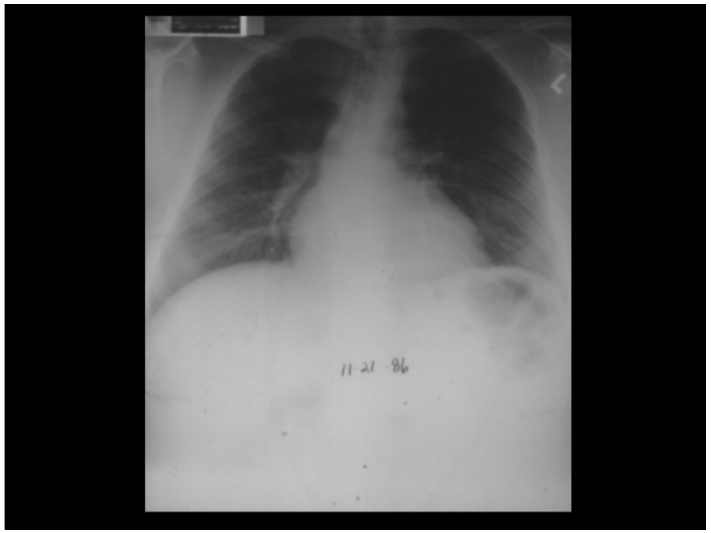
- Pathogenic antibody capable of causing alveolar hemorrhage and rapidly progressive glomerulonephritis
- Only one randomized, controlled trial: ***Johnson et al. Medicine 64:219, 1985***
- Plasmapheresis results in rapid lowering of anti-GBM antibody, lower post RX creatinine and reduced incidence of ESRD

Anti-GBM ANTIBODY DISEASE & GOODPASTURE'S SYNDROME



Lockwood et al. Br Med J 1975;2:252





Plasmapheresis in anti-glomerular basement membrane disease: How much is enough?

Nitin Relia, Yusra Cheema, Jennifer Tuazon, and James Paprello

Clinical Nephrology, Vol. 85 – No. 3/2016 – Letter to the editor

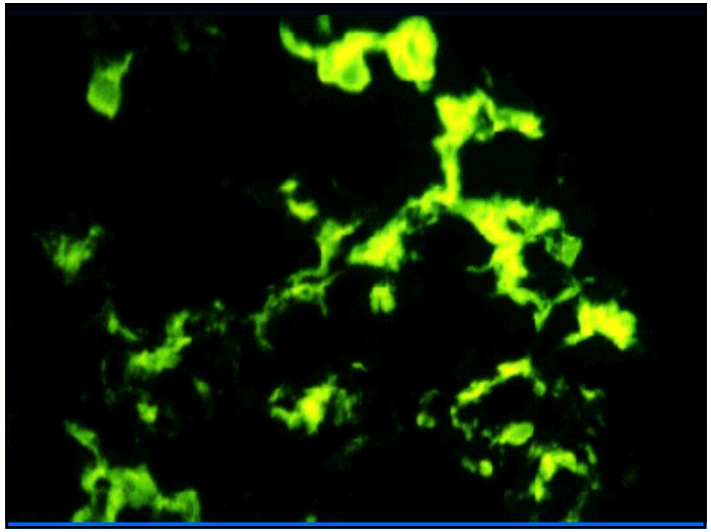
Table 1. Patient characteristics.

Patient characteristics	Patient 1	Patient 2	Patient 3
Age/sex	25 years/male	19 years/female	43 years/female
Creatinine at presentation (mg/dL)	3.0	4.2	3.4
Peak creatinine (mg/dL)	9.5	7.6	13.0
% of crescents on renal biopsy	60%	75%	100%
Dialysis (Y/N)	N	Y	Y
Number of plasmapheresis sessions	40	25	39
Immunosuppression	Steroids, 3 monthly doses of cytoxan, 2 doses of rituximab	Steroids, 4 monthly doses of cytoxan	Steroids, 6 monthly doses of cytoxan
Follow-up (months)	36	36	16
S.Cr (mg/dL) at most recent f/u	1.8	1.6	2.3

Y = yes; N = no; S.Cr = serum creatinine; f/u = follow-up.

Apheresis for Renal Disease

- Primary Renal Disease
  - Goodpasture's disease
  - IgA nephritis/HSP
  - Pauci-immune RPGN
  - Focal segmental glomerulosclerosis
- Secondary Renal Disease
  - SLE
  - APA syndrome
  - Cryoglobulinemia
  - Multiple Myeloma
  - TTP/HUS
  - Transplantation



IgA Nephropathy and Henoch Schonlein Purpura

In general, IgA nephropathy is treated with supportive therapy including ACE and ARBs to lower blood pressure and minimize proteinuria.

Immunotherapy with glucocorticoids and mycophenolate mofetile are recommended for severe cases.

TPE has been evaluated in patients with severe disease….

Plasmapheresis as the sole therapy for RPGN in Henoch Schonlein Purpura

Hattori et al. Am J Kidney Dis 33:427, 1999

- 9 children with RPGN: proteinuria: 4.9 gm/m2/d, GFR: 46.5 mL/min, crescents in > 56 % of glomeruli
- TPE as sole therapy, thrice weekly for 2 weeks then weekly for 6 weeks
- Improvement in renal function, purpuric rash and abdominal pain
- 87% longterm renal survival (9.6 y) vs. less than 33% in previous studies

Plasma Exchange as an Adjunctive Therapy for Crescentic IgA Nephropathy.

Xie X[1], Lv J, Shi S, Zhu L, Liu L, Chen M, Wang Y, Cui Z, Wang X, Liu L, Yu X, Zhou F, Zhao MH, Zhang H.

Renal Division, Peking University First Hospital, Peking University Institute of Nephrology, Key Laboratory of Renal Disease, Ministry of Health of China, and Key Laboratory of Chronic Kidney Disease Prevention and Treatment, Peking University, Ministry of Education, Beijing, China

Am J Nephrol. 2016;44(2):141-9. doi: 10.1159/000448767. Epub 2016 Aug 17.

BACKGROUND:

Crescentic IgA nephropathy (CreIgAN) has a poor prognosis despite aggressive immunosuppressive therapy. The efficacy of plasma exchange (PE) is not well defined.

TPE FOR CRESENTERIC IGA NEPHRITIS

METHODS:

Twelve patients with severe CreIgAN who received PE as addition to routine immunosuppressive therapy, followed for more than 6 months, were involved. Twelve matched historical controls who received immunosuppressive therapy alone were selected. Renal survival, plasma IgA-IgG complex and active complement products were assessed.

RESULTS:

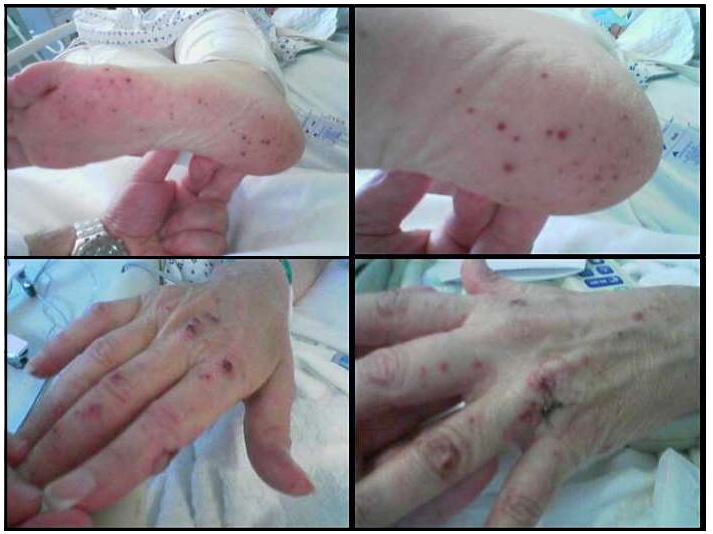
Nine men and 3 women received a median of **7 PE courses** (range 5-10). Their baseline urine protein excretion rate was 5.8 (4.5-8.7) g/day, and their serum creatinine level was 705.3 ± 296.4 μmol/l. **During a mean follow-up of 15.6 months (6-51 months), 6 of the 12 PE group patients were free of dialysis, while all the control patients were dialysis dependent** (6 of 12 vs. 0 of 12, p = 0.014). In the PE group, dialysis had to be restarted for 1 patient owing to the development of severe pneumonia and pulmonary failure. **PE was associated with a higher kidney survival rate** (log rank test, p = 0.026) during follow-up. It also significantly decreased plasma IgA-IgG complex levels (pre-PE: 85.3 ± 25.9% vs. post-PE: 38.4 ± 12.4%, p < 0.001) and plasma and urinary active complement product levels, including C3a, C5a and soluble C5b-9. The latter levels remained low until the last follow-up.

CONCLUSION:

This study indicated that PE could increase renal recovery rates in severe CreIgAN.

Apheresis for Renal Disease

- Primary Renal Disease
  - Goodpasture's disease
  - IgA nephritis/HSP
  - Pauci-immune RPGN
  - Focal segmental glomerulosclerosis
- Secondary Renal Disease
  - SLE
  - APA syndrome
  - Cryoglobulinemia
  - Multiple Myeloma
  - TTP/HUS
  - Transplantation



Are ANCA pathogenic?

Lionaki & Falk, JASN 18:1987-8, 2007

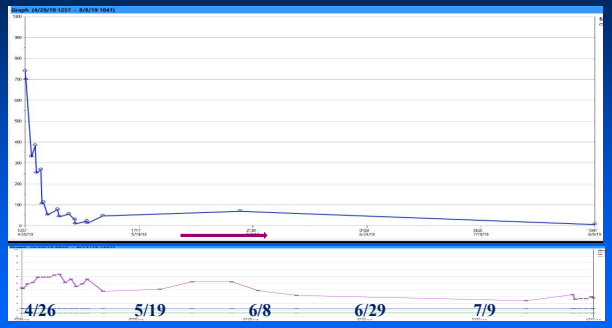
- ANCA are capable of activating leukocytes *in vitro*: *Falk & Jennette, JASN 13:1977-9, 2002, Jennette et al. JASN 17:1235-42, 2006*
- In animals, anti-myeloperoxidase ABs can induce necrotizing GN and vasculitis. *Xiao et al. Am J Path 167:39-45, 2995, Little et al. Blood 106: 2050-58, 2005.*
- Case of transplacental transfer of ANCA resulting in vasculitis in newborn infant. *Schlieben et al. Am J Kidney Dis 45:758-61, 2005*

Controlled trials of TPE for severe RPGN

	Index of Severity	TPE	no TPE
Mauri et al. 1985 (ref 1)	Creatinine > 9		
Initial creatinine (# pts)		13.5 (6)	13.1 (5)
Creatinine after 3 years		**8.7***	**13.4**
Glockner et al. 1988 (ref 2)	Dialysis dependent		
Initial creatinine (# pts)		7.4 (8)	9.2 (4)
Creatinine after 6 months		**1.7***	**5.5**
Pusey et al. 1991 (ref 3)	Dialysis dependent		
Initial # pts on dialysis		11	8
Patients off dialysis at 12 months		**10@**	**3**
Cole et al. 1992 (ref 4)	Dialysis dependent		
Initial # pts on dialysis		4	7
Patients off dialysis at 12 months		**3**	**2**

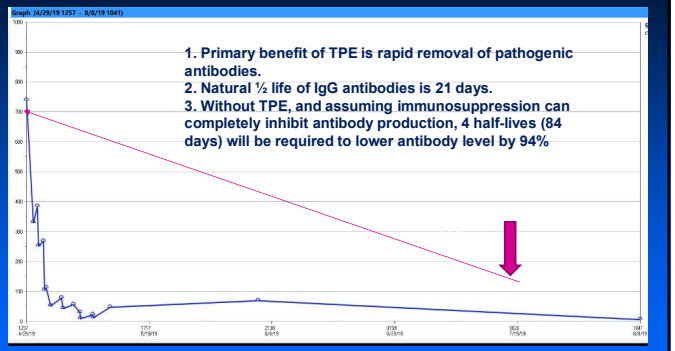
Kaplan AA. Ther Apheresis 1997;1:255-259

Rapid lowering of PR-3 antibodies with TPE



On Dialysis 0ff Dialysis

Rapid lowering of PR-3 antibodies with TPE



Kidney Int 40:1991, 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

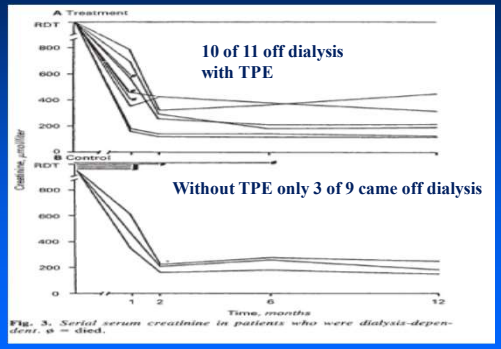


Fig. 3. Serial serum creatinine in patients who were dialysis-dependent. ϕ = died.

Pusey et al, Kidney Int 40: 757-763, 1991

Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis (MEPEX)

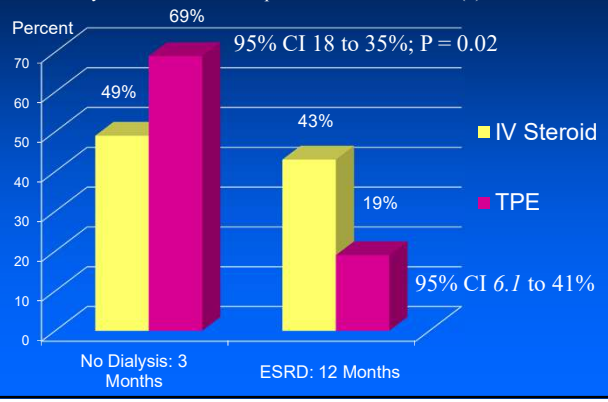
Jayne DR - *J Am Soc Nephrol* - 01-JUL-2007; 18(7): 2180-8

137 patients with ANCA-associated systemic vasculitis with serum creatinine >500 micromol/L (5.8 mg/dl)
Randomized to TPE vs. intravenous methylprednisolone.
Both groups received oral cyclophosphamide and oral prednisolone.
70 received 7 plasma exchanges, 67 received 3000 mg of IV methylprednisolone

Results: In patients presenting with renal failure, TPE increased the rate of renal recovery in ANCA-associated systemic vasculitis

Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis (MEPEX).

Jayne DR - *J Am Soc Nephrol* - 01-JUL-2007; 18(7): 2180-8



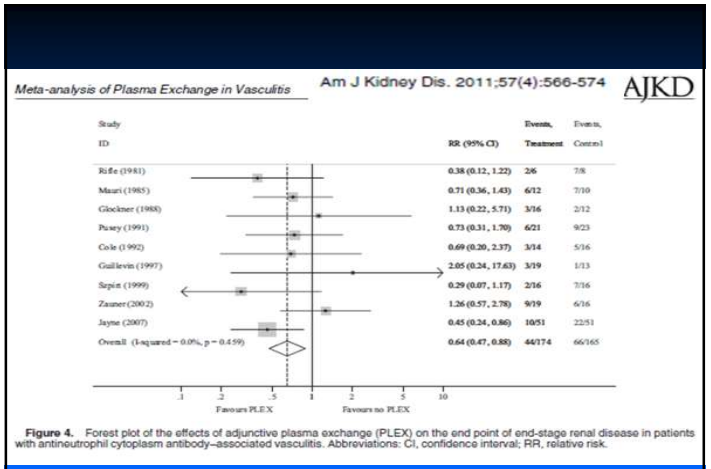


Figure 4. Forest plot of the effects of adjunctive plasma exchange (PLEX) on the end point of end-stage renal disease in patients with antineutrophil cytoplasm antibody–associated vasculitis. Abbreviations: CI, confidence interval; RR, relative risk.

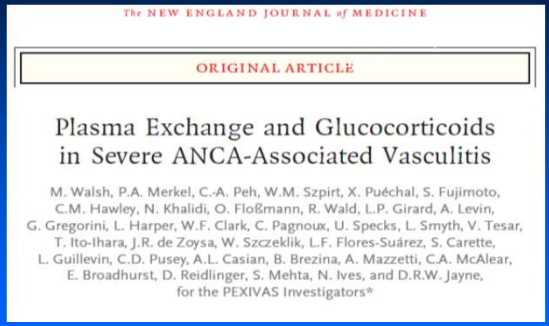
Journal of Clinical Apheresis: 2016 ASFA Guidelines

Current management/treatment

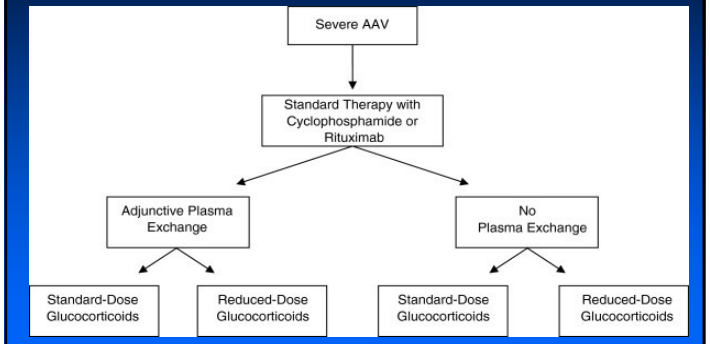
The current management is combination therapy consisting of high-dose corticosteroids and cytotoxic immunosuppressive drugs (cyclophosphamide and rituximab). Two randomized trials indicate that rituximab is an effective alternative to cyclophosphamide in new or relapsing patients.

Overall, existing controlled trials suggest no benefit of TPE for many cases with kidney involvement. Important exceptions are: **Patients with (1) severe active kidney disease, i.e., requiring dialysis therapy or with serum creatinine concentration above 6 mg/dL; (2) severe pulmonary hemorrhage; and (3) anti-GBM disease who are also ANCA-positive.**

PEXIVAS



PEXIVAS



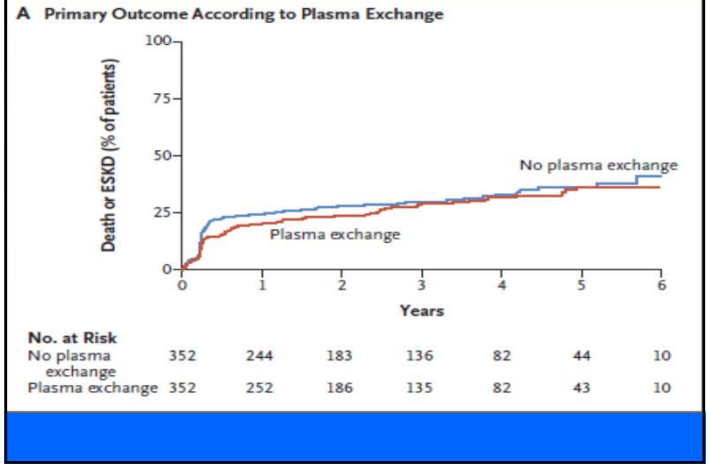
PEXIVAS

Table 1. Characteristics of the Patients at Baseline.*

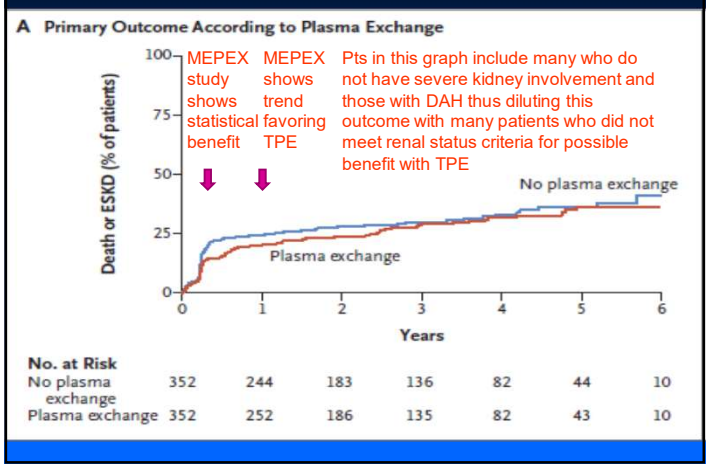
Characteristic	Plasma Exchange (N = 352)	No Plasma Exchange (N = 352)
Kidney function		
Median serum creatinine level (IQR) — μmol/liter	327 (206–491)	336 (209–495)
Serum creatinine level ≥500 μmol/liter or undergoing dialysis — no. (%)	101 (28.7)	104 (29.5)
Undergoing dialysis — no. (%)	66 (18.8)	74 (21)

In patients without DAH, this is the only group found to improve with TPE in previous studies evaluating ANCA disease.

PEXIVAS



PEXIVAS



Editorial *382;7 nejm February 13, 2020*
ANCA-Associated Vasculitis — Refining Therapy with Plasma Exchange and Glucocorticoids
Vimal K. Derebail, M.D., M.P.H., and Ronald J. Falk, M.D.

"The trial has limitations that are potentially of clinical importance. **A kidney biopsy was not required** for entry into the trial. Patients with ANCA-associated vasculitis frequently have a relapsing and remitting course; thus, diffuse tubulointerstitial and glomerular scarring can occur before initial diagnosis. At the time of entry, severe ANCA-induced kidney disease that caused an estimated glomerular filtration rate of less than 50 ml per minute per 1.73 m2 could have resulted from active inflammatory injury, chronic sclerotic injury, or both. **Without baseline biopsy data, the proportion of patients who had kidney dysfunction caused by active inflammation, which may respond to immunomodulatory therapy, as compared with chronic sclerosis, which would not respond to this therapy, is unknown. A subgroup of patients with aggressive kidney disease with minimal scarring may benefit from plasma exchange."**

MEPEX VS. PEXIVAS for patients with creatinines of ≥5.7 mg/dL or on dialysis

- MEPEX
- 137 Pts randomized
- Statistical benefit in 3 months for TPE showing more patients off dialysis
- At 1year, increased likelihood of being off dialysis
- **All patients with renal biopsies**

- PEXIVAS
- 206 Pts randomized
- Despite clear separation on provided figure, there is no statistical assessment at 3 months
- At 1 year, no statistical benefit but provided figure is diluted with the majority of patients having creatinines <5.7mg or DAH
- **No biopsy data provided.**

Why should PEXIVAS results negate MEPEX?

PEXIVAS: Correspondence

NEJM 282:22, MAY 28, 2020

- Authors asked how many patients did not receive 7 TPE treatments?
- Authors response: Of 317 patients in TPE group:
- 20 (6%) received between one and 6 exchanges
- 15 (4%) received **no** exchanges
- **Thus: 35/317 = 11% of patients in TPE group did not get full dose of TPE**

- Of potentially greater concern…….
- There was only 101 patients in the renal failure group with high creatinine (>5.7), or on dialysis. How many of these patients had reduced number of TPE treatments
- It is possible that up to 35 pts in TPE group who had creatinine greater than 5.7, or were on dialysis, did not receive full dose of TPE … the group previously identified as most likely to respond …. 35/101 is a big percentage…

Relative costs of TPE for AKI with ANCA

- ESRD with HD = $90,000/y (USRDS 2018)
- Assume that ANCA patients will survive on dialysis for one year.
- 7 TPE treatments at $2000/TPE = $14,000
- $14,000/90,000 = 0.16
- **CCL: If only 16% of all TPE treated patients avoid dialysis for one year, the cost of providing TPE to all patients will be less than no TPE.**

Conclusion

- **Previous studies show benefit for TPE in pts with advanced renal disease (creatinine ≥ 5.7 mg/dL or requiring dialysis)**
- **PEXIVAS found no benefit for TPE in patients with advanced renal disease**
- **Lack of renal biopsy data is a substantial deficiency in the ultimate assessment of negative TPE data**
- **35 patients in PE group did not get full dose of TPE. The effect of these undertreated patients may be very significant if a substantial number of these undertreated patients were in the group of 101 patients with creatinines ≤ 5.7 or those on dialysis.**
- **Cost of providing TPE with possible benefit is far less than need for chronic dialysis if no TPE is provided.**
- **PEXIVAS data is not sufficient to negate previous recommendations that TPE may benefit ANCA patients with advanced renal disease**

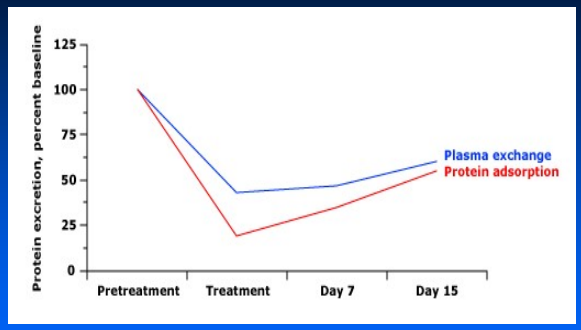
Apheresis for Renal Disease

- Primary Renal Disease
  - Goodpasture's disease
  - IgA nephritis/HSP
  - Pauci-immune RPGN
  - Focal segmental glomerulosclerosis
- Secondary Renal Disease
  - SLE
  - APA syndrome
  - Cryoglobulinemia
  - Multiple Myeloma
  - TTP/HUS
  - Transplantation

Focal Segmental Glomerulosclerosis (FSGS)

- 15-55% of patients with ESRD due to FSGS will have recurrence of proteinuria after renal transplantation.
- 30-50,000 dalton protein can increase glomerular permeability.
- Protein adsorption and plasmapheresis can lower proteinuria and maintain normal histology. *Dantal et al. NEJM 330: 1994, Artero et al. Am J Kidney Dis 23:1994*

Removal of circulating factor lowers protein excretion in FSGS



Mean reduction in protein excretion following treatment with a protein adsorption column in eight patients with recurrent FSGS after renal transplantation. ***Dantal, J, et al, N Engl J Med 1994; 330:7.***

878 THE NEW ENGLAND JOURNAL OF MEDICINE April 4, 1996

CIRCULATING FACTOR ASSOCIATED WITH INCREASED GLOMERULAR PERMEABILITY TO ALBUMIN IN RECURRENT FOCAL SEGMENTAL GLOMERULOSCLEROSIS

VIRGINIA J. SAVIN, M.D., RAM SHARMA, M.S., MUKUT SHARMA, PH.D., ELLEN T. MCCARTHY, M.D., SUZANNE K. SWAN, M.D., EILEEN ELLIS, M.D., HELEN LOVELL, M.D., BRADLEY WARADY, M.D., SRIPAD GUNWAR, PH.D., ARNOLD M. CHONKO, M.D., MARY ARTERO, M.D., AND FLAVIO VINCENTI, M.D.*

Plasma Exchange lowers glomerular permeability and protein excretion in patients with recurrent Focal Segmental Glomerulosclerosis post transplant

882 THE NEW ENGLAND JOURNAL OF MEDICINE April 4, 1996

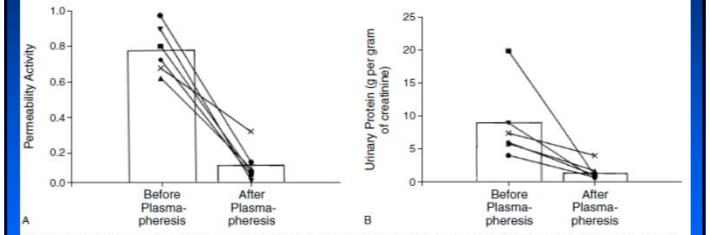


Figure 4. Permeability Activity (Panel A) and the Ratio of Urinary Protein to Creatinine (Panel B) before and after 4 to 14 Plasmapheresis Treatments in Six Transplant Recipients with Recurrent Focal Segmental Glomerulosclerosis.
Plasmapheresis was carried out daily for two to four days and then on alternate days. Permeability activity was measured in serum samples obtained immediately before the first treatment and within 24 hours after the last treatment. Urinary protein and creatinine were measured before treatment and 4 to 10 days after the last treatment. The bars indicate the mean values.

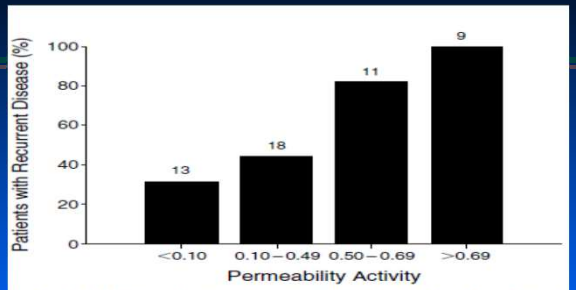


Figure 2. Relation between Permeability Activity and Recurrent Focal Segmental Glomerulosclerosis after Renal Transplantation.
Patients followed for six months or more after renal transplantation were divided arbitrarily into four groups according to the serum value for permeability activity. The frequency of recurrent focal segmental glomerulosclerosis increased with increasing values ($P<0.001$). The number of patients in each group is shown above the bars.

Table 2. Frequency of Recurrent Focal Segmental Glomerulosclerosis in 30 Patients after Transplantation, According to the Value for Permeability Activity in Serum Samples Obtained before Transplantation.

PERMEABILITY ACTIVITY*	NO RECURRENCE	RECURRENCE
	no. of patients (%)	
<0.50	19	4 (17)
≥0.50	1	6 (86)
Total	20	10 (33)

*$P<0.001$ for the comparison between the patients with values under 0.50 and those with values greater than or equal to 0.50.

CONCLUSIONS: FGS recurs in approximately 30% of allografts and causes graft loss in half of these. Patients who have lost a first allograft to recurrent FGS are at high risk for developing recurrent disease in a second allograft. Prolonged allograft survival is possible in patients with recurrent FGS and may best be obtained with a combination of treatment modalities including cyclosporine (perhaps in higher dosages than are routinely used in clinical renal transplantation), ACE inhibitors, and early use of plasmapheresis. The efficacy of these modalities supports the notion that recurrent FGS is caused by a circulating humoral mediator.

Response to Plasmaphersis for FSGS

TABLE 4. Treatment regimens, responses, and current graft status for KTx recipients with unequivocal FSGS that received plasmapheresis therapy

Case	Age at KTx	Sex	Donor	PP start	PP start (days from KTx)	Total PP duration (d)	Ritux[a]	Ritux start (days from KTx)	FSGS recur (d)	Initial response to PP[b]	F/U (d)	Current KTx status[c]	Current proteinuria status[d]
1	13	F	LRD	Post-KTx	2	78	No	N/A	Yes (1)	NR	4	HD	N/A
2	42	F	LRD	Post-KTx	20	51	No	N/A	Yes (14)	NR	516	HD	N/A
3	30	M	LRD	Post-KTx	1	36	No	N/A	Yes (1)	PR	37	HD	N/A
4	65	M	LRD	Post-KTx	315	179	No	N/A	Yes (2)	PR	443	1.1	alb/Cr 1773
5	38	F	LRD	Post-KTx	52	1248	No	N/A	Yes (14)	CR	1328	1.1	alb/Cr 1811
6	50	M	LRD	Post-KTx	119	251	No	N/A	Yes (70)	CR	365	1.3	Tot. Pr. 3.7
7	19	F	LRD	Post-KTx	2	138	Yes	12	Yes (1)	NR	359	1.5	alb/Cr 2
8	18	F	LRD	Pre-KTx	−5	293	No	N/A	Yes (5)	CR	494	PD[e]	N/A
9	67	M	LRD	Pre-KTx	−5	124	No	N/A	Yes (1)	CR	134	PD[e]	N/A
10	42	M	LURD	Pre-KTx	−5	709	No	N/A	Yes (1)	PR	850	HD/died	N/A
11	23	F	LRD	Pre-KTx	−5	4	No	N/A	No	N/A	1717	2.5	Tot. Pr. 0.3
12	6	M	LRD	Pre-KTx	−8	28	Yes	7	Yes (1)	NR	392	0.8	alb/Cr 20
13	13	M	LRD	Pre-KTx	−5	933	Yes	928	Yes (1)	CR	916	1.0	alb/Cr 11
14	5	M	LRD	Pre-KTx	−7	93	Yes	63	Yes (1)	CR	208	0.6	alb/Cr 7

[a] Rituximab dose = 375 mg/m^2 given once every 2 wk for 2 or 4 doses.
[b] NR defined as proteinuria reduction ≤50% of post-KTx peak after initial PP course; PR defined as proteinuria reduction >50% of post-KTx but not normalized; CR defined as normalization of proteinuria after initial PP course.
[c] Dialysis status or most recent serum creatinine concentration (mg/dL).
[d] Most recent urine protein measurement. Normal values: alb/Cr <17 mg/g; Tot. Pr. <0.15 g/24 hr.
[e] These subjects relapsed after discontinuation of PP, were subsequently unresponsive, and progressed to graft loss.
KTx, kidney transplant; PP, plasmapheresis; Ritux., rituximab; LRD, living-related donor; LURD, living-unrelated donor; N/A, not applicable; NR, no response; PR, partial response; CR, complete response; HD, hemodialysis; PD, peritoneal dialysis; alb/Cr, albumin/creatinine ratio in urine; Tot. Pr., total 24 h protein in urine; FSGS, focal segmental glomerulosclerosis.

Kidney Transplantation for Primary Focal Segmental Glomerulosclerosis: Outcomes and Response to Therapy for Recurrence. Hickson, LaTonya, Transplantation. 87(8):1232-1239, 2009.

Indications: ASFA Guidelines

LDL Apheresis

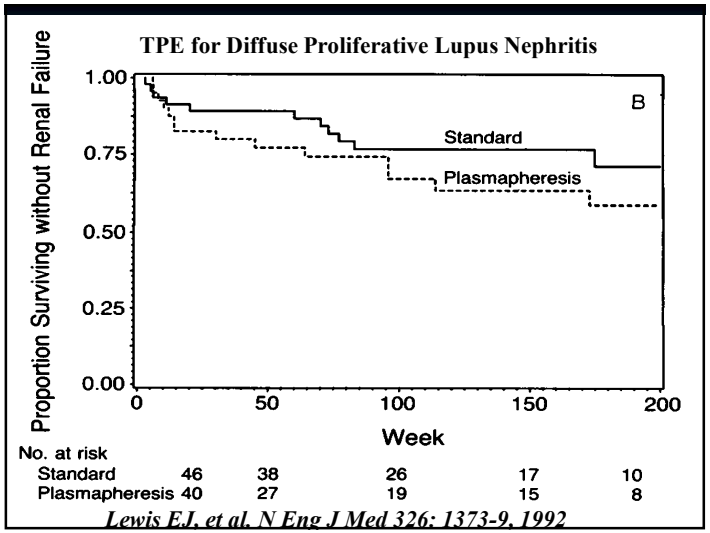
- Homozygous FH: Cat I, Grade 1A
- Heterozygous FH: Cat II, Grade 1A
- Homozygotes with small blood volume: TPE, Cat II, Grade 1C
- Lipoprotein (a): Category II, Grade 1B
- FSGS, steroid resistant: Cat III, Grade 2C
- Peripheral vascular diseases: Cat II, Grade 1B
- Phytanic acid storage disease (Refsum's disease): Cat II, Grade 2C
- Sudden sensorineural hearing loss: Cat III, Grade 2A

Journal of Clinical Apheresis 31:149–338 (2016)

UC San Diego Health

Apheresis for Renal Disease

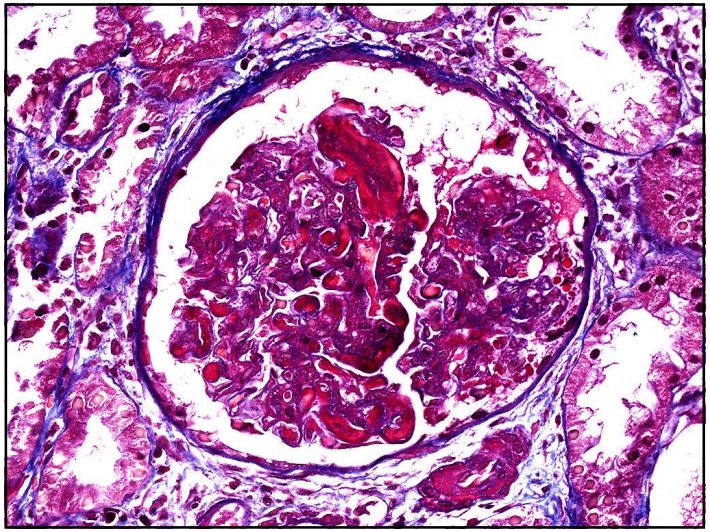
- Primary Renal Disease
  - Goodpasture's disease
  - IgA nephritis/HSP
  - Pauci-immune RPGN
  - Focal segmental glomerulosclerosis
- Secondary Renal Disease
  - SLE
  - APA syndrome
  - Cryoglobulinemia
  - Multiple Myeloma
  - TTP/HUS
  - Transplantation

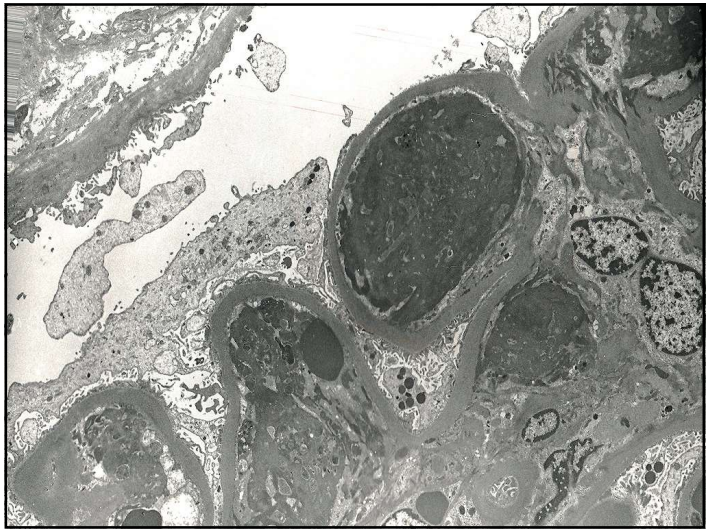


Lewis EJ, et al. N Eng J Med 326: 1373-9, 1992

Apheresis for Renal Disease

- Primary Renal Disease
  - Goodpasture's disease
  - IgA nephritis/HSP
  - Pauci-immune RPGN
  - Focal segmental glomerulosclerosis
- Secondary Renal Disease
  - SLE
  - APA syndrome
  - Cryoglobulinemia
  - Multiple Myeloma
  - TTP/HUS
  - Transplantation





Are anti-phospholipid antibodies pathogenic?

"Antiphosphospholipid antibodies (aPL) have been demonstrated to have procoagulant actions upon protein C, annexin V, platelets, serum proteases, toll-like receptors, tissue factor, and via impaired fibrinolysis.

Aside from increasing the risk of vascular thrombosis, aPL increase vascular tone, thereby increasing the susceptibility to atherosclerosis, fetal loss and neurological damage."

BL Bermas, PH Schur, UpToDate, 2010

Catastrophic Antiphospholipid Antibody Syndrome (CAPS)

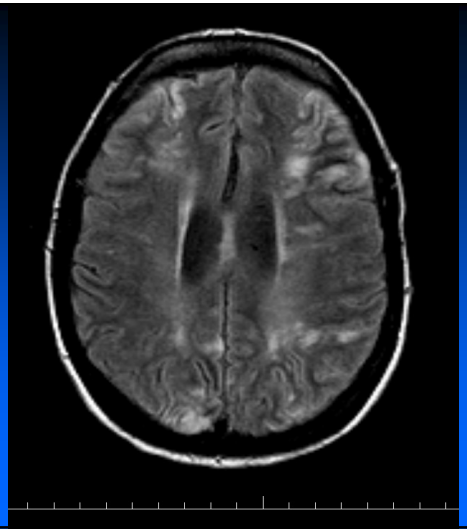
CAPS is a rare life-threatening form of antiphospholipid antibody syndrome (APS)

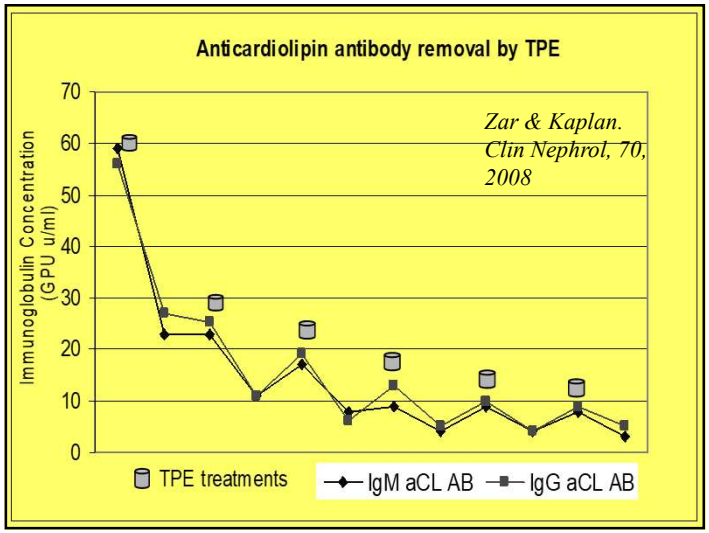
Associated mortality rate is >50%.

Treatment consists of IV heparin, IV steroids, IVIG and/or TPE.

Catastrophic Antiphospholipid Antibody Syndrome: Case Report

- 33 year old caucasian female with history of primary APS with multiple miscarriages and deep venous thrombosis
- Presented with headaches and visual field defects.
- Non-compliance with coumadin. Her INR was 1.3.
- At presentation, patient had acute renal failure and non-ST elevation myocardial infarction. Serum creatinine (S.Cr) was 1.9 mg/dl, which peaked at 2.8 mg/dl by the third day.
- She was transferred to ICU and started on IV heparin.
- Within 24 hours of admission, her mental status deteriorated and she developed seizures and left sided hemiplegia. She subsequently developed malignant hypertension (BP 225/130 mmHg), flash pulmonary edema and required intubation for severe respiratory distress.





TPE for CAPS

CAPS has never been investigated in a prospective, randomized trial

But, a review of the first 250 patients entered into the CAPS Registry demonstrated that the combination of TPE, anticoagulants and steroids was associated with an overall 78% survival. The authors concluded that this treatment combination should be the first line of therapy for patients with CAPS

Bucciarelli S. et al. Arthritis Rheum 2006;54:2568

Anti-Phospholipid Antibody Syndrome

- Lupus anticoagulant and anticardiolipin antibody associated with arterial and venous thrombosis, recurrent fetal loss and renal disease.
- Plasmapheresis has resulted in successful pregnancy and reversal of renal disease. *Frampton et al. Lancet ii:1023, 1987, Fulcher et al. Lancet ii:171, 1989, Kincaid-Smith et al. Quart J Med 258:795, 1988*

Are anti-phospholipid antibodies pathogenic?

Anti-ß2-glycoprotein-I antibodies

ß2-GP-I (apolipoprotein H) binds to negatively charged phospholipids and inhibits both contact activation of the clotting cascade and the conversion of prothrombin to thrombin.

The properties of this protein as a clotting inhibitor may explain why neutralizing antibodies can promote thrombosis.

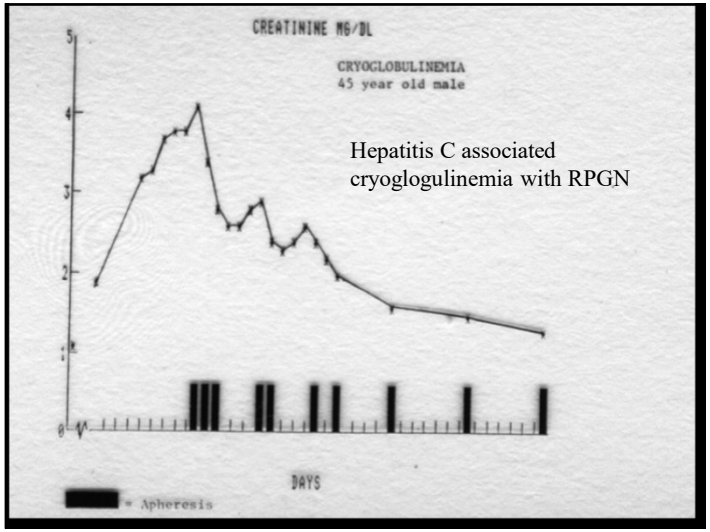
Schousboue I: Blood 1985, 66:1086
Nimpf J et al: Biochim Biophys Acta, 1986, 884:142

Apheresis for Renal Disease

- Primary Renal Disease
  - Goodpasture's disease
  - IgA nephritis/HSP
  - Pauci-immune RPGN
  - Focal segmental glomerulosclerosis
- Secondary Renal Disease
  - SLE
  - APA syndrome
  - Cryoglobulinemia
  - Multiple Myeloma
  - TTP/HUS
  - Transplantation

Cryoglobulinemia

- Despite lack of randomized, controlled trials, there is a general consensus that plasmapheresis is useful for rapid removal of cryoglobulins.
- Concomittant hepatitis C infection may render chemotherapy problematic.
- Some patients may respond to plasmapheresis alone. ***Ferri et al. Nephron 43, 246, 1986***

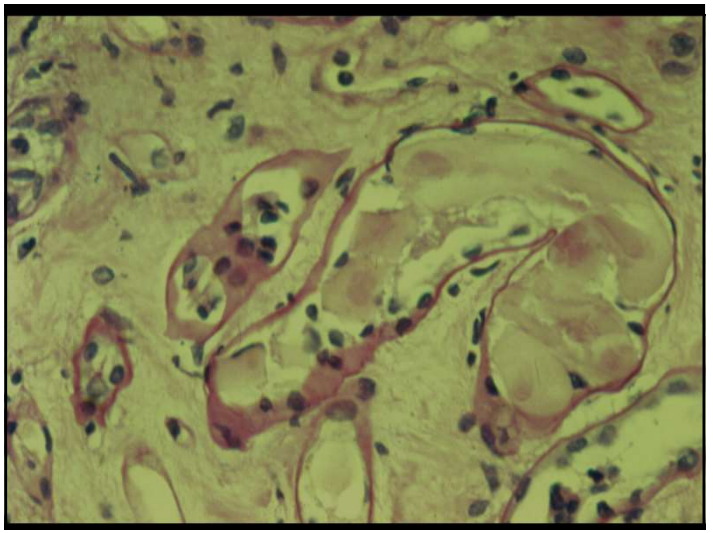


Cryoglobulin Removal with Therapeutic Plasma Exchange (TPE)

DATE	IGM mg/dL	Crycrit %
Day 1 pre TPE	294	8%
post TPE	97	
Day 2 pre TPE	119	
post TPE	61	trace

Apheresis for Renal Disease

- Primary Renal Disease
  - Goodpasture's disease
  - IgA nephritis/HSP
  - Pauci-immune RPGN
  - Focal segmental glomerulosclerosis
- Secondary Renal Disease
  - SLE
  - APA syndrome
  - Cryoglobulinemia
  - Multiple Myeloma
  - TTP/HUS
  - Transplantation



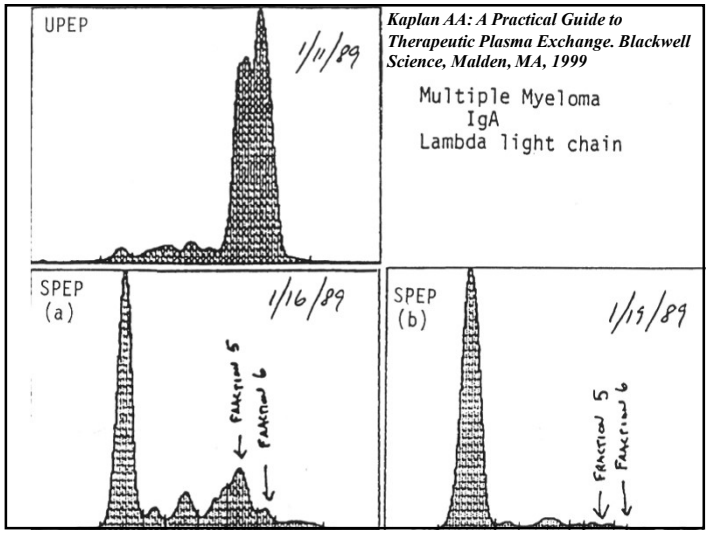
"Cast Nephropathy" in Multiple Myeloma

- Light chains (Bence Jones protein) can be tubulo-toxic and result in obstruction of nephron lumen and acute renal failure
- Plasmapheresis, as an adjunct to chemotherapy, results in a more rapid lowering of serum light chains and a lower post RX creatinine. *Zucchelli et al. Kidney Int 33:1175, 1988*

Table 2. Short-term effects of therapy in the two groups of patients

	Group I	Group II	*P*
Number in group	15	14	
Number of patients requiring dialysis	13	11	NS
Number of patients interrupting dialysis	11	2	<0.01
Number of patients who died within the first 2 months	1	5	NS
Serum creatinine at the end of the 2nd month mean ± SD *mg/dl*	2.6 ± 2.1	7.7 ± 1.9	<0.001

Zuchelli et al. K.I. 1988



Kaplan AA: A Practical Guide to Therapeutic Plasma Exchange. Blackwell Science, Malden, MA, 1999

Plasma Exchange When Myeloma Presents as Acute Renal Failure: A Randomized, Controlled Trial

William F. Clark, et al.and the Canadian Apheresis Group
Annals of Internal Medicine 6 December 2005 | Volume 143 Issue 11 | Pages 777-784

97 with acute renal failure at the onset of multiple myeloma were randomized to conventional therapy plus 5 to 7 plasma exchanges for 10 days or conventional therapy alone.

The primary composite outcome: death, dialysis dependence, or GFR<30 mL/min .

Results: Composite end point occurred in 33 of 57 (57.9%) in PE v. 27 of 39 (69.2%) in controls = NS. One third of patients in each group died.

Limitations: The study was small, used a composite outcome, and did not use renal biopsy as an inclusion criterion. Recruiting physicians were blinded to treatment allocation but not to treatment thereafter.

Conclusions: In patients with acute renal failure at the onset of multiple myeloma, there is no conclusive evidence that 5 to 7 plasma exchanges substantially reduce a composite outcome of death, dialysis dependence, or GFR<30 mL/min at 6 months.

Baseline characteristics were similar between groups.

43 participants had a monoclonal kappa light chain,
36 participants had a monoclonal lambda light chain,
the remainder had a monoclonal Bence–Jones protein in excess.

The monoclonal protein occurred in both the plasma and urine in 59 participants, in the plasma in 76 participants, in the urine in 79 participants, and in the casts of the renal biopsy in 1 participant.

Hence: of 97 patients, only 80 had definitive evidence of free light chains in plasma. Given that the only rationale for plasma exchange is to remove free light chains from the plasma, at least 17 patients may not have a condition which could have possibly benefited from plasma exchange.

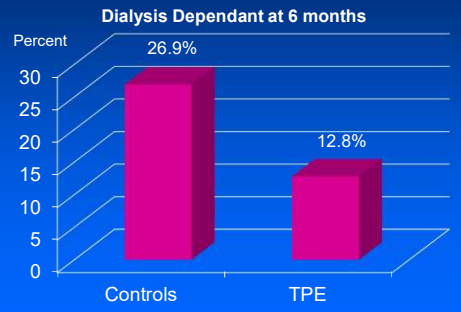
Relative costs of TPE for AKI in MM and ESRD

- ESRD with HD = $90,000/year
- Average lifepan of MM pt on HD = 2 years
- 2 years of HD = $180,000
- 6 TPE treatments for light chain removal = $12,000
- $12,000/$180,000 = 0.07
- CCl: if only 7% of treated patients avoid HD, net costs of TPE are less expensive option

Plasma Exchange When Myeloma Presents as Acute Renal Failure: A Randomized, Controlled Trial

William F. Clark, et al .and the Canadian Apheresis Group

Annals of Internal Medicine Vol 143, 777-784, 2005



difference 14.1% [CI, –5.1% to 34.6%]; *P* = 0.20

Apheresis for Renal Disease

- Primary Renal Disease
  - Goodpasture's disease
  - IgA nephritis/HSP
  - Pauci-immune RPGN
  - Focal segmental glomerulosclerosis
- Secondary Renal Disease
  - SLE
  - APA syndrome
  - Cryoglobulinemia
  - Multiple Myeloma
  - TTP/HUS
  - Transplantation

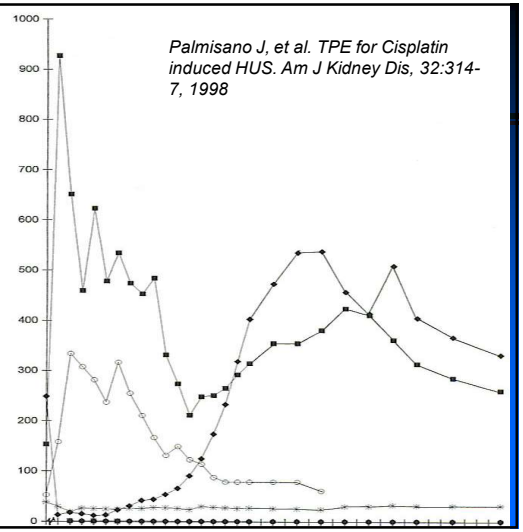
Therapeutic Apheresis
4(3):201–206, Blackwell Science, Inc.

Therapeutic Apheresis for Cancer Related Hemolytic Uremic Syndrome

Andre A. Kaplan

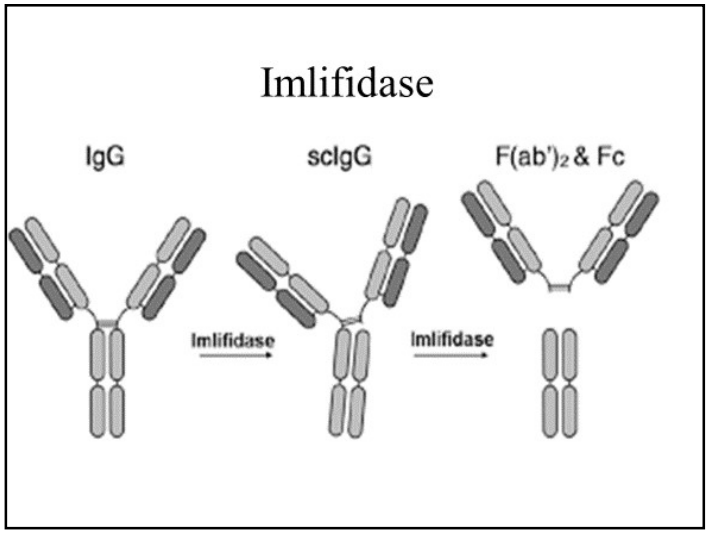
TABLE 1. *Chemotherapy and drugs associated with HUS*

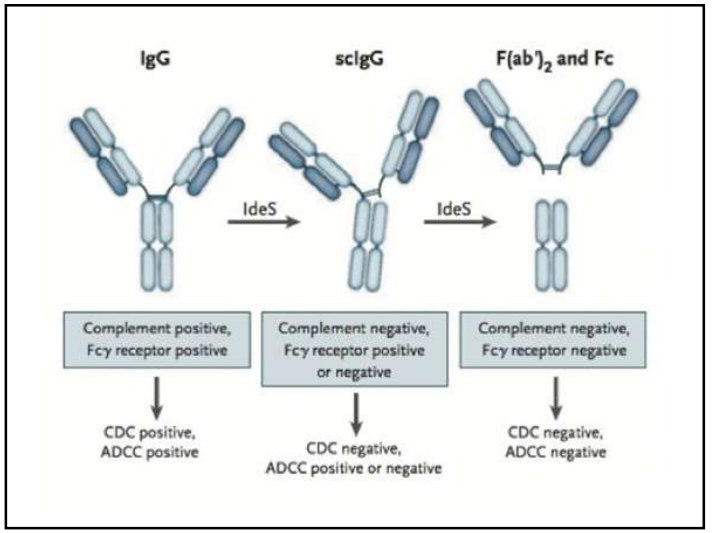
Mitomycin C
5 Flourouracil
Bleomycin
Cisplatin
Methyl CCNU
Cytosine Arabinoside
Daunomycin
Alpha-Interferon
Gemcitabine
Estramustine
Cyclosporin A
Tacrolimus



Palmisano J, et al. TPE for Cisplatin induced HUS. Am J Kidney Dis, 32:314-7, 1998

Fig 1. Clinical course of cisplatin-induced HUS during treatment with TPE. To convert creatinine from micromoles per liter to milligrams per deciliter, divide by 88.4. Hemodialysis treatments and TPE occurred on days 2, 4, and 6. Baseline values graphed on the *Y* axis represent laboratory data from 9 days before admission. (-●-), TPE; (-■-), LDH U/L; (-◆-), PLT K/μL; (-▪-), HCT %; (-○-), and creatinine μmol/L.





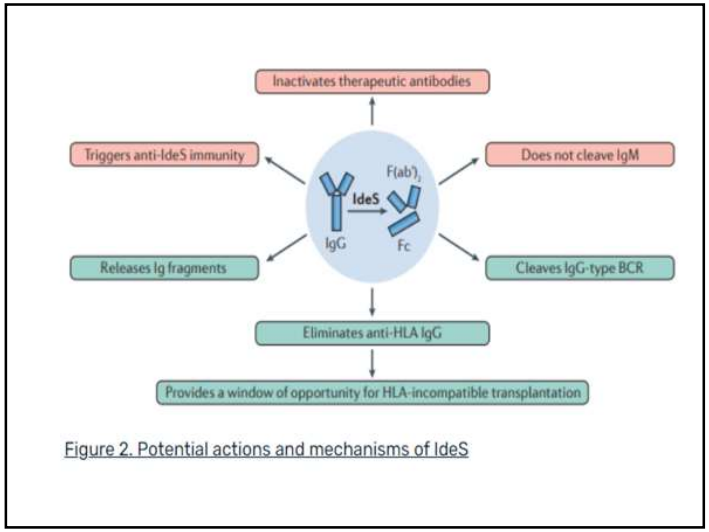
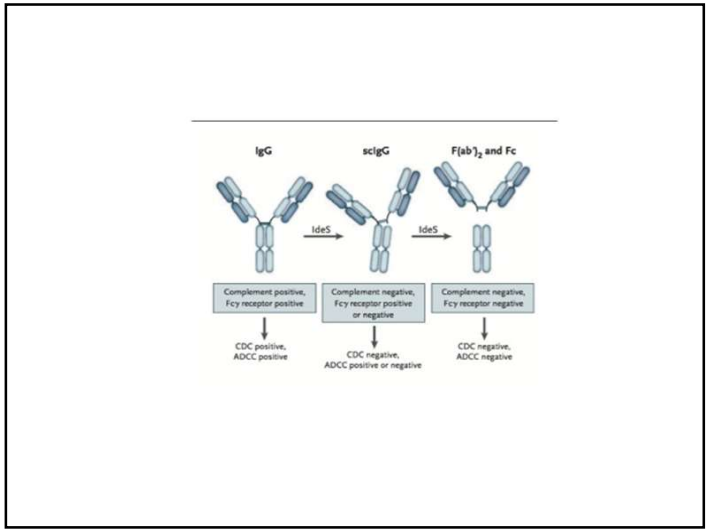


Figure 2. Potential actions and mechanisms of IdeS



Imlifidase desensitization for highly sensitized kidney transplant candidates:

Proposed list price for imlifidase is $170,000 per 11 mg vial. An average cost of treatment is expected to be $355,000. Considering the cost of hemodialysis in the US is $90,000/year, $355,000 would be equal to the cost of 3.9 years of dialysis.

Technology July 20, 2022