Secondary Glomerular Disease, Vasculitis – Plasmapheresis Therapy

György Deák
Semmelweis University, Budapest
# Clinical approach to glomerulonephritis

<table>
<thead>
<tr>
<th>Clinical syndrome</th>
<th>Histology</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated hematuria</td>
<td><strong>Non-proliferative</strong></td>
<td>Primary</td>
</tr>
<tr>
<td>Isolated proteinuria</td>
<td>MCD, FSGS, MGN</td>
<td>Infection</td>
</tr>
<tr>
<td>Hematuria-proteinuria</td>
<td>DN, Amyloid, Alport</td>
<td>Tumor</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td><strong>Proliferative</strong></td>
<td>Autoimmune</td>
</tr>
<tr>
<td>Acute glomerulonephritis</td>
<td>Mesangial-</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Rapidly progressive GN</td>
<td>Focal-</td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td>Diffuse-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Membrano-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extracapillary-</td>
<td></td>
</tr>
</tbody>
</table>

- MCD: Minimal change disease
- FSGS: Focal segmental glomerulosclerosis
- MGN: Membranous glomerulonephritis
- DN: Diabetic nephropathy
- Amyloid: Amyloidosis
- Alport: Alport syndrome
- Mesangial: Mesangial proliferative
- Focal: Focal proliferative
- Diffuse: Diffuse proliferative
- Membrano: Membranous proliferative
- Extracapillary: Extracapillary proliferative
- Heavy metal: Heavy metal toxicity
Therapeutic plasma exchange (TPE)

- centrifugation-

- anticoagulant (citrate)
- plasma (waste)
- centrifuge

- replacement fluid
- crystalloid
- albumin
- fresh frozen plasma

- replacement fluid pump
- plasma pump
- blood pump
- anticoagulant pump

Diagram showing the separation of blood components using centrifugation and the processes involved in TPE.
Therapeutic plasma exchange (TPE) - membrane separation -
Immune adsorption (IA)

- **blood pump**
- **plasma pump**
- **membrane**
- **Protein A column to bind Ig-s**
## Evidence based indication categories for PEX


<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Disorders for which apheresis is accepted as first-line therapy either as a primary standalone treatment or in conjunction with other modes of treatment.</td>
</tr>
<tr>
<td>II.</td>
<td>Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.</td>
</tr>
<tr>
<td>III.</td>
<td>Optimum role of apheresis therapy is not established. Decision making should be individualized.</td>
</tr>
<tr>
<td>IV.</td>
<td>Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful.</td>
</tr>
</tbody>
</table>

Grading of recommendations

1: Strong recommendation
2: Weak recommendation

A: High quality evidence - RCTs without important limitations or overwhelming evidence from observational studies.

B: Moderate quality evidence - RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies.

C: Low quality evidence - Observational studies or case series

Guyatt G. Chest 2006;129:174
Rapidly progressive glomerulonephritis

Clinical features

• Dysmorphic hematuria, active urinary sediment
• Proteinuria - nephrotic in 1/3 of patients
• Hypertension
• Progressive loss of renal function - GFR halves over 3 months
• Histology: extracapillary proliferation - crescentic GN
Crescentic GN (RPGN)

I. Anti GBM antibodies (linear IF)
   • Goodpasture’s sy.,
   • Renal localized form

II. Immunecomplex-mediated GN (granular IF)
   • Primary GN: IgA GN, Membranoproliferative GN
   • Henoch Schönlein purpura
   • Autoimmune: SLE
   • Postinfectious

III. ANCA associated GN (no IF = pauci immune)
   • Wegener`s granulomatosis
   • Microscopic polyangiitis (MPA)
   • Churg Strauss sy
Goodpasture’s syndrome

Pathogenesis

Anti- GBM antibody (Antigene: IV. collagene α-3 chain NC1 domaine)
Binding to basal membrane - complement activation - inflammation

Clinical features

• Renal-pulmonary syndrome
• RPGN
• Shortness of breath, hemoptysis - diffuse alveolar haemorrhage (DAH)
  DAH associated with exposure to hydrocarbons, cocaine, marijuana, hard metal dust, fire smoke, cigarette smoking
• Association with HLA allele DR B1-1501
• Diagnosis: a-GBM antibody, ANCA (positive in 30%), renal biopsy
• The disease does not relapse
Goodpasture’s syndrome

Alveolar bleeding

Extracapillary proliferative GN

Linear IgG immunofluorescence
### Therapy of Goodpasture’s syndrome

- **Plasma exchange daily, 1-1.5 x PV x 7-14**

<table>
<thead>
<tr>
<th>Indication category</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Dialysis independence</td>
<td>I 1A</td>
</tr>
<tr>
<td>- Diffuse alveolar hemorrhage</td>
<td>I 1B</td>
</tr>
<tr>
<td>In case of DAH replace fresh frozen plasma</td>
<td></td>
</tr>
<tr>
<td>- Dialysis dependent, no DAH</td>
<td>IV 1A</td>
</tr>
</tbody>
</table>

- **Metylprednisone pulse x3, Prednisone 1 mg/kg x 6 months**

- **Cyclophosphamide 2-3 mg/kg x 2-3 months**

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Prognosis depends on initial renal function in Goodpasture’s syndrome.
Systemic vasculitis

- Capillary
- Henoch-Schönlein Purpura
- Cryoglobulinaema
- Wegener’s granulomatosis
- Microscopic polyangiitis
- Churg Strauss syndrome
- Polyarteritis nodosa and Kawasaki disease
- Giant cell (temporal) arteritis
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Antiphospholipid syndrome
- Sjögren’s syndrome

Jennette et al., Arthritis Rheum, 1994
Anti-neutrophyl cytoplasmic antibodies

IIF

C-ANCA

P-ANCA

ELISA:

anti-Proteinase-3 (PR3) antibodies

anti-Myeloperoxidase (MPO) antibodies
Wegener’s granulomatosis
Clinical features

• General: malaise, weight loss, fever, anemia
• Arthralgia, myalgia
• Palpable purpura, livedo reticularis, necrosis
• Gastrointestinal symptoms - pain, bleeding
• Uveitis, retinitis
• Mononeuritis multiplex, seizures
• Upper respiratory tract inflammation
• Alveolar hemorrhage, capillaritis
• RPGN; focal necrotizing, extracapillary GN
• Granuloma formation
• Serology: C-ANCA - anti proteinase-3 antibody
Sinusitis
Saddlenose deformity
septal perforation
uveitis
Palpable purpura:
Microscopic (leukocytoclastic) vasculitis

• Wegener´s granulomatosis
• Microscopic polyangiitis
• Cryoglobulinemia
• Henoch-Schönlein purpura
• Anti Phospholipid Sy
• Drug-induced
Lower respiratory tract inflammation

Cough, SOB
Hemoptysis
Alveolar capillaritis
Intraalveolar bleeding
Migrating infiltrates
May resemble pneumonia
Microscopic polyangiitis

• Less frequent upper respiratory tract inflammation
• No granuloma
• Serology: P-ANCA - anti myeloperoxidase antibody

Churg-Strauss syndrome

• Asthma
• Upper and lower respiratory tract inflammation
• Peripheral/tissue eosinophylia
• Granuloma formation
• Serology: P-ANCA
ANCA plays a role in the pathogenesis of microscopic vasculitis

Mesenteric microvascular hemorrhage in a WKY rat after infusion of anti-MPO antibodies and superfusion with Chemokine ligand-1 (CXCL-1)

ANCA titer and relapse rate

101 PR3+ WG-patients in sustained remission

Serial capture ELISA of mature PR3

(Finkielman for WGET, Ann. Int. Med. 2007)
### Factors associated with Wegener granulomatosis relapse

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Risk of relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>A fourfold rise in C ANCA/PR3 ANCA titre</td>
<td>RR 42.5</td>
</tr>
<tr>
<td>Chronic nasal carriage of <em>Staphylococcus aureus</em></td>
<td>RR 7.16</td>
</tr>
<tr>
<td>Creatinine clearance &gt; 60 ml/min</td>
<td>RR 2.94</td>
</tr>
<tr>
<td>The presence of ANCA at diagnosis</td>
<td>RR 2.89</td>
</tr>
<tr>
<td>Cardiac involvement at diagnosis</td>
<td>RH 2.87</td>
</tr>
<tr>
<td>Cumulative cyclophosphamide dose &lt; 10 g in the first 6 months</td>
<td>RH 2.83</td>
</tr>
<tr>
<td>Prednisolone ≥ 20 mg/day for &lt; 2.75 months</td>
<td>RH 2.41</td>
</tr>
<tr>
<td>Co-trimoxazole as adjuvant to remission maintenance therapy</td>
<td>RR 0.32</td>
</tr>
</tbody>
</table>

Clinical trials in ANCA associated vasculitis

**Induction**
- 3 - 6 mo.

**Maintenance**

**Alternative agents**
- MAINRITSAN - Rituximab
- RAVE - Rit vs CYC
- ABAVAS - Abatacept
- RATTRAP - Rit vs infliximab

- NORAM: MTX vs CYC
- MEPEX: PE vs MP
- CYCLOPS: CYC iv vs oral
- WEGET: Etanercept vs placebo
- SOLUTION: ATG
- MYCYC: MMF Vs CYC
- RITUXIVAS

- LEM: LEF vs MTX
- NORAM: MTX vs CYC
- CYCAZAREM: AZA vs CYC
- IMPROVE: AZA vs MMF
- REMAIN: AZA, 24 mo vs 48 mo
### Microscopic vasculitis: therapy of severe disease

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remission induction</strong></td>
<td></td>
</tr>
<tr>
<td>• Metyl-prednisone oral, 1 mg/kg/d oral, decrease dose</td>
<td></td>
</tr>
<tr>
<td>• Cyclophosphamide, (iv pulse)</td>
<td>1A, (1B)</td>
</tr>
<tr>
<td>• Solu-Medrol iv daily 250-1000 mg x 3 days</td>
<td>3</td>
</tr>
<tr>
<td>• Sumetrolim (PCP prophylaxis) (?)</td>
<td></td>
</tr>
<tr>
<td>• Plasma exchange:</td>
<td>Indication category</td>
</tr>
<tr>
<td>Dialysis dependence (recent)</td>
<td>I</td>
</tr>
<tr>
<td>Diffuse alveolar hemorrhage (DAH)</td>
<td>I</td>
</tr>
<tr>
<td>Dialysis independence, no DAH</td>
<td>III</td>
</tr>
<tr>
<td><strong>Remission maintenance:</strong></td>
<td></td>
</tr>
<tr>
<td>Low dose Metyl-prednisone +</td>
<td></td>
</tr>
<tr>
<td>- Azathioprin 1,5 -2 mg/kg/day</td>
<td>1B</td>
</tr>
<tr>
<td>or: - Leflunomide 30 mg/day</td>
<td>1B</td>
</tr>
<tr>
<td>or: - Methotrexate 0,3 mg/kg/w: if creat &lt; 180 µmol/l</td>
<td>2B</td>
</tr>
</tbody>
</table>
### Alternative therapies for remission induction in relapsing, refractory or persistent disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycophenolate mofetil</td>
<td>2 g/day</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m² body surface area weekly for 4 weeks</td>
</tr>
<tr>
<td>15-Deoxyspergualin</td>
<td>0.5 mg/kg/day x 21 days, 7 days washout x 6 cycles</td>
</tr>
<tr>
<td></td>
<td>wait until the white cell count returns to &gt; 4000/ml</td>
</tr>
<tr>
<td>IVIG</td>
<td>2 g/kg over 5 days</td>
</tr>
<tr>
<td>Infliximab</td>
<td>3–5 mg/kg/infusion every 1 to 2 months</td>
</tr>
<tr>
<td>Anti-thymocyte globulin</td>
<td>2.5 mg/kg/day for 10 days adjusted according to lymphocyte count:</td>
</tr>
<tr>
<td></td>
<td>no anti-thymocyte globulin if &lt;150/ml, 1.5 mg/kg/day if 150–300/ml,</td>
</tr>
<tr>
<td></td>
<td>full dose if &gt;300/ml</td>
</tr>
</tbody>
</table>

EULAR. Ann Rheum Dis 2009;68;310-7
Methylprednisolone versus Plasma Exchange (MEPEX) trial

- N=100, randomized design
- ANCA-associated vasculitis
- Necrotizing, crescentic GN
- Creatinine > 500 µmol/l, 2/3: on dialysis, 1/3: predialysis
- Therapy:
  - Metylprednisolon 1000 mg/day x 3
  vs
  - Plazma exchange 60 ml/kg x 7
- Metylprednisolon 1 mg/kg/day starting dose with dose decrease + cyclophosphamide 2,5 mg/kg/day x 3 mo, followed by azathioprin
- F/U: 1 yr
MEPEX: probability of end stage renal failure

Immunecomplex-mediated RPGN

- IgA nephropathy
- Henoch Schönlein purpura
- Primary membranoproliferative GN
  C4NeF, C3NeF: antibodies that stabilize classic or alternative C3 convertases
- Lupus nephritis

<table>
<thead>
<tr>
<th>WHO Class</th>
<th>Renal histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Minimal mesangial</td>
</tr>
<tr>
<td>II.</td>
<td>Mesangial proliferative</td>
</tr>
<tr>
<td>III.</td>
<td>Focal proliferative</td>
</tr>
<tr>
<td>IV.</td>
<td>Diffuse proliferative</td>
</tr>
<tr>
<td>V.</td>
<td>Membranous</td>
</tr>
<tr>
<td>VI.</td>
<td>Advanced sclerosing</td>
</tr>
</tbody>
</table>
IV. Diffuse proliferative lupus nephritis

wire loops
Crescentic glomerulonephritis
No studies with homogenous groups of patients with immune complex RPGN were conducted except for diffuse proliferative lupus nephritis

Analysis of PEX studies in diffuse proliferative LN

<table>
<thead>
<tr>
<th>Plasma exchange + cytotoxics v cytotoxics</th>
<th>No. of studies</th>
<th>NN</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>2</td>
<td>125</td>
<td>1.62</td>
<td>0.64 to 4.09</td>
</tr>
<tr>
<td>ESRD</td>
<td>3</td>
<td>143</td>
<td>1.24</td>
<td>0.60 to 2.57</td>
</tr>
<tr>
<td>Doubling of serum creatinine</td>
<td>2</td>
<td>51</td>
<td>0.17</td>
<td>0.02 to 1.26</td>
</tr>
<tr>
<td>Major infection</td>
<td>2</td>
<td>125</td>
<td>0.69</td>
<td>0.35 to 1.37</td>
</tr>
<tr>
<td>Herpes zoster virus</td>
<td>2</td>
<td>104</td>
<td>1.69</td>
<td>0.10 to 29.42</td>
</tr>
</tbody>
</table>

### PEX in immune complex RPGN and SLE

<table>
<thead>
<tr>
<th>Disease</th>
<th>Indication category</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Immune complex RPGN</td>
<td>III</td>
<td>2B</td>
</tr>
<tr>
<td>• Systemic lupus erythematosus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>II</td>
<td>2C</td>
</tr>
<tr>
<td><strong>Cerebritis, Alveolar hemorrhage,</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Catastrophic APS, Cryoglobulinemia,</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hyperviscosity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thrombotic Thrombocenic purpura</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephritis</td>
<td>IV</td>
<td>1B</td>
</tr>
</tbody>
</table>

Therapy of severe focal proliferative and diffuse proliferative lupus nephritis

**Remission induction**

**NIH protocol**

- Solu-Medrol 1 g/m² iv, monthly x at least 1yr
- Prednisone (methyl-prednisone) 0,5 mg/kg/d → 0,25 mg/kg qOD
- Cyclophosphamide
  
  0,5-1 g/ m² monthly x  6 mo., then 3 monthly x 24 mo.

- 25-35%: major infection
- 50% of women : amenorrhoea

Euro-lupus trial

• Solu-Medrol 750 mg iv for 3 days
• Methyl-prednisone 0,5 mg/kg/day → 0,25 mg/kg qOD
• Cyclophosphamide
  - 500 mg iv 2 weekly x 6
  vs
  - 0,5 g/m²/mo x 6 (↑ by 250 mg), then 3 monthly x 2
• Maintenance: Azathioprin 2 mg/kg/day x 30 months + low dose MP

Houssiau F. Arthritis & Rheumatism 2002;46:2121–31
10-year follow-up data of the Euro-Lupus Trial

Cumulative CYC dose

<table>
<thead>
<tr>
<th>HD</th>
<th>LD</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.5 g</td>
<td>5.5 g</td>
</tr>
<tr>
<td>2/3: 3g</td>
<td></td>
</tr>
</tbody>
</table>

Houssiau F. Ann Rheum Dis 20 Jan 2009
Mycophenolate mofetil for severe lupus nephritis (classes III, IV, V)

- **MMF**: 2-3 g/day x 6-12 mo
- **CYC**: Iv pulse CYC (Ginzler, Ong) Oral CYC (Chan)

Cryoglobulininemia

Type I. Monoclonal IgM: plasmacell dyscrasia, NonHodgkin Lymphoma

Type II. Monoclonal IgM-polyclonal IgG - Rheumatoid factor: HCV, HBV

Type III. Polyclonal IgM-polyclonal IgG - Rheumatoid factor: SLE, infections
**Clinical features**

- Hyperviscosity
- Microthrombi, gangrena, Raynaud, livedo reticularis
- Microscopic vasculitis
- Membranoproliferative GN (80%)
- Mesangial proliferative GN, Membranous GN
- Peripheral neuropathy
- Arthritis, myalgia
- Sicca sy

**Diagnosis**

Low complement levels (type II, III)

Screening: separate serum at 37 °C - keep serum at 4 °C x 5 days

Type II-III: Rheumatoid factor

Quantitative measurement: no close relationship with symptoms

Characterization: immunofixation
Hyperviscosity

- Mucous membrane bleeding
- Visual disturbancies, retinopathy
- Tinnitus, hearing loss
- Headache, vertigo, nystagmus,
- Somnolency
- Muscle cramps
- Heart failure, respiratory failure
- Coma

Ostwald viscometer
Waldenstöm's macroglobulinemia

Pre - PEX

Post - PEX
globular accumulations of cryoglobulin in the capillary lumens

membranoproliferative GN
tubular structures in subendothelial deposits
palpable purpura, necrosis

Raynaud

livedo reticularis
# Plasma exchange in cryoglobulinemia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Indication category</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoglobulinemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe/symptomatic</td>
<td>I (TPE)</td>
<td>1B</td>
</tr>
<tr>
<td><em>Systemic vasculitis</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Acute glomerulonephritis sy</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Acute renal failure</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Nephrotic sy</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Neuropathy</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Hyperviscosity</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary to HCV</td>
<td>II (IA)</td>
<td>2B</td>
</tr>
</tbody>
</table>

Cryofiltration

Plasma $\rightarrow$ 36°C $\rightarrow$ patient

Immunoglobulins, IFN, albumin, and fibrinogen are preserved.
Therapy of HCV-related cryoglobulinemia

• No severe symptoms
  Antiviral therapy: α - IFN or PEG - IFN
  Ribavirin

• Severe symptoms
  - Antiviral therapy as above
    Ribavirin dose adjusted to GFR
    No Ribavirin and PEG - IFN if GFR < 50 ml/min
  - Methylprednisolon pulse 0,5-1 g x3
  - Immune adsorption or cryofiltration, (PEX)
  - Cyclophosphamide or Rituximab

Stefanutti C. J Clin Apher. 2009;24:241
Antiphospholipid syndrome
Clinical features

• Antiphospholipid antibodies
  - anti-cardiolipin antibody (ELISA)
  - anti β2-glycoprotein (ELISA)
  - lupus anticoagulant - prolonged APTT

• Venous thrombosis: deep veins, renal-, hepatic-, retinal veins, vena cava
  and/or

• Arterial thrombosis: cerebral-, renal-, mesenteric arteries, coronaries
  pulmonary hypertension, amaurosis fugax

• Precipitating factors: smoking, anticoncipients, pregnancy, tumors,
  autoimmunity, immobilization, hyperlipidemia

• Habitual abortion, preeclampsia/eclampsia

• Hematology: Thrombotic microangiopathy - thrombopenia, hemolysis;
  bleeding

• Renal (25%): Thr. renal artery- glomerular capillary - vein, secondary FSGS

• Mitral-, aortic regurgitation / stenosis
Arteriole with thrombus

Glomerular capillaries occluded by agglutinated red blood cells
Glomerular capillaries filled with fibrin thrombi
Catastrophic antiphospholipid syndrome

- Involvement of at least three organs/tissues
- Symptoms develop within one week
- Histological proof of vessel thrombosis
- Presence of antiphospholipid antibodies
- Life threatening condition
Therapy of antiphospholipid syndrome

- Aspirin/clopidogrel (prophylaxis!)
- Heparin/warfarin
  - INR 2.5-3.0
  - life-long
- Catastrophic APS
  - Anticoagulation with heparin
  - Glucocorticoids
  - Intravenous immunoglobulin
  - Plasma exchange indication category grade
    II. 2C
  - rituximab
  - autologous bone marrow transplantation
    experimental
PEX - complications

- Fever
- Urticaria
- Hypocalcemia
- Hypotension
- Bleeding diathesis
- Hypogammaglobulinemia - immunosuppression
- Premature termination of procedure 0.2%
- ICU admission 0.1%
  - Anaphylaxis
  - Bronchospasm
  - Cardiac failure, respiratory failure
- Viral infection (FFP)
- Catheter-related: Thrombosis, sepsis, bleeding
- Death

MEPEX: outcome at one year

<table>
<thead>
<tr>
<th>Baseline</th>
<th>1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not on dialysis</td>
<td></td>
</tr>
<tr>
<td>N=31 (31%)</td>
<td>Not on dialysis n=20 (64%)</td>
</tr>
<tr>
<td></td>
<td>On dialysis n= 4 (13%)</td>
</tr>
<tr>
<td></td>
<td>Death n=7 (23%)</td>
</tr>
<tr>
<td>On dialysis</td>
<td></td>
</tr>
<tr>
<td>N=69 (69%)</td>
<td>Not on dialysis n=30 (43%)</td>
</tr>
<tr>
<td></td>
<td>On dialysis n=22 (32%)</td>
</tr>
<tr>
<td></td>
<td>Death n=17 (25%)</td>
</tr>
</tbody>
</table>

p=0.016

CYCLOPS (Cyclophosphamide Daily Oral Versus Pulsed) trial in ANCA associated vasculitis

N = 149, creatinine 150-500 µmol/l
Prednisone +
CYC 15 mg/kg iv pulse 2-3 weekly to remission ➔ monthly x3
   vs 2 mg/kg /day oral to remission ➔ 1,5 mg/kg/d x 3 mo
followed by AZA
   f/u: 18 mo
Primary endpoint: disease free survival at 9 mo

**CYCLOPS: main results**

**Time to remission**
- Daily oral:  
- IV pulse:  

\[ p = 0.65 \]

**Time to relapse**
- Daily oral:  
- IV pulse:  

\[ p = 0.63 \]

No difference in any endpoint

Cumulative CYC dose: daily oral - 15.9 g; IV pulse - 8.2 g

Leukopenia: daily oral - 45%; IV pulse - 26%, \( p < 0.02 \)

Ann Intern Med 2009;150:670
<table>
<thead>
<tr>
<th>Disease</th>
<th>Indication category</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Goodpasture’s syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis independence</td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td>Diffuse alveolar hemorrhage</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>Dialysis dependent, no DAH</td>
<td>IV</td>
<td>1A</td>
</tr>
<tr>
<td>• ANCA- associated RPGN</td>
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<tr>
<td>Dialysis dependence</td>
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<td>1A</td>
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<tr>
<td>Diffuse alveolar hemorrhage (DAH)</td>
<td>I</td>
<td>1C</td>
</tr>
<tr>
<td>Dialysis independence, no DAH</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>• Catastrophic antiphospholipid syndrome</td>
<td>II</td>
<td>2C</td>
</tr>
<tr>
<td>• Cryoglobulinemia</td>
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<tr>
<td>Severe/symptomatic</td>
<td>I (TPE)</td>
<td>1B</td>
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<tr>
<td>Secondary to HCV</td>
<td>II (IA)</td>
<td>2B</td>
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<tr>
<td>• Immune complex RPGN</td>
<td>III</td>
<td>2B</td>
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<tr>
<td>• Systemic lupus erythematosus</td>
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<tr>
<td>Severe</td>
<td>II</td>
<td>2C</td>
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<td><em>Cerebritis, Alveolar hemorrhage, Catastrophic APS, Cryoglobulinemia, Hyperviscosity</em></td>
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<tr>
<td>Nephritis</td>
<td>IV</td>
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</table>

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<thead>
<tr>
<th>Disease</th>
<th>Indication category</th>
<th>Grading</th>
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<tbody>
<tr>
<td>Scleroderma</td>
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<tr>
<td>Focal segmental glomerulosclerosis, recurrent</td>
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<td>Myeloma cast nephropathy</td>
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<td>Renal transplantation</td>
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<td>Antibody mediated rejection</td>
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<tr>
<td>Desensitization, donor specific HLA AB</td>
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</tr>
<tr>
<td>High PRA; cadaveric donor</td>
<td>III</td>
<td>2C</td>
</tr>
</tbody>
</table>
Inactivation of factors Va, VIIIa in the presence of protein S and phospholipids

Extrinsic pathway

Intrinsic pathway

X

V

Ca

PROTHROMBIN

Coagulation cascade

Activated protein C

*Thrombomodulin

Endothelial cell protein C receptor

Protein C

Thrombin

Phospholipid surface

Fibrinogen

Fibrin (clot)

Clot propagation

Clot lysis (Fibrinolysis)

Extrinsic pathway

Intrinsic pathway