Therapeutic Plasma Exchange: Current Perspectives and Renal Indications

Renal Week
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Plasmapheresis for antibody associated GN: Rationale

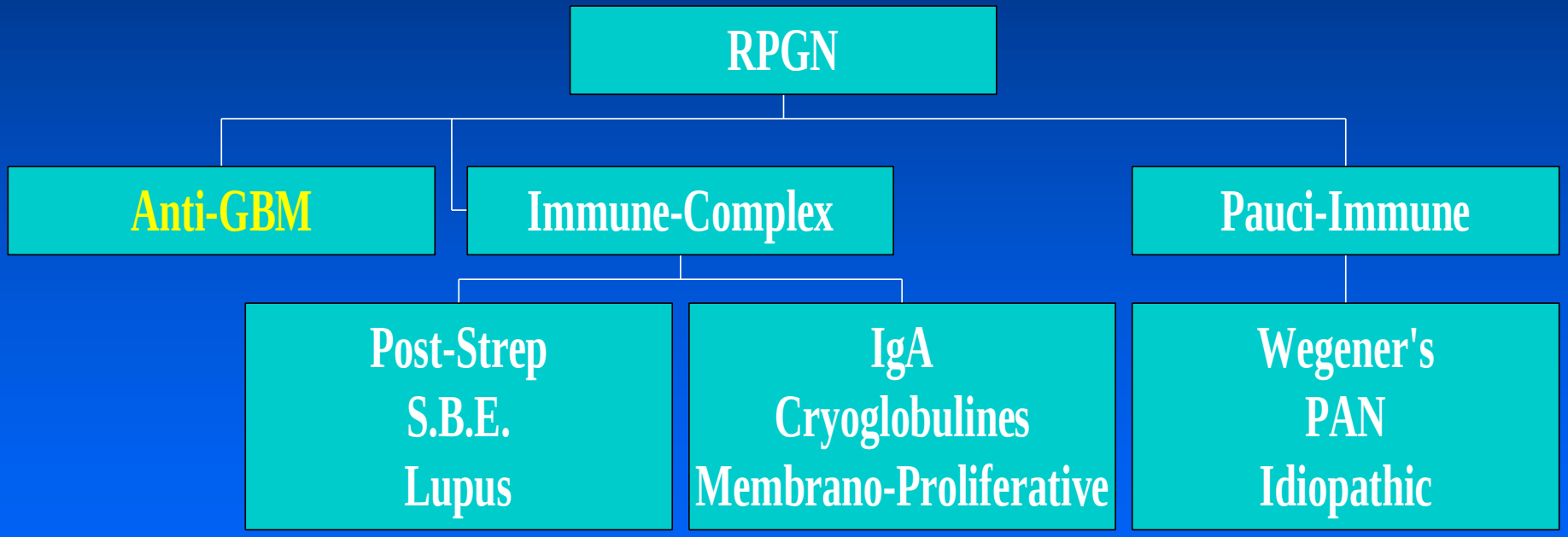
- IgG half life is 21 days: Even with complete cessation of production, there is prolonged period with substantial amount of antibody still present
- Plasmapheresis is the most reliable and rapid means of lowering antibody levels

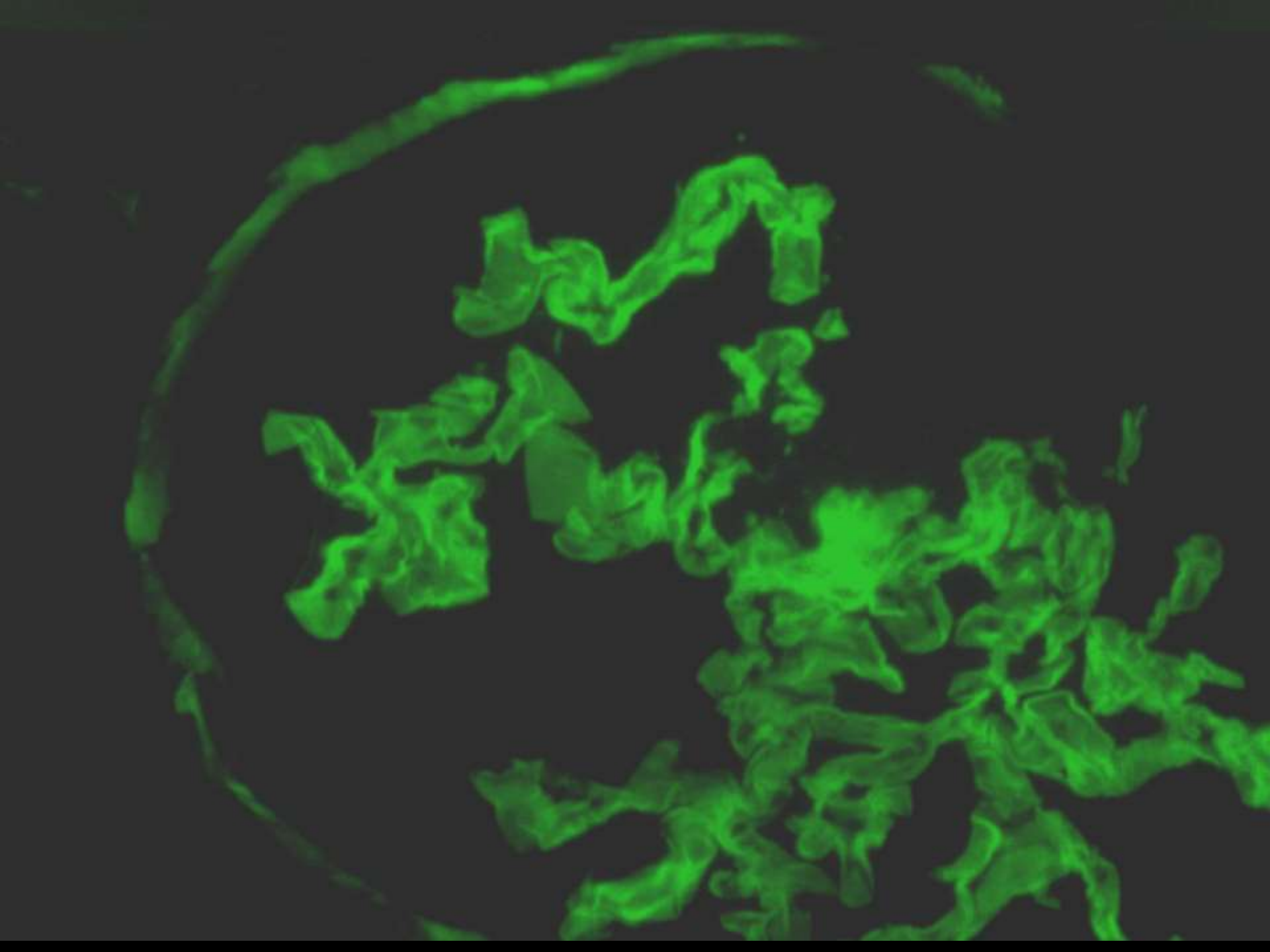
Apheresis for Renal Disease

- 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

Rapidly Progressive Glomerulonephritis

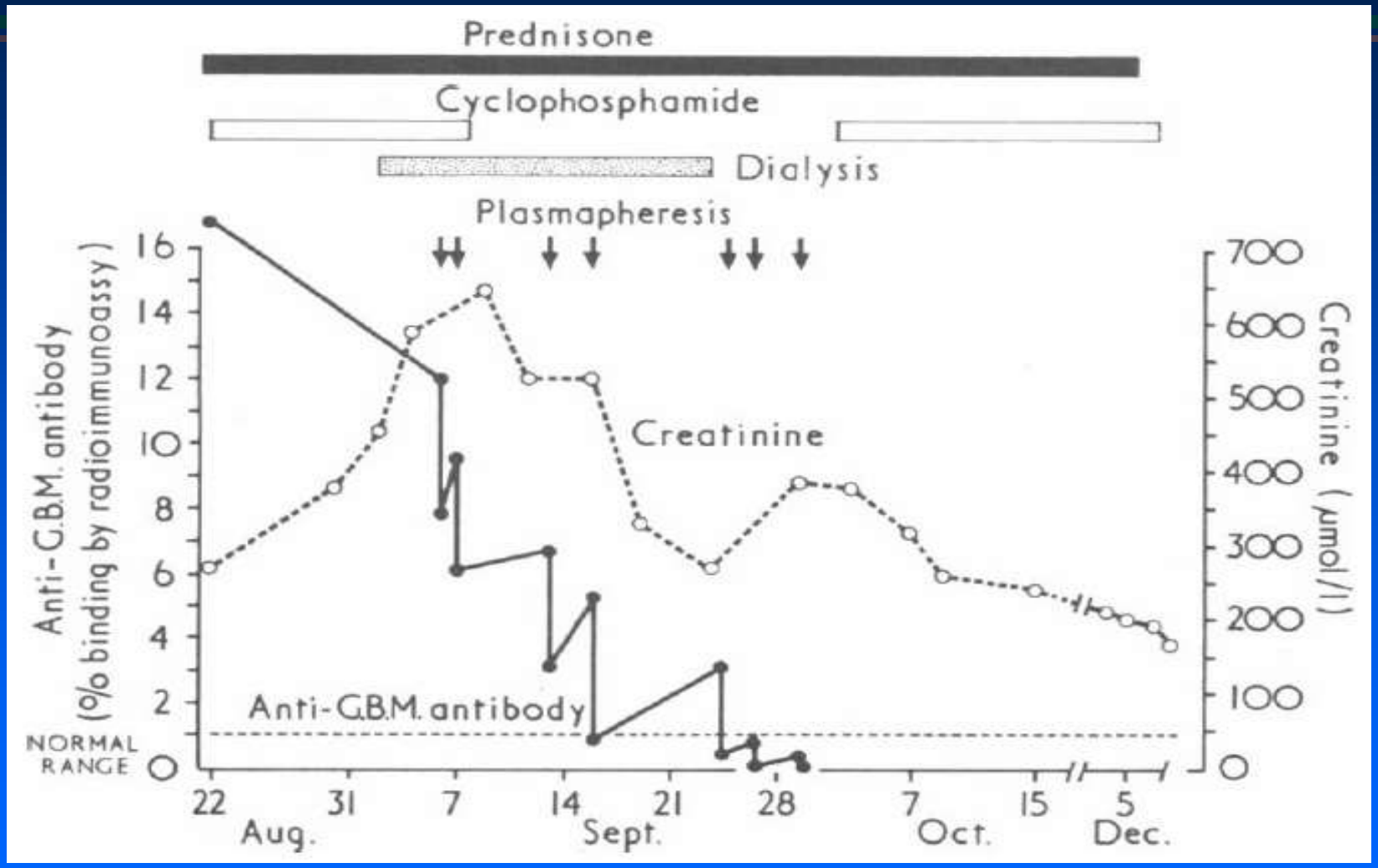




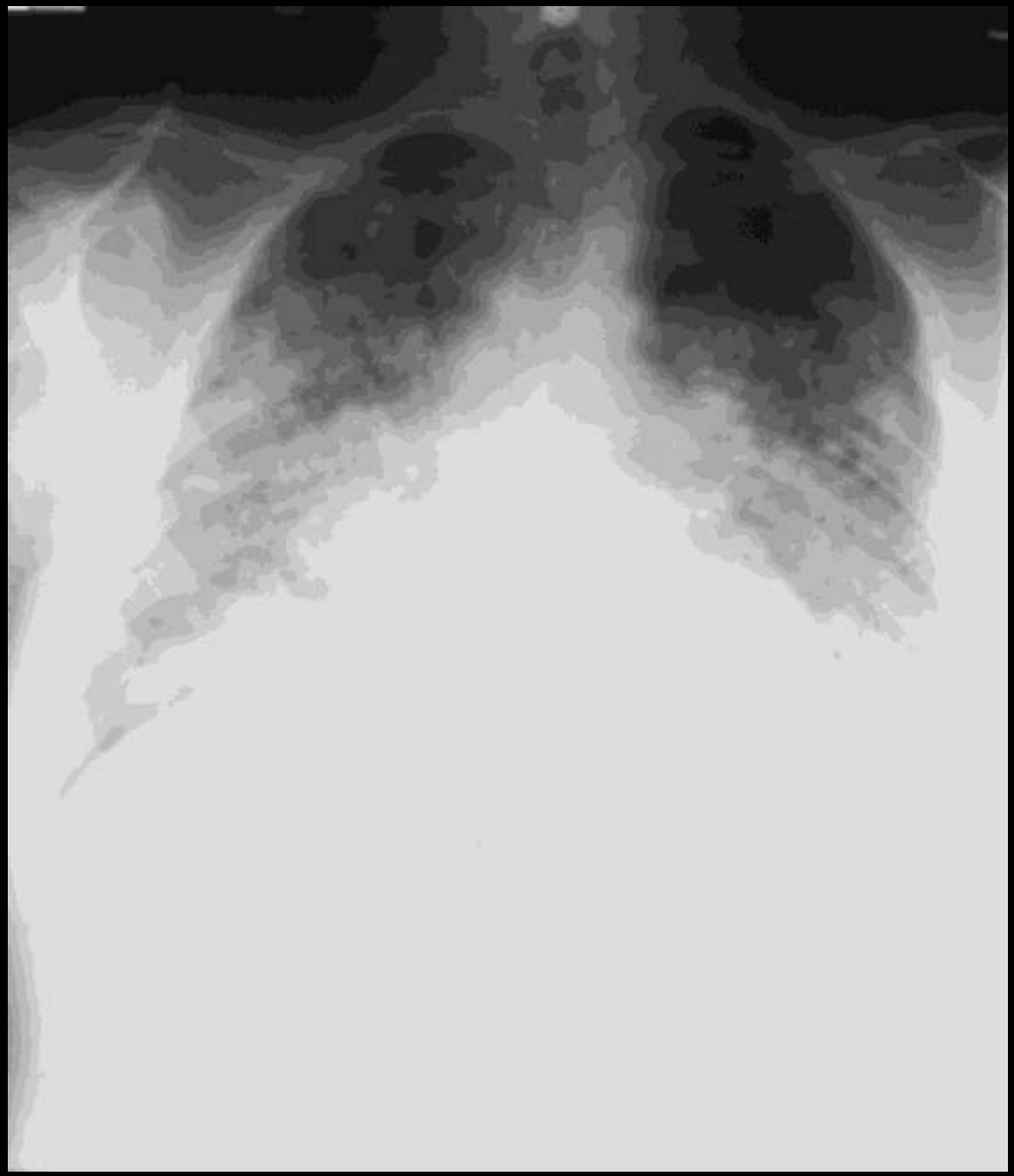
Anti-GBM Antibody and Goodpasture's Syndrome

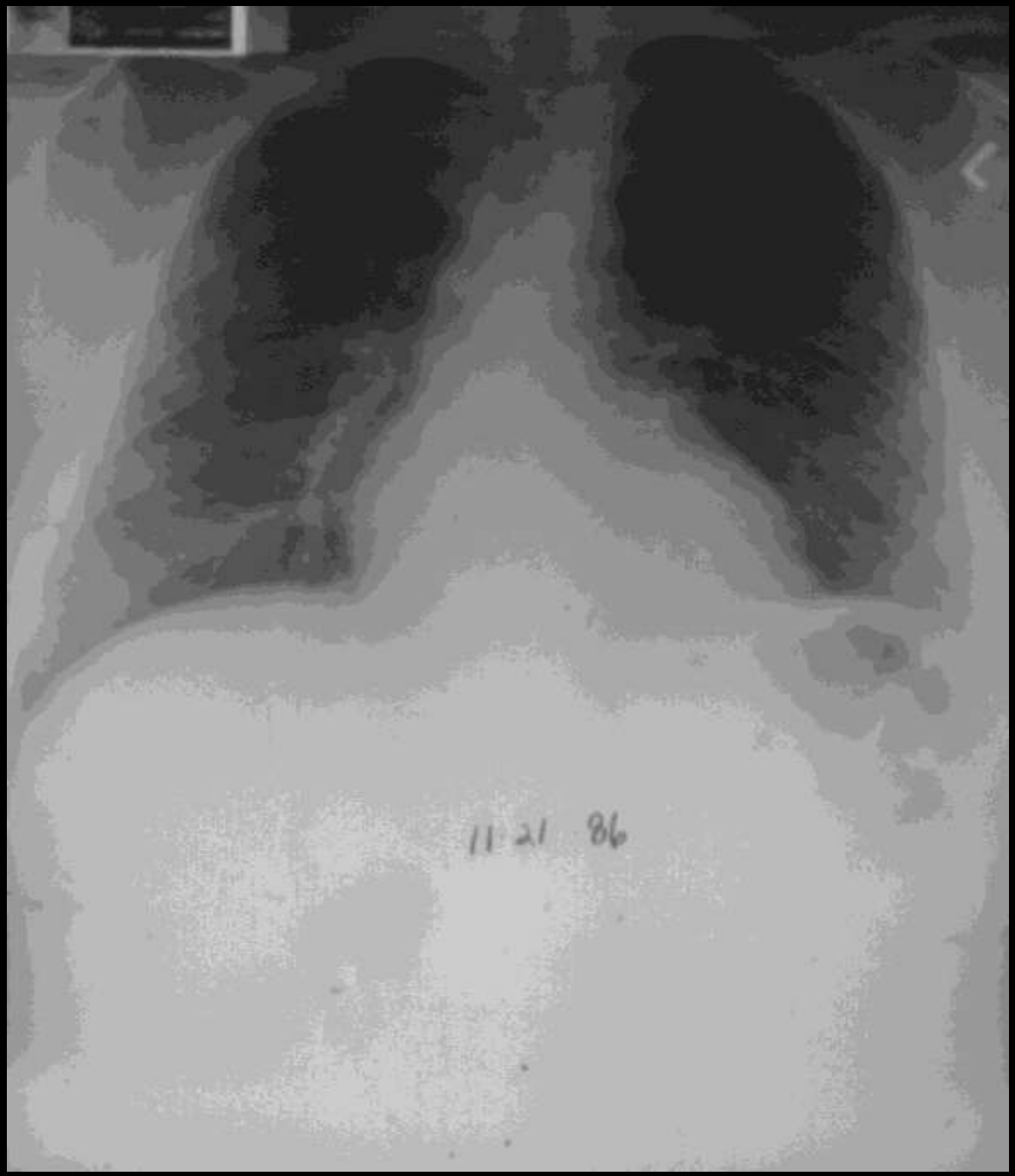
- Pathogenic antibody capable of causing alveolar hemorrhage and rapidly progressive glomerulonephritis
- Only one randomized, controlled trial: ***Johnson et al. Medicine 64:219, 1985***
- Plasmapheresis results in rapid lowering of anti-GBM antibody, lower post RX creatinine and reduced incidence of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

Anti-GBM ANTIBODY DISEASE & GOODPASTURE'S SYNDROME



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

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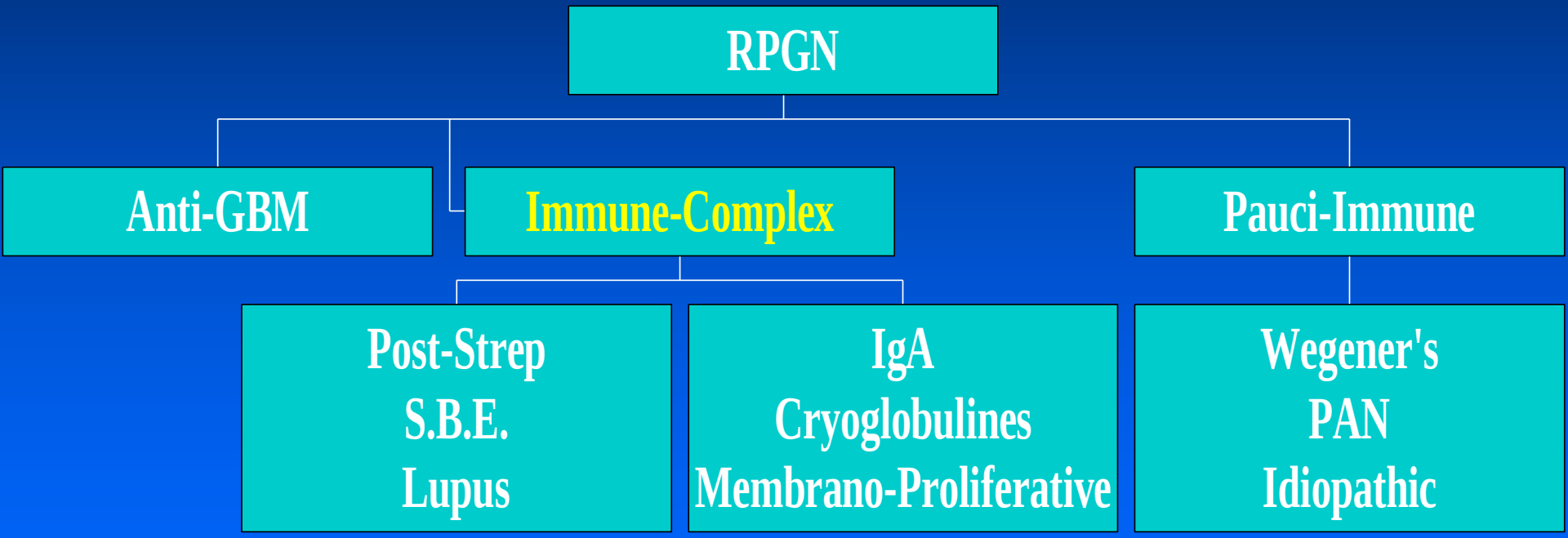
Nitin Relia MD, Yusra Cheema MD, Jennifer Tuazon MD, James Paprello MD

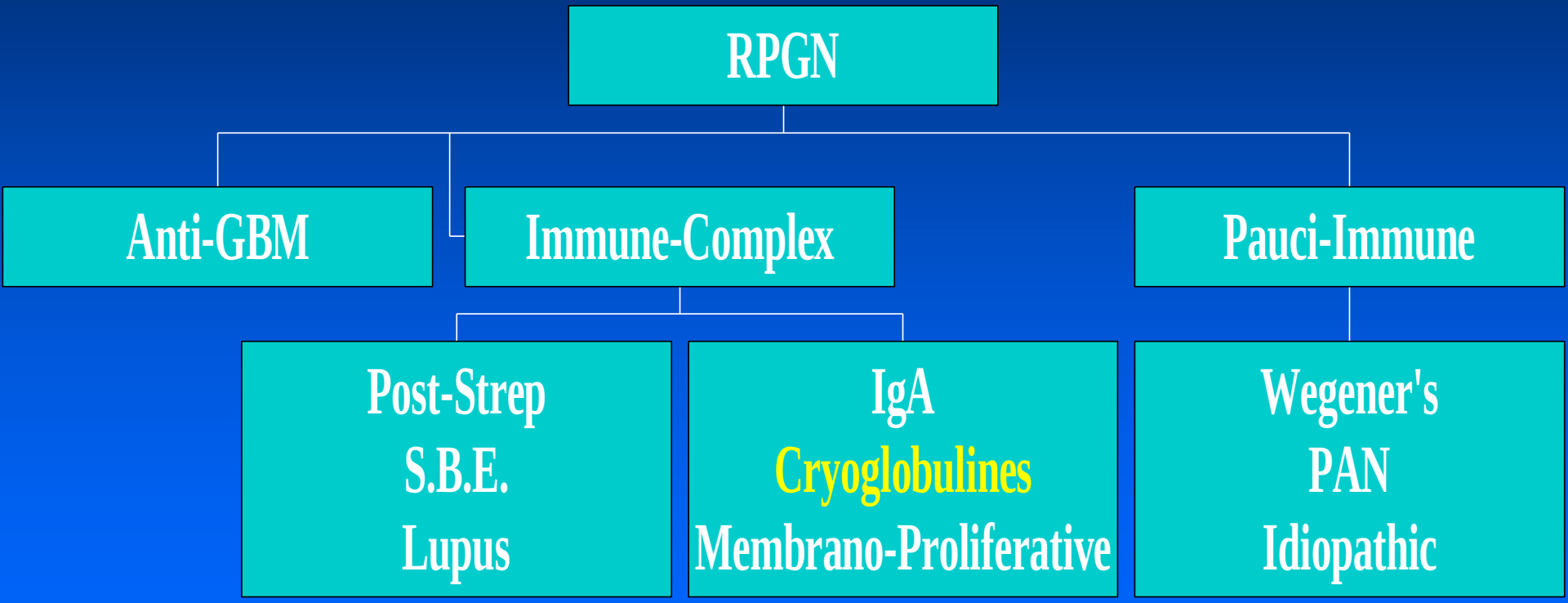
Title: Plasmapheresis in Anti- Glomerular Basement Membrane Disease, How much is enough?

Patient characteristics	Patient 1	Patient 2	Patient 3
Age/Sex	25 yr/Male	19 yr/Female	43 yr/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	40	25	39
Patient characteristics	Patient 1	Patient 2	Patient 3
sessions			
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

Rapidly Progressive Glomerulonephritis

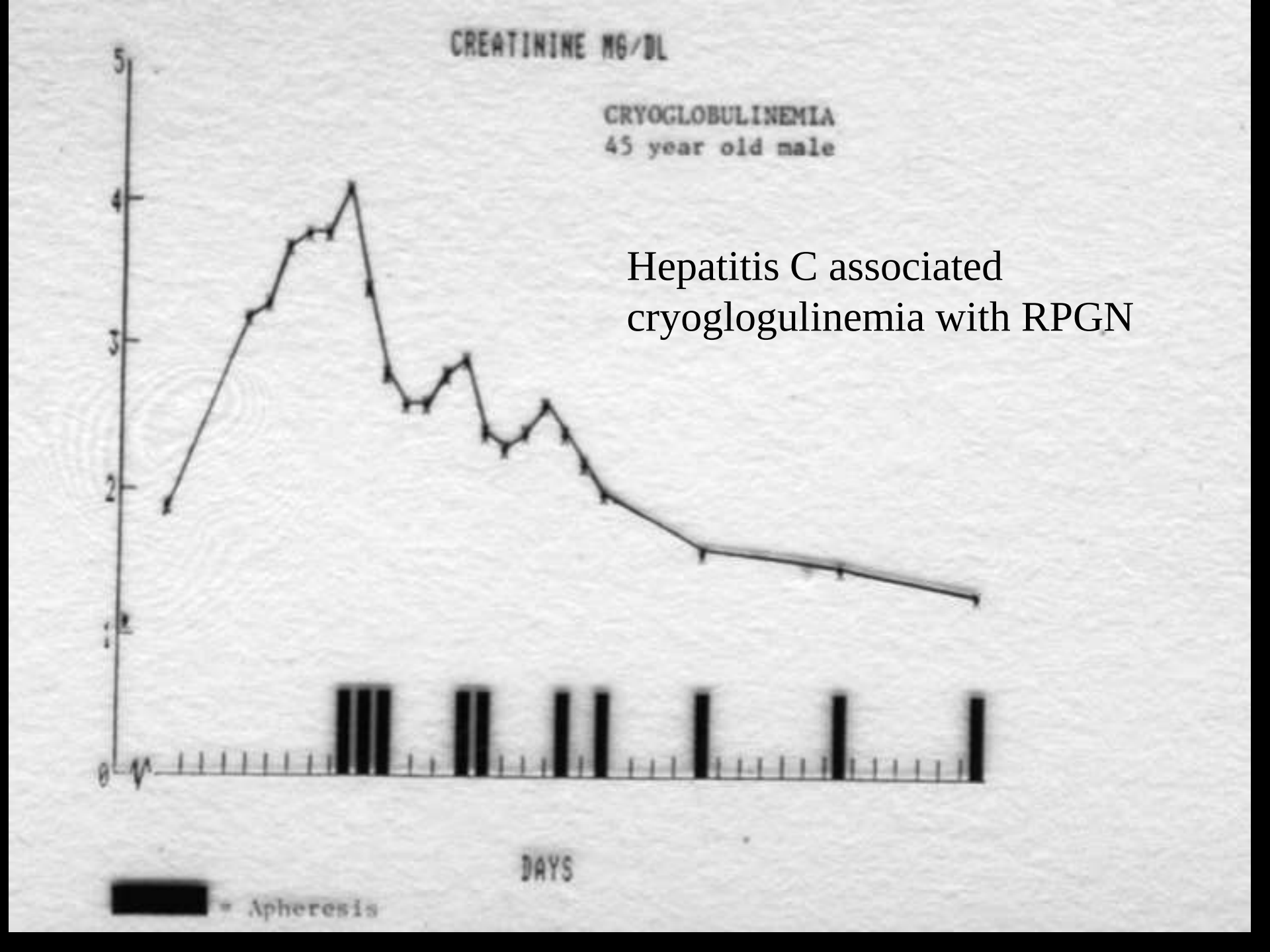


Rapidly Progressive Glomerulonephritis



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*

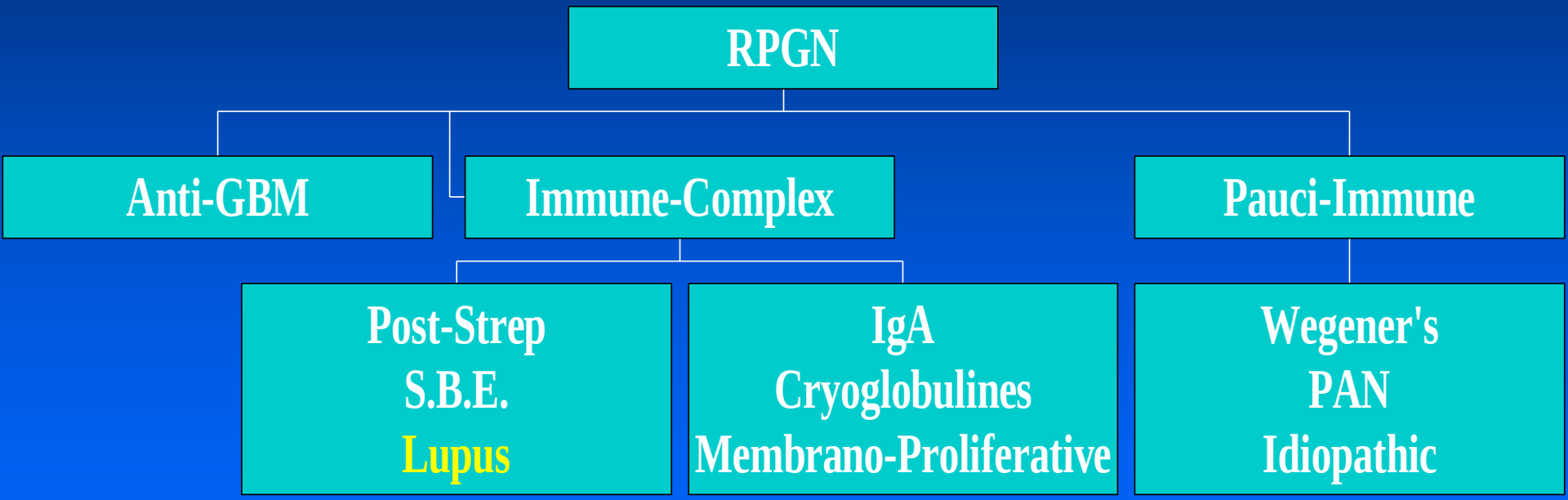


Hepatitis C associated cryoglogulinemia with RPGN

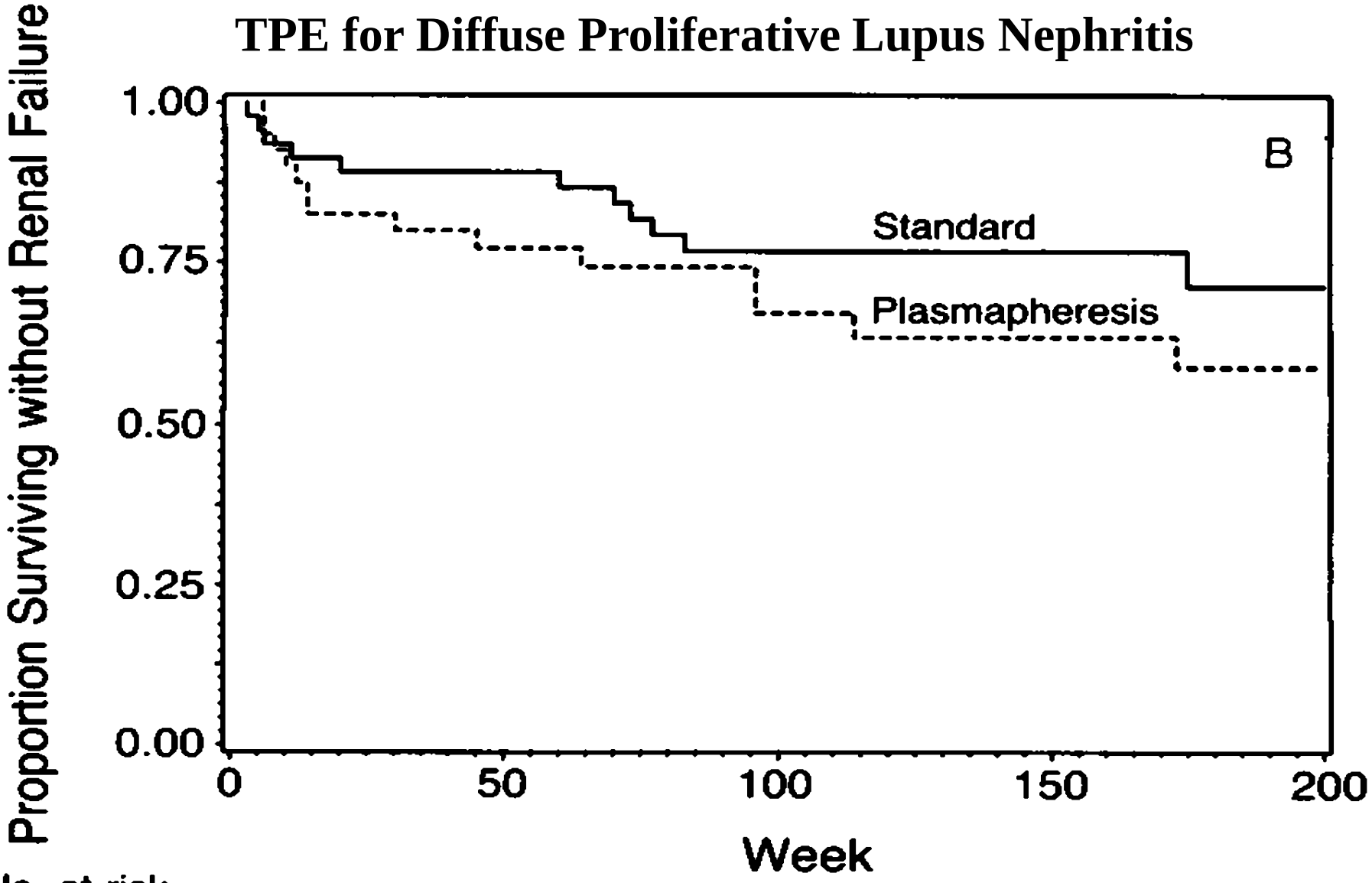
Cryoglobulin Removal with Therapeutic Plasma Exchange (TPE)

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

Rapidly Progressive Glomerulonephritis



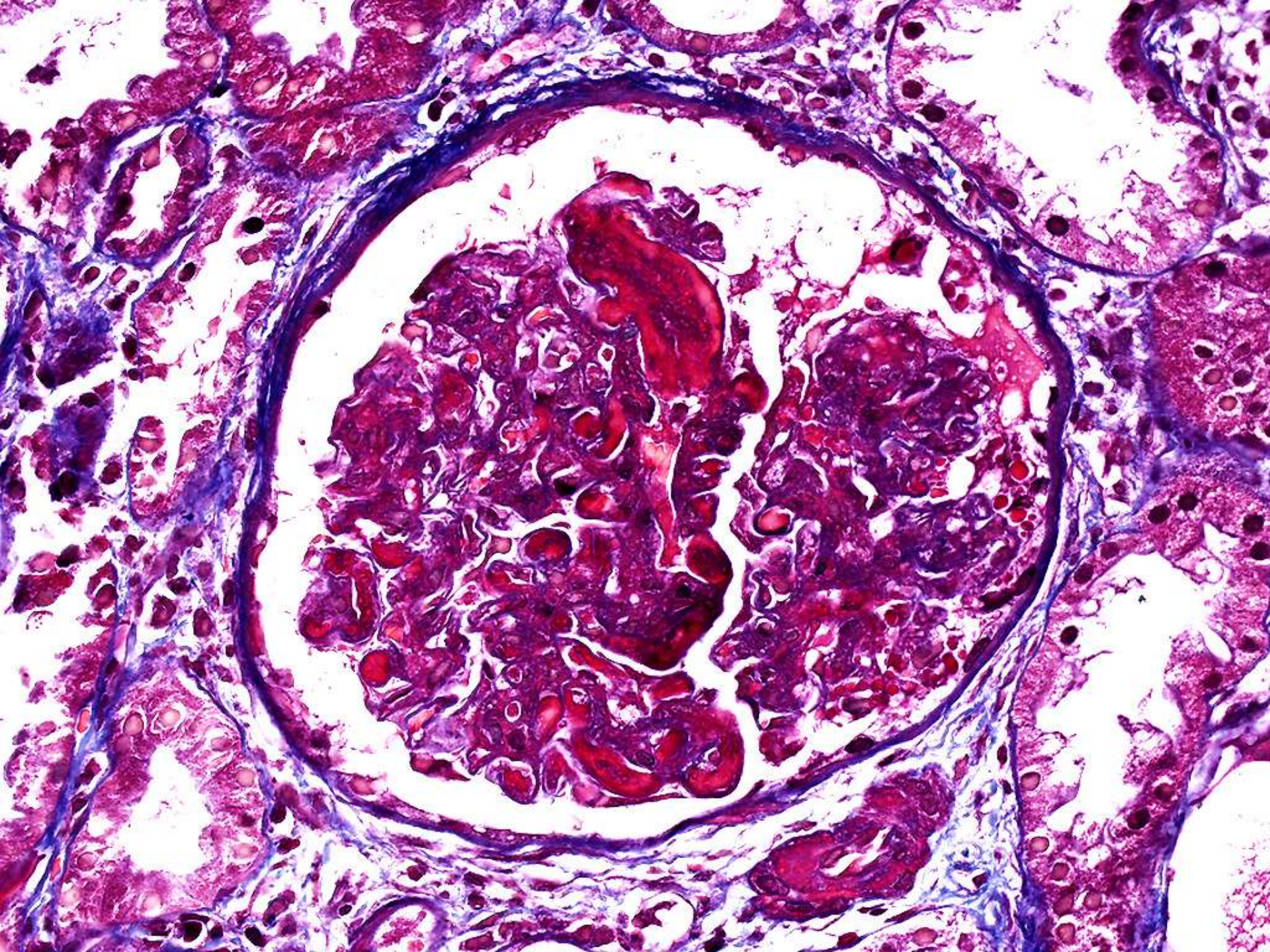
TPE for Diffuse Proliferative Lupus Nephritis

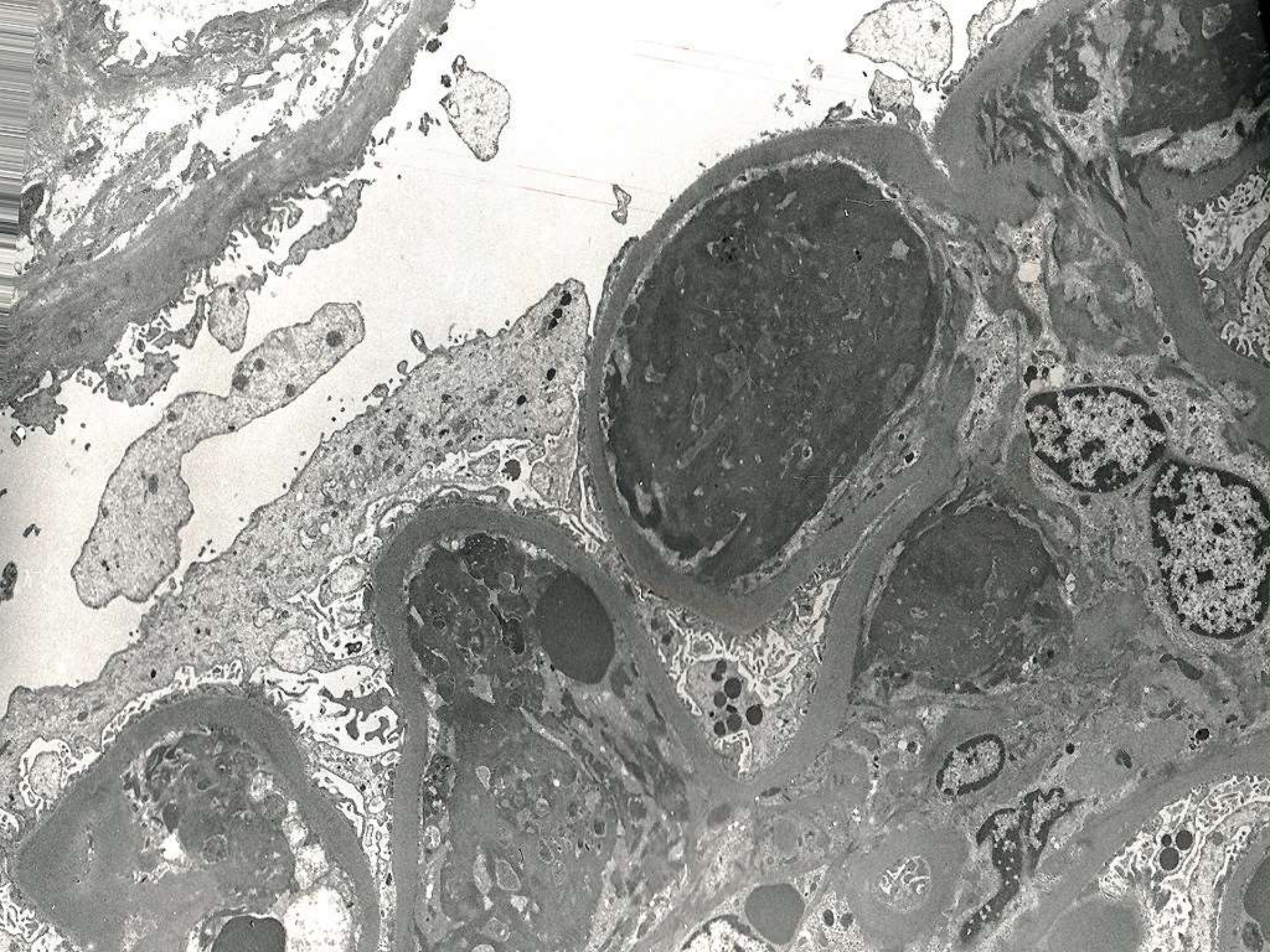


No. at risk

Standard	46	38	26	17	10
Plasmapheresis	40	27	19	15	8

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





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

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)

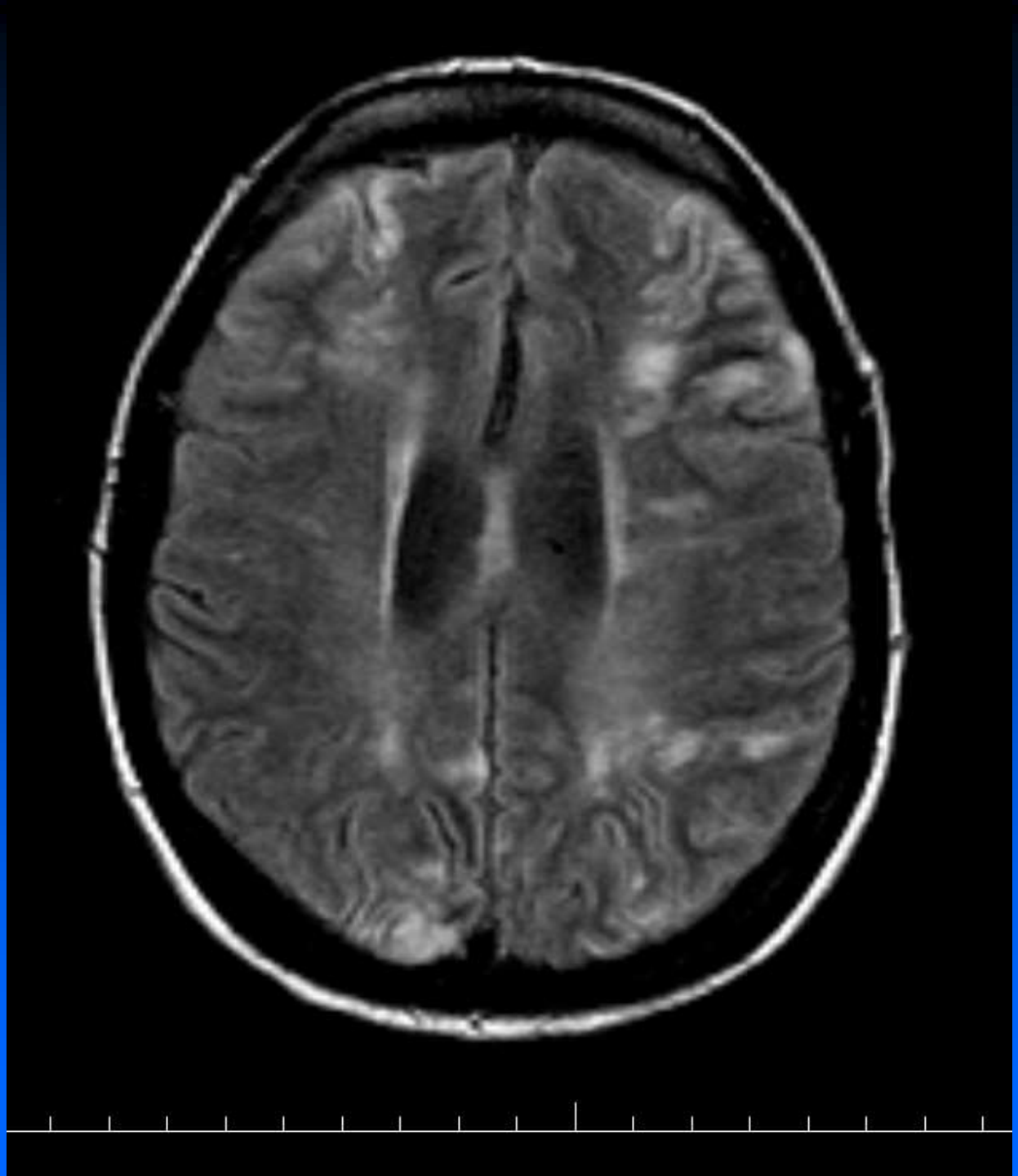
CAPS is a rare life-threatening form of antiphospholipid antibody syndrome (APS)

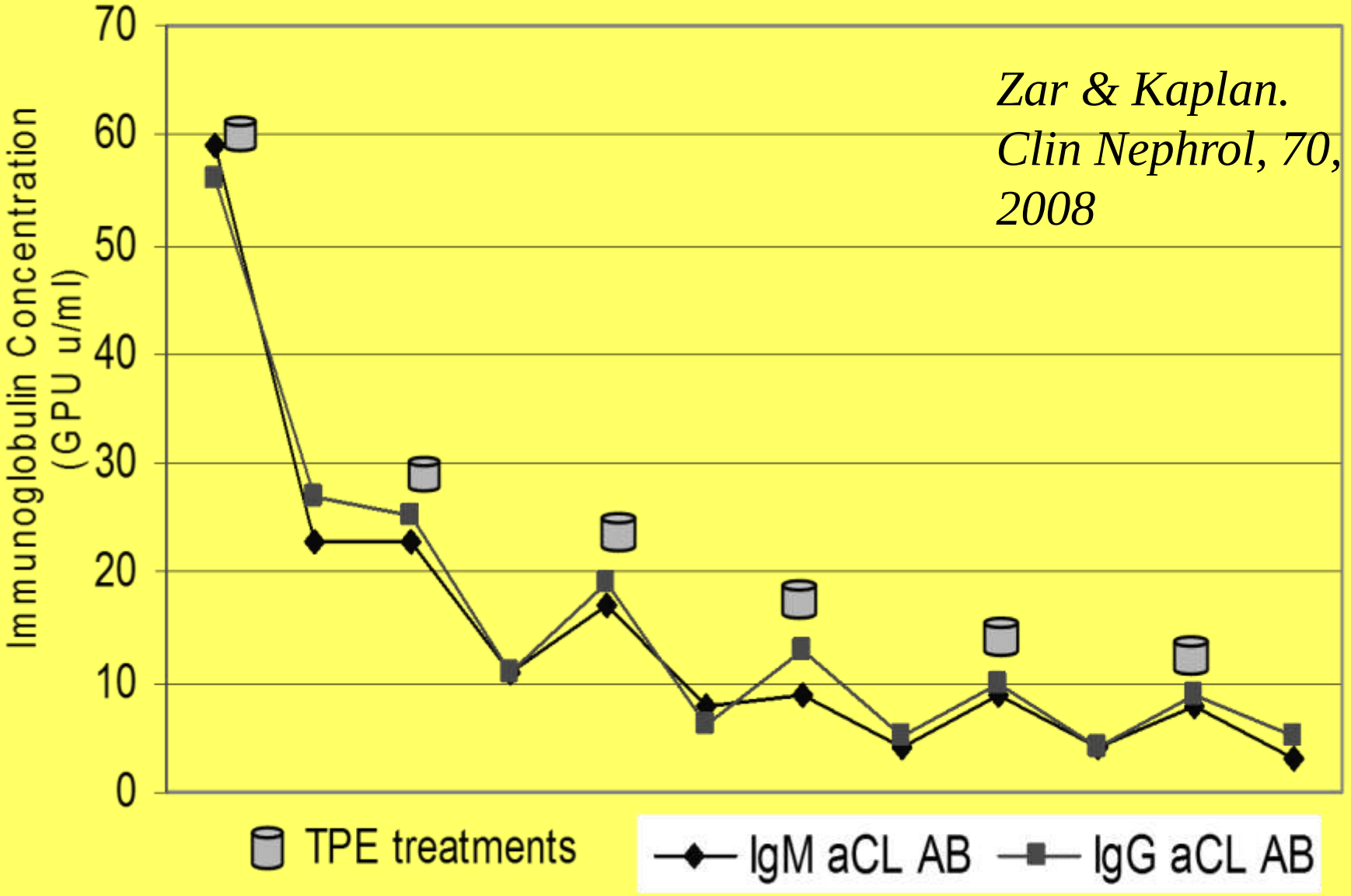
Associated mortality rate is >50%.

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.




Anticardiolipin antibody removal by TPE
Immunoglobulin Concentration (GPU u/ml)
70
60
50
40
30
20
10
0
TPE treatments
IgM aCL AB
IgG aCL AB
Zar & Kaplan. Clin Nephrol, 70, 2008

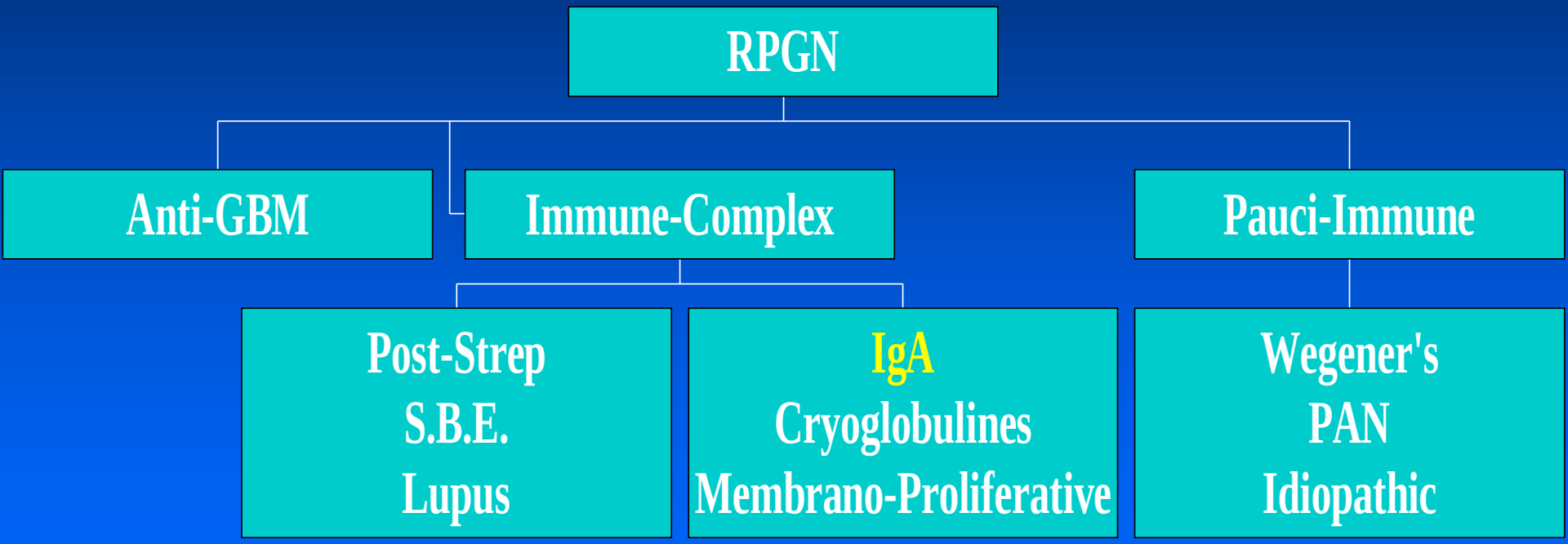
TPE for CAPS

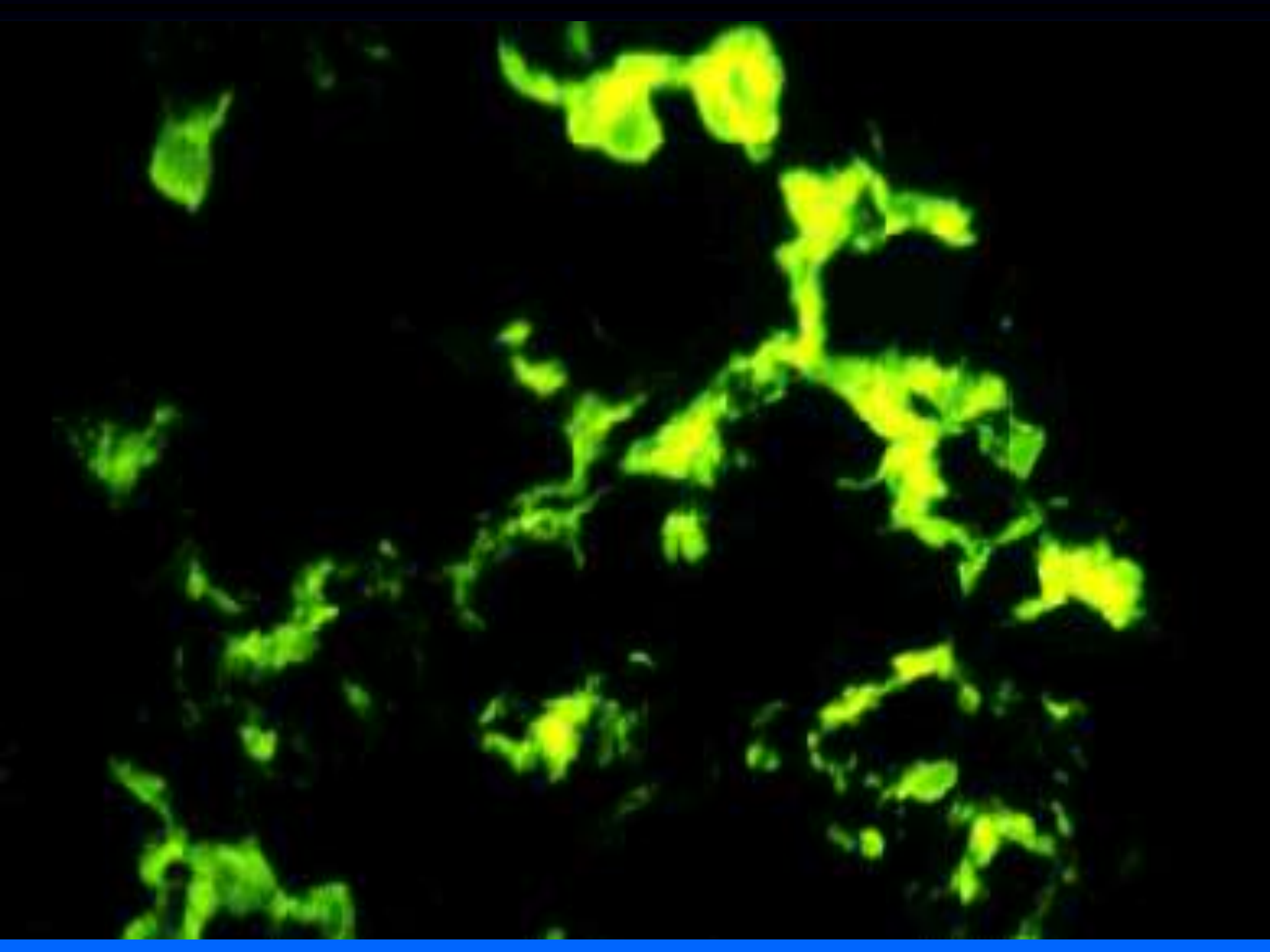
CAPS has never been investigated in a prospective, randomized trial

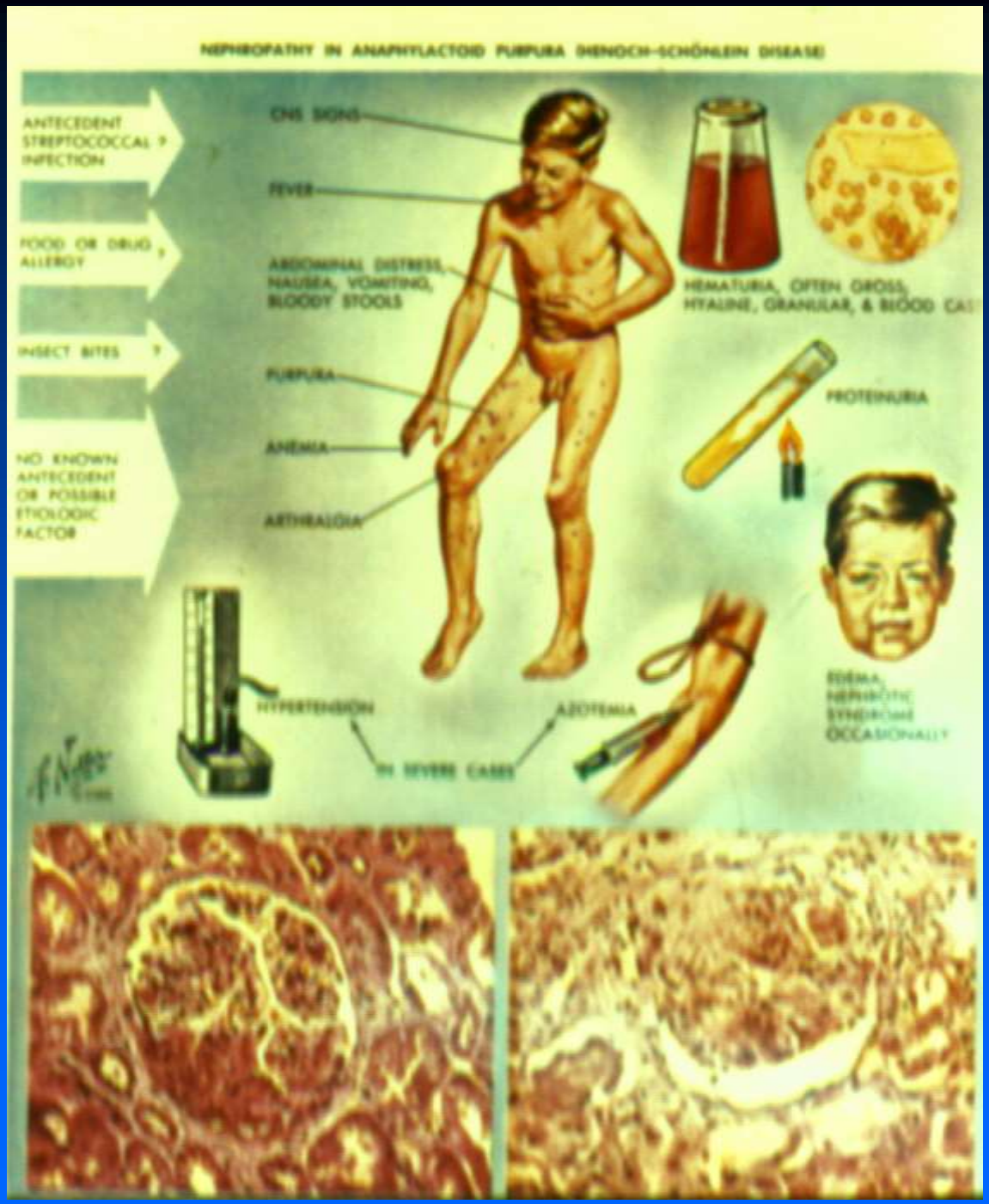
But, a review of the first 250 patients entered into the CAPS Registry demonstrated that the combination of TPE, anticoagulants and steroids was associated with an overall 78% survival. The authors concluded that this treatment combination should be the first line of therapy for patients with CAPS

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

Rapidly Progressive Glomerulonephritis






NEPHROPATHY IN ANAPHYLACTOID PURPURA (HENOCH-SCHÖNLEIN DISEASE)
ANTECEDENT STREPTOCOCCAL ? INFECTION
FOOD OR DRUG ALLERGY
INSECT BITES ?
NO KNOWN ANTECEDENT OR POSSIBLE ETIOLOGIC FACTOR
CNS SIGNS
FEVER
ABDOMINAL DISTRESS, NAUSEA, VOMITING, BLOODY STOOLS
PURPURA
ANEMIA
ARTHRALGIA
HEMATURIA, OFTEN GROSS, HYALINE, GRANULAR, & BLOOD CA
PROTEINURIA
EDEMA, NEPHROTIC SYNDROME OCCASIONALLY
HYPERTENSION
IN SEVERE CASES
AZOTEMIA

IgA Nephropathy and Henoch Schonlein Purpura

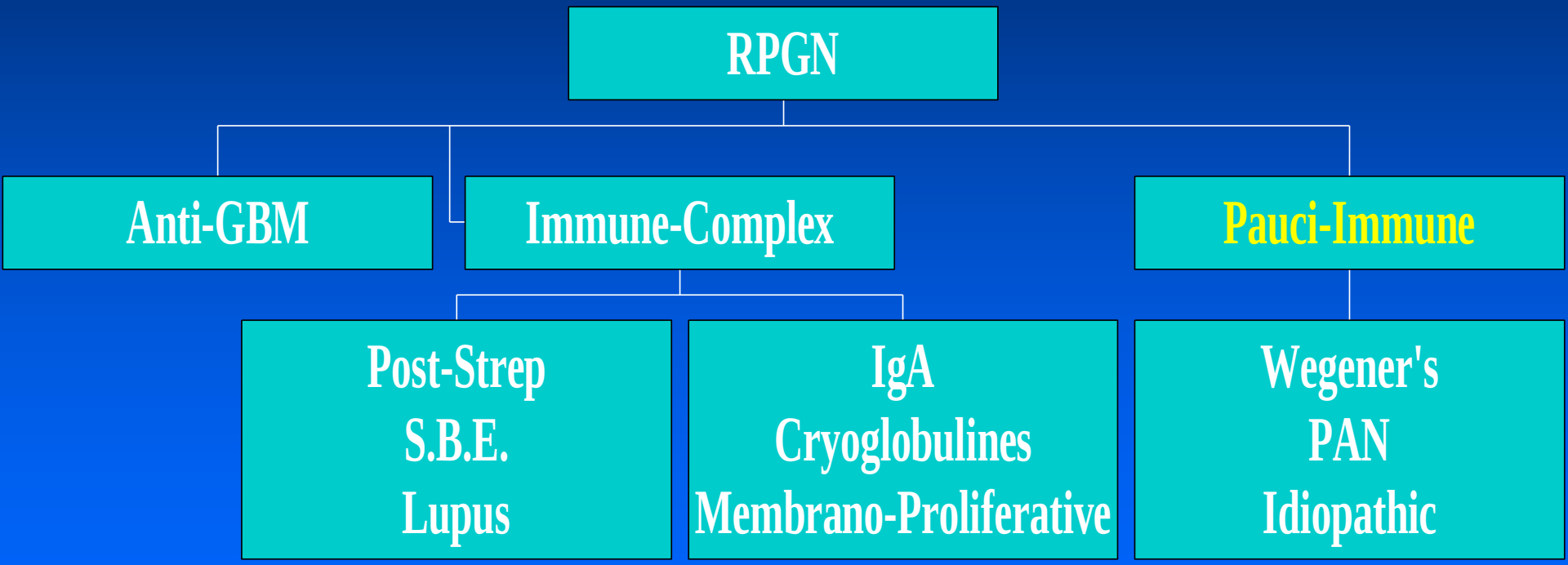
- Removal of circulating IgA complexes may improve outcome of RPGN. *Coppo et al. Nephron 40:488, 1985, Nicholls et al. J Clin Apheresis 5:128, 1990*
- Plasmapheresis can result in successful treatment even without immunosuppression. *Hene & Kater. Plasma Ther Transfus Technol 4:165, 1983, Coppo et al. Plasma Ther Transfus Technol 6:705, 1985*
- *Hattori et al. Am J Kidney Dis 33:427, 1999*

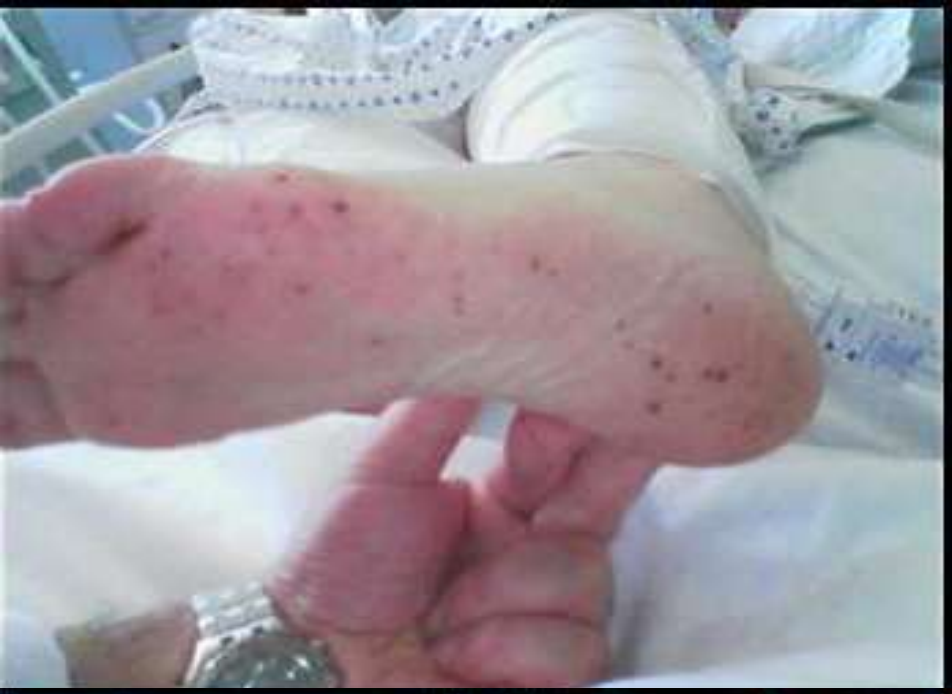
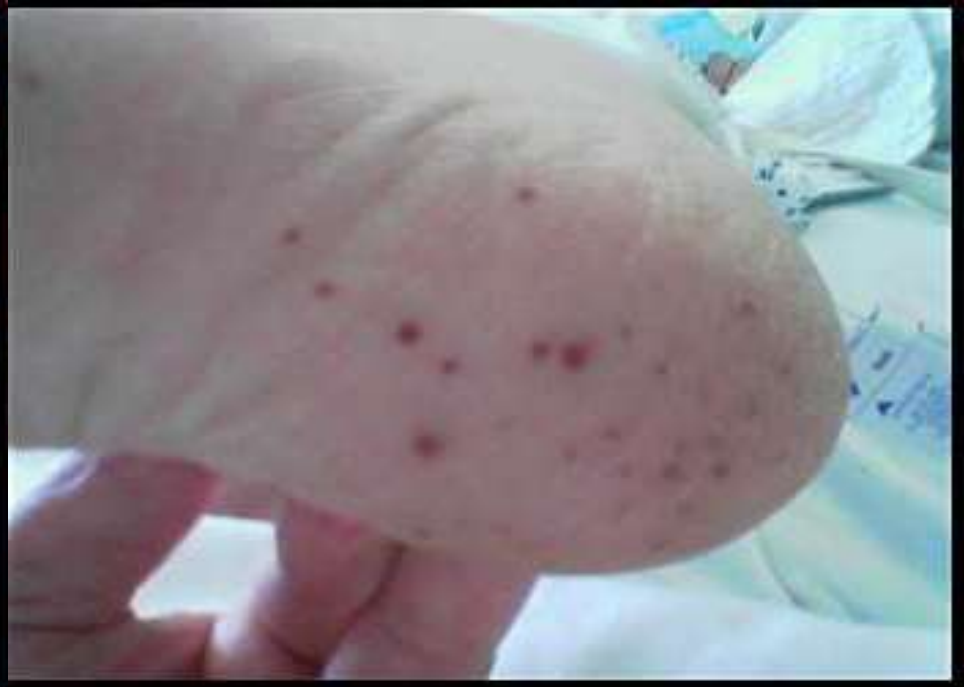
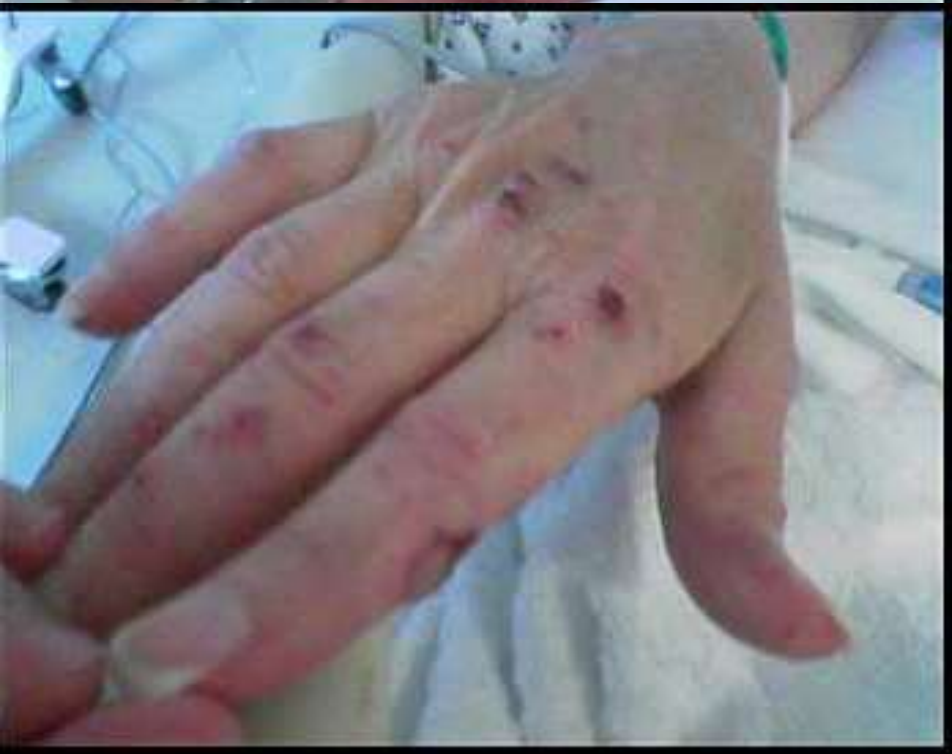
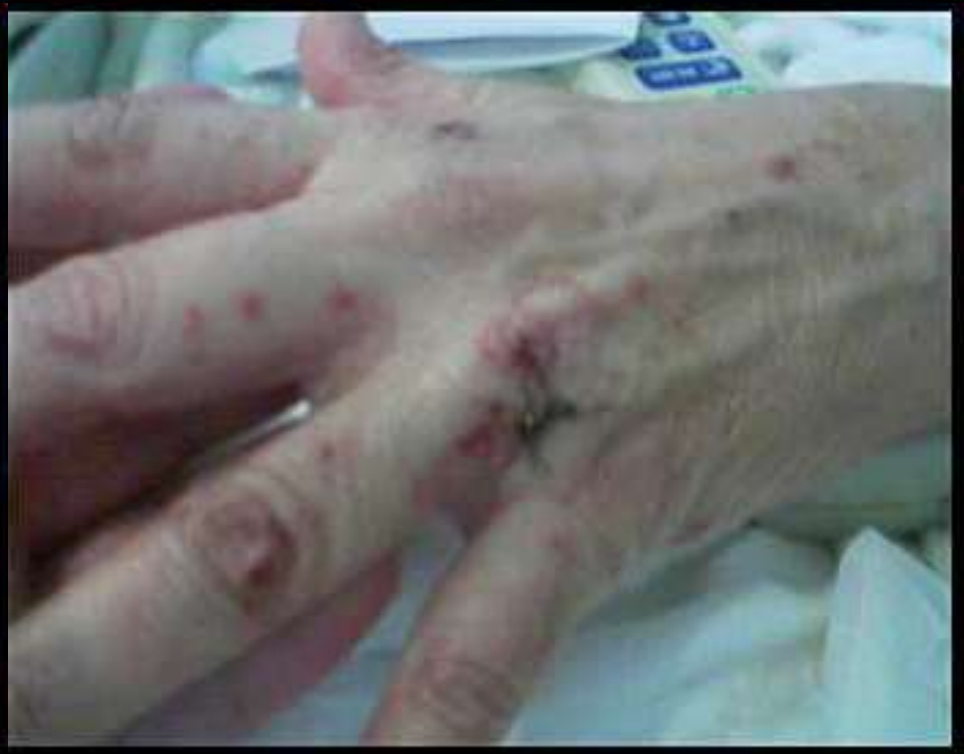
Plasmapheresis as the sole therapy for RPGN in Henoch Schonlein Purpura

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

Rapidly Progressive Glomerulonephritis



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***

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

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.

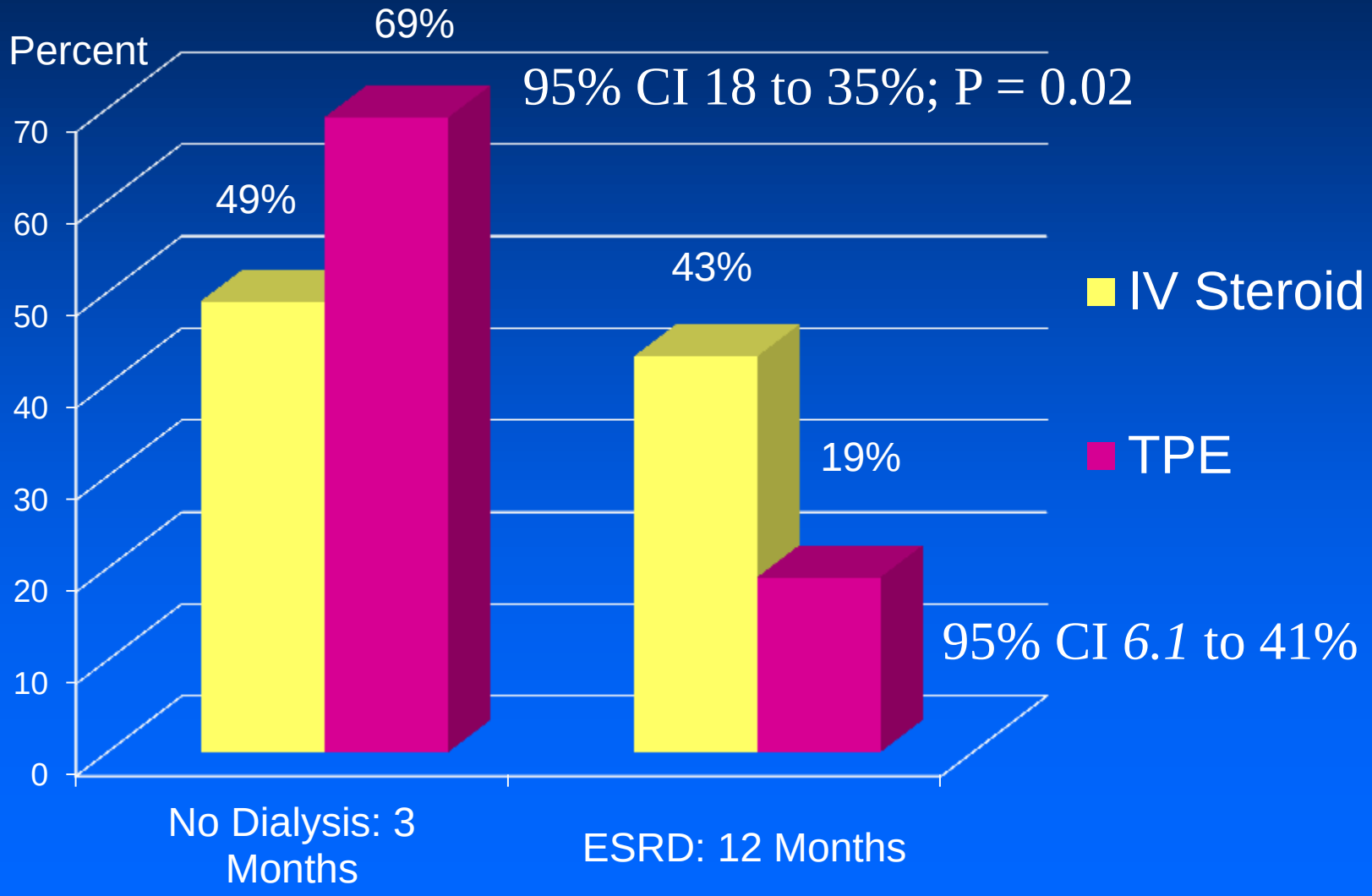
Both groups received oral cyclophosphamide and oral prednisolone.

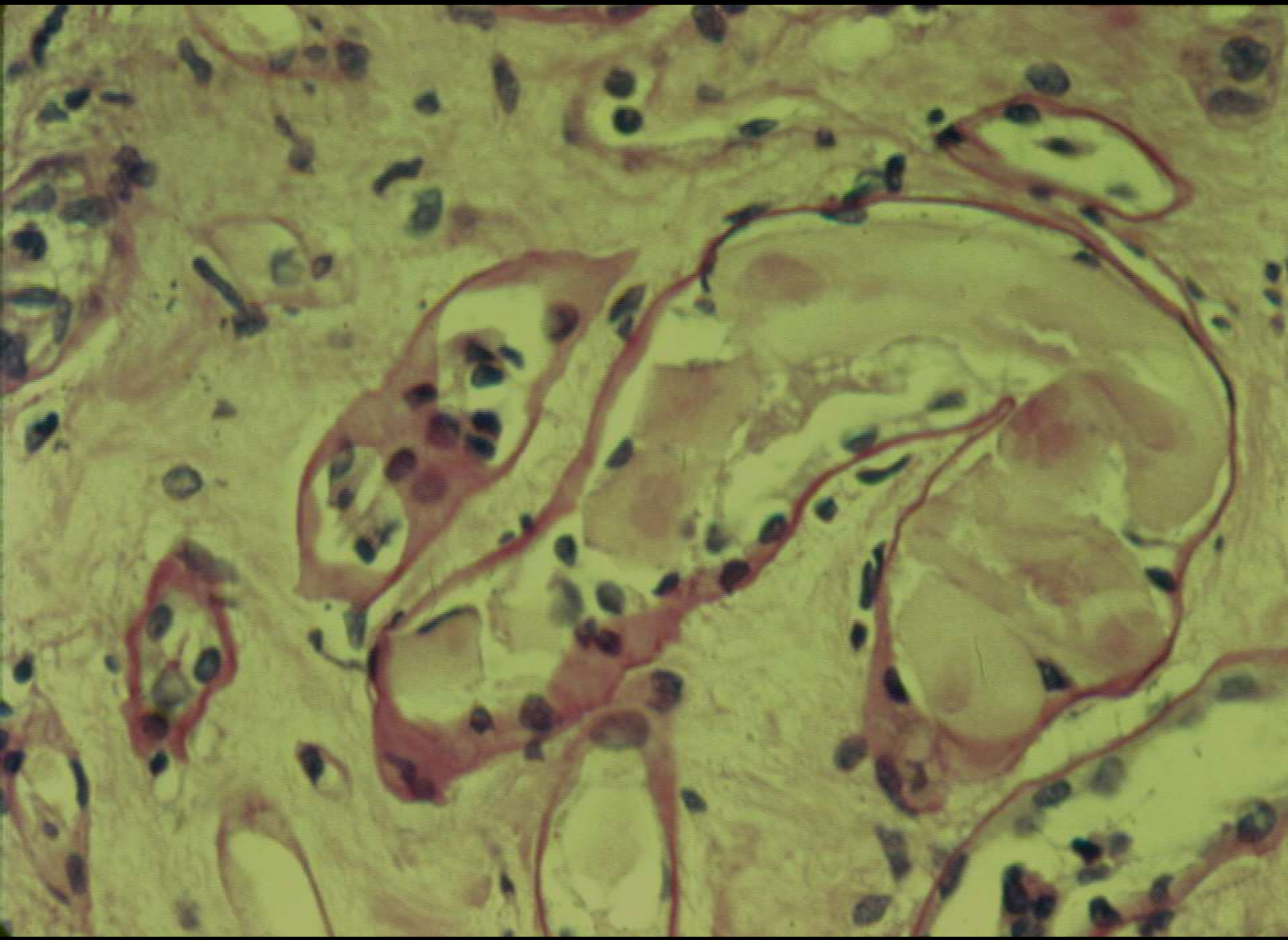
70 received 7 plasma exchanges, 67 received 3000 mg of IV methylprednisolone

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.

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





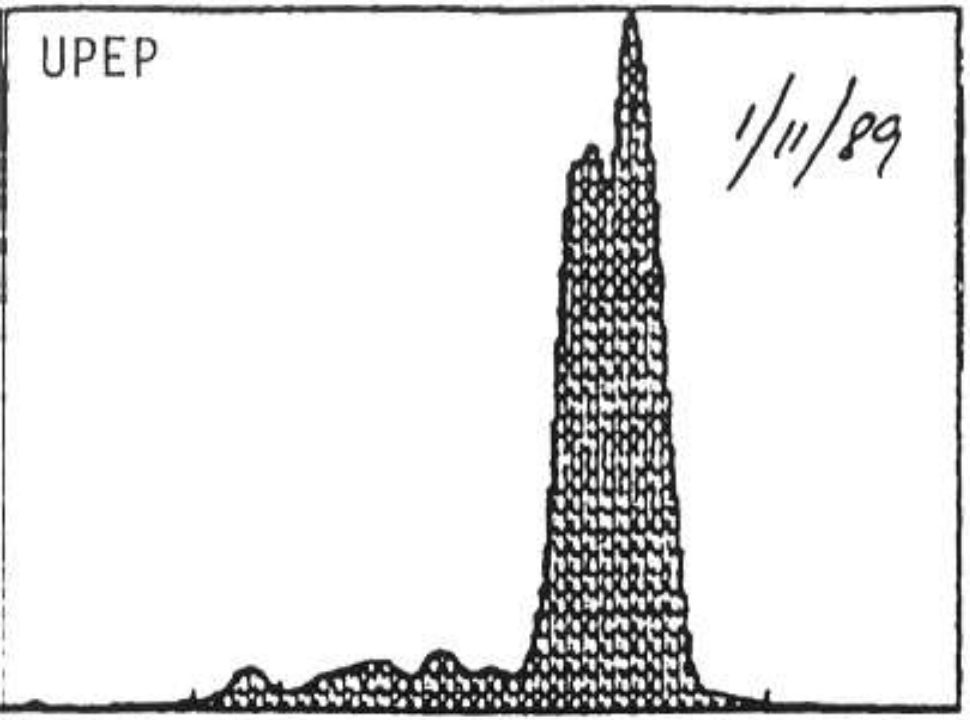
“Cast Nephropathy” in Multiple Myeloma

- 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

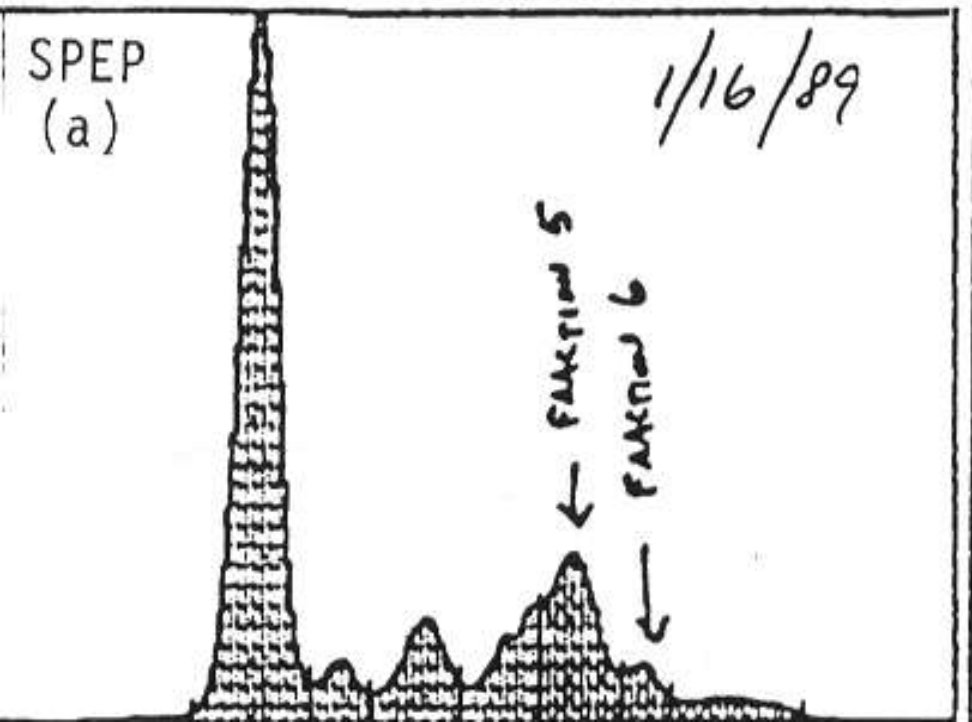
	Group I	Group II	*P*
Number in group	15	14	
Number of patients requiring dialysis	13	11	NS
Number of patients interrupting dialysis	11	2	<0.01
Number of patients who died within the first 2 months	1	5	NS
Serum creatinine at the end of the 2nd month mean ± SD *mg/dl*	2.6 ± 2.1	7.7 ± 1.9	<0.001

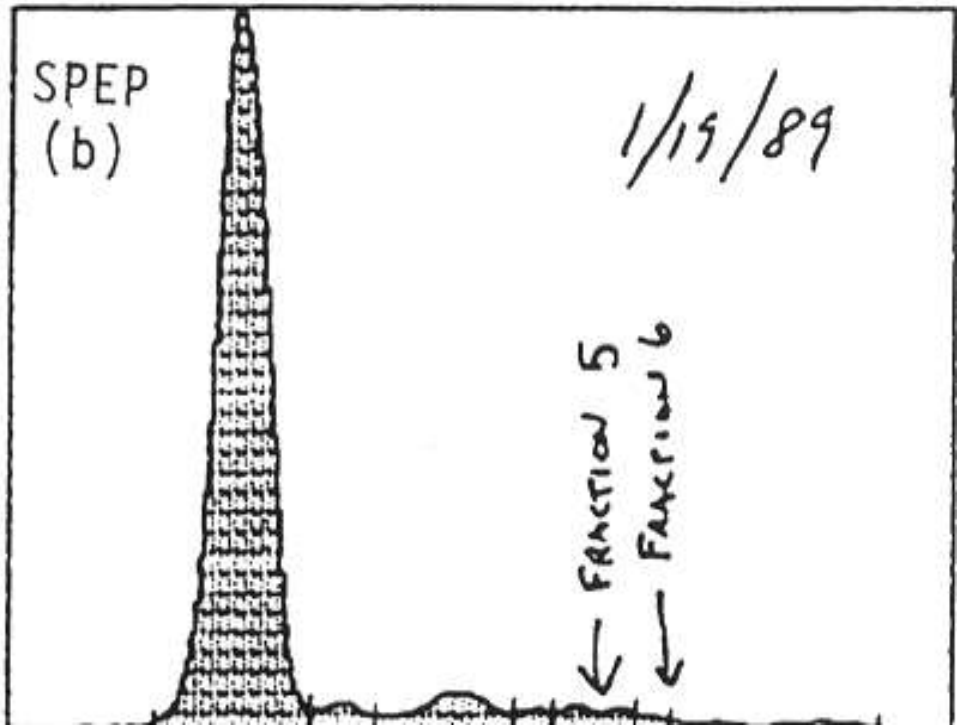
Zuchelli et al. K.I. 1988



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

Multiple Myeloma
IgA
Lambda light chain

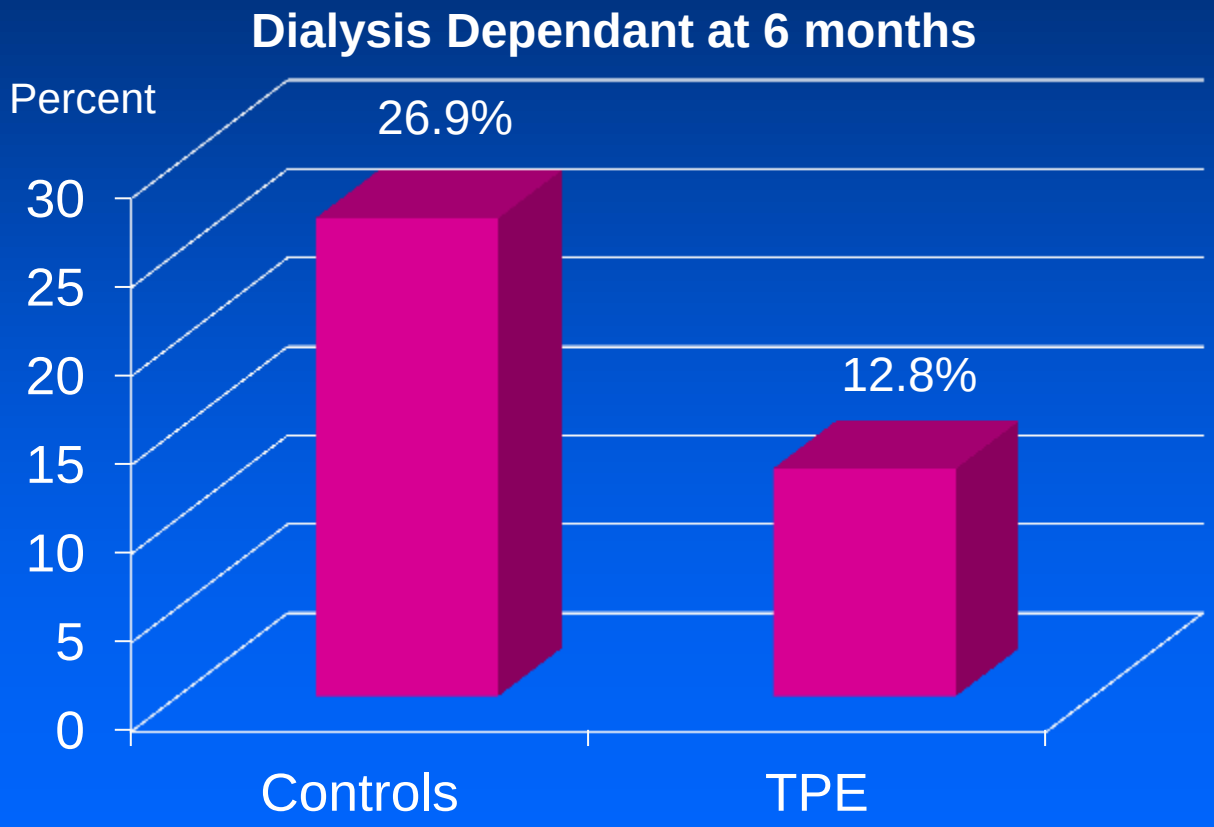




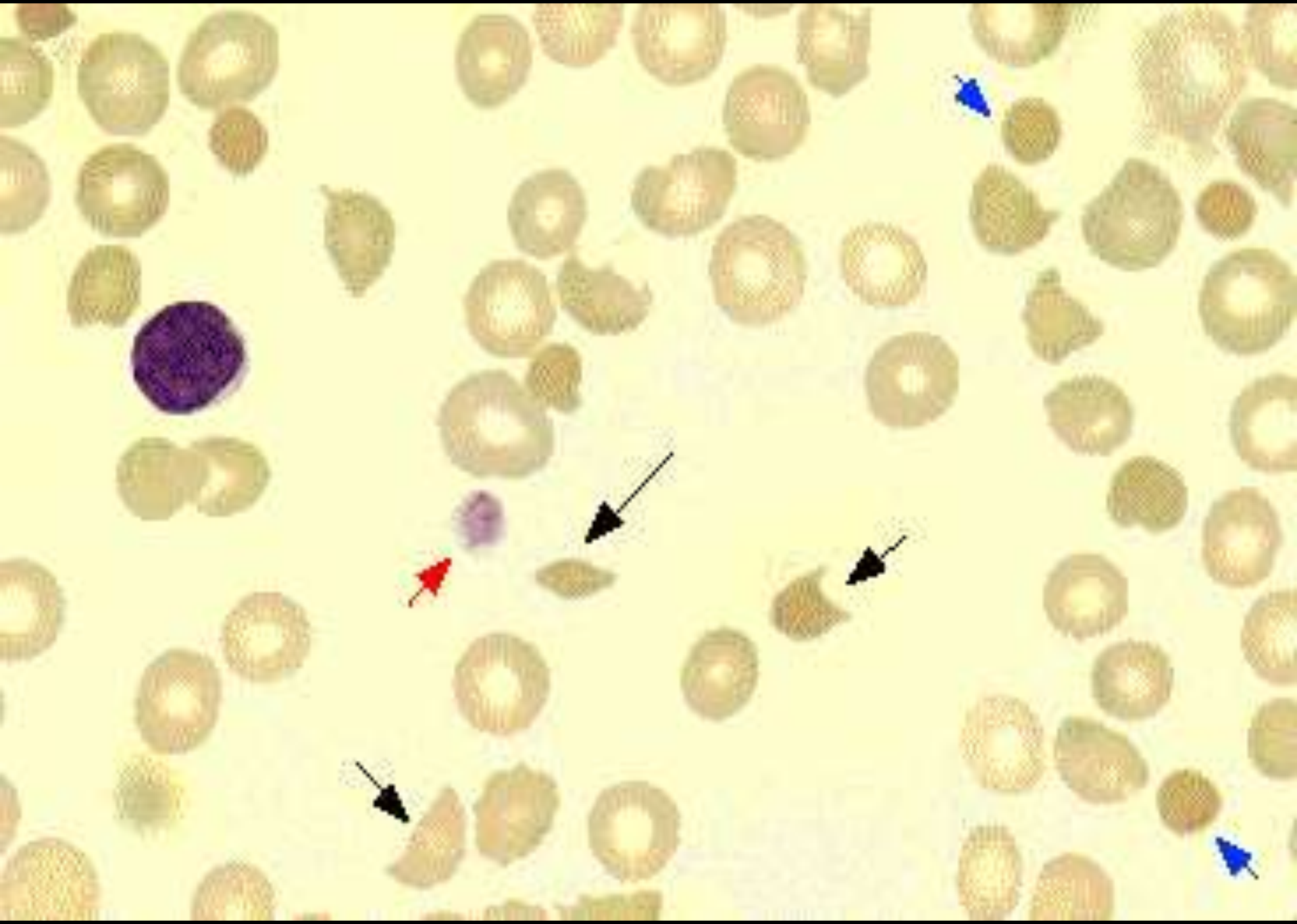
Plasma Exchange When Myeloma Presents as Acute Renal Failure: A Randomized, Controlled Trial

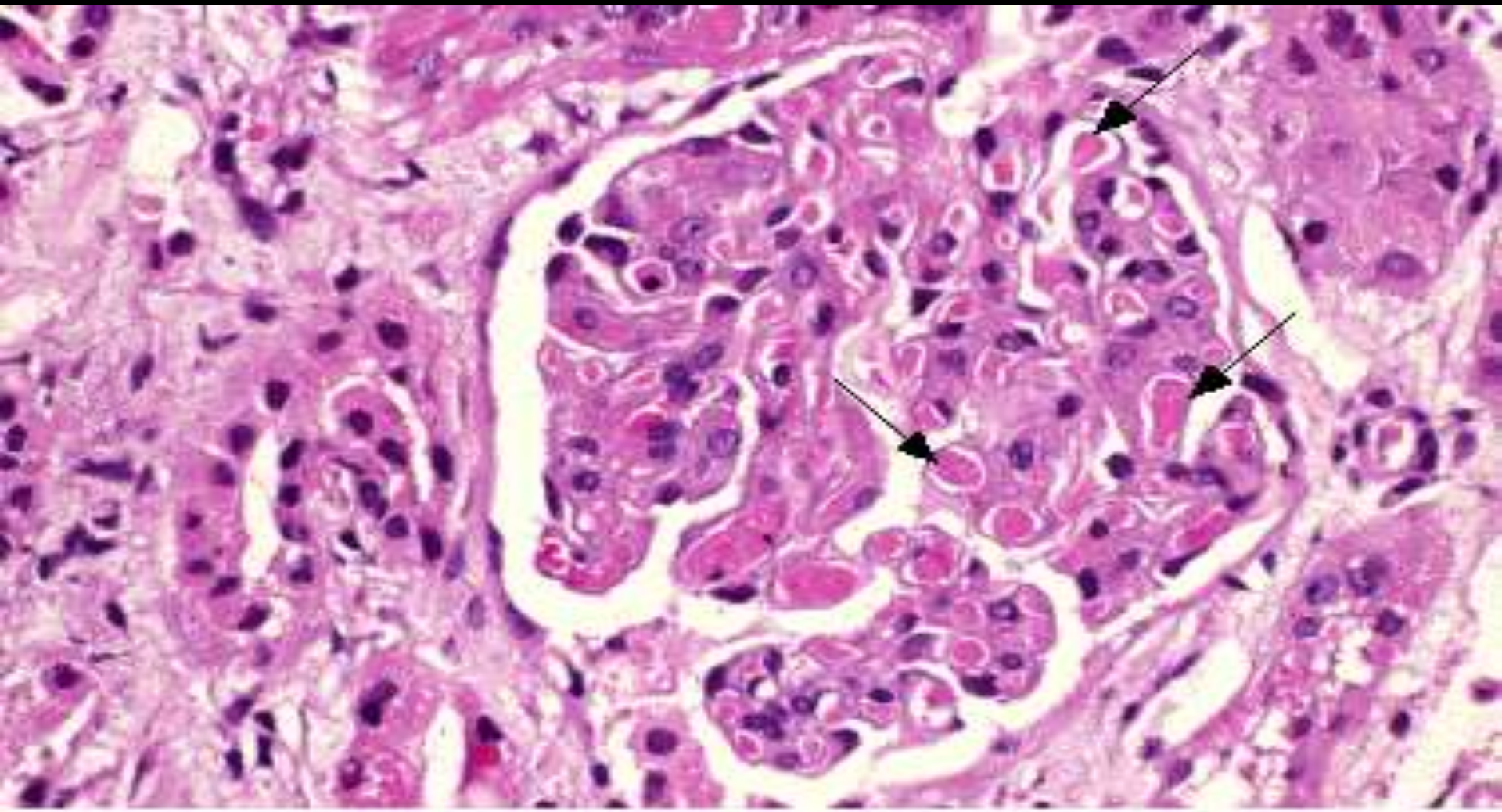
William F. Clark, et al .and the Canadian Apheresis Group

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



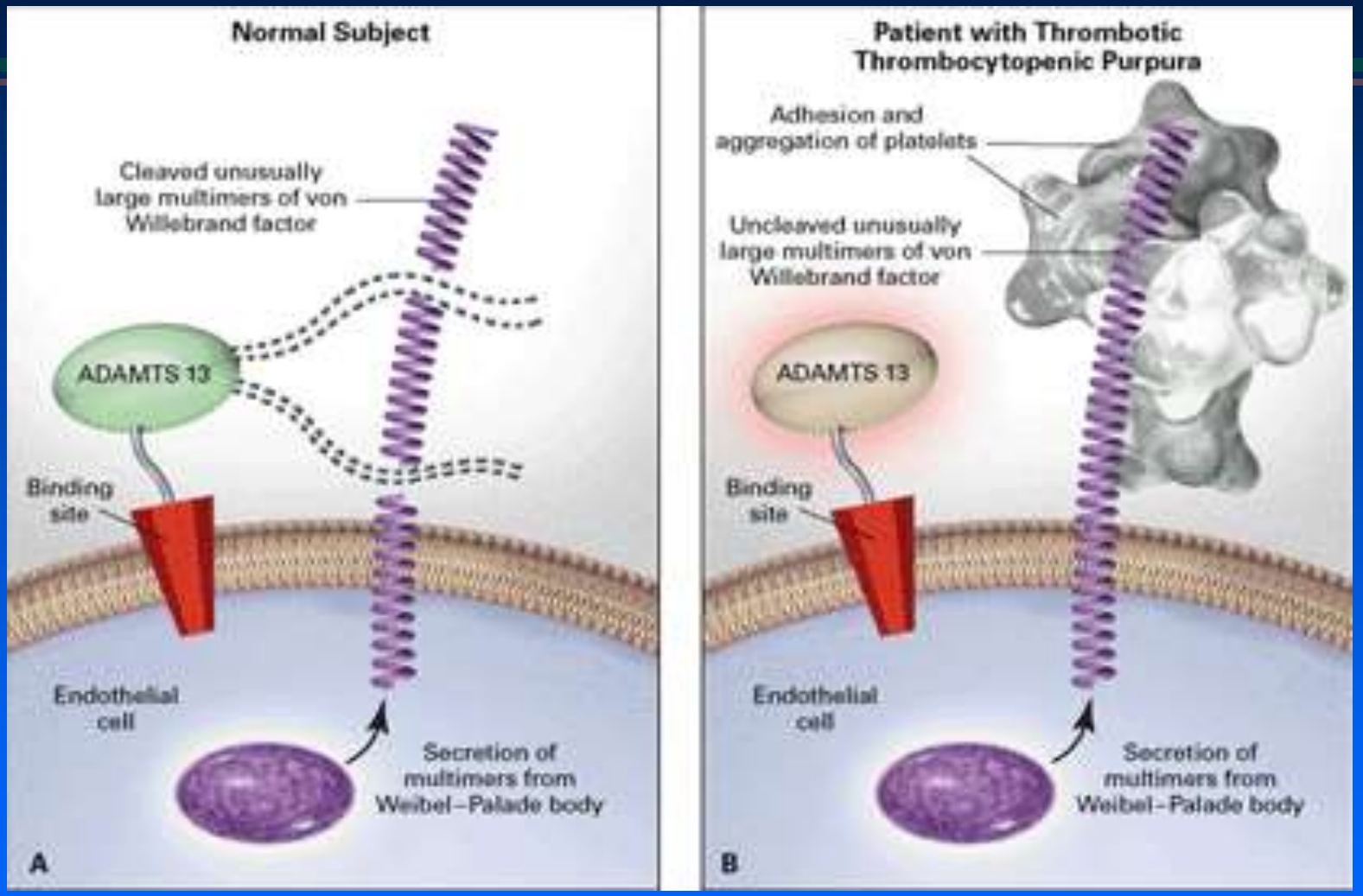
difference 14.1% [CI, –5.1% to 34.6%]; *P* = 0.20





Hemolytic uremic syndrome Light micrograph showing multiple intracapillary glomerular thrombi (arrows) typical of a thrombotic microangiopathy as can be seen in any of the forms of the hemolytic-uremic syndrome. Courtesy of Helmut Rennke, MD.

PATHOGENESIS OF TTP



N Engl J Med 2002;347:589

a disintegrin and metalloprotease with thrombospondin type I repeats (ADAMTS)

TTP and HUS

- Plasmapheresis clearly beneficial in TTP.
  Rock et al. NEJM 325:393, 1991
- Benefit of plasmapheresis in HUS is less clear and may depend on associated factors:
  E. Coli 0157 induced verotoxin, cancer, chemotherapy/drug induced, post renal transplant, pediatric versus adult, etc.

Rock et al. NEJM 325:393, 1991

Table 4. Results after Six Months.

Outcome	Plasma Exchange	Plasma Infusion		
		No Crossover	Crossover	Total
Response*				
No. of patients	51 (100)	32 (100)	19 (100)	51 (100)
Success	40 (78)	10 (31)	15 (79)	25 (49)
Failure	11 (22)	22 (69)	4 (21)	26 (51)
Survival†				
No. of patients	51 (100)	20 (100)	31 (100)	51 (100)
Success	40 (78)	10 (50)	22 (71)	32 (63)
Failure	11 (22)	10 (50)	9 (29)	19 (37)

*P = 0.002 by two-tailed exact binomial test for all comparisons between groups. The difference between the plasma-exchange and plasma-infusion groups in the percentage with a successful response was 29 percent (95 percent confidence interval, 11 to 47 percent).

†The difference between the plasma-exchange and plasma-infusion groups in the percentage who survived was 15 percent (95 percent confidence interval, −2.5 to +32.5 percent).

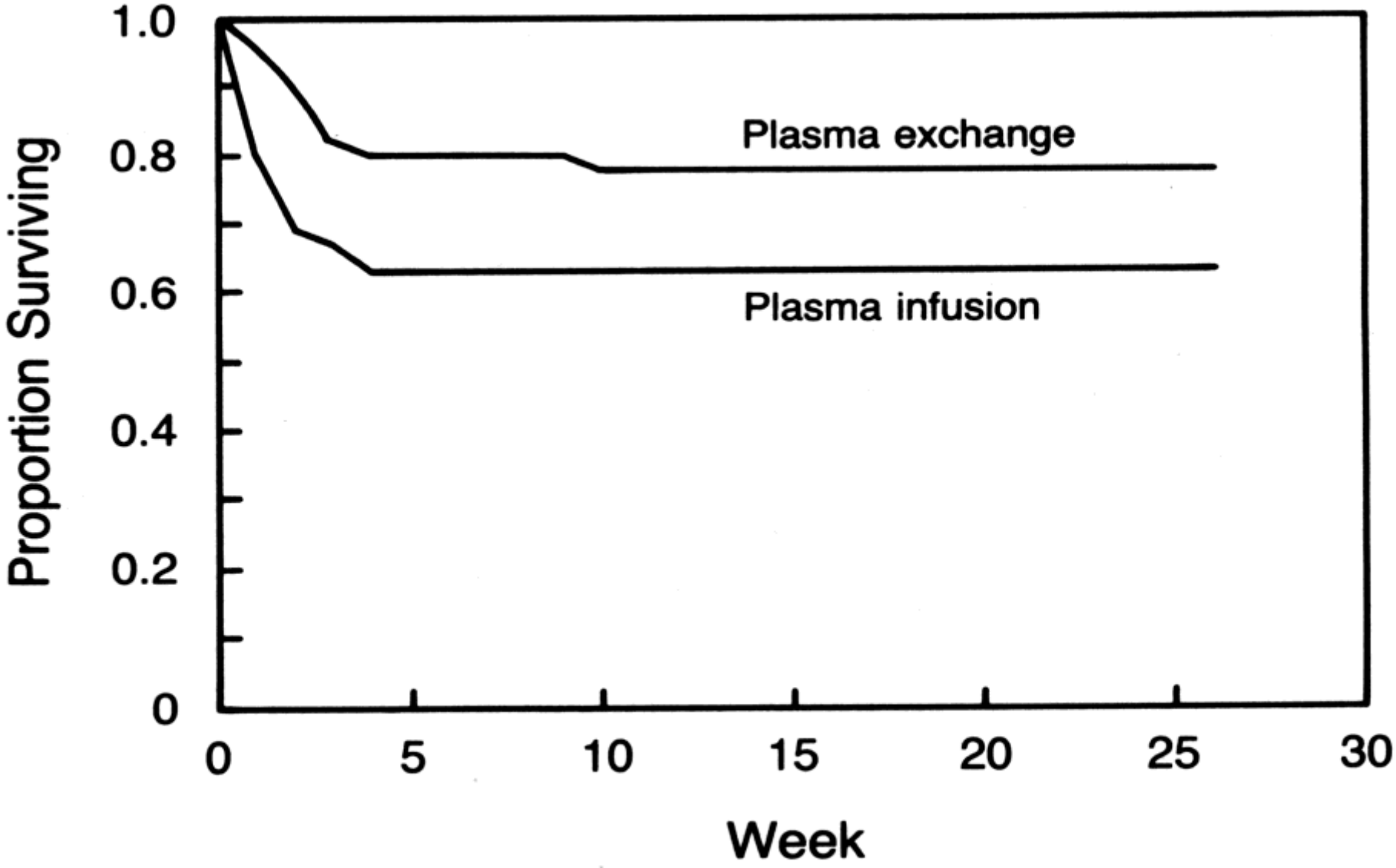


Figure 1. Survival of Patients with Thrombotic Thrombocytopenic Purpura.

Table 2. Classification and treatment of different forms of HUS*

Disease	Causes	Treatment
Stx-HUS	Stx-producing *Escherichia coli*	Supportive
	Shigella dysenteriae type 1	Supportive, antibiotics
Non-Stx-HUS	Bacteria (*Streptococcus pneumoniae*)	Antibiotics, no plasma
sporadic	Viruses (HIV)	Plasma
	Drugs (antineoplastic, antiplatelet, immunosuppressive)	Drug withdrawal, plasma
	Pregnancy associated	Delivery, plasma
	Postpartum	Plasma
	Systemic diseases	
	lupus	Steroids, plasma
	scleroderma	BP control
	antiphospholipid syndrome	Oral anticoagulants
	Idiopathic	Plasma
	Genetic (factor H, MCP, factor I)	Plasma
familial	Genetic (factor H, MCP, factor I), plasma	Plasma

Hemolytic Uremic Syndrome

Marina Noris* and Giuseppe Remuzzi*†

**Transplant Research Center, "Chiara Cucchi de Alessandri e Gilberto Crespi," Mario Negri Institute for Pharmacological Research; and †Department of Medicine and Transplantation, Ospedali Riuniti di Bergamo, Bergamo, Italy*

J Am Soc Nephrol 16: 1035–1050, 2005. doi: 10.1681/ASN.2004100861

Effectiveness of therapeutic plasma exchange in the 1996 Lanarkshire *Escherichia coli* O157:H7 outbreak

Lancet 1999; **354:** 1327–30

S Dundas, J Murphy, R L Soutar, G A Jones, S J Hutchinson, W T A Todd

Findings 22 adults developed HUS/TTP. They had a mean age of 71 years. 16 cases received TPE. Six cases had contraindications to TPE or died before the procedure could be done. Ten of the 22 (45%) adults with HUS/TTP died. Five of the 16 (31%) TPE-treated cases died, four of eight aged over 70 years compared with one of eight aged less than 70 years. Premorbid illness, neurological features,

Interpretation The mortality rate is high in adults who develop HUS/TTP induced by *E coli* O157. TPE appears to be a promising treatment that was well tolerated in our elderly patients. A national register of adult cases of HUS/TTP induced by *E coli* O157 should be established.

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

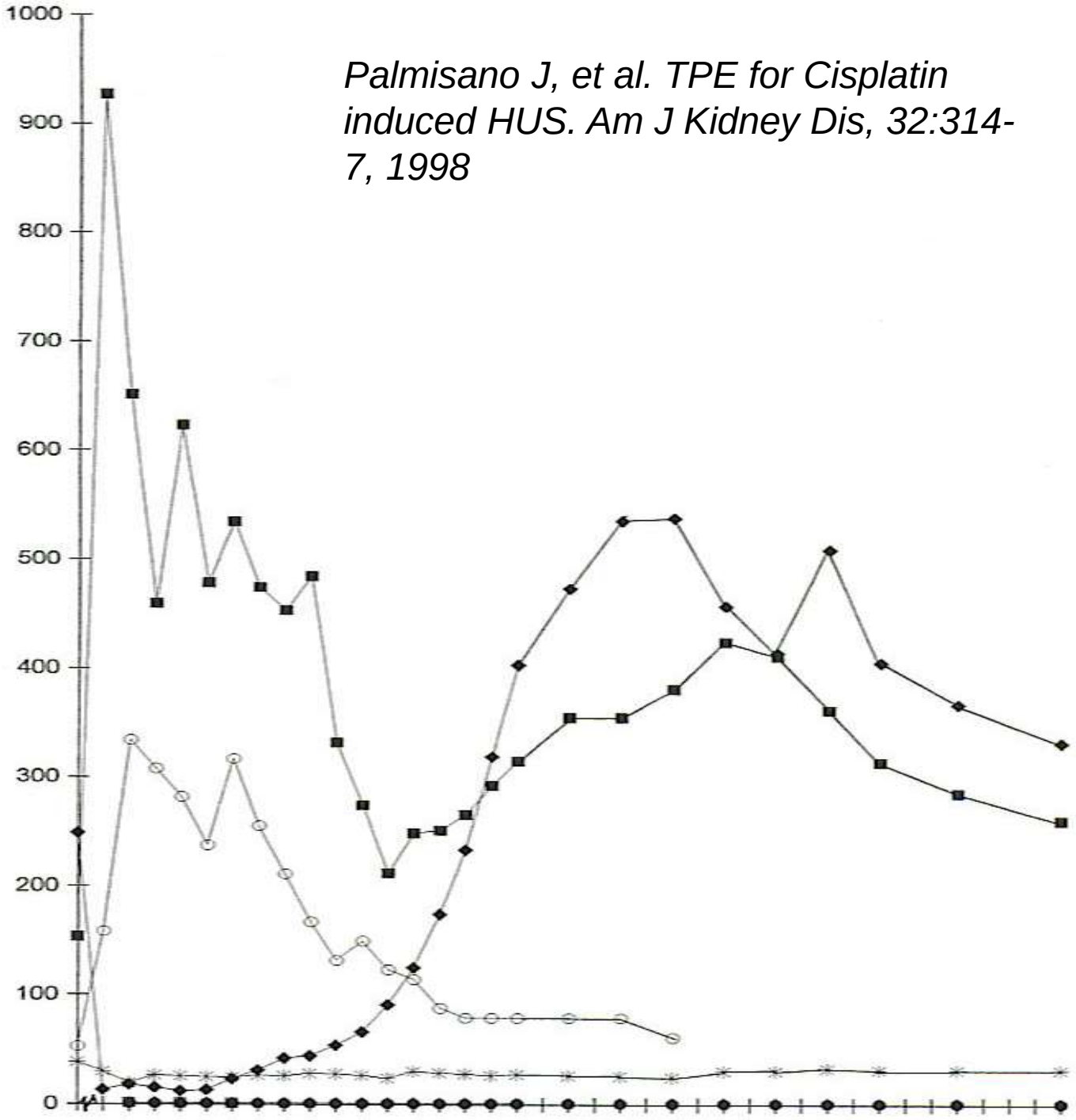


Fig 1. Clinical course of cisplatin-induced HUS during treatment with TPE. To convert creatinine from micromoles per liter to milligrams per deciliter, divide by 88.4. Hemodialysis treatments and TPE occurred on days 2, 4, and 6. Baseline values graphed on the *Y* axis represent laboratory data from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

Drug-induced HUS

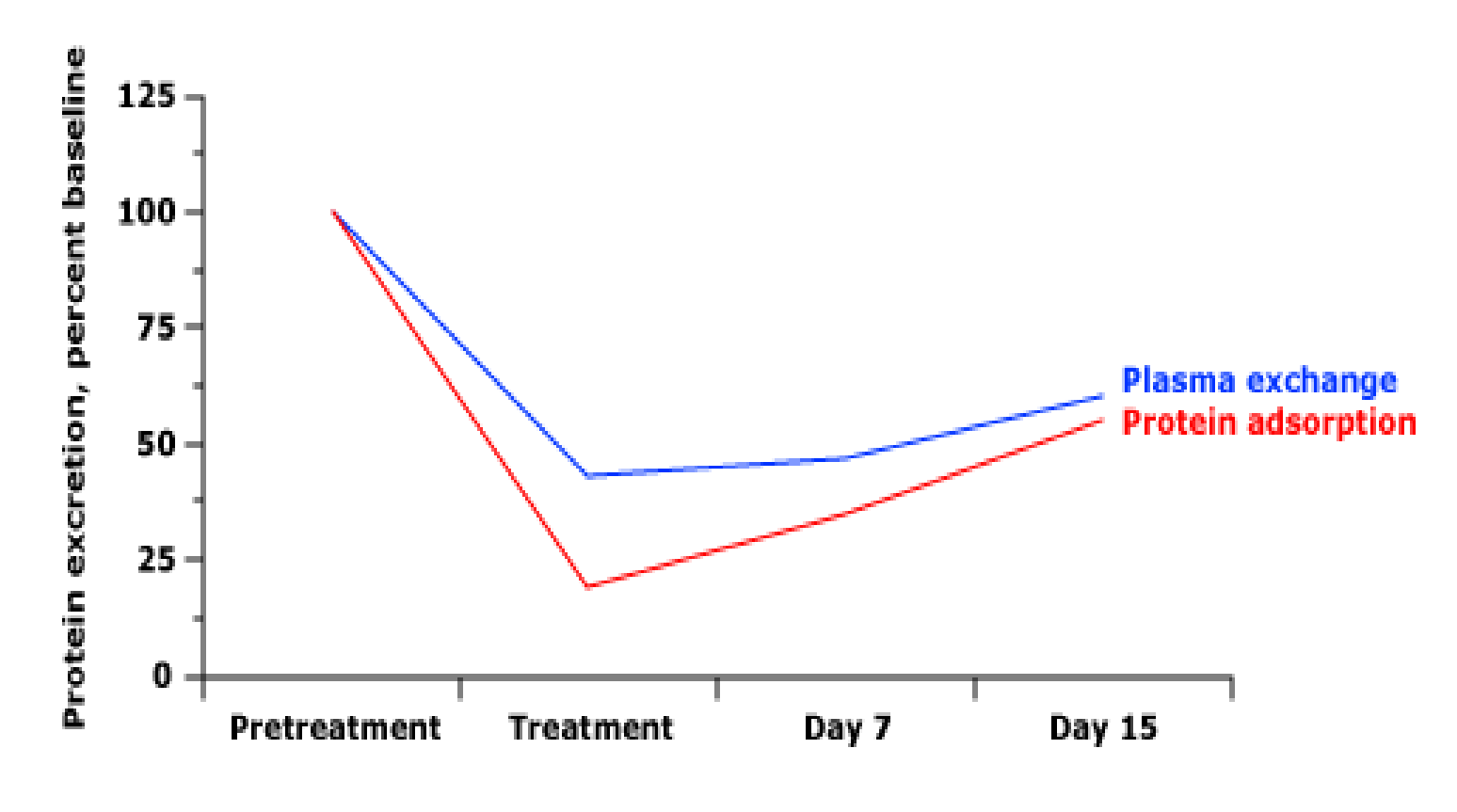
In two series consisting of 158 cases of TTP-HUS associated with ticlopidine, the mortality rate in patients receiving TPE was significantly lower than in those who did not (24 versus 50 percent and 18 versus 57 percent, respectively).

Bennett CL et Ann Intern Med 1998;128:541
Bennett CL et Arch Intern Med 1999;159:2524

Focal Segmental Glomerulosclerosis (FSGS)

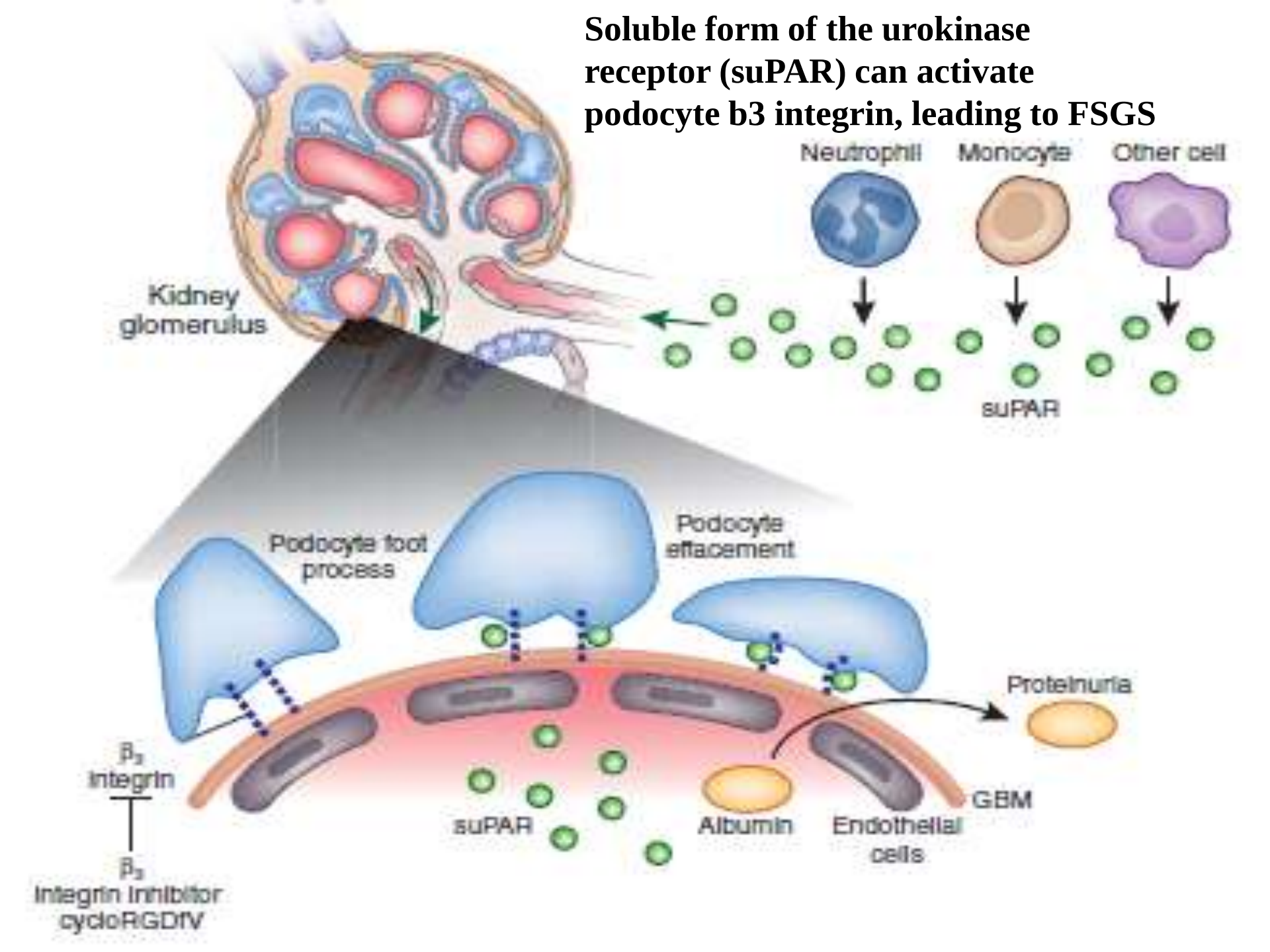
- 15-55% of patients with ESRD due to FSGS will have recurrence of proteinuria after renal transplantation.
- 30-50,000 dalton protein can increase glomerular permeability.
- Protein adsorption and plasmapheresis can lower proteinuria and maintain normal histology. *Dantal et al. NEJM 330: 1994, Artero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

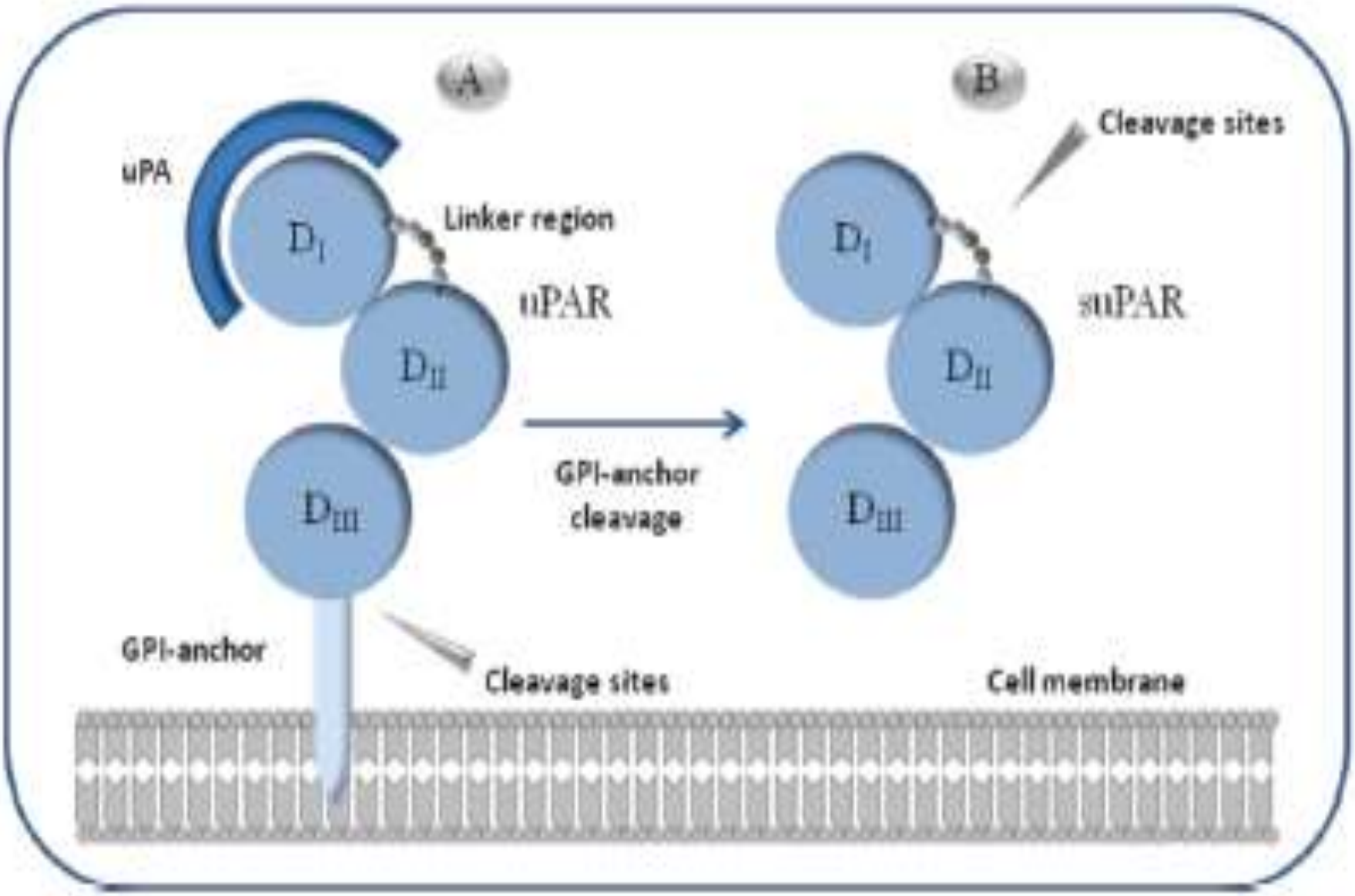
Removal of circulating factor lowers protein excretion in FSGS



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.*

Soluble form of the urokinase receptor (suPAR) can activate podocyte b3 integrin, leading to FSGS



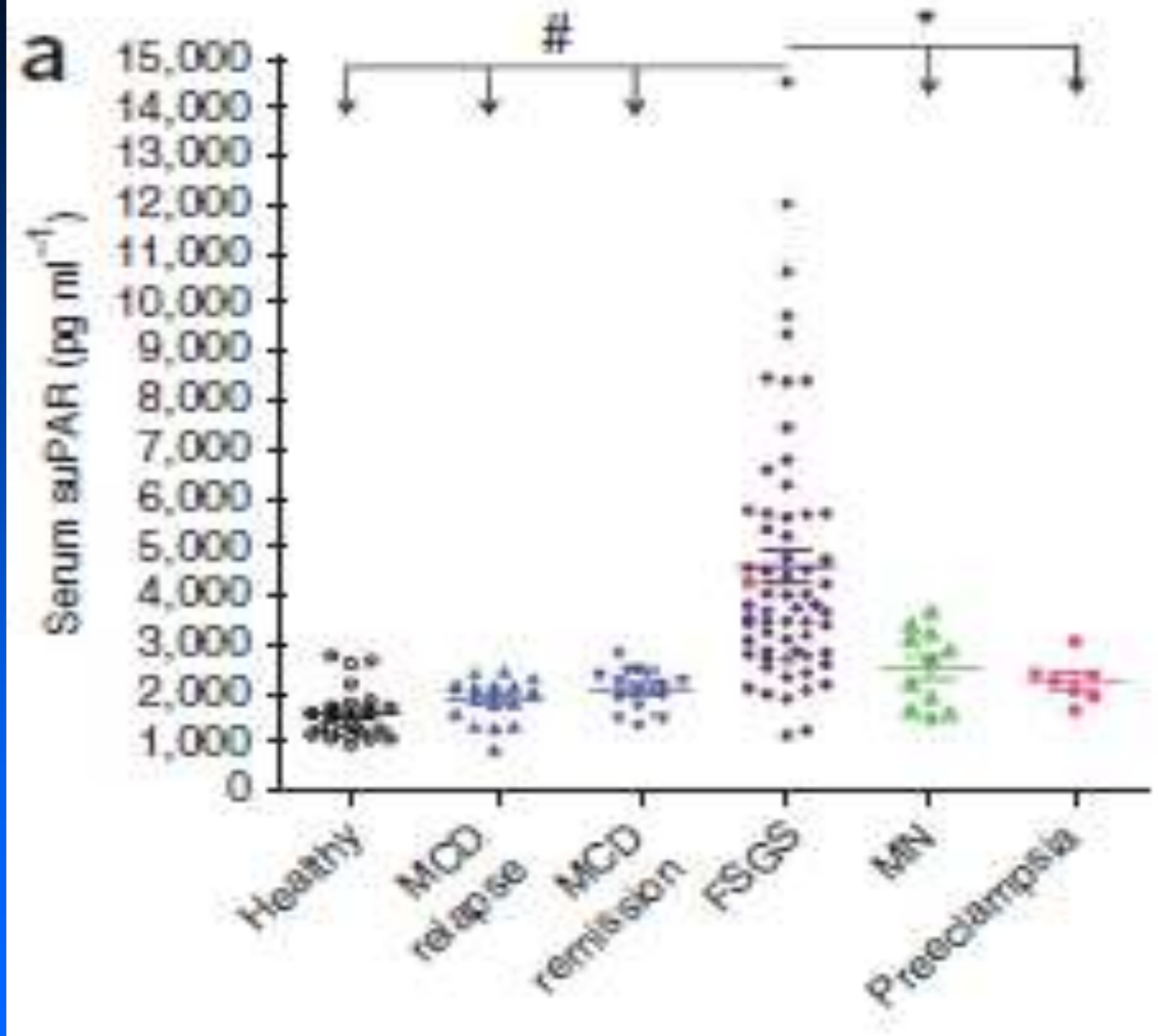

A
B
uPA
Linker region
D_I
D_{II}
D_{III}
uPAR
GPI-anchor cleavage
Cleavage sites
suPAR
GPI-anchor
Cleavage sites
Cell membrane

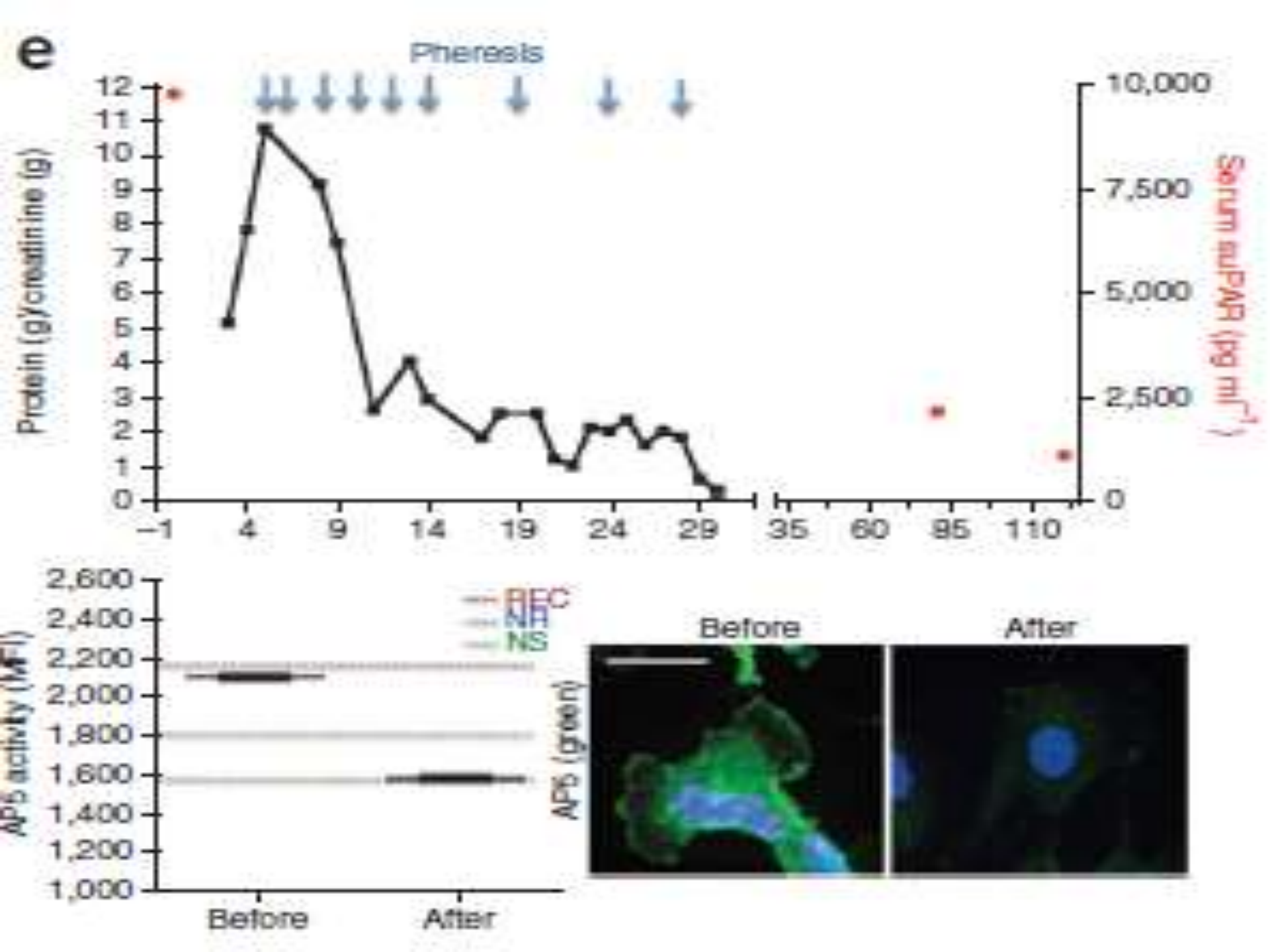
suPAR is a circulating protein ranging from 20 to 50 kDa, depending on the degree of glycosylation and proteolytic cleavage

Fragments	Structure	Physical Characteristics	Molecular Mass kDa*	Localization
$uPAR_{I-III}$		Full length + GPI anchor	~55-60 (35) [1,2]	Membrane-bound
$uPAR_{II-III}$		Cleaved + GPI anchor	~45-50 (27)[3]	Membrane-bound
$suPAR_{I-III}$		Full length - GPI anchor	~55-60 (35)[4,5]	Soluble
$suPAR_{II-III}$		Cleaved - GPI anchor	~40-45 (27)[6,7]	Soluble
$suPAR_{I}$		Cleaved - GPI anchor	~16 (9)[8]	Soluble

GPI-anchor Domain Linker region D_I: Domain 1 D_{II}: Domain 2 D_{III}: Domain 3

*The molecular mass is listed for glycosylated proteins . The molecular mass for non-glycosylated proteins is shown in parentheses .[1] Nielsen *et al.*, 1988 ; [2] Roldan *et al.*, 1990; [3] Høyer-Hansen *et al.*, 1992; [4] Ploug *et al.*, 1991; [5] Ploug *et al.*, 1992a; [6] Wahlberg *et al.*, 1998; [7] Høyer Hansen et al 2001; [8] Behrendt *et al.*, 1991.


a
#
15,000
14,000
13,000
12,000
11,000
10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
0
Serum suPAR (pg ml^{-1})
Healthy
MCD relapse
MCD remission
FSGS
MN
Preeclampsia


e
Pheresis
Protein (g/creatinine (g)
Serum suPAR (pg ml^{-1})
12
11
10
9
8
7
6
5
4
3
2
1
0
10,000
7,500
5,000
2,500
0
−1
4
9
14
19
24
29
35
60
95
110
2,600
2,400
2,200
2,000
1,800
1,600
1,400
1,200
1,000
APS activity (MFI)
REC
NA
NS
Before
After
Before
After
APS (green)

Transplant candidate with cytotoxic antibodies

- Preformed cytotoxic antibodies preclude renal transplantation due to risk of hyperacute rejection.
- Immunoadsorption in highly sensitized patients can allow for successful transplant. *Charpentier et al. Kidney Int 42:suppl 38:S-176,1992, Ross et al. Tansplantation 55:785, 1993*

Renal transplantation across ABO groups

- Pretreatment with plasmapheresis to remove anti-A or anti-B antibodies is necessary in order to prevent acute vascular rejection
- 5 year graft survival as high as 78% when kidneys from donors in blood groups A2 or B subgroups are transplanted into group O recipients *Modlin et al.. Urolog Clin N Am 28:687-707, 2001..*
- donor specific skin grafting is used to predict outcome *Karakayali et al. Transplantation Proceedings, 31:256-257, 1999.*