Secondary Glomerular Disease, Vasculitis – Plasmapheresis Therapy

György Deák
Uzsoki Hospital, Budapest, Hungary
Therapeutic plasma exchange (TPE) - centrifugation -

- Anticoagulant (citrate)
- Plasma (waste)
- Centrifuge
- Replacement fluid pump
- Plasma pump
- Blood pump
- Anticoagulant pump
- Cristalloid
- Albumin
- Fresh frozen plasma
- Whole blood in
- Component to be removed out
- Plasma
- Platelet rich plasma
- Leukocytes
- Erythrocytes
Therapeutic plasma exchange (TPE) - membrane separation -
Immune adsorption (IA)

Protein A column to bind Ig-s

Blood pump

Plasma pump

Membrane
<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
# Clinical approach to glomerular disease

<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, MGP</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, metals</td>
</tr>
<tr>
<td></td>
<td>Diffuse-</td>
<td>Metabolic</td>
</tr>
<tr>
<td></td>
<td>Membrano-</td>
<td>Hereditary</td>
</tr>
<tr>
<td></td>
<td>Extracapillary-</td>
<td></td>
</tr>
</tbody>
</table>
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 seldom relapses
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</td>
</tr>
<tr>
<td>Diffuse alveolar hemorrhage</td>
<td>I</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</td>
</tr>
</tbody>
</table>

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

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

---

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

- Capillary
- Arteriole
- Venule
- Vein
- Large to medium-sized artery
- Small artery
- Aorta
- Cutaneous leucocytoclastic angiitis
- Henoch-Schönlein Purpura
- Cryoglobulinaemia
- Wegener’s granulomatosis
- Microscopic polyangiitis
- Churg-Strauss syndrome
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Antiphospholipid syndrome
- Sjögren’s syndrome
- Polyarteritis nodosa
- Giant cell (temporal) arteritis

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

I I F

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)

### 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 $\geq 20$ 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>

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)
Clinical trials in ANCA associated vasculitis

**Induction**
3 - 6 mo.

**Maintenance**

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

**Alternative agents**
MAINRITSAN - Rituximab
RAVE - Rit vs CYC
ABAVAS - Abatacept
RATTRAP - Rit vs infliximab
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 x3
  - 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

Risk of requiring renal replacement therapy at 12 months in patients treated with or without plasma exchange

Risk ratio (95% CI)

Cole 1992 0.60 [0.17, 2.10]
Jayne 2007 0.45 [0.24, 0.86]
Mauri 1985 0.48 [0.18, 1.26]
Pusey 1991 0.81 [0.05, 12.01]
Rifle 1980 0.27 [0.04, 1.73]
Subtotal (95% CI) 0.47 [0.30, 0.75]

Walters et al. BMC Nephrology 2010, 11:12
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

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
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>1A, (1B)</td>
</tr>
<tr>
<td>• Cyclophosphamide, (iv pulse)</td>
<td></td>
</tr>
<tr>
<td>• Solu-Medrol iv daily 250-1000 mg x 3 days</td>
<td>2C</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 21days, 7 days washout x 6 cycles 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: no anti-thymocyte globulin if &lt;150/ml, 1.5 mg/kg/day if 150–300/ml, full dose if &gt;300/ml</td>
</tr>
</tbody>
</table>

EULAR. Ann Rheum Dis 2009;68;310-7
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
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
- Metyl-prednisolone 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

Therapy of severe focal proliferative and diffuse proliferative lupus nephritis

Euro-lupus trial

- Solu-Medrol 750 mg iv for 3 days
- Methyl-prednisolone 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>

**A**

Free of death (%)

HR: 2.78 (0.54-14.32)

$p = 0.203$

B

Free of ESRD (%)

HR: 0.53 (0.10-2.90)

$p = 0.457$

C

Free of SDSC (%)

HR: 1.34 (0.41-4.40)

$p = 0.628$

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)

Analysis of PEX studies in diffuse proliferative LN

<table>
<thead>
<tr>
<th>Plasma exchange + cytotoxics vs 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>Cerebritis, Alveolar hemorrhage,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catastrophic APS, Cryoglobulinemia,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperviscosity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic Thrombopenic purpura</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephritis</td>
<td>IV</td>
<td>1B</td>
</tr>
</tbody>
</table>
New and evolving therapies for lupus nephritis

**B cell depletion**
- Rituximab: anti CD20 (1)
- Epratuzumab: anti-CD22 (2)

**Induction of B cell tolerance**
- Abetimus (ds-oligoDNA molecule) (3)
- IVIG

**Anti - C5, IL1, IL10, IFN, TNF-α**

**Blockade of B-T cell costimulation**
- Abatacept: CD28-Ig fusion (4)
- IDEC-131: anti CD40L (5)

**Blockade of B-cell stimulation**
- Belimumab: anti BlyS (6)

**Autologous stem cell transplantation**

Cryoglobulinemia

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

Type I.

Type II.-III.

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
globular accumulations of cryoglobulin in the capillary lumens

membranoproliferative GN
tubular structures in subendothelial deposits
Raynaud, palpable purpura, necrosis, livedo reticularis
### Plasma exchange in cryoglobulinemia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Indication category</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cryoglobulinemia</strong></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 $\rightarrow$ cooler $\rightarrow$ pre-treatment $\rightarrow$ post-treatment $\rightarrow$ $36^\circ$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
  
  - Metylprednisolon 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: II
    - grade: 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

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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Indication category</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Scleroderma</td>
<td>III</td>
<td>2C</td>
</tr>
<tr>
<td>• Focal segmental glomerulosclerosis, recurrent</td>
<td>I</td>
<td>1C</td>
</tr>
<tr>
<td>• Myeloma cast nephropathy</td>
<td>II</td>
<td>2B</td>
</tr>
<tr>
<td>• Renal transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody mediated rejection</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>Desensitization, donor specific HLA AB</td>
<td>II</td>
<td>1B</td>
</tr>
<tr>
<td>High PRA; cadaveric donor</td>
<td>III</td>
<td>2C</td>
</tr>
</tbody>
</table>
### MEPEX: outcome at one year

#### Baseline

<table>
<thead>
<tr>
<th>Not on dialysis</th>
<th>1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=31 (31%)</td>
<td></td>
</tr>
<tr>
<td>Not on dialysis</td>
<td>n=20 (64%)</td>
</tr>
<tr>
<td>On dialysis</td>
<td>n=4 (13%)</td>
</tr>
<tr>
<td>Death</td>
<td>n=7 (23%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>On dialysis</th>
<th>1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=69 (69%)</td>
<td></td>
</tr>
<tr>
<td>Not on dialysis</td>
<td>n=30 (43%)</td>
</tr>
<tr>
<td>On dialysis</td>
<td>n=22 (32%)</td>
</tr>
<tr>
<td>Death</td>
<td>n=17 (25%)</td>
</tr>
</tbody>
</table>

#### Chart

- PEX
- IV MP

\[ p = 0.016 \]
Hyperviscosity

• Mucous membrane bleeding
• Visual disturbancies, retinopathy
• Tinnitus, hearing loss
• Headache, vertigo, nystagmus,
• Somnolency
• Muscle cramps
• Heart failure, respiratory failure
• Coma
Waldenstöm's macroglobulinemia

Pre - PEX

Post - PEX
Targeted therapies for SLE

- Rituximab
- Ocrelizumab
- Epratuzumab
- Anti-CD40L
- CD20
- CD22
- CD40
- CD40L
- TACI
- BAFF-R
- BCMA
- B7.1/2
- CD28/CTLA-4
- BLyS/BAFF
- TCR
- MHC II Ag
Novel B Cell Therapeutic Targets in Immune-Mediated Glomerular Diseases

IgG subclass switching

Nephritogenic Ig subclasses

Final stage

Antigen

CD40 CD40L

IFN-γ

IL-4

TGF-β IL-10

IL-2, 4, 5

IgG2a, IgG3

IgE, IgG1

IgA

IgM

C3