

**Special Considerations During Apheresis in  
Patients with Renal Disease**  
2011 Annual Meeting ASFA  
Nephrology Division  
University of Virginia



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# Disclosure

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- Conference Unrestricted educational grants: UVA TAA
- Slides
  - Dr Danny Hu
  - Dr Torloni
  - Dr Timothy Bunchman

# Outline

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- Drug Removal
- Fluid Shifts
- Concomitant need for Renal Replacement Therapy (Hemodialysis) Requirement
- Depletion Coagulopathy

# Extracorporeal Therapies RPA 2001

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- Hemodialysis
- Hemofiltration
- Hemodiafiltration
- Continuous renal replacement therapies
- Hemoperfusion
- **Apheresis (TPE)**
- Immunoabsorption
- Liver dialysis

# Therapeutic Plasma Exchange

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## Logical reasons

- High molecular weight  $\geq 15000$  Da
- Intravascular distribution (or freely moves b/n compartments)  $V_d < 0.3$
- Long half life
- Low turnover (slow rate of formation)
- Toxic substance

# ASFA Guidelines

Every seven years

## Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Apheresis Applications Committee of the American Society for Apheresis

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The American Society for Apheresis (ASFA) Apheresis Applications Committee is charged with a review and categorization of indications for therapeutic apheresis. This elaborate process had been undertaken every 7 years resulting in three prior publications in 1986, 1993, and 2000 of "The ASFA Special Issues." This article is the integral part of the Fourth ASFA Special Issue. The Fourth ASFA Special Issue is significantly modified in comparison to the previous editions. A new concept of a fact sheet has been introduced. The fact sheet succinctly summarizes the evidence for the use of therapeutic apheresis. A detailed description of the fact sheet is provided.

Journal of Clinical Apheresis 22:106–175 (2007) and by the ASFA. Category I therapeutic apheresis has been assigned category I and category IV are discussed in

apheresis; categories;

## Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Apheresis Applications Committee of the American Society for Apheresis

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ally to this work.

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It is Wiley InterScience

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# Indications for Therapeutic Apheresis: ASFA & AABB Categories I -IV

I: Standard & acceptable  
1<sup>st</sup> line therapy or  
valuable adjunctive  
+randomized cont. trials

II: Generally accepted  
2<sup>nd</sup> line therapy or Case  
reports + small studies

III: Insufficient evidence  
to establish efficacy Only  
anecdotal reports or  
conflicting

IV: controlled trials show  
no efficacy  
(IRB approved research  
protocols)

# Outline: TPE- Renal Indications

Disease/Condition	ASFA Category
Immune Complex related Glomerulonephritis	
Anti-glomerular basement membrane antibody disease	I
SLE	IV
Pauci-Immune Glomerulonephritis	
ANCA + Rapidly progressive glomerulonephritis (Crescentic GN)	II
IgA Nephropathy & Henoch Schonlein Purpura	
Cryoglobulinemia	
Hemolytic uremic syndrome	III
Thrombotic Thrombocytopenic Purpura	I
Multiple Myeloma associated Acute Kidney Injury	II
Renal transplanation	
Rejection	IV (III?)
Presensitization	III
Recurrent focal glomerulosclerosis	III

*Couser, WG RPGN: Pathogenic Mechanisms and Therapy. AJKD 1988;6:449-464*

- separates crescentic GN based on suspected immune mediated mechanisms & Rx modalities
- Type I Anti-GBM 20%
- Type II Immune Complex 40%
  - Post infectious
  - IgA/HSP
  - MPGN
  - Lupus
- Type III Pauci-immune 40%
  - PAN
  - Wegener's
  - Hypersensitivity
  - Idiopathic

# Anti-Glomerular Basement-Antibody Disease And Other Forms of Rapidly Progressive Glomerulonephritis

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- Untreated RPGN leads to ESRD
- Different diseases can result in RPGN
- Three major subgroups:
  - Goodpasture's syndrome (GPS)
  - Wegener's granulomatosis (WG) or Microscopic polyarteritis (mPA)
  - (pauci) or no tissue immune deposits and circulating antineutrophil cytoplasmic autoantibodies (ANCA)

# Anti-Glomerular Basement Membrane Antibody Disease (Goodpasture's)

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- **Autoantibody to the c terminus of  $\alpha 3$  chain of Type IV collagen**
  - **Restricted to glomerular and alveolar basement membrane**
- **Results in complement mediated damage to these membranes producing:**
  - **Glomerulonephritis**
  - **Alveolar hemorrhage**
- **Role of TPE**
  - **More rapid decline in anti-GBM Ab titers**
  - **Lower serum creatinine levels**
  - **Fewer patients progressing to renal failure**
  - **Decreased mortality (40% versus 85%)**

## ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE (GOODPASTURE'S SYNDROME)

<b>Disease Group:</b> Renal					<b>Procedure</b>	<b>Category</b>
<b>Incidence:</b> 1 per 100,000/year					TPE	I
<b># of reported patients*:</b> >300						
<b>RCT</b>	<b>CT</b>	<b>CS</b>	<b>CR</b>		<b>Strength of evidence</b>	
1 (17)	0	17 (430)	17		Type I	

- **Anti-glomerular Basement Membrane Antibody Mediated Disease**
  - Single CT (Johnson et al. Medicine 1985), case studies
  - TPE useful in rapid lowering of Anti-GBM Ab
  - Lower post-treatment serum creatinine, decreased incidence of ESRD
    - Should use immunosuppression
    - Can follow Ab levels for end point

# Therapy of anti-GBM Ab: analysis of prognostic significance of clinical, pathologic & Rx factors

Johnson ... Medicine (Baltimore). 1985 Jul;64(4):219-27

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- compared immunosuppression alone to immunosuppression + TPE
- 17 patients (9 + 8)
- clinical course + rate of disappearance of Ab
- Rate of disappearance of anti-GBM Ab more rapid in TPE patients
- Cr in TPE grp at end of Rx was half that of other
- ASFA Category 1

# Case presentation

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- JK is a 65 year-old Caucasian man with hx of interstitial lung disease, asbestos exposure. He presented in July 2002 with hemoptysis, acute renal failure, P-ANCA 1:80
- Kidney biopsy showed necrotizing vasculitis, consistent with pauci-immune, ANCA-associated vasculitis.

# Case presentation

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- Patient received oral cyclophosphamide 50mg per day for 3 days, pulse dose 1gm IV methylprednisolone for 3 days.
- His pulmonary symptoms resolved, renal failure improved, discharged on oral cyclophosphamide 75mg qd, then up to 100mg qd and prednisone taper. Creatinine on discharge 1.2 mg/dL

# Case presentation

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- One year later, he had no evidence of relapse, oral cyclophosphamide was gradually tapered over 3 months.
- 2 months after cyclophosphamide discontinued, he developed rapid weight loss, weakness, fatigue, cough and respiratory distress, admitted to OSH.

# Case presentation

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- ESR 96, p-ANCA 1:80. CXR and CT showed no clear evidence for infiltrate. Urine was bland, no protein, creatinine 1.2.
- He was empirically treated with IV antibiotics and 3 days of oral cyclophosphamide 100mg daily.
- His respiratory symptoms improved and was discharged.

# Case presentation

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- Shortly after discharge, Oral cyclophosphamide 100mg qd and 1mg/kg prednisone were restarted. His malaise, weakness, cough did not improve. Dyspnea is somewhat better.
- He subsequently developed epistaxis. Endoscopic exam by ENT did not reveal any suspicious lesions, biopsy was not performed.
- 3 weeks later he developed leukopenia, oral cyclophosphamide was discontinued.

# ANCA+ RPGN “Crescentic” GN (pauci-immune non anti GBM)

- Case reports (favorable)
- CT-no favorable generalized benefit (Cole et al. 1992, AJKD) (TPE + standard immn)
- Subset analysis revealed that TPE was beneficial for patients with severe disease or those requiring dialysis (Kaplan Ther Apheresis, 1997)

## ANCA-ASSOCIATED RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (WEGENER'S GRANULOMATOSIS)

Disease Group: Renal					Procedure	Category
Incidence: 8.5 per 100,000/year					TPE	II
# of reported patients*: >300						
RCT	CT	CS	CR	Strength of evidence		
8 (296)	1 (26)	21 (294)	NA	Type I		

De Groot K et al. Value of pulse cyclophosphamide in ANCA-Associated Vasculitis: meta-analysis and critical review. *Nephrol Dial Transplant* 2001;16;2018-2027.

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- A meta-analysis summarized the results from 3 RCT's comparing pulse IV cyclophosphamide and continuous therapy.
  - Studies were too small to make conclusion about efficacy
    - show pulse therapy were less likely to fail to induce remission.
    - showed adverse effects were more frequent with daily oral therapy.
    - No difference in ESRD or mortality rates.

# European Vasculitis Study Group (EUVAS)

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- Created in early 1990's to investigate diagnostic role of ANCA, standardization of ANCA testing, assessment and classification of all AASV.
- Despite different clinical and pathological characteristics, all ANCA-associated vasculitides were studied together.
- New classification based on disease severity.
- Goal was to facilitate therapeutic clinical trials.

**Table 3. Prospective therapeutic trials coordinated by EUVAS**

Trials	Design	Patient subgroup	Test limb	Control limb	End-point
First wave					
NORAM	RCT	Early systemic	MTX + PRED	CYC + PRED	Remission
CYCAZAREM	RCT	Generalized	3 months CYC, then AZA	12 months CYC	Relapse
MEPEX	RCT	Severe renal	Plasma exchange	Intravenous methylprednisolone	Renal survival
SOLUTION	Single limb	Refractory	Antithymocyte globulin	-	Remission
Second wave					
CYCLOPS	RCT	Generalized	"Plus" CYC + PRED	Oral CYC + PRED	Disease-free period
MUPIBAC	RCT	WG, stable remission	Nasal mupirocin	Placebo	Relapse
REMAIN	RCT	Renal vasculitis, stable remission	AZA + PRED for 4 years	Stop treatment at 2 years	Relapse

AZA, azathioprine; CYC, cyclophosphamide; MTX, methotrexate; PRED, prednisolone; RCT, randomized controlled trial; WG, Wegener granulomatosis.

Jayne D. Update on the European Vasculitis Study Group trials  
 Current Opinion in Rheumatology. 2001, 13:48-55

## Renal survival in prospective trials in patients with renal vasculitis.

### Treatment with or without plasma exchange

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<u>Author</u>	<u>Year</u>	<u>n</u>	<u>PE</u>	<u>no PE</u>
Glockner	1988	12	5/8	3/4
Pusey	1991	19	10/11	3/8
Cole	1992	11	3/4	2/7
Guillevin	1997	8	4/6	1/2
Haubitz	1998	22	6/12	2/10
Jayne	2002	26	9/16	4/10
Total		88	9/16 (67%)*	20/50 (40%)

\*p<0.05

# MEPEX

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Randomized trial of plasma exchange versus methyl prednisolone as additional therapy for severe ANCA + glomerulonephritis

*Jayne, Mayo Clin Proc 1997*

Chances of Renal Recovery for Dialysis-Dependent ANCA-Associated Glomerulonephritis

J. Am. Soc. Nephrol., Jul 2007; 18: 2189 - 2197.

**EUVAS**

*de Lind van Wijngaarden*

# MEPEX - Design

**ANCA+ RPGN with creatinine >6mg/dL**

**Entry and randomization  
Standard drug treatment**

**+ plasma exchange  
60 ml/kg x 7  
(max. PE volume 4L)**

**+ i.v. methyl prednisolone  
15 mg/kg x 3  
(max. pulse dose 1g)**

**Dialysis-independent?**

# **MEPEX** – Patients recruited

**151 entered 1995-2001**

**13 withdrawn –  
other diagnoses**

**138 studied**

**69 plasma exchange**

**69 methyl prednisolone**

**Data on 134**

**From 9 European countries, mean age 64,  
diagnoses MP > WG, 2/3 dialysis requiring / oliguric**

# Significant differences at 3 months

- In surviving patients

	Dialysis- independent	On dialysis	
PLEX	80%	20%	p=0.018
iv MP	59%	41%	

- In the patient group as a whole

	Alive and dialysis-independent	On dialysis or dead	
PLEX	66%	34%	p=0.036
iv MP	48%	52%	

# **Plasmapheresis Therapy for Diffuse Alveolar Hemorrhage in Patients with Small-Vessel Vasculitis**

Philip J. Klemmer, MD, W. Chalermkulrat, MD, Michael S. Reif, MD, Susan L. Hogan, PhD,

David C. Henke, MD, and Ronald J. Falk, MD

AJKD 2003, 42 (6) 1149-1153

## **Plasmapheresis Therapy for Diffuse Alveolar Hemorrhage in Patients with Small-Vessel Vasculitis**

**AJKD 2003, 42 (6) 1149-1153**

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- Goal: study the role of PLEX in treating diffuse alveolar hemorrhage (DAH) associated with AASV.
- Retrospective: all patients treated at UNC hospital with PLEX for their first episode of AASV with DAH from 1995 to 2001. N=20
- No patients had no linear IgG stain of GBM on renal biopsy, no detectable serum Anti-GBM antibodies.
- All except one patient were ANCA positive

# Plasmapheresis Therapy for Diffuse Alveolar Hemorrhage in Patients with Small-Vessel Vasculitis

AJKD 2003, 42 (6) 1149-1153

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- All patients received:
  - daily PLEX until DAH improved, qod PLEX until DAH resolved.
  - IV methylprednisolone 7mg/kg/day for 3 days.
  - All except 2 patients received IV cyclophosphamide 0.5gm/m<sup>2</sup>

# Results

- DAH resolved in 20/20 (100%) of patients
- Mean number of PLEX was 6.15 (4-9)
- One mortality from PE, occurred 16 days after resolution of DAH.
- 6/6 patients had normal renal function on admission, all 6 maintained normal renal function.
- 14 patients had renal on admission, 7/14 (50%) required HD. 7/14 (50%) did not require HD, had improved renal function at discharge.
  - 1/7 HD dependent patient came off HD after discharge.

# Conclusion

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- Patients presented with hemoptysis and pulmonary Infiltrate caused by DAH related to pauci-immune small vessel vasculitis benefit from PLEX and aggressive immunosuppression.
- No control. Patients with AASV related DAH that did not get PLEX all presented before 1995. These patients were younger, less azotemic, less anemic than the study cohort. Therefore were not included.

# Conclusion

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- ANCA vasculitis is a disease that presents with varying severity. No standard treatment for all patients.
  - For induction therapy, IV cyclophosphamide may be an alternative for patients in whom reducing exposure to drug is important.
    - meta-analysis. Nephrol Dial Transplant 2001;16;2018-2027
  - For long-term maintenance therapy, azathioprine may an effective alternative to cyclophosphamide.
    - NEJM 2003;349;36-44

# Conclusion

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- Role of plasma exchange
  - For severe renal disease, plasma exchange may increase dialysis free survival.
    - MEPEX trial
- From UVA data
  - Call for more collection of patient data, follow up information to make meaningful observations.

# Multiple Myeloma associated AKI

- Cast Nephropathy from light chain toxicity
- TPE + anti-neoplastic Rx desired
- Evidence: CT (n=29) (Zucchelli et al. KI, 1988)- strong support
- Recommend- 5 consecutive daily TPE treatments-early in course

## MYELOMA WITH ACUTE RENAL FAILURE

**Disease Group:** Hematologic; renal

**Incidence:** 1 per 100,000/year

**Procedure**

TPE

**Category**

III

**# of reported patients\*:** 100-300

RCT	CT	CS	CR	Strength of evidence
5 (182)	0	6 (105)	NA	Type I

# Multiple Myeloma associated AKI issues

- other causes of renal failure
- advanced renal failure: results not as good better before onset of oligoanuria (Johnson et al. Arch Intern med, 1990)

## MYELOMA WITH ACUTE RENAL FAILURE

Disease Group: Hematologic; renal

Incidence: 1 per 100,000/year

Procedure

TPE

Category

III

# of reported patients\*: 100-300

RCT

5 (182)

CT

0

CS

6 (105)

CR

NA

Strength of evidence

Type I

# IgA Nephropathy & Henoch Schonlein Purpura

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- ~ 10% of IgA presents as RPGN
- TPE rationale--removal of circulating IgA
- Evidence No CTs, case reports Treatment +/- other immunosuppressive agents
- Recommend:
  - Useful in RPGN presentation (Coppo et al. Plasma Ther Transfus Technol, 1985)
  - Likely minimal role in chronic disease

# Henoch Schonlein Purpura

(Hattori et al, Am J Kid Dis, 1999, 33:427-33)

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- 9 children with RPGN with HSP Rx with PP without immunosuppression
  - Proteinuria ~ 4.9 gms/m<sup>2</sup>
  - GFR ~ 46 mls/min/1.73 m<sup>2</sup>
- 6/9 complete recovery
- 2/9 rebound with proteinuria with progression to ESRD

# Cryoglobulinemia

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- Renal Manifestations- glomerular capillary deposition of cryoglobulin or immune complex disease with complement activation and vasculitis
- Evidence: No CTs, case reports and uncontrolled trials
- Consensus: Useful adjunct in treatment of severe disease (progressive RF, coalescing purpura, advanced neuropathy) (D'Amico et al. KI, 1989)

# Hemolytic Uremic Syndrome

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- Difficult at times to differentiate between TTP and HUS (TTP tends to have more neurological manifestations while renal failure predominates in HUS)
- May be HUS associated with Shiga toxin, congenital (factor H deficiency) or caused by inciting drugs-cyclosporine, tacrolimus, quinine, Oral Contraceptives, or other diseases like SLE and carcinoma)

# Hemolytic Uremic Syndrome

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- Evidence- limited-works in TTP? Why not HUS- adult outcome usually worse
  - SUBGROUPS:
    - Recurrent HUS in renal Transplantation- (Agarwal et al. JASN, 1995) Reviewed case reports- suggest TPE effective but endpoint unclear (ie continue until renal function returns)
    - HUS in Children- No RCTs, case reports suggest benefit of limiting renal damage in children with no diarrheal prodrome, neurologic manifestations or those >5 yrs of age (Gianviti et al. AJKD, 1993)
    - Recommend: Minimal data to support use except in subgroups above

# Systemic Lupus Erythematosus

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- Evidence- early case reports suggested some benefit but CTs have not supported TPE when added to standard Immunosuppression (Lewis et al., NEJM, 1992)
- May be some role in pregnancy when use of cytotoxic agents are not desired
- ? Treatment refractory disease
- Recommend: no evidence to support use

# Focal Segmental Glomerulosclerosis

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- Group: Recurrence Post-transplant (15-55% recurrence)- thought to be due to a circulating factor not yet specifically isolated
- Evidence - strong no CTs, case reports with clinical and proteinuria improvement (Artero et al., AJKD, 1994)
- Recommend: Daily therapy (early) for up to 2 weeks

# Focal Segmental Glomerulosclerosis

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- Group: Native FSGS
  - Multiple etiologies, therefore need to evaluate carefully
- Evidence: equivocal- may offer benefit in treatment resistant forms of primary FSGS
- Recommend: Clinically based

# Panel Reactive Antibody Reduction

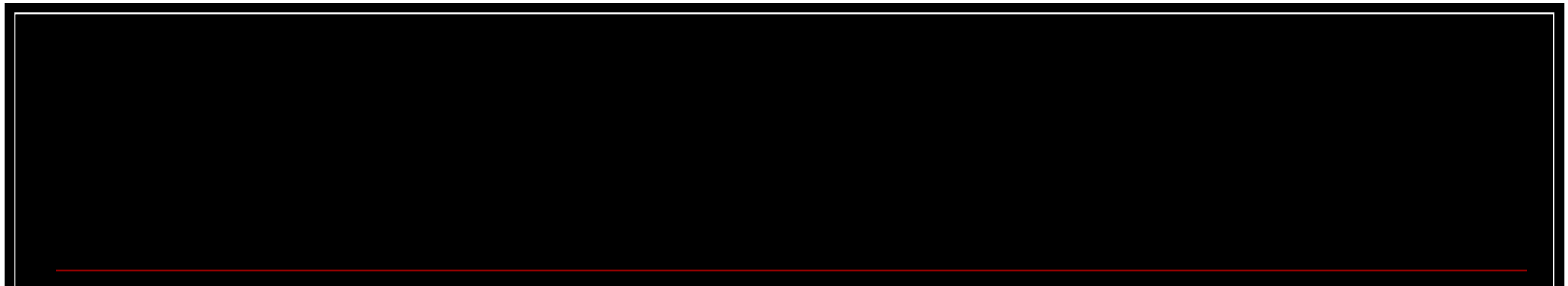
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- Transplant Candidates with high titers of cytotoxic antibodies- high rate of hyperacute rejection of transplanted grafts
- Other therapies also offered-ie monthly IVIG infusions-currently undergoing trials
- Evidence: used immunoabsorption column treatments- No CTs, some encouraging results in several case studies (Ross et al., Transplantation, 1993)
- Recommend: High consideration in those unable to receive renal transplants due to elevated PRA

# Acute Renal Vascular Rejection

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- Evidence: 2 controlled trials no significant benefit noted (Allen et al., Transplantation, 1983)
- Recommend: No supportive evidence for TPE in this treatment



**TABLE I. Indication Categories for Therapeutic Apheresis in Renal and Metabolic Diseases**

Disease	Procedure	Indication category
<b>Renal and metabolic diseases</b>		
Anti-glomerular basement membrane antibody disease	Plasma exchange	I
Rapidly progressive glomerulonephritis	Plasma exchange	II
Hemolytic uremic syndrome	Plasma exchange	III
<b>Renal transplanation</b>		
Rejection	Plasma exchange	IV
Presensitization	Plasma exchange	III
Recurrent focal glomerulosclerosis	Plasma exchange	III
Heart transplant rejection	Plasma exchange	III
	Photopheresis	III
Acute hepatic failure	Plasma exchange	III
Familial hypercholesterolemia	Selective adsorption	I
	Plasma exchange	II
Overdose/poisoning	Plasma exchange	III
Phytanic acid storage disease	Plasma exchange	I