When Both Renal Replacement Therapy and Apheresis are Needed: Are Tandem Procedures Practical?

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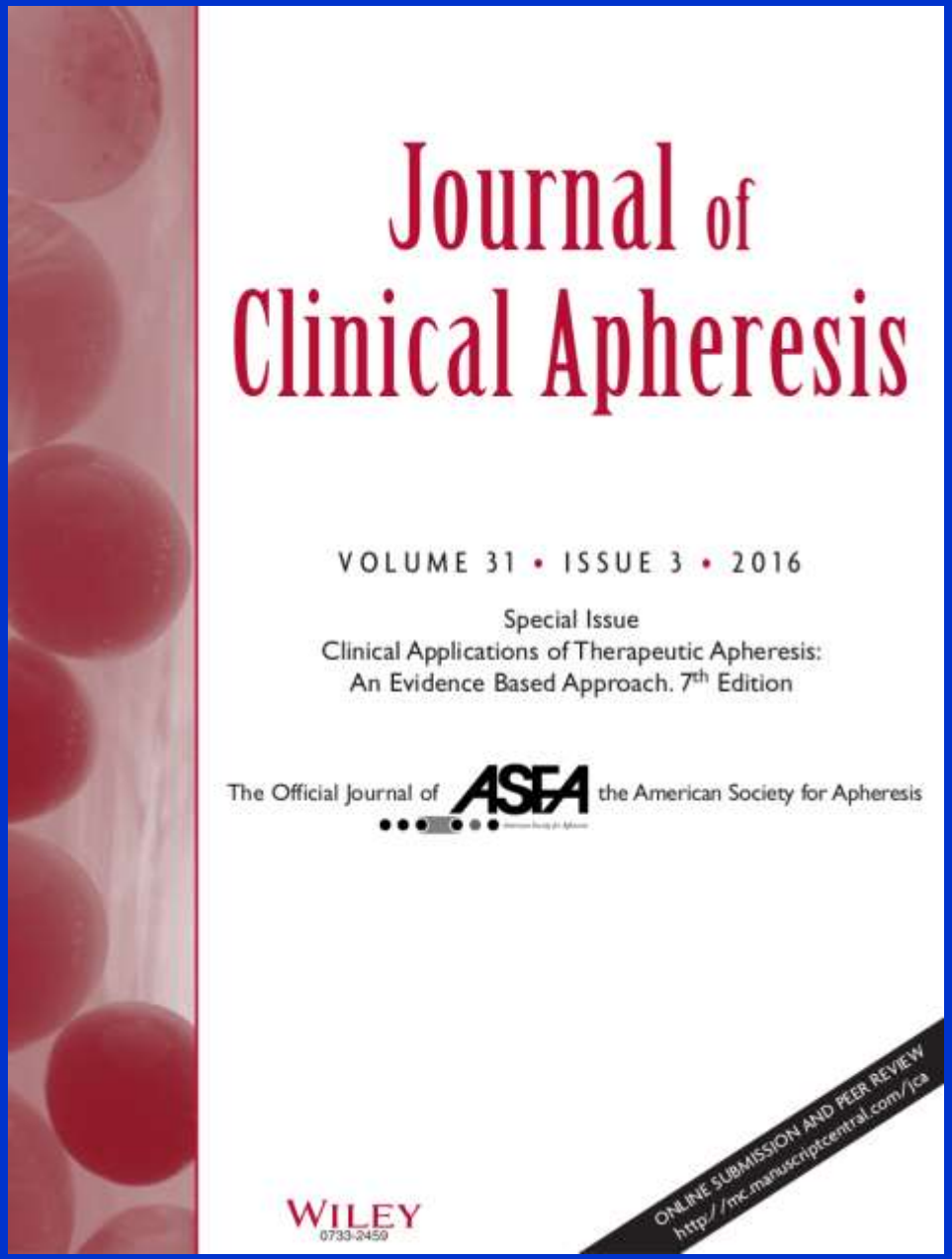

Journal of Clinical Apheresis 2016;31:149-162; 163-338

Clinical Applications of Therapeutic Apheresis: An Evidence Based Approach. 7th Edition

Description of Clinical Disorder	Apheresis Modality	Indication	Category	Grade
ANCA-associated rapidly progressive glomerulonephritis (Granulomatosis with polyangiitis; and Microscopic Polyangiitis)	TPE	Dialysis dependence	**I**	1A
	TPE	DAH	**I**	1C
	TPE	Dialysis independence	III	2C
Anti-glomerular basement membrane disease (Goodpasture's syndrome)	TPE	Dialysis dependence, no DAH	III	2B
	TPE	DAH	**I**	1C
	TPE	Dialysis independence	**I**	1B
Focal segmental glomerulosclerosis	TPE	Recurrent in transplanted kidney	**I**	1B
	LDL apheresis	Steroid resistant in native kidney	III	2C
Henoch-Schönlein purpura	TPE	Crescentic	III	2C
	TPE	Severe extrarenal disease	III	2C
Immunoglobulin A nephropathy	TPE	Crescentic	III	2B
	TPE	Chronic Progressive	III	2C
Myeloma cast nephropathy	TPE		II	2B
Nephrogenic systemic fibrosis	ECP		III	2C
	TPE		III	2C
Renal transplantation, ABO compatible	TPE/IA	Antibody mediated rejection	**I**	1B
	TPE/IA	Desensitization, Living Donor	**I**	1B
	TPE/IA	Desensitization, Deceased Donor	III	2C
Renal transplantation, ABO incompatible	TPE/IA	Desensitization, Living Donor	**I**	1B
	TPE/IA	Antibody mediated rejection	II	1B
Thrombotic microangiopathy				
Coagulation Mediated	TPE	*THBD* mutation	III	2C
Complement mediated	TPE	Complement factor gene mutations	III	2C
		Factor H autoantibodies	**I**	2C
		MCP mutations	III	1C
Drug associated	TPE	Ticlopidine	**I**	2B
		Clopidogrel	III	2B
		Calcineurin inhibitors	III	2C
HPC transplantation associated	TPE		III	2C
Shiga toxin mediated	TPE/IA	Severe neurological symptoms	III	2C
	TPE	*Streptococcus pneumonia*	III	2C
	TPE	Absence of severe neurological symptoms	IV	1C

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Anti-glomerular basement membrane disease (Goodpasture's syndrome)
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Renal transplantation, ABO incompatible
Thrombotic microangiopathy

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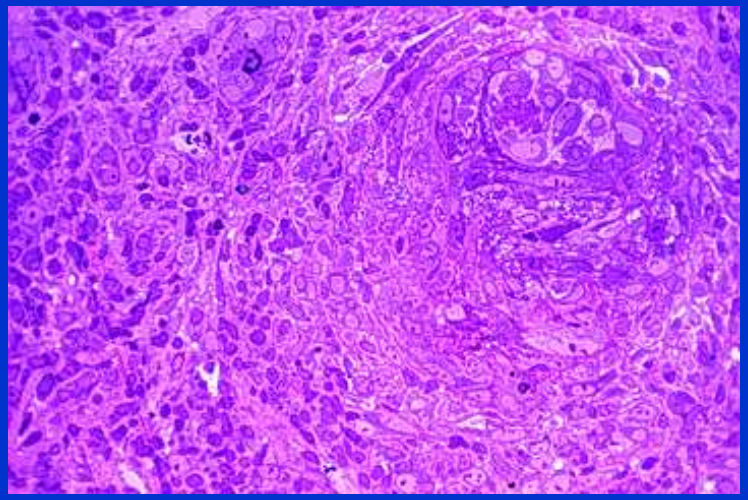
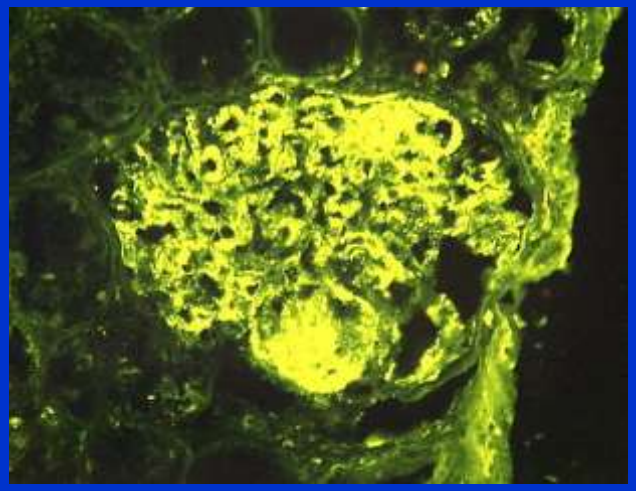
ANCA-Associated Rapidly Progressive Glomerulonephritis

- Acute kidney injury
- Hematuria, proteinuria
- Renal inflammation (RPGN)
  - Crescent formation
  - Glomerular necrosis
- Immune vasculitis
  - pulmonary-renal syndrome
  - ANCA (small, medium)
    - GPA (c-ANCA)
    - MPA (p-ANCA)
- 70% with severe presentation (creat ≥ 5.8 mg/dL) require hemodialysis (MEPEX)





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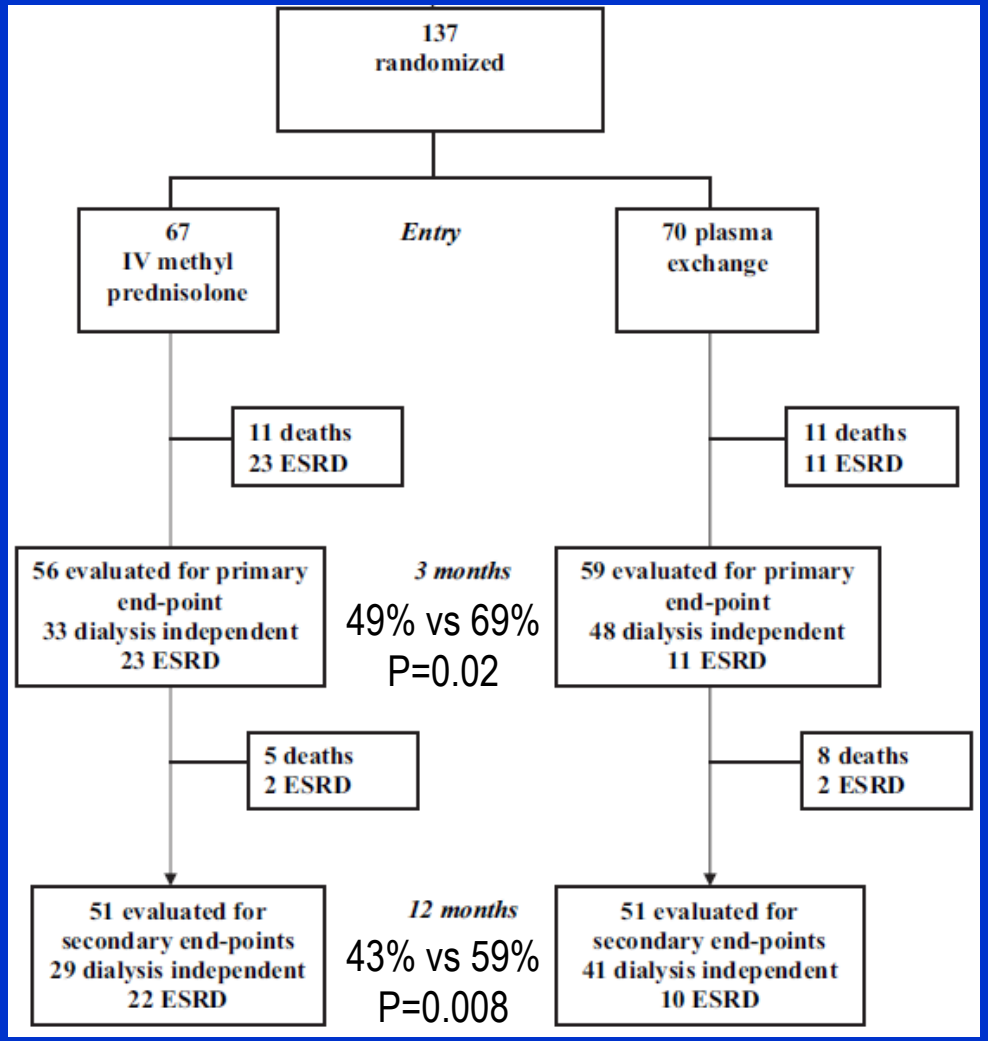
Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis

- 137 patients with biopsy-proven ANCA-associated RPGN
- Creatinine ≥ 5.8 mg/dL
- All received oral cyclophosphamide and predisolone
- Randomized to receive TPE x 7 or 3000 mg IV methylprednisolone
- 1° outcome measure: dialysis independence at 3 months
- 2° outcome measures
  - Renal survival at 1 year
  - Patient survival at 1 year
  - Severe adverse event rates



Jayne DRW et al. J Am Soc Nephrol 18: 2180-8, 2007

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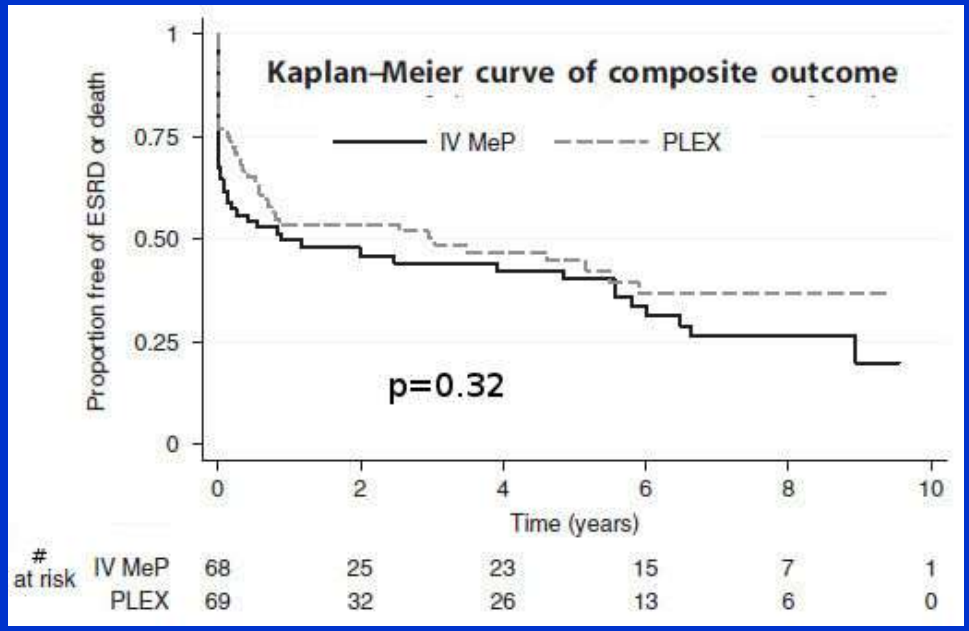
Benefit of Plasma Exchange Less Certain After Median 3.95 Years of Follow-up

Long-term primary and secondary outcomes by

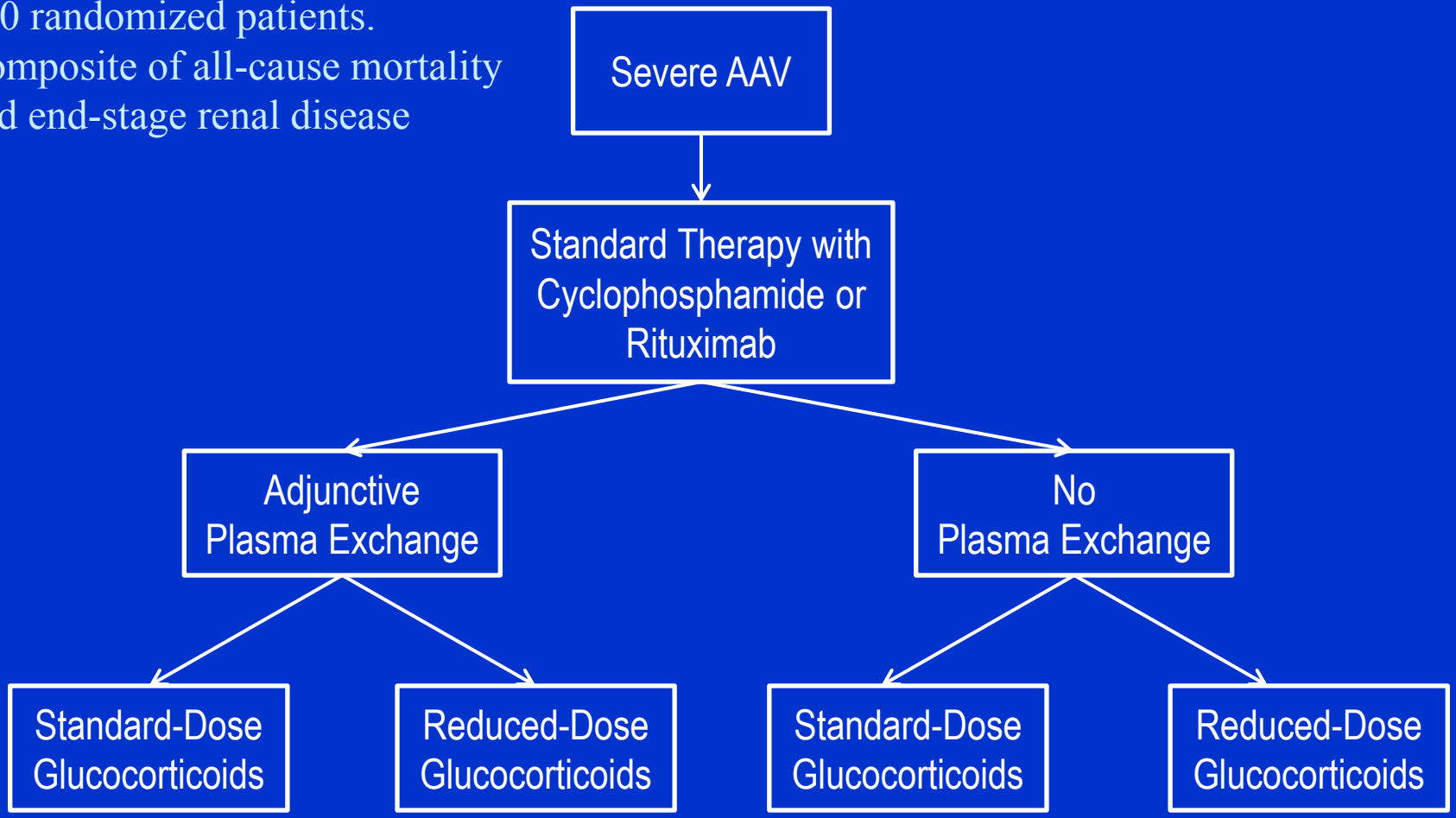
Outcome	IV MeP, $n = 68$ (%)	PLEX, $n = 69$ (%)	HR (95% CI)	*P*-value
Death or ESRD	46 (68)	40 (58)	0.81 (0.53–1.23)	0.32
Death	35 (51)	35 (51)	1.08 (0.67–1.73)	0.75
ESRD[a]	33 (49)	23 (33)	0.64 (0.40–1.05)	0.08
Relapse[a]	16 (21)	10 (14)	0.56 (0.26–1.21)	0.14



Walsh M et al. Kidney International 84:397-402, 2013

Pexivas: Randomized Controlled Trial

500 randomized patients.
Composite of all-cause mortality and end-stage renal disease



Walsh et al. Trials 2013, 14:73

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ASFA Recommendations Regarding Plasma Exchange for ANCA-Associated RPGN

ANCA-ASSOCIATED RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (GRANULOMATOSIS WITH POLYANGIITIS AND MICROSCOPIC POLYANGIITIS)

Incidence: 8.5/1000,000/yr	**Indication**	**Procedure**	**Recommendation**	**Category**
	Dialysis dependence[a]	TPE	Grade 1A	I
	DAH	TPE	Grade 1C	I
	Dialysis independence	TPE	Grade 2C	III
No. of reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	8 (296)	1 (26)	22 (347)	NA

[a]At presentation, defined as Cr > 6 mg/dL. DAH=diffuse alveolar hemorrhage

Schwartz J et al. J Clinical Apheresis 2016;31:163-338

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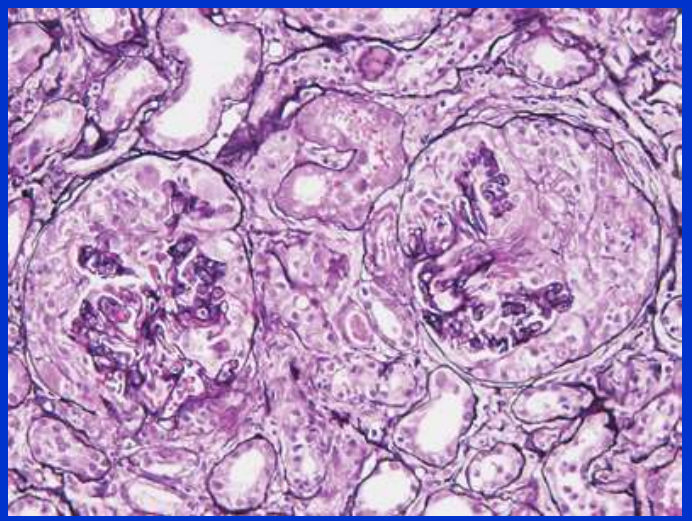
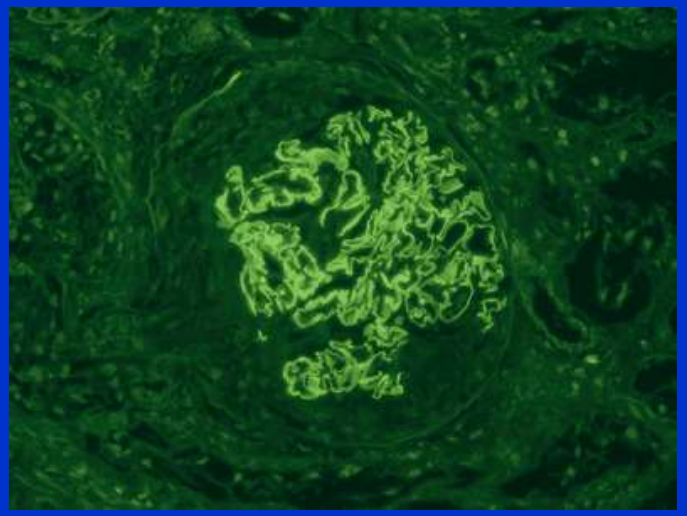
Anti-Glomerular Basement Membrane Disease

- Autoantibodies to NC1 domains of α3 and α5 chains of Type IV collagen in GBM
- Linear pattern on IF staining
- Renal inflammation
  - Crescent formation (>50% glomeruli)
  - Glomerular necrosis
- Pulmonary-renal syndrome
- TPE rapidly lowers anti-GBM ab
  - Avoid ESRD if start when creat ≤ 6 mg/dL
  - Treat anyway for DAH
  - Patients on HD may still respond to TPE if early diagnosis and acute presentation
- One randomized trial: Johnson, JP et al. Medicine 1985;64:219-227.





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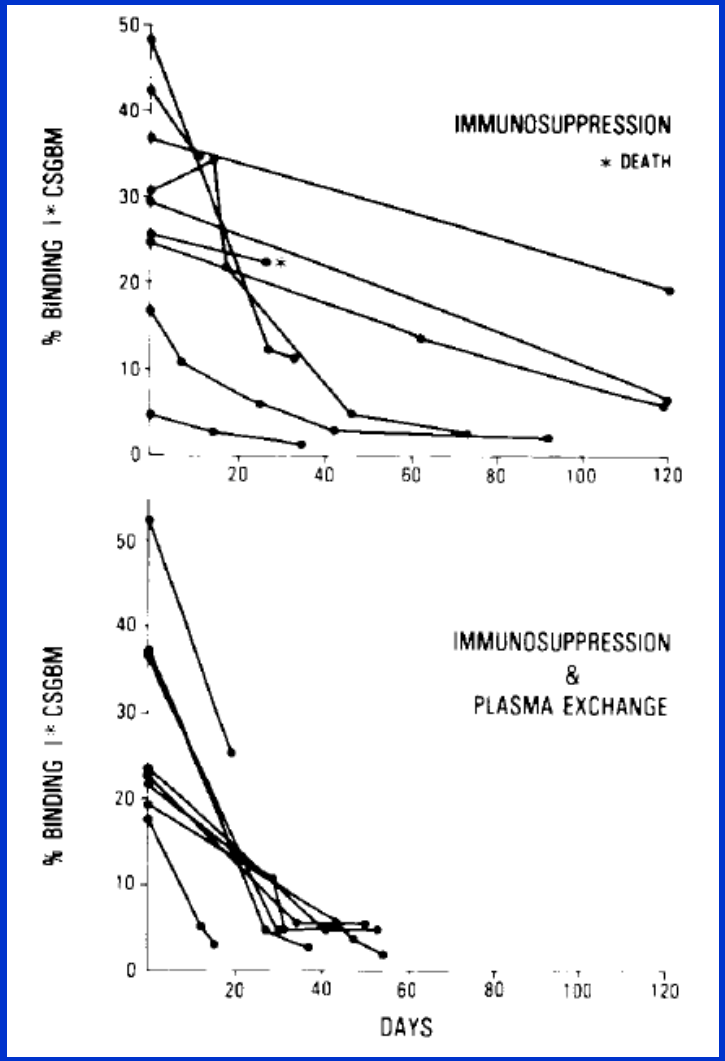
Randomized Trial of Immunosuppression ± Plasma Exchange for Anti-GBM Disease

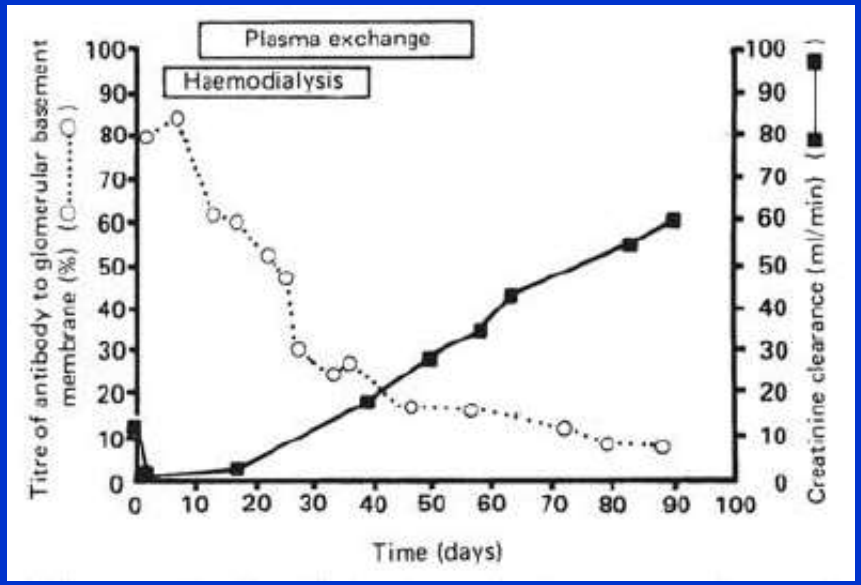
- 5 year randomized prospective study
- Immunosuppression ± TPE
- Randomization scheme
  - Group I: pred/cyc
  - Group II: pred/cyc + TPE (4 L Q 3 d)
- Almost all patients with >50% crescents on presentation required HD on completion of study treatment
- Anti-GBM antibody disappearance faster in TPE group than in immunosuppression group ($p < 0.05$)



Johnson JP et al. Medicine 1985;64:219-227

Reversal of Renal Failure with Immunosuppression and Plasma Exchange in Dialysis-Dependent Anti-GBM Disease

- 35 y/o woman with fatigue, nausea, hematuria, oliguria x 1 month
- Cr 5.05 mg/dL (435 µmol/L) and CrCL 12 mL/min on presentation
- Cr 8.29 mg/dL (715 µmol/L) and CrCl 2 mL/min 2 days later
- Florid necrotising crescentic glomerulonephritis with anti-GBM
- Hemodialysis-dependent x 4 weeks
- Treatment regimen
  - Cyc 3 mg/kg/d, pred 60 mg/d x 8 weeks
  - TPE (4 L) daily x 6 weeks
- Cr improved to 1.62 mg/dL, CrCl to 60 mL/min



Maxwell AP et al. BMJ 1988;297:333-334

ASFA Recommendations Regarding Plasma Exchange for Anti-GBM-Mediated RPGN

ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE (GOODPASTURE'S SYNDROME)				
Incidence: 1/1000,000/yr	**Indication**	**Procedure**	**Recommendation**	**Category**
	Dialysis dependence[a], no DAH	TPE	Grade 2B	III
	DAH	TPE	Grade 1C	I
	Dialysis independence	TPE	Grade 1B	I
No. of reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	1(17)	0	19 (468)	21

[a]At presentation, defined as Cr > 6 mg/dL. DAH=diffuse alveolar hemorrhage

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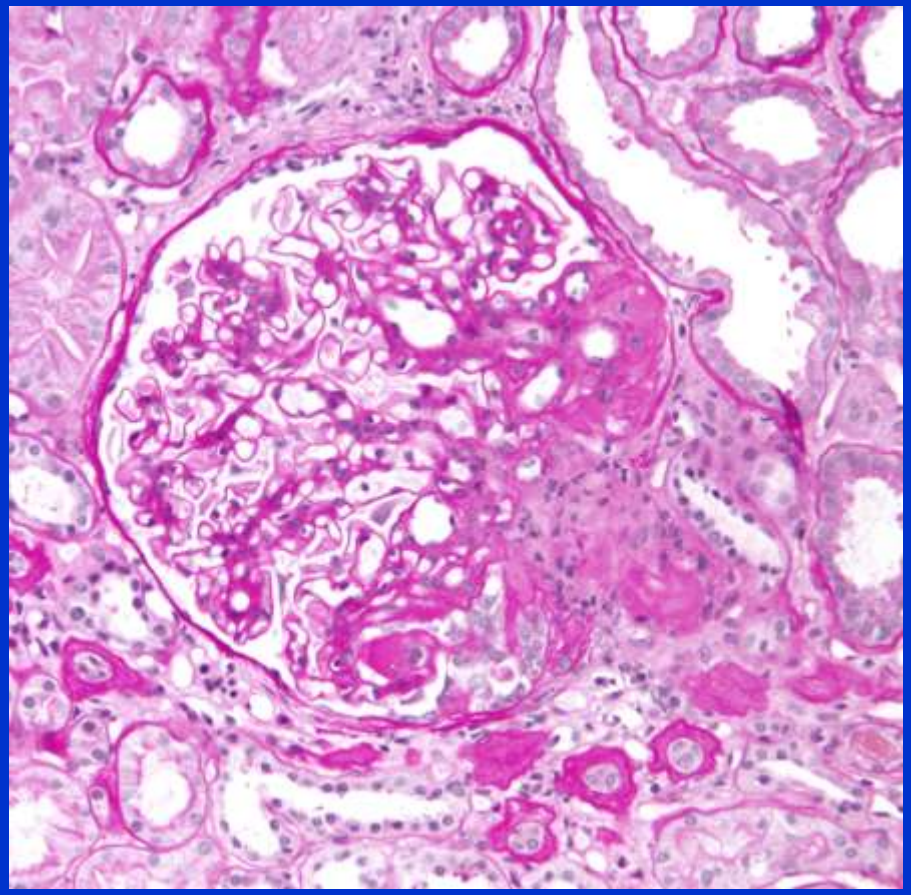
Focal Segmental Glomerulosclerosis

- Focal areas of sclerosis adjacent to normal areas of glomerulus
- Podocytopathy
- Disease associations
  - Podocyte gene mutations
    - NPHS1 (nephrin)
    - NPHS2 (podocin)
  - HIV, parvovirus B19
  - Heroin, IFN, pamidronate
  - Cancer, ↑BP, ageing
- 80% idiopathic (1° FSGS)
  - 40% of 1° nephrotic syndrome
  - ~7 per 1 million adults worldwide



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Focal Segmental Glomerulosclerosis

- 30-40% recurrence post-transplant (hours to years)
  - 50% graft loss within 2 years
  - Higher risk if idiopathic, age <20, living donor, prior recurrence post tp
  - Up to 80% recurrence in subsequent graft
- Circulating permeability factor?
  - Recurrences in renal allografts
  - Disease transferable to animals with patient plasma
  - 30-50 kDa protein sensitive to heat, proteolysis, $[NH_4]_2SO_4$
  - suPAR? CLC-1? Anti-CD40?
- Treatment: controversial?
  - Corticosteroids, cytotoxic drugs, cyclosporine, rituximab, ACE inhibitors
  - Apheresis approach to circulating permeability factor?

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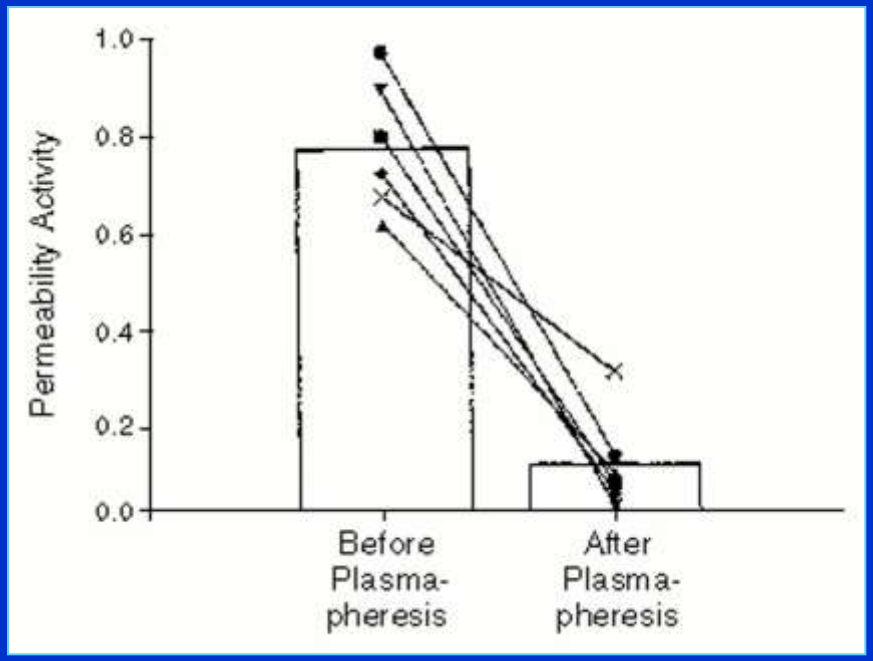
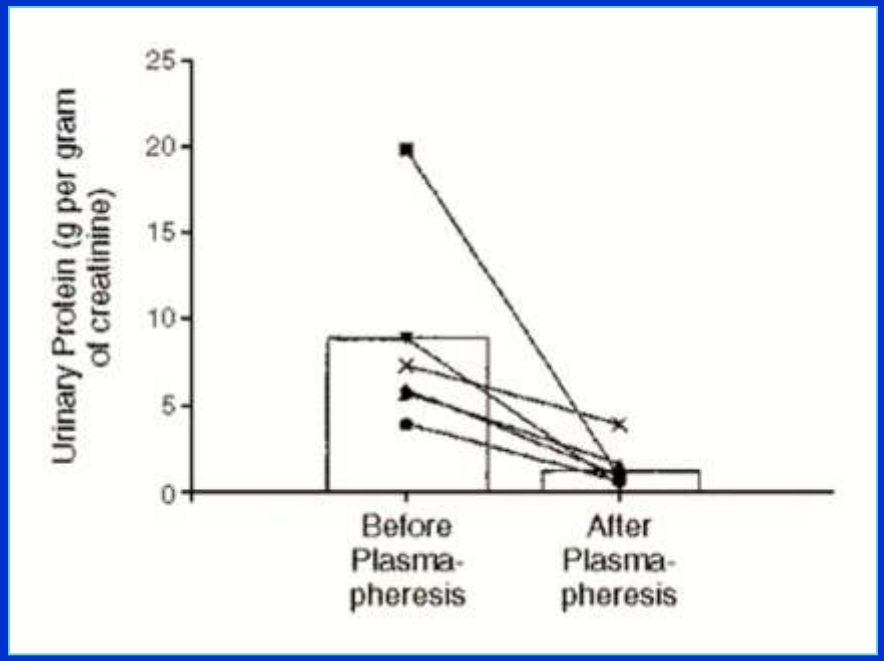
Permeability Factor and Proteinuria in Focal Segmental Glomerulosclerosis





from Savin VJ et al. N Engl J Med 1996;334:878-83

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ASFA Recommendations Regarding Plasma Exchange for FSGS

FOCAL SEGMENTAL GLOMERULOSCLEROSIS				
Incidence: 7/1000,000/	**Indication**	**Procedure**	**Recommendation**	**Category**
	Recurrent in transplanted kidney	TPE	Grade IB	I
	Steroid resistant in native kidney	LDL Apheresis	Grade 1C	III
No. of reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Recurrent in transplanted kidney	0	3 (48)	49 (224)	15 (17)
Steroid resistant in native kidney	0	0	1 (11)	4(4)

Schwartz J et al. J Clinical Apheresis 2016;31:163-338

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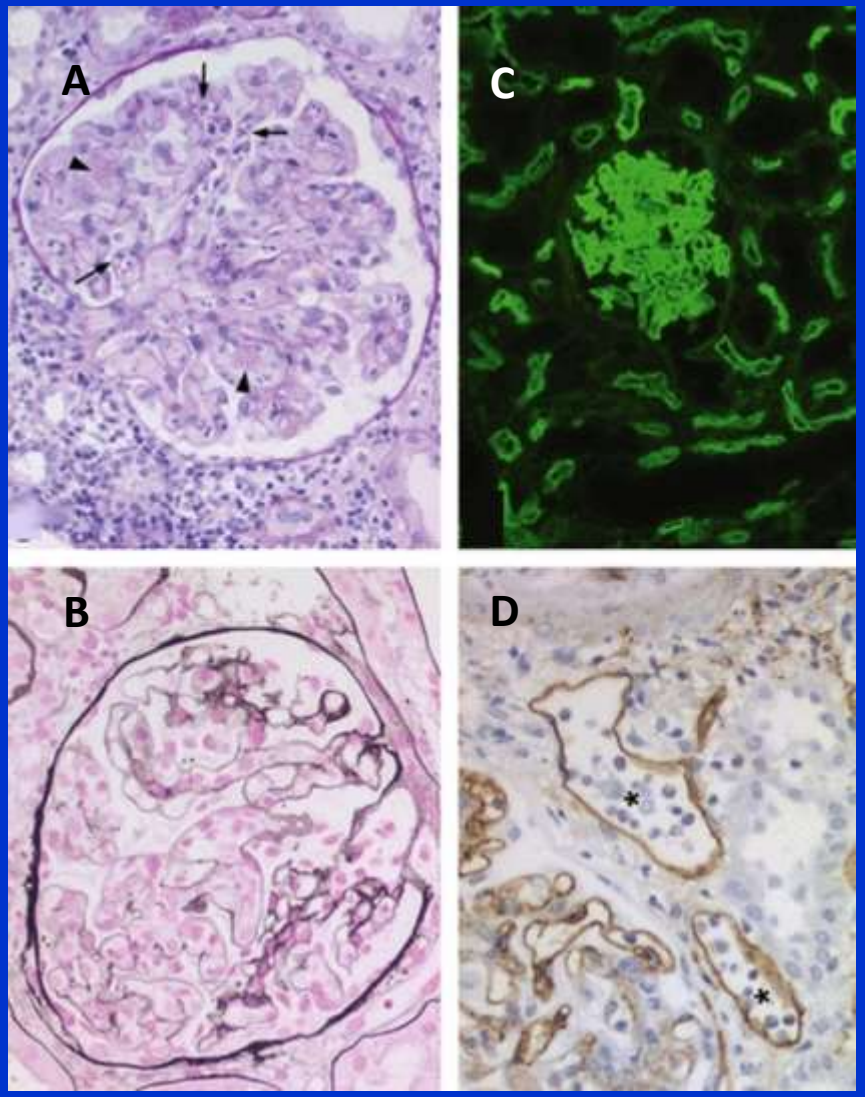
Antibody-Mediated Renal Allograft Rejection

- B-cell mediated humoral rejection
- 20-30% allograft loss at 1 year if unsuccessfully treated
- Complement fixing antibodies against donor HLA determinants (DSA)
- Days to years post-transplant
- Diagnosis includes
  - Detectable DSA
  - Deposition of C4d in peritublar capillaries and other typical histological features
  - Allograft dysfunction
    - Declining GFR
    - Rising proteinuria



Adapted from Fehr T, Gaspert A. Transplant International 2012;25:623-632

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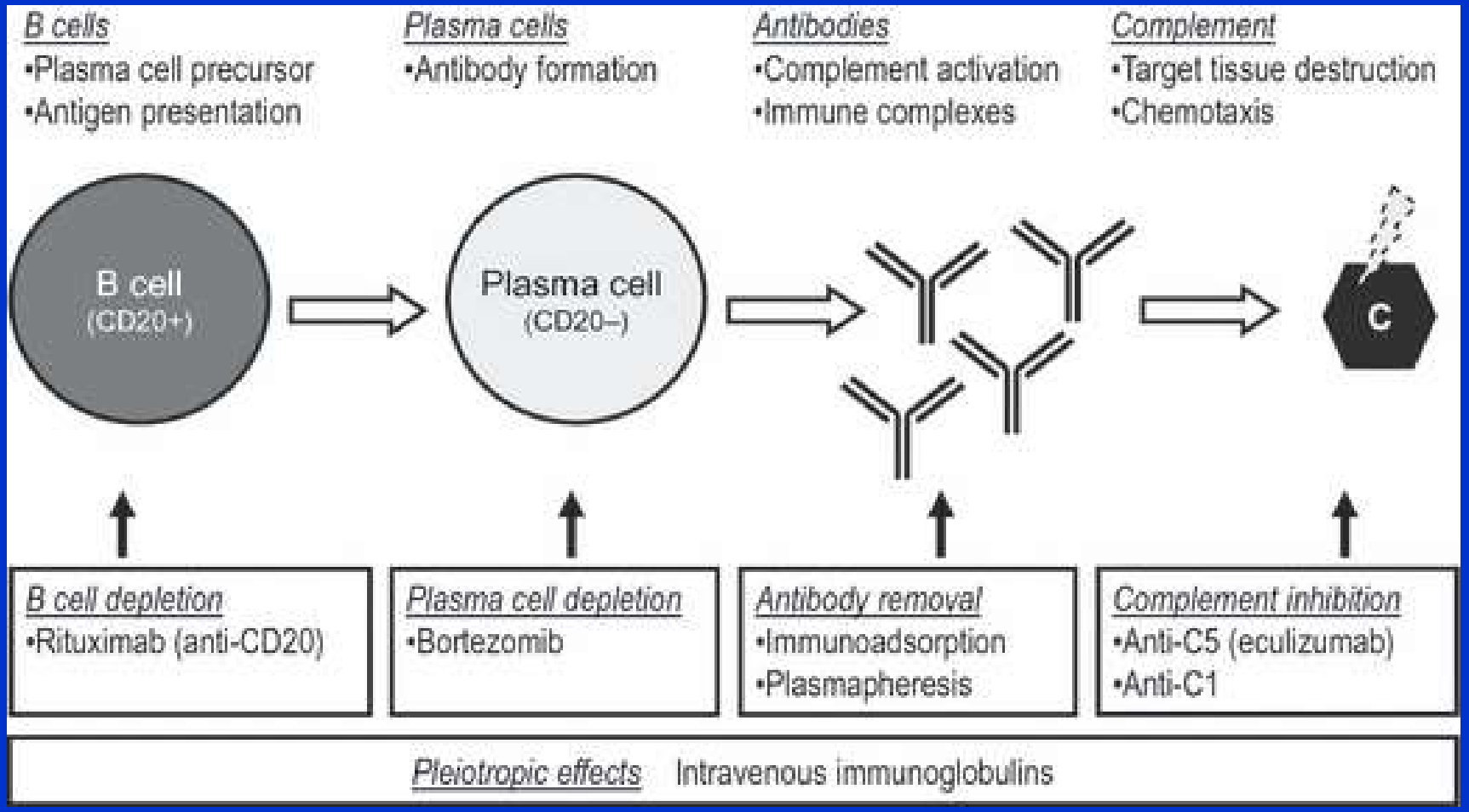
Treatment of Antibody-Mediated Rejection: Opposing the B-Cell Immune Response



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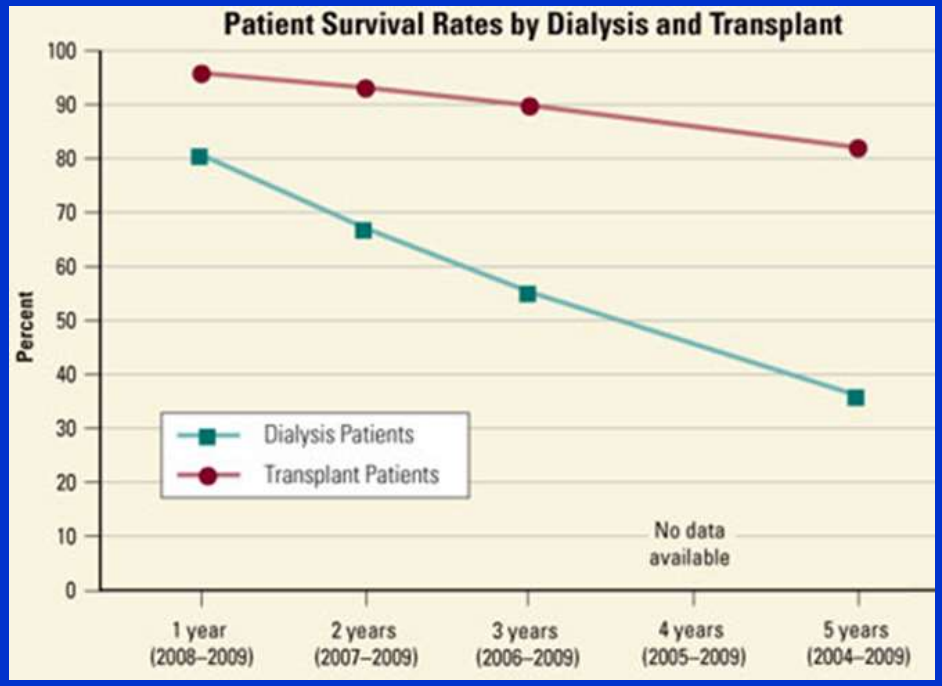
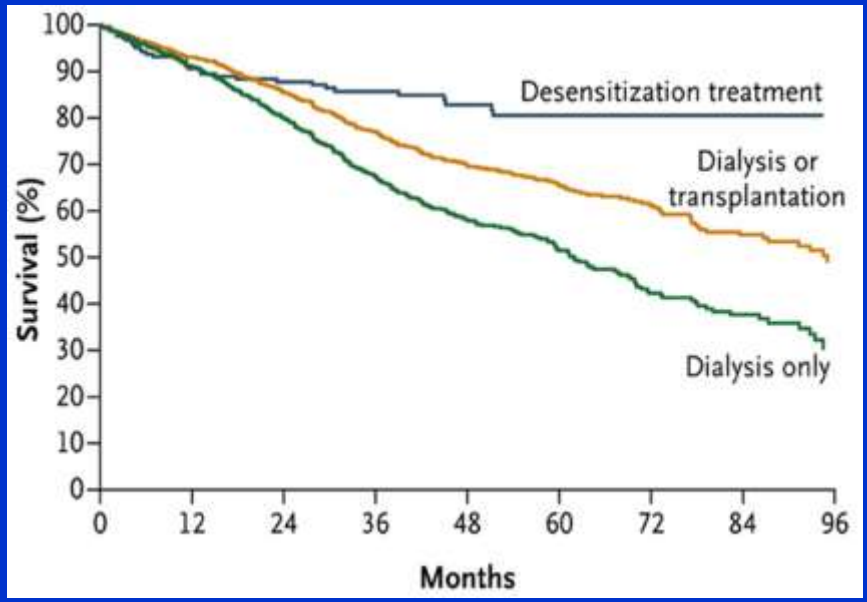


- Five-year survival of patients with ESRD
  - 85.5% if transplanted
  - 35.8% if remain on hemodialysis
  - 5-year graft survival rates are 66-74%.
- 99,344 Americans on wait list for kidney
- 12,508 kidney transplants as of 23 Sept 2016
- Average wait time 4-5 years depending on PRA

Source: NIDDK, UNOS

- Patients with HLA incompatibility to living donor
  - + CDC or FC crossmatch
  - DSA detectable by Luminex assay
- Desensitization protocol to permit transplant
  - Plasma exchange
  - IVIG (or CMV-Ig)
  - Immunosuppression
- 80.6% patient survival at 5 and 8 years

Source: Montgomery, RA et al. NEJM 2011;165:318-26



ASFA Recommendations Regarding Plasma Exchange for Renal Allograft AMR

RENAL TRANSPLANTATION, ABO COMPATIBLE

Incidence: AMR: 10% renal transplant recipients; 40% renal transplant recipients who underwent desensitization; 30% of waiting list patients	**Indication**	**Procedure**	**Recommendation**	**Category**
	AMR	TPE/IA	Grade 1B	I
	Desensitization, LD	TPE/IA	Grade 1B	I
	Desensitization, DD	TPE/IA	Grade 2C	III

No. of reported patients: >300	**RCT**	**CT**	**CS**	**CR**
AMR	3 (61)	8 (342)	37 (727)	13 (14)
Desensitization	0	5 (441)	29 (466)	11 (11)
High PRA	0	0	1 (20)	0

AMR = antibody-mediated rejection; DD = deceased donor; HLA = human leukocyte antigen; LD = living donor; PRA = panel reactive antibodies

Schwartz J et al. J Clinical Apheresis 2016;31:163-338

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When Both Hemodialysis and Apheresis are Indicated, Perform Them in Tandem

- Enhanced convenience for the patient
  - Minimize time spent in treatment
  - Minimize visits to outpatient treatment center
- Venous access issues
  - Hemodialysis requires venous access device
  - Tandem treatment would minimize use of device
    - ↓ risk of infection of venous access device
    - ↓ risk of failure of venous access device
- Does tandem treatment compromise the efficiency of hemodialysis?

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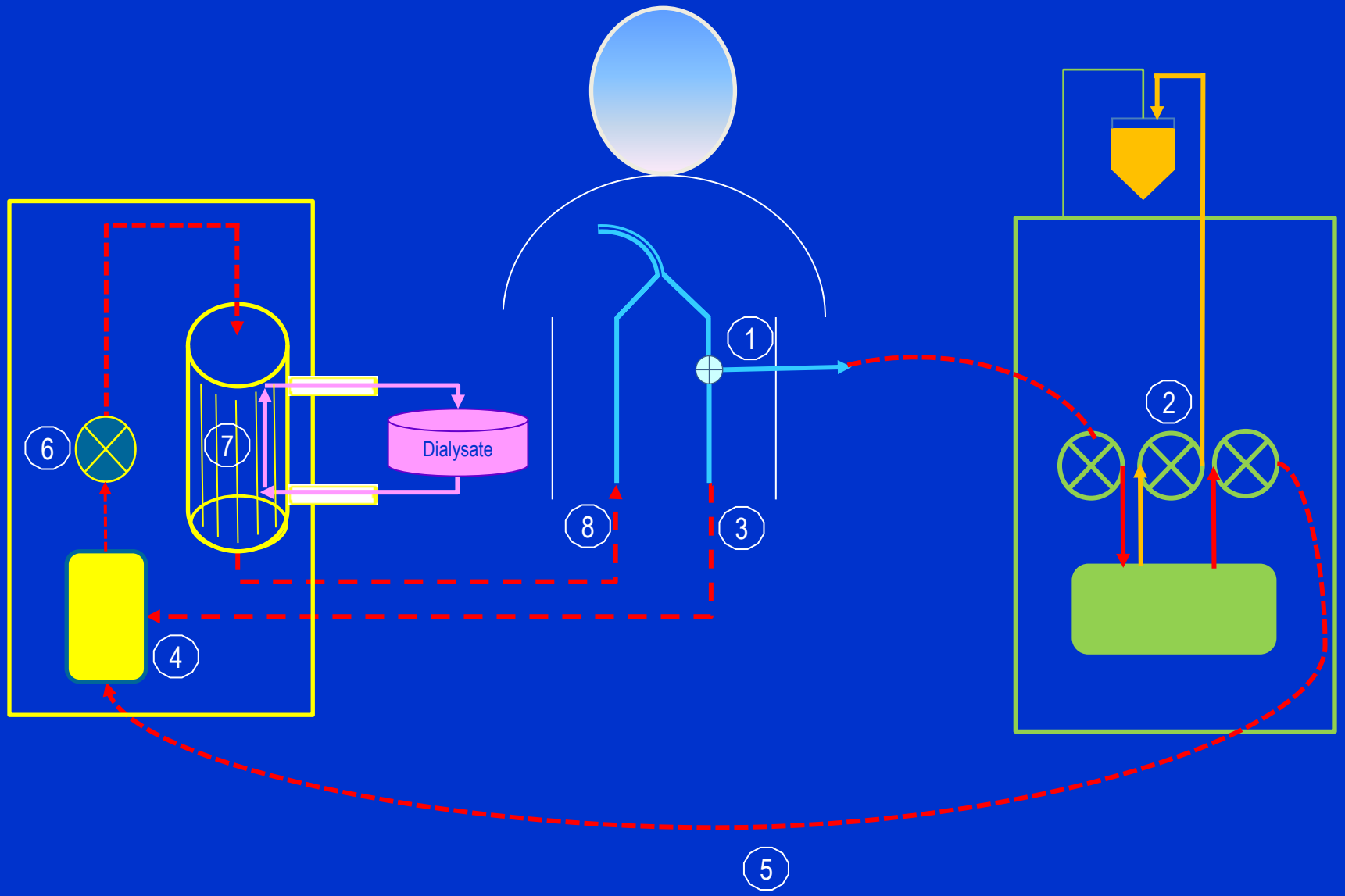
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2
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Dialysate

Tandem Hemodialysis/Plasma Exchange without Supplemental Calcium

Patient Information		Plasma Volume (mL)	Plasma Ionized Calcium[a] (mg/dL)			Urea Reduction Ratio[b] (%)
			Start	Mid	End	
Patient #1	51 y/o ♂ with recurrent focal segmental glomerular sclerosis after second renal transplant.	6735	5.3		5.0	75.3
Patient #2	63 y/o ♀ with anti-glomerular basement membrane disease.	3677 3786 3687	4.6 4.6 4.8	4.4 4.4 4.5	4.4 4.2 4.2	67.8 67.1 61.5
Patient #3	53 y/o ♂ with AMR 1 month after transplant for hypertensive renal disease.	3597 3509	4.4 4.5	4.2 4.6	4.1 4.3	64 84.6
			P = 0.024[c]			

[a]Patient plasma ionized calcium just prior to starting plasma exchange (Start), at the midpoint of plasma exchange (Mid) and at the end of plasma exchange (End) in each tandem procedure. Reference range = 4.6–5.3 mg/dL.

[b]$URR = 100 \times \frac{[BUN]pre - [BUN]post}{[BUN]pre}$

[c]Friedman Repeated Measures ANOVA on Ranks.

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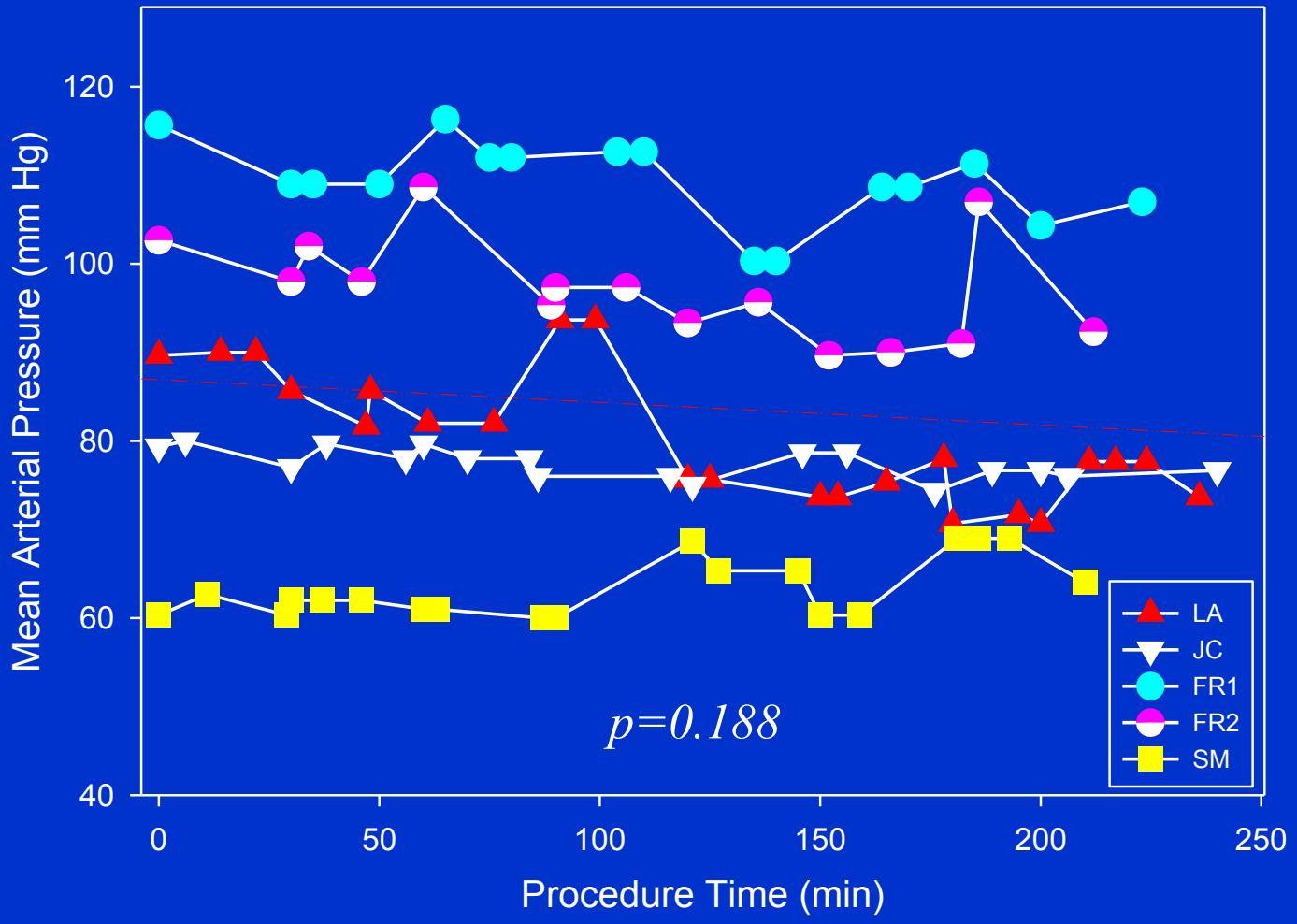
Mean Arterial Pressure Remains Stable During Tandem HD/HPC Collection



Conclusions

- Certain rapidly progressing renal disorders may require a period of renal replacement therapy
- Apheresis may be also be required in management of these disorders
- These extracorporeal therapies can be safely performed in tandem for patient safety and convenience
- Neither the efficacy of hemodialysis nor the outcome of apheresis are compromised by tandem procedures
- Plasma ionized calcium is maintained if the blood return from the apheresis circuit is routed through the dialyzer

Спасибо!