Apheresis in renal diseases

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Apheresis treatments

• Separation of blood components
  • Centrifugation or membrane filtration

• Apheresis of Plasma
  • Plasma exchange
  • Secondary Plasma treatment
    • Double filtration
    • Affinity columns (Immunoadsorption...)

• Apheresis of Blood Cells
  • Erythrocyte exchange
  • Extracorporeal photo-chimiotherapy
Indications of Plasma Exchange in renal diseases

• 1. Anti-GBM disease (Goodpasture)
• 2. ANCA associated rapidly progressive glomerulonephritis
• 3. Thrombotic Microangiopathies
• 4. Cryoglobulinemic glomerulonephritis
• 5. Myeloma cast Nephropathy (?)
• 6. (Transplantation)
1964: Goodpasture’s syndrome: a clinicopathologic entity
Benoit & al, Am J Med
52 patients. Survival 4 %, Renal survival 2%.
<table>
<thead>
<tr>
<th>Year</th>
<th>N Patients</th>
<th>1-year patient survival (%)</th>
<th>1-year kidney survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1964 (1)</td>
<td>52</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>1976 (2)</td>
<td>7</td>
<td>53</td>
<td>43</td>
</tr>
<tr>
<td>2001 (3)</td>
<td>71</td>
<td>79</td>
<td>41</td>
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</tbody>
</table>


<table>
<thead>
<tr>
<th></th>
<th>N Patients</th>
<th>1-year patient survival (%)</th>
<th>1-year kidney survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creat &lt; 500 µmol/L</td>
<td>19</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>Creat &gt; 500, not dialysed</td>
<td>13</td>
<td>83</td>
<td>82</td>
</tr>
<tr>
<td>Dialysed before 72h</td>
<td>39</td>
<td>65</td>
<td>8</td>
</tr>
<tr>
<td>Dialysed and 100% crescents</td>
<td>0</td>
<td></td>
<td></td>
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</table>

*Levy & al, Ann Int Med, 2001*
KDIGO guidelines (Kidney Int., 2012, Supp 2)

• Plasmapheresis is indicated in all patients with anti-GBM GN except those who are dialysis-dependent at presentation and have 100% crescents in an adequate biopsy sample, and do not have pulmonary hemorrhage.

• Methylprednisolone 500–1000 mg/d i.v. for 3 days, followed by prednisone, 1 mg/kg/d/IBW (maximum 80 mg/d)

• Cyclophosphamide: 2 mg/kg/d orally for 3 months.

• Plasmapheresis: One 4-liter exchange per day with 5% albumin; should be continued for 14 days or until anti-GBM antibodies are no longer detectable.

• Add 150–300 ml fresh frozen plasma at the end of each pheresis session if patients have pulmonary hemorrhage, or have had recent surgery, including kidney biopsy.
Retrospective study of Goodpasture patients treated with plasma-exchange in France.

Aim of the study: to describe patients’ characteristics, current therapeutic practice and 1-year results

based on **SFH Registry** (Société Française d’Hémaphérèse)

- 1985-2006: 270 patients with Goodpasture
- Study on 122 patients
SFH Registry
1-year patient and kidney survival according to cyclophosphamide use

<table>
<thead>
<tr>
<th></th>
<th>N Patients</th>
<th>1-year patient survival (%)</th>
<th>1-year kidney survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>122</td>
<td>86</td>
<td>28</td>
</tr>
<tr>
<td>no Cyclophosphamide</td>
<td>10</td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td>i.v. Cyclophosphamide</td>
<td>72</td>
<td>82</td>
<td>26</td>
</tr>
<tr>
<td>p.o. Cyclophosphamide</td>
<td>32</td>
<td>97</td>
<td>33</td>
</tr>
</tbody>
</table>
• The experience from the SFH Registry is not a controlled study
• It just emphasizes the importance of adhering precisely to the guidelines

*Cyclophosphamide: 2 mg/kg/d orally for 3 months.*
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Does plasma replacement with Albumin play a role in the therapeutic effect of Plasma Exchange?

• No direct proof available, but:
• Very likely, because:
  - Daily Plasma exchange with albumin replacement effectively decreases complement factors levels
  - The complement system participates in the injury to the kidney
Intensive Plasma Exchange on the Cell Separator: Effects on Serum Immunoglobulins and Complement Components

A. J. Keller and S. J. Urbaniak

Table II. Cumulative percentage reductions* (mean ± SEM) in post-exchange serum immunoglobulin and complement component concentrations during consecutive daily exchanges

<table>
<thead>
<tr>
<th>Serum component</th>
<th>Day 1</th>
<th>Day 5</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>34.6 ± 2.6</td>
<td>19.9 ± 7.1</td>
<td>3.8</td>
</tr>
<tr>
<td>IgA</td>
<td>39.1 ± 5.2</td>
<td>23.1 ± 6.0</td>
<td>4.0</td>
</tr>
<tr>
<td>IgM</td>
<td>31.1 ± 3.9</td>
<td>20.5 ± 10.8</td>
<td>2.0</td>
</tr>
<tr>
<td>CH&lt;sub&gt;50&lt;/sub&gt;</td>
<td>42.9 ± 3.6</td>
<td>40.3 ± 8.0</td>
<td>28.0</td>
</tr>
<tr>
<td>C4</td>
<td>34.0 ± 3.5</td>
<td>28.3 ± 9.3</td>
<td>7.5</td>
</tr>
<tr>
<td>C3</td>
<td>32.1 ± 3.9</td>
<td>14.9 ± 2.4</td>
<td>6.0</td>
</tr>
</tbody>
</table>
Involvement of the Complement system in the kidney injury of anti-GBM nephritis

• Local formation of immune complexes GBM-anti-GBM should activate the classical pathway of Complement
    • C5a and sC5-b9 increased in plasma and urine
    • The plasma level of sC5b-9 predictor for renal failure (p < 0.005)
    • Glomerular deposition of factor B and Properdin, as well as C1q
    • Involvement of both activation pathways (classical and alternate)
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- Plasmapheresis: One 4-liter exchange per day with 5% albumin; should be continued for 14 days or until anti-GBM antibodies are no longer detectable.
- Add 150–300 ml fresh frozen plasma at the end of eachpheresis session if patients have pulmonary hemorrhage, or have had recent surgery, including kidney biopsy.
For repeated plasma exchanges, use:
- 10-20 ml/kg FFP for maintaining plasma Fibrinogen > 1 g/L
- 30 ml/kg FFP in case of disease-related haemorrhagic risk
- 100 % substitution with FFP in case of overt or major risk of haemorrhage
To summarize the choice between Albumin and Fresh Frozen Plasma as substitution fluid,

• Albumin is likely more efficient than FFP, through non specific elimination of mediators including complement proteins
• Some FFP is needed at the end of plasma exchange, in the context of renal biopsy or alveolar haemorrhage
• The volume of FFP at the end of session is to be chosen:
  • Smaller volume for more efficacy?
  • Larger volume for more safety?
ANCA associated rapidly progressive glomerulonephritis

• Granulomatosis with Polyangeitis (Wegener)
• Microscopic Polyangeitis
• Renal-limited

• Crescentic glomerulonephritis
• Pauci-immune
Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis

David R.W. Jayne,* Gill Gaskin,† Niels Rasmussen,‡ Daniel Abramowicz,§ Franco Ferrario,¶ Loic Guillevin,‖ Eduardo Mirapeix,** Caroline O.S. Savage,†† Renato A. Sinico,‖ Coen A. Stegeman,†† Kerstin W. Westman,§§ Fokko J. van der Woude,¶¶ Robert A.F. de Lind van Wijngaarden,¶¶ and Charles D. Pusey; on behalf of the European Vasculitis Study Group†

## European MEPEX trial

<table>
<thead>
<tr>
<th></th>
<th>Methylprednisolone</th>
<th>Plasma Exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>N pts</td>
<td>67</td>
<td>70</td>
</tr>
<tr>
<td>(N dialysed)</td>
<td>(48)</td>
<td>(47)</td>
</tr>
<tr>
<td>Alive, not dialysed at 3 mo</td>
<td>33</td>
<td>*</td>
</tr>
<tr>
<td>Alive at 1 year</td>
<td>51</td>
<td>NS</td>
</tr>
<tr>
<td>Alive, not dialysed at 1 year</td>
<td>29</td>
<td>**</td>
</tr>
</tbody>
</table>

* p = 0.02  
** p = 0.008
• Meta-analysis of 9 Randomized Controlled Trials (1981 to 2007)
• Total 387 patients (201 treated with Plasma exchange; 186 without)
• End-point = death
  • RR = 1.0 (95% CI = 0.71-1.42)
  • P= 0.9
• End-point = end stage renal disease
  • RR = 0.64 (95% CI = 0.47-0.88)
  • P=0.007
KDIGO guidelines (Kidney Int., 2012, Supp 2)

• Plasmapheresis is indicated in ANCA-vasculitis with GN for patients presenting with either advanced kidney failure (SCr > 500 µmol/l]) or with diffuse alveolar hemorrhage.

• + Methylprednisolone 500 mg/d i.v. for 3 days, followed by prednisone, 1 mg/kg/d/IBW (maximum 60 mg/d)

• Cyclophosphamide: 1.5 mg/kg/d orally or i.v. 0.75 g/m2 q 3–4 weeks, for 3 to 6 months

• Plasmapheresis: 60 ml/kg volume replacement with 5% albumin; Seven treatments over 14 days

• Add 150–300 ml fresh frozen plasma at the end of each pheresis session if patients have pulmonary hemorrhage, or have had recent surgery, including kidney biopsy.
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Involvement of the alternate pathway of Complement in the kidney injury of ANCA vasculitis

• Experimental data
  • Primed neutrophils activate the alternate pathway of complement
  • Mouse model of anti-MPO vasculitis

• Clinical studies
  • Gou SJ et al, Kidney Int 2012
    • C3a, C5a, Bb, sC5b-9 increased in serum/urine of patients with ANCA vasculitis
    • Higher in active disease than in remission
Plasma exchange in ANCA vasculitis: 1 question

• Could plasma exchange be also useful in the initial treatment for less severe cases than MEPEX criteria?
  → on-going European study PEXIVAS
Thrombotic microangiopathies

- Idiopathic TTP (auto-antibody anti-ADAMTS13)
- Constitutionnal TTP (genetically abnormal ADAMTS13)

- Typical HUS: post-diarrhea (E.Coli producing Shigatoxin)
- Atypical HUS: abnormal alternate pathway of Complement

- Secondary Thrombotic microangiopathy
  - Malignant Hypertension; Renal Scleroderma crisis; Anti-phospholipid syndrome
  - Allogenic Stem cells transplantation
  - Cancer
  - Pregnancy
  - Drugs (Mitomycin, calcineurin inhibitor, Clopidogrel, Interferon...)
  - Infections (HIV, S.pneumoniae...)
Thrombotic thrombopenic purpura (Moschowitz) treatment

- Constitutionnal ADAMTS13 deficiency
  - Fresh frozen plasma infusion corrects the deficiency
  - Chronic replacement therapy

- Acquired ADAMTS13 deficiency with inhibitory antibody
  - Plasma exchange removes abnormal multimers of Willebrand factor
  - Plasma exchange removes the inhibitory antibody anti-ADAMTS13
  - Fresh frozen plasma provides normal ADAMTS13

- Association with immunosuppressive (corticosteroids, Rituximab...

Rock GA, et al

Figure 1. Survival of Patients with Thrombotic Thrombocytopenic Purpura.

The survival curves differ significantly (P = 0.036 by the Breslow-Gehan test).
TTP : Guidelines
of the French National Reference Center

• Start immediately daily plasma exchanges with FFP
• First session : 60 ml/kg, thereafter 40 ml/kg/session
• At least 7 days
• Associate corticosteroids 1 mg/kg
• Decrease frequency when platelets > 150 000/mm3 on 2 consecutive days and neurologic signs corrected
• If unresponsive after 5 days, increase exchange volume to 60 ml/kg and associate Rituximab (375 mg/m2/wk x 4 weeks)
But the consequences of these pharmacokinetics changes on the immunological and clinical effects of the drug are not known.
Typical Hemolytic and Uremic syndrome (E.coli, Shiga toxin +)

- Supportive treatment generally sufficient, but still some mortality (2%) or renal sequellae (30%)
- Plasma infusion, plasma exchange with FFP or Eculizumab have been used as additive treatments
- Each one has been described as useful in case reports or short series in children or adults
- No one has demonstrated efficacy in controlled trial
German epidemic of HUS

- Started on 19 Mai 2011
- Cause: Escherichia Coli O154 H4
- Food contamination (Fenugrec seeds)
- 4,321 patients had infectious diarrhea / E.Coli
- 852 HUS cases
- 50 deaths
- In a subgroup, 251 patients had plasma exchanges with FFP and 67 Eculizumab
Validation of treatment strategies for enterohaemorrhagic Escherichia coli O104:H4 induced haemolytic uraemic syndrome: case-control study
Menne J et al, *BMJ* 2012;345:e4565

**WHAT THIS STUDY ADDS**

No benefit of plasmapheresis or glucocorticoid treatment was found for patients with enterohaemorrhagic *E.coli* O104:H4 induced haemolytic uraemic syndrome, and prolonged treatment may even do more harm than good.

An aggressive antibiotic treatment strategy was not harmful in patients with established haemolytic uraemic syndrome and might even be beneficial.

No benefit of eculizumab could be found when short term outcome was compared with a patient group with similar severity of disease.
Atypical Hemolytic Uremic Syndrome

- Children and adults
- May be recurrent or familial
- Much worse prognosis than typical HUS
- Dysfunction of alternate pathway of complement demonstrated in > 60 %
- Constitutionnal: gene mutation, with
  - loss of function: factors H, I, MCP, CFHR, Thrombomodulin …
  - gain of function: factors C3, B…
- Acquired
  - Auto-antibodies against factor H
Atypical Hemolytic Uremic Syndrome

Treatment

• aHUS with abnormal complement factor
  – Plasma exchange with FFP associated with transient remission in > 50 %
  – Mechanism:
    • Removal of over-functionning factor: B, C3, replaced by normal
    • Or restoring levels of normal regulating factor: H, I (not MCP)
  – But recurrence, plasma exchange dependancy, plasma exchange resistance
  – Progression to death or ESRD > 60 % in the long term

• aHUS with antibody anti-factor H
  – Mechanism of plasma exchange: removal of anti-factor H and factor H supply
  – Association with immunosuppressive treatment for long-term remission
Atypical Hemolytic Uremic Syndrome Treatment

• Eculizumab
  – Monoclonal antibody anti-C5
  – Cases and series reports of more than 70 patients
  – Corrects thrombopenia and improves renal function in almost all cases, with demonstrated complement abnormality or not
  – Now approved by FDA and EMA
Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome


Secondary thrombotic microangiopathies

- Plasma exchange with Fresh frozen plasma is
  - Contra-indicated in S.pneumoniae invasive infection
    - FFP contains antibodies against T-antigen unmasked by neuraminidase
  - Useless in TMA associated with malignant hypertension, metastatic cancer or allogenic stem cells transplantation
  - May be useful in other etiologies
Cryoglobulinemic glomerulonephritis

- Membrano proliferative glomerulonephritis
- Type II cryoglobulinemia with monoclonal IgM
- 80 % associated with chronic HCV infection
- Treatment
  - anti-viral + immunosuppressive (Rituximab)
  - case reports suggest improvement with plasma exchange in 70-80 % in symptomatic/severe cases (but no controlled trial)
- What will change with the new anti-HCV drugs?
Myeloma cast nephropathy

- At the moment, not an evidence-based indication of plasma-exchange
- Largest randomized controlled study (Clark WF, 2005) «negative»
- However, the pathogenic role of filtered circulating free light chains is demonstrated
Are circulating free light-chains effectively reduced by plasma-exchange?

- The rate of reduction depends on:
  - The exchange volume
  - The rhythm and total number of sessions
  - The effects of chemotherapy on plasma cells
    (Dexamethazone, Bortezomib, Thalinomide)
- Individual response of each patient
  - Reduction > 50% in 17/24 patients (60%)
    (Leung N, 2008)
- Free light-chains may also be reduced by other extracorporeal techniques:
  - Hemodialysis with High Cut Off membrane
  - Hemodiafiltration
39 patients
Myeloma casts on biopsy
Dialyse initiated in 24/39
Plasma exchange in 20
Hemodialysis HCO in 19
Alternative Apheresis techniques

• Double Filtration and Immunoadsorption have the major advantage of using no blood-derived products (Albumin or FFP)

• Few specific studies
  • Double filtration:
    • one open series of 25 patients with TTP (Valbonesi, 2004): results as would be expected with plasma exchange
  • Immunoadsorption:
    • One study comparing ProteinA immunoadsorption with plasma exchange in 20 patients with rapidly progressive glomerulonephritis: no difference (Stegmayr, 1999)
    • one randomized controlled trial of Protein A immunoadsorption in antibody-mediated rejection of kidney transplant: was positive (Bohmig, 2007)
    • Several series of ProteinA immunoadsorption as part of protocols for desensitization of HLA immunized recipients before kidney transplantation
    • Immunoadsorption with specific ABO antigens columns before ABO incompatible graft
Conclusions

• More randomised controlled trials needed !...
• Some are on-going : PEXIVAS, (MYRE)
• Improvement of protocols could also result from studies addressing the mechanisms of action: antibodies depletion, complement system changes, free light chains reduction...
• Apheresis techniques other than plasma exchange have the major advantage of needing no blood-derived product, and should be evaluated comparatively