Therapeutic Apheresis
Behrouz Mansouri Taleghani
What means hemapheresis

- Old Greek: Aphairesis
  = removal, depletion

- Aristoteles used the word “aphairesis” for a systematic perception of the essential part
Therapeutic Apheresis

Plasmapheresis

Thrombapheresis

Leukapheresis

Erythrapheresis

Donor Apheresis
Milestones of hemapheresis I

1914: Term “plasmapheresis”
Abel JJ, Rowntree LG, Turner BB: Plasma removal with return of corpuscles (Plasmapheresis)
J Pharmacol Exp Ther 1914; 5:625-641

1926: Plasmapheresis in humans
Gilbert A, Tzanck A, Negroni T: Emmission sanguine avec restitution globulaire
Paris méd 1926; 21:217
Milestones of hemapheresis II

1944: Blood centrifuge
Tui C, Bartter FC, Wright AM, Holt RB: Red cell re-infusion and the frequency of plasma donations. Preliminary report of multiple donations in eight weeks by each of six donors. JAMA 1944; 124:331

1952: Plastic blood bags
Walter CW, Murphy WP: A closed gravity technique for the preservation of whole blood in ACD solution utilizing plastic equipment. Surg Gynec Obstet 1952; 94:687
Milestones of hemapheresis III

1968: Plasmapheresis by cell separators

Blood constituents (plasma, cells) show differences in size and density.
Therapeutic Apheresis (TA)

**Rationale**

- The disease is caused by pathological or pathologically elevated blood constituent(s) and/or
- by (a) missing blood constituent(s).
- TA is sufficiently effective in depleting any putative causative constituent(s) and/or
- in replacing any hypothetical missing factor in order to achieve a (symptomatic) remission of the disease.
Indication categories as established by ASFA

- **Category I**
  … Accepted as **first-line therapy**, either as a primary **standalone** treatment **or in conjunction with other** modes of treatment.

- **Category II**
  … Accepted as **second-line therapy**, either as a **standalone** treatment **or in conjunction with other** modes of treatment.

- **Category III**
  … Optimum **role of apheresis therapy is not established.**
  **Decision making should be individualized.**

- **Category IV**
  … Published evidence demonstrates or suggests apheresis to be **ineffective or harmful** (“research setting only”)

- **Category P** …
  = pending, devices **not available/not FDA approved in USA**

Definition of level of evidence for assignment of indications to specific categories by ASFA

<table>
<thead>
<tr>
<th>Grade</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>… at least 1 properly designed randomized controlled trial</td>
</tr>
<tr>
<td>Type II-1</td>
<td>… well-designed controlled trials without randomization</td>
</tr>
<tr>
<td>Type II-2</td>
<td>… well-designed cohort or case-control analytic studies, preferably from more than one center or research group</td>
</tr>
<tr>
<td>Type II-3</td>
<td>… multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence</td>
</tr>
<tr>
<td>Type III</td>
<td>Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees</td>
</tr>
</tbody>
</table>
### Kategorie I: Erstlinienbehandlung, alleine oder mit anderen Modalitäten

<table>
<thead>
<tr>
<th>Diagnosen / Indikationen</th>
<th>DGTI</th>
<th>ASFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwere Babesiose</td>
<td>EA</td>
<td>EA</td>
</tr>
<tr>
<td>Therapie Hyperleukozytose / Leukostase</td>
<td>LA</td>
<td>LA</td>
</tr>
<tr>
<td>Hyperviskositätssyndrom bei Paraproteinämie (inkl. Prophylaxe vor Rituximab-Therapie)</td>
<td>PA</td>
<td>PA</td>
</tr>
<tr>
<td>Kryoglobulinämie</td>
<td>PA</td>
<td>PA</td>
</tr>
<tr>
<td>Erythrodermes, kutanes T-Zelllymphom (CTCL)</td>
<td>ECP</td>
<td>ECP</td>
</tr>
<tr>
<td>Akuter Zerebralinsult infolge Sichelzellerkrankung &amp; kombiniert heterozygote Varianten</td>
<td>EA</td>
<td>EA</td>
</tr>
<tr>
<td>Thrombotisch thrombozytopenische Purpura (TTP)</td>
<td>PA</td>
<td>PA/I</td>
</tr>
<tr>
<td>Atypisches HUS (aHUS) mit Inhibitor gegen Komplementfakor H</td>
<td>PA</td>
<td>PA</td>
</tr>
<tr>
<td>Medikamenten-assoziierte MAHA durch Ticlopidin/Clopidogrel</td>
<td>PA</td>
<td>PA</td>
</tr>
<tr>
<td>Fam. Hypercholesterinämie (Homozygote*, unzureichend behandelbare Heterozygote)</td>
<td>LPA</td>
<td>LPA*</td>
</tr>
<tr>
<td>Guillain-Barré-Syndrom</td>
<td>PA &amp; IA</td>
<td>PA</td>
</tr>
</tbody>
</table>

**Legende:**
- LA = leukocytapheresis
- EA = erythocytapheresis
- TPE = therapeutic plasma exchange
- ECP = extracorporeal photochemotherapy
- IA = immunoaddserption
- LPA = lipidapheresis

**Quelle:** J Clin Aph 2010;25:83–177
Kategorie I: Erstlinienbehandlung, alleine oder mit anderen Modalitäten

<table>
<thead>
<tr>
<th>Diagnosen / Indikationen</th>
<th>DGTI</th>
<th>ASFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronisch inflammatorische demyelinisierende Polyradikoloneuropathie</td>
<td>PA &amp; IA</td>
<td>PA</td>
</tr>
<tr>
<td>Mittelschwere bis schwere Myasthenia gravis und vor Thymektomie</td>
<td>PA &amp; IA</td>
<td>PA</td>
</tr>
<tr>
<td>PANDAS &amp; Sydenham-Chorea</td>
<td>PA</td>
<td>PA</td>
</tr>
<tr>
<td>Paraproteinämische Polyneuropathien (PNP) bei IgG/IgA/IgM-Paraprotein</td>
<td>PA</td>
<td>PA</td>
</tr>
<tr>
<td>Rezidivierende fokal segmentale Glomerulosklerose</td>
<td>PA</td>
<td>PA</td>
</tr>
<tr>
<td>Wegener-Granulomatose mit dialysepflichtiger RPGN oder diffuser alveolärer Blutung</td>
<td>PA</td>
<td>PA</td>
</tr>
<tr>
<td>Goodpasture-Syndrom mit <strong>nicht</strong> dialysepflichtiger RPGN</td>
<td>PA &amp; IA</td>
<td>PA</td>
</tr>
<tr>
<td>Goodpasture-S mit RPGN mit diffuser alveolärer Blutung (± dialysepflichtig)</td>
<td>PA &amp; IA</td>
<td>PA</td>
</tr>
<tr>
<td>Immunkomplex-bedingte RPGN</td>
<td>IA (PA/III)</td>
<td>PA</td>
</tr>
<tr>
<td>Antikörper-vermittelte Abstoßung nach Nierentransplantation</td>
<td>PA &amp; IA</td>
<td>PA</td>
</tr>
<tr>
<td>Zelluläre Abstoßung nach Lungentransplantation</td>
<td>ECP</td>
<td>ECP</td>
</tr>
<tr>
<td>Morbus Wilson, fulminantes Leberversagen und Hämolyse</td>
<td>PA</td>
<td>PA</td>
</tr>
<tr>
<td><strong>LA = leukocytapheresis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IA = immunoaddsortion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EA = erythocytapheresis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LPA = lipidapheresis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TPE = therapeutic plasma exchange</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ECP = extracorporeal photochemotherapy</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A 74-year-old female with low-grade fever, confusion, and anorexia for 3 weeks was treated for a presumed viral illness. She returned 10 days later unimproved. She was thin (51 kg), afebrile; significant dyspnoea; massive splenomegaly extending below her umbilicus. WBC count 375 G/l; Hb 95 g/L, Hct 0.28; PLT count 110 G/l.

What is your suggested diagnosis/complication?

What is your suggested acute intervention?

≈ 1.2 kg
Hyperleukocytosis Syndrome

**Lungs**
pulmonary leukostasis $\rightarrow$ dyspnoea/tachypnoea etc.;
diffuse pulmonary infiltrates without evidence of pneumonia

**Cerebrovascular leukostasis**
Often non-specific signs and symptoms of cerebrovascular leukostasis, e.g. head age, confusion; but also (secondary!) CNS bleeds!!

**Eyes**
e.g. visual deficits, papillary oedema, retinal bleedings, occlusion of central artery or vein

**Other**
Myocardial infarction (even without CHD!), priapism, ....
Leukapheresis
ASFA & DGTI Cat I (symptomatic cases) or III (prophylactic)
Rationale and indications

Physiology: ... and regulation of capillary blood flow

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Trigger</th>
<th>Indication</th>
<th>Grade</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>Leukostasis</td>
<td>Treatment</td>
<td>1 B</td>
<td>I</td>
</tr>
<tr>
<td>AML/CML</td>
<td>WBC &gt; 100 G/l</td>
<td>Prophylaxis</td>
<td>2 C</td>
<td>III</td>
</tr>
<tr>
<td>ALL/CLL</td>
<td>WBC &gt; 400 G/l</td>
<td>Prophylaxis</td>
<td>2 C</td>
<td>III</td>
</tr>
</tbody>
</table>

... In the presence of unequivocal retinal findings, leukapheresis may be performed for even lower WBC counts ...
... cave-at: transfusion!

**Thrombapheresis**

ASFA & DGTI Cat II (symptomatic cases) or III (prophylactic)

**Rationale and indications in PV and ET**

<table>
<thead>
<tr>
<th>Thrombocytosis</th>
<th>Trigger</th>
<th>Indication</th>
<th>Grade</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive</td>
<td>not defined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in ET / MPN (usually &gt; 1’000 G/l)</td>
<td>Risk profile</td>
<td>Prophylaxis</td>
<td>2C</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>Symptoms (Microcirculation, organ dysfunction, bleedings)</td>
<td>Treatment</td>
<td>2C</td>
<td>II</td>
</tr>
</tbody>
</table>

Physiology: Haemostasis and ...

Erythrapheresis and RBC-exchange
Rationale and indications

- **Polycythaemia vera:** Cat III for symptomatic patients
- **Sickle cell disease:** Cat I for cerebral infarction, 
  Cat II for prim/sec stroke prophylaxis + prophylaxis of iron overload
- **Severe Malaria, Babesiosis, Filariosis:** Cat II for severe cases
- **Haemochromatosis:** Fe-depletion Cat III

# Erythropheresis and RBC-exchange

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Trigger / Indication</th>
<th>Goal</th>
<th>#</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycythemia vera</td>
<td>♂ Hct &gt; 0,60 l/l ♂ Hct &gt; 0,56 l/l</td>
<td>Hct 0,40-0,45 l/l</td>
<td>1-2</td>
<td>III</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Clinic, Ferritin &gt; 300 µg/l</td>
<td>Hct-reduction &lt; 0,20 l/l Ferritin &lt; 50 µg/l</td>
<td>1-3 / month</td>
<td>III</td>
</tr>
<tr>
<td>Sickle cell disease or compound</td>
<td>Acute CNS infarction</td>
<td>path. RBC &lt; 30 %</td>
<td>1-2</td>
<td>I</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>Acute pulmonary reaction</td>
<td></td>
<td></td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis CNS infarction, Prophylaxis iron-overload</td>
<td>path. RBC 30-50 %</td>
<td>1 / month</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>Multi organ failure</td>
<td>path. RBC &lt; 30 %</td>
<td>1-2</td>
<td>III</td>
</tr>
<tr>
<td>Babesiosis</td>
<td>&gt; 10 % affected RBC, neurologic symptoms, lung edema</td>
<td>path. RBC &lt; 5 %</td>
<td>1-2</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>&lt; 10 % affected RBC, but high-risk patients</td>
<td>path. RBC &lt;&lt; 5 %</td>
<td>1-2</td>
<td>II</td>
</tr>
<tr>
<td>Malaria</td>
<td>&gt;10 % affected RBC, neurologic symptoms, lung edema</td>
<td>path. RBC &lt; 5 %</td>
<td>1-2</td>
<td>II</td>
</tr>
<tr>
<td>Stem cell transplantation</td>
<td>AB0-minor or–bidirectional incompatible transplant</td>
<td>Exchange of recipient-RBC with group 0 RBC</td>
<td>1-2</td>
<td>III</td>
</tr>
</tbody>
</table>

Separation of plasma from whole blood by centrifugation and/or filtration.

Maintenance of volemia by replacement with a variable substitution fluid.
## Replacement Fluids: Advantages, Disadvantages, and Special Issues

<table>
<thead>
<tr>
<th>Replacement Fluid</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Special Issues</th>
</tr>
</thead>
</table>
| Normal Saline (crystalloid)| • Inexpensive  
• No risk of allergic reactions and …  
• disease transmission         | • Hypo-oncotic  
• Lacks coagulation factors & Ig                                           |                                                                              |
| Albumin (colloid)          | • Iso-oncotic;  
• Low risk of reactions  
• Low risk of disease transmission                                         | • More expensive  
• Lacks coagulation factors & Ig                                             |                                                                              |
| Plasma                     | • Contains coagulation factors & Ig                                          | • Risk of transfusion (allergic!) reactions  
• increased [citrate]                                                          | • Special transfusion requirements (i.e. AB0-, …)                             |
| Red Blood Cells            |                                                                              | • Risk of transfusion reactions                                               | • History RBC alloimmunization                                                  |

McLeod BC, Transfusion 2012;52:38S
Changing trends in use of plasma exchange by members of the Canadian Apheresis Group (1981-1997)

Changing trends in use of plasma exchange by members of the Canadian Apheresis Group (1981-1997)

Multiple Sclerosis

Evidence: several case series and one placebo-controlled trial, Curr Opin Neurol 2007;20:286-93

Multiple Sclerosis Therapy Consensus Group (MSTCG), J Neurol 2008;255:1449–1463

* In cases of ≥ 2 severe relapses per year it may also be used as basic therapy
** Change of these therapies at this stage of escalation not yet formally evaluated
*** Considered in some European countries as second line treatments but not indicated in France
§ Option in severe, steroid-resistant relapses

Fig. 1 Escalating immunotherapy of RRMS (update 2008)
Severe exudative pancreatitis by extreme hypertriglyceridemia (71.7 mmol/l, normal < 2 mmol/l). In addition to standard treatment plasmapheresis was performed at the ICU. Triglycerids decreased to 16 mmol/l. Caesarean section in the 34th week, birth of a healthy daughter.

Fontana S et al: Transfusion 2006;46:1853-1854
Plasma Exchange:
Kinetics of remaining fraction

\[
\text{Remaining patient plasma (\%)}
\]

\[
\text{Plasma exchange volume (in patient’s plasma volumes)}
\]

1 – 1,5 x PPV

36.8%

22.3%

13.5%

extravascular compartment

active + passive

active + passive

synthesis

intravascular compartment

whole blood removal

therapeutic plasma exchange

degradation

substitution fluids + blood cells + anticoagulants

Modifiziert nach Weinstein 2003
Selective Apheresis

- **Regenerative / non-regenerative systems;**
  Whole blood / component processing systems

- **Precipitation**
  e.g. HELP system (LDL-elimination)

- **Secondary Filtration**
  e.g. hollow-fibre membranes (e.g. LDL-elimination)

- **Adsorption**
  e.g. LDL-Immuno- / -dextran sulphate adsorption,
  Ig- Immunoadsorption, Protein A Immunoadsorption,
  other ligands like tryptophan, phenylalanin, ……..

- **Selective cytapheresis procedures**
  e.g. progenitor cells; dentritic cells; photopheresis;

---

Bundesausschuss Ärzte und Krankenkassen zum Thema therapeutische Hämapheresen mit selektiver Plasmadifferentialtrennung (ca. 800 Seiten):
The majority of diseases treated by TPE are linked by a common theme of pathogenesis: (Tissue) damage due to auto-antibodies and immune complexes (IC)

REMOVAL OF ANTIBODIES AND IC
Therapeutic Plasma Exchange (TPE)  
*Limitations: Causes and Consequences*

- Short lasting and symptomatic approach:  
  ➤ Supplementary medication recommended

- Antibody removal always incomplete, because:
  1. Extravascular reservoir not accessible  
     ➤ Multiple TPE at 1 - 3 day intervals
  2. Limited exchange volume per procedure  
     ➤ Selective removal of antibodies and IC
Ig Immunoabsorption

Rationale

Advantages of Ig IA (in comparison to TPE)

➢ Very efficient and selective removal of IgG and IC
➢ No need for substitution fluids
➢ Intensified treatment schedule possible

Clinical conditions with the necessity of repeated and/or intensified removal of circulating IgG and IC

Need of controlled ± randomized studies
Selective Removal of Immunoglobulins

**Indications (categories DGTI / ASFA)**

- **“Accepted” indications:**
  - HLA-sensitised (kidney) transplant rejection (I / pend)
  - Goodpasture’s syndrome (I / pend)
  - Myasthenia gravis (I / pend)
  - Guillain-Barré-Syndrome (I / pend)
  - CIDP (I / pend)
  - Rapid-progressive GN in Goodpasture-syndrome (I / pend)
  - Acquired autoimmune coagulopathy (II / III)
  - IgG/IgA/IgM-paraproteinemic polyneuropathy (II / III)
  - AB0-major-incompatible stem cell and kidney Tx (II / pend)
  - Severe Pemphigus (II / pend)
  - Lambert-Eaton-Syndrome (II / pend)
  - focal and segmental glomerulosklerosis (II / pend)
  - Idiopathic dilated cardiomyopathy (III / III)

Protein A Immunoabsorption (PAIA)
Protein A Immunoadsorption (PAIA)
Protein A Immunoabsorption (PAIA)

- Immunoglobulins adsorbed with Staph Protein A bound to Sepharose
- Column regenerated with sodium citrate 0.13 M buffer at a pH of 2.2
- Removes 97% IgG1, 98% IgG2, 40% IgG3, 77% IgG4, 56% IgM, 55% IgA

Graphics: Fresenius HemoCare
Coagulation Factor VIII Inhibitors
Causes and consequences

Haemophiliacs
- **Allo**-antibodies
- Overall prevalence 5-7 %
  Severe disease: 12-13 %

Non-haemophiliacs
- **Auto**-antibodies
- rare

➢ (Life-threatening) bleedings
➢ Serious treatment problems

F VIII Inhibitors in Non-haemophiliacs

Case 1
F VIII Inhibitors

Therapeutic strategies

Goals:

Control / prevent acute haemorrhages

Induce immune tolerance
**Therapeutic Strategies**

*Modified Malmoe Protocol*

- **Induction therapy (repeated on day 21, if required)**
  - Removal of F VIII inhibitors (Prot-A-IA, 3-5x)
  - Cyclophosphamide 12-15 mg/kg i.v. on days 1 and 2
  - IV-IgG 0.4 g/kg for 5 days

- **Long-term maintenance therapy**
  - Prot-A-IA (weekly ➔ tapered off)
  - Cyclophosphamide and/or Corticosteroids p.o. (daily)

*Main differences to the original Malmoe protocol*

1) No F VIII application with view to immunomodulation
2) Supplementation of maintenance therapy
F VIII Inhibitors in Non-haemophiliacs

Case 1

Patient characteristics
63 years, female
Life-threatening bleedings in mouth and neck
F VIII activity 9%; F VIII inhibitor 123 BU/mL

Treatment
Initial stabilization by porcine F VIII
3 cycles of induction therapy
12 months of maintenance therapy
F VIII Inhibitors in Non-haemophiliacs

Treatment course of case 1

Ongoing complete remission since March 1996
F VIII Inhibitors in Non-haemophiliacs
Results of different treatment strategies (I)

- Immunosuppressive single agent therapy¹
  - Corticosteroids: 22/45 patients with PR or CR
  - Cyclophosphamide: 37/80 patients with PR or CR

- Immunosuppressive combination therapy²
  - Corticosteroids + Cycloph.: 5/10 patients with CR

F VIII Inhibitors in Non-haemophiliacs

Results of different treatment strategies (II)

Immunoabsorption + immunosuppression:

• Meanwhile > 100 patients
• CR in > 90% with up to 20 Y of follow-up

F VIII Inhibitors in Non-haemophiliacs

Substitution and treatment costs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>~Price (SFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemate HS</td>
<td>1‘000 IE i.v.</td>
<td>1’000</td>
</tr>
<tr>
<td>Recombinate</td>
<td>1‘000 IE i.v.</td>
<td>1’250</td>
</tr>
<tr>
<td>Hyate C</td>
<td>1‘000 IE i.v.</td>
<td>2’200</td>
</tr>
<tr>
<td>FEIBA S-TIM 4</td>
<td>1‘000 IE i.v.</td>
<td>1’500</td>
</tr>
<tr>
<td>Novoseven</td>
<td>4.8 mg i.v.</td>
<td>4’000</td>
</tr>
<tr>
<td>Prednison</td>
<td>100 mg p.o.</td>
<td>1</td>
</tr>
<tr>
<td>Endoxan</td>
<td>1.0 g i.v.</td>
<td>35</td>
</tr>
<tr>
<td>Octagam</td>
<td>10 g i.v.</td>
<td>750</td>
</tr>
<tr>
<td>Mabthera</td>
<td>500 mg i.v.</td>
<td>2’500</td>
</tr>
</tbody>
</table>
F VIII inhibitors in non-haemophiliacs

Conclusions

A combination of immunosuppression with immunoadsorptions to Protein A seems to be efficient, safe and cost-effective in patients with F VIII autoantibodies.

DGTI / ASFA category II / III for IA

**Pemphigus vulgaris** is an autoimmune blistering disease of the skin and mucous membranes caused by circulating antibodies to desmogleins.
Pemphigus vulgaris

Therapeutic strategies

Goals:

- Control acute disease activity
- Induce immune tolerance
Patient # 4 before and after 4 x PAIA
Treatment Protocol*

*Arch Dermatol Res 2010;302:241–253
“Latest data 2010”*

- Meanwhile more than 50 patients with severe pemphigus were successfully treated with a treatment protocol including PAIA.

- The majority showed a dramatic clinical response within 2 weeks after the initiation of PAIA.

- In the majority of patients, PAIA has been tapered off completely without clinical relapse.

*Arch Dermatol Res 2010;302:241–253
Conclusions

The implementation of PAIA into a concept of immunomodulatory / immunosuppressive treatment seems to be efficient, safe and cost-effective in the therapy of otherwise refractory or life-threatening autoimmune diseases. Controlled studies are mandatory.
Thrombotic Thrombocytopenic Purpura (TTP) (Moschcowitz 1924)

- Microangiopathic haemolytic anaemia
- Thrombocytopenia
- Fever
- Neurological signs / symptoms
- Renal dysfunction
Acute non-familial TTP

- 20/24 and 37/37 patients had vWF-cleaving protease deficiency (< 5%)

- 20/24 and 26/37 had a protease inhibitor
  (IgG in 5/5 and 26/26 tested)
TTP and vWF-cleaving protease deficiency

vWF multimere

ADAMTS 13
(Swiss model)
TTP and vWF-cleaving protease deficiency

*Implications for Therapy*

- Extensive plasma exchange
- Immunosuppressive therapy
- Ig(G!) Immunoadsorption (?)
- Splenectomy

Fontana S et al. Vox Sang 2006;90:245-254
PAIA: pathophysiological insights in TTP

Adverse Reactions (AR)

- **AR related to Central venous catheters:** dysfunction, occlusion, thrombosis ± lung embolism, haemato-/pneumothorax, infections

- **AR related to anticoagulation:**
  - Paraesthesia, nausea, vomiting, tetany
  - Alkalosis, hypokaliaemia
  - Possibly increased bleeding tendency

- **Hypotension:**
  hypovolaemia (extracorporeal volume, bleeds), vasovagal reaction, anti-hypertensive drugs, allergic reactions, pre-existing infections or neurological or cardiovascular diseases

- **Allergic Reaction:**
  possibly aggravated due to ACE-inhibitors

Citrate use and duration of different apheresis procedures

Buchta C et al., Transfusion 2003;43:1615-1621
Ca2+ support increased subjective tolerance towards LVL, as assessed by an ordinal scale and the VAS rating system

Buchta C et al., Transfusion 2003;43:1615-1621
Calcium substitution indicated?

Stem cell apheresis Yes
Plasma exchange Yes
Leukocyte depletion Yes
Platelet depletion Yes
Donor platelet-apheresis ?
Donor red cell apheresis ?

- Bolan: 0.1 mmol Ca++ / mmol citrate
- NIH: 0.11 mmol Ca++ / mmol citrate
- Buchta: 0.053 mmol Ca++ / mmol citrate