# SD-Plasma transfusion protocols in children

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# Disclosure

- Head of the apheresis unit, blood blank and tissue bank, pediatric hemoncologist, neonatologist and pediatric intensivist at the St. Anna Kinderspital, Vienna, Austria
- Medical director of plasmapheresis unit Plasmapunkt, Vienna, Austria
- Working as a physician in transfusion medicine at the austrian red cross blood bank, Vienna, Austria
- Worked as a physician in transfusion medicine at the Medical University of Vienna, Department of Transfusion medicine

# Indication

- The main indication for the transfusion of plasma is to correct deficiencies of clotting factors, for which a specific concentrate is not available, **in patients with active bleeding**.

Liumbruno G. (SIMTI) Blood Transfus 2009; 7: 132-150

# Products available

- FFP = fresh frozen plasma
- Plasma with viral inactivation
  - SD FFP = solvent detergent treated plasma
  - MB FFP = methylene blue treated plasma
  - Psoralen FFP = amatoselen (S59) plus UVA treated plasma
  - Riboflavin FFP = riboflavin plus UV light treated
  - UVC FFP = UVC treated plasma

Liumbruno G. (SIMTI) Blood Transfus 2009; 7: 132-150

# Solvent/detergent-treated plasma

- S/D FFP is a pharmaceutical product, obtained from a pool of about 1,000 units of FFP, with the following characteristics:
  - high batch per batch standardisation;
  - declared concentration/activity of the biologically active proteins;
  - reduced immunological risks related to the presence of antibodies, cells (or their fragments);
  - inactivation of the majority of potentially transmissible pathogens;
  - selective elimination of units contaminated by hepatitis A virus or parvovirus B19

Liumbruno G. (SIMTI) Blood Transfus 2009; 7: 132-150

# Side effects

- “Anaphylactic or anaphylactoid reactions due to hypersensitivity to infused plasma proteins or anti-IgA following the transfusion of Solvent Detergent Plasma (SDP) are rare (<1: 1000) and are likely to be of the same order as for FFP.”

Liumbruno G. (SIMTI) Blood Transfus 2009; 7: 132-150

# The usual starting dose of SDP is 12-15 mls/Kg.

- Monitor the response both clinically and with measurement of prothrombin time (PT), partial thromboplastin time (PTT)
- The infusion of SDP should begin as soon as clinical circumstances permit after thawing.
- Beware volume overload if rapid infusion is used in patients with limited cardiac reserve. (max rate 2-4mls/kg per hour in such patients)
- Each unit of SDP contains a standard volume of 200mls, in contrast to a unit of FFP, which contains 220-300mls.
- Plasma therapy should only be given where there is a clear clinical indication and where the expected benefit outweighs the inherent risks.

# Firm indications for giving plasma include:

- The correction of haemostatic disorders where no other more suitable therapy exists or is available.
- Emergency warfarin reversal where prothrombin complex concentrates are unavailable.

**SDP is only required for the reversal of over anticoagulation in the presence of major bleeding.**

- Haemostatic failure associated with major blood loss
- Liver disease, either in the presence of haemorrhage, or prior to an elective procedure
- Acute Disseminated Intravascular Coagulation
- Factor V deficiency and acetyl cholinesterase deficiency
- The treatment of choice in thrombotic thrombocytopenic purpura (TTP) in conjunction with plasma exchange

*Vox Sanguinis* (2007) **92**, 206–212

**ORIGINAL PAPER**

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DOI: 10.1111/j.1423-0410.2006.00884.x

# Normal levels of ADAMTS13 and factor H are present in the pharmaceutically licensed plasma for transfusion (Octaplas®) and in the universally applicable plasma (Uniplas) in development

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[2]*Octapharma Pharmazeutika Produktionsges.m.b.H, Molecular Biochemistry, Arnimallee 22, D-14195 Berlin, Germany*

| Plasma products | ADAMTS13 activity (U/ml) | ADAMTS13 antigen (µg/ml) | Factor H antigen (mg/ml) |
|---|---|---|---|
| Single-donor FFP ($n$ = 20) | 1·24 ± 0·11 | 0·96 ± 0·08 | 0·48 ± 0·09 |
| Octaplas® ($n$ = 24) | 0·96 ± 0·06[a] | 0·89 ± 0·07[a] | 0·47 ± 0·03 |
| Uniplas ($n$ = 3) | 0·99 ± 0·05 | 0·90 ± 0·06 | 0·49 ± 0·01 |

[a]Statistically significant difference compared with mean of single-donor fresh-frozen plasma (FFP) units.
Mean levels ± standard deviation are presented.

Acta Pædiatr 91: 1056–1059. 2002

Taylor&Francis healthsciences

# Remission of thrombotic thrombocytopenic purpura in a patient with compound heterozygous deficiency of von Willebrand factor-cleaving protease by infusion of solvent/detergent plasma

K Kentouche[1], U Budde[2], M Furlan[3], V Scharfe[4], R Schneppenheim[5] and F Zintl[1]

*Department of Paediatrics[1], Friedrich-Schiller-University , Jena, Germany; Laboratory Arndt and Partners[2], Hamburg, Germany; Central Haematology Laboratory[3], University Hospital, Inselspital, Bern, Switzerland; Hospital Dresden Neustadt[4], Department of Paediatrics, Dresden, Germany; Department of Paediatric Haematology and Oncology[5], University Hospital Hamburg-Eppendorf, Hamburg, Germany*

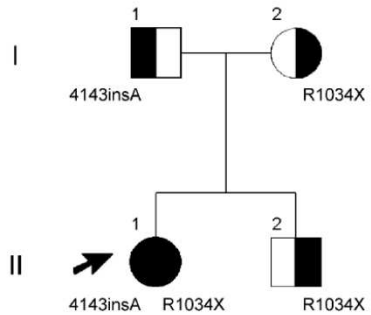


*Fig. 4.* The pedigree of the patient's family depicts the inherited transmission of mutations in the ADAMTS13 gene. The patient (arrow) is compound heterozygous for two mutations, whereas the heterozygous family members are clinically unaffected.

Kentouche K, Budde U, Furlan M, Scharfe V, Schneppenheim R, Zintl F. Remission of thrombotic thrombocytopenic purpura in a patient with compound heterozygous deficiency of von Willebrand factor-cleaving protease by infusion of solvent/detergent plasma. Acta Pædiatr 2002; 91: 1056–1059. Stockholm. ISSN 0803-5253

Plasma exchange or plasma infusion is considered to be the therapy of choice in patients with thrombotic thrombocytopenic purpura (TTP) who are deficient in von Willebrand factor-cleaving protease (VWF-CP). Recently, mutations in the ADAMTS13 gene were identified as being responsible for VWF-CP deficiency in patients with familial TTP (VWF-CP deficiency in the absence of an inhibitor). Here we report on a girl who presented with recurrent thrombocytopenia and anaemia since birth, developing the full pentad of characteristic TTP at the age of 16 y. Congenital TTP was confirmed on the basis of severe VWF-CP deficiency in the absence of an acquired inhibitor. The patient was found to be compound heterozygous for two hitherto undescribed mutations in the ADAMTS13 gene: a truncating frame shift mutation, 4143insA in exon 29, and the nonsense mutation 3100A $>$T in exon 24 (R1034X). After infusion of solvent/detergent plasma, the patient went into remission and remained asymptomatic under regular plasma therapy at 2-wk intervals for over two years.

*Conclusion:* TTP in childhood may be mild and oligosymptomatic. Determination of VWF-CP activity is helpful in the differential diagnosis of thrombocytopenia.

*Table 1.* Laboratory data prior to and after one year of solvent/detergent plasma therapy.

| | Before | After (1 d after the last plasma infusion) |
|---|---|---|
| Hb (mmol/L) | 4.8 | 8.5 |
| WBC ($\times 10^9$/L) | 4.8 | 5.5 |
| Platelets ($\times 10^9$/L) | 37 | 162 |
| Reticulocytes (‰) | 336 | 10 |
| LDH (U/L) | 908.4 | 120 |
| Haptoglobin (g/L) | <0.06 | n.d. |
| Bilirubin (μmol/L) | 43.6 | 8.4 |
| Creatinine (μmol/L) | 214 | 61 |
| Glomerular filtration rate (ml/min/L.73 $m^2$) | 37.3 | 115.8 |
| Albuminuria (mg/mmol crea) | 71.8 | 9.5 |
| Alpha-1-microglobulin (mg/mmol crea) | 7.16 | 0.52 |
| VWF: Ag (%) | 220 | 100 |
| VWF: RCo (%) | 358 | 70 |

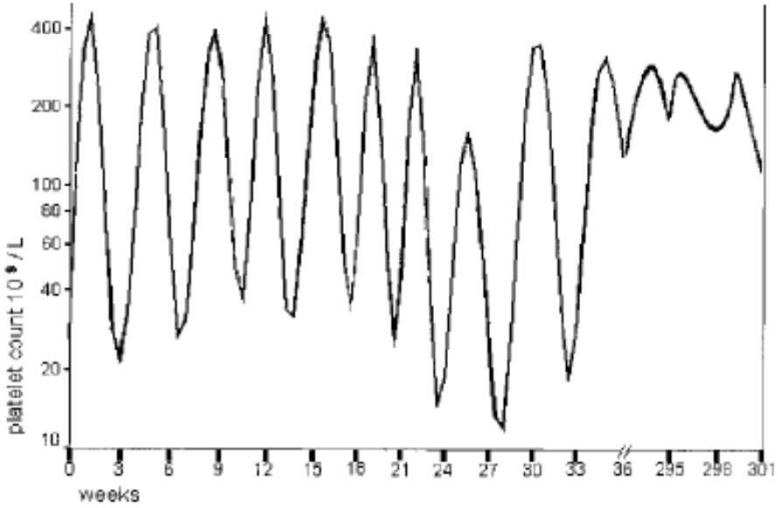


*Fig. 3.* Platelet counts during treatment with plasma infusion. The first 10 infusions at intervals of 3 wk kept the patient free of symptoms of thrombocytopenic purpura (TTP) but there was still remarkable platelet consumption. Shortening the intervals to 2 wk maintained the platelet count above $200 \times 10^9$/L.

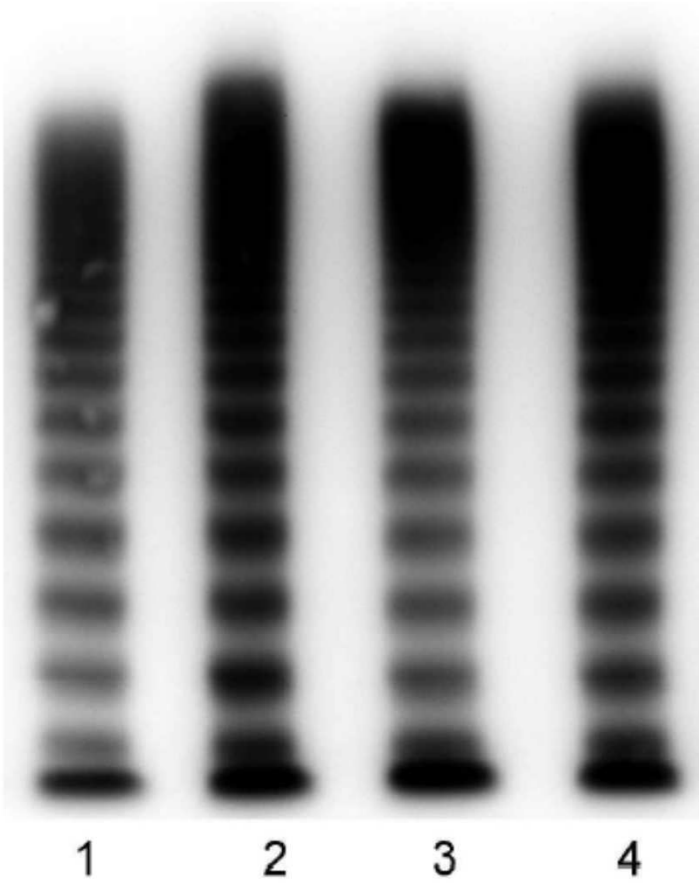


*Fig. 1.* Multimeric analysis of plasma von Willebrand factor (VWF) in a low affinity SDS agarose gel: 1 = pooled normal human plasma, 2 = patient's plasma before SD- (solvent/detergent) plasma infusion, 3 = patient's plasma after SD-plasma infusion, 4 = plasma from the patient's father. The patient's plasma samples were both analysed during remission of acute thrombocytopenic purpura (TTP). Plasma infusion reduces the slowly migrating large VWF multimers of the patient to a level comparable with that of the clinically asymptomatic father, but not to pool plasma.

# Acquired, noncongenital thrombotic thrombocytopenic purpura in children and adolescents: clinical management and the use of ADAMTS 13 assays

Vickie McDonald[a], Ri Liesner[b], John Grainger[c], Michael Gattens[d], Samuel J. Machin[a] and Marie Scully[a]

| CASE | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| PEX to 1st clinical remission | 15 | 41 | Nil: 6 doses BPL 8Y | 30 | 30 | 15 | 10 |
| Adjunctive treatment | Rituximab (×4), MP × 3 doses | Rituximab (×6) MP × 3 doses | Rituximab (×4) prednisolone | Prednisolone | Rituximab (×4) MP × 3 doses | Rituximab (×4) MP | Rituximab (×6), MP × 3 doses |
| ADAMTS13 activity in remission (%) | <5 | 39 | 73 | ND | 66 | 70 | <5 |
| Anti ADAMTS13 IgG in remission (%) | 34–120 | <4 | <4 | ND | 48 (noninhibitory) | <4 | 90 |
| Time to relapse (months) | 19 | 12 | No relapse | 24 | No relapse | No relapse | No relapse |
| Total follow up (months) | 24 | 35 | 38 | 25 | 9 | 16 | 12 |

LDH, Lactate dehydrogenase; MP, methylprednisolone; NA, not applicable; ND, not done; PEX, plasma exchange. Normal ranges: creatinine: a: 49–92 mmol/l; b: 35–125 mmol/l; LDH 470–900 IU/l; Troponin T <0.01 μg/l, ADAMTS13 activity >66%, ADAMTS13 mixing study >50%, Anti-ADAMTS13 IgG <4%.

for PEX Octaplas was used

Blood Coagul Fibrinolysis 21:245 – 250 2010

*Vox Sanguinis* (2008) **94**, 48–55

**ORIGINAL PAPER**

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# A biochemical quality study of a pharmaceutically licenced coagulation active plasma (Octaplas®) thawed by the SAHARA-III dry tempering system compared to the regular use of a water bath

**A. Heger, J. Römisch & T.-E. Svae**

*Octapharma Pharmazeutika Produktionsges.m.b.H, Pre-Clinical Research & Development Department, Oberlaaer Strasse 235, A-1100 Vienna, Austria*

| Parameters | Octaplas® thawed in a water bath | Octaplas® thawed by the SAHARA-III dry tempering system | Statistical significance *P* value |
|---|---|---|---|
| Visual control | Passed[a] | Passed[a] | |
| Total protein (mg/ml) | 60 (58–61) | 60 (59–60) | |
| pH value | 7·3 (7·2–7·4) | 7·2 (7·2–7·2) | ≤ 0·05 |
| Osmolality (mosmol/kg) | 367 (358–382) | 364 (356–375) | |

Parameter levels are shown as mean (minimum–maximum) values ($n = 6$); $P \leq 0{\cdot}05$, statistically significant difference between Octaplas® thawed in a water bath or by the SAHARA-III dry tempering system.

[a]The thawed plasma is clear to slightly opalescent and free of solid or gelatinous particles.

# Presence of HLA antibodies in single-donor-derived fresh frozen plasma compared with pooled, solvent detergent-treated plasma (Octaplas®)

**P. Sinnott,* S. Bodger,* A. Gupta* & M. Brophy†**

© 2004 Blackwell Publishing Ltd, *European Journal of Immunogenetics* **31**, 271–274

**Table 1.** Prevalence of HLA antibodies in SDFFP (Octaplas®) and single-donor units of FFP using HLA-specific ELISA

| ELISA kit | SDFFP (Octaplas®) ($n$ = 12) | Single-donor units FFP ($n$ = 58) |
|---|---|---|
| GTI Quikscreen/B screen (Screen for HLA class I and II IgG, IgA and IgM) | All samples negative | Two of 58 samples positive for class I only |
| GTI Quest Quik/B screen (Screen for HLA class I and II IgG only) | All samples negative | Five of 58 class I positive, of which three were also class II positive |

**Table 2.** Summary of results for ELISA, CDC and flow cytometric analyses of the HLA-specific antibody-positive FFP samples

| Sample | ELISA | CDC | Flow cytometry |
|---|---|---|---|
| 1 | Weak positive (HLA class I) | Negative | Weak positive |
| 2 | Weak positive (HLA classes I and II) | Negative | Weak positive |
| 3 | Weak positive (HLA classes I and II) | Negative | Weak positive |
| 4 | Weak positive (HLA classes I and II) | Negative | Weak positive |
| 5 | Strong positive (specific HLA-B15 and B17) | Positive (specific HLA-B15 and B17) | Strong positive |

## COMPARISON OF P … E TREATMENT OF

GAIL A. RO … RD, M.D.,
VICTOR S. BLANCHETTI … RT A. SPASOFF, M.D.,

**Abstract** *Background.* … and after six months.
purpura is an uncommon … t treatment cycle patients
even with current treatme … a higher rate of response
and its optimal treatmen … platelet count (24 of 51
plasma exchange and pla … d plasma infusion (13 of
treatments, it is not clear … nts treated with plasma
we describe a prospecti … the 51 patients who re-
plasma exchange with pla … = 0.035).
thrombotic thrombocytope … in the plasma-exchange
*Methods.* One hundre … sponse observed in 40 of
thrombocytopenic purpura … tients in the plasma-infu-
ceive either plasma exc … 2). Eleven patients in the
fresh-frozen plasma on s … s did 19 patients in the
entry into the trial. The tot … 36). The overall mortality
patients undergoing plas … ge is more effective than
that received by patients … of thrombotic thrombocy-
the patients also receive … topenic purpura. (N Engl J Med 1991; 325:393-7.)
outcomes in the two groups were compared at the end of

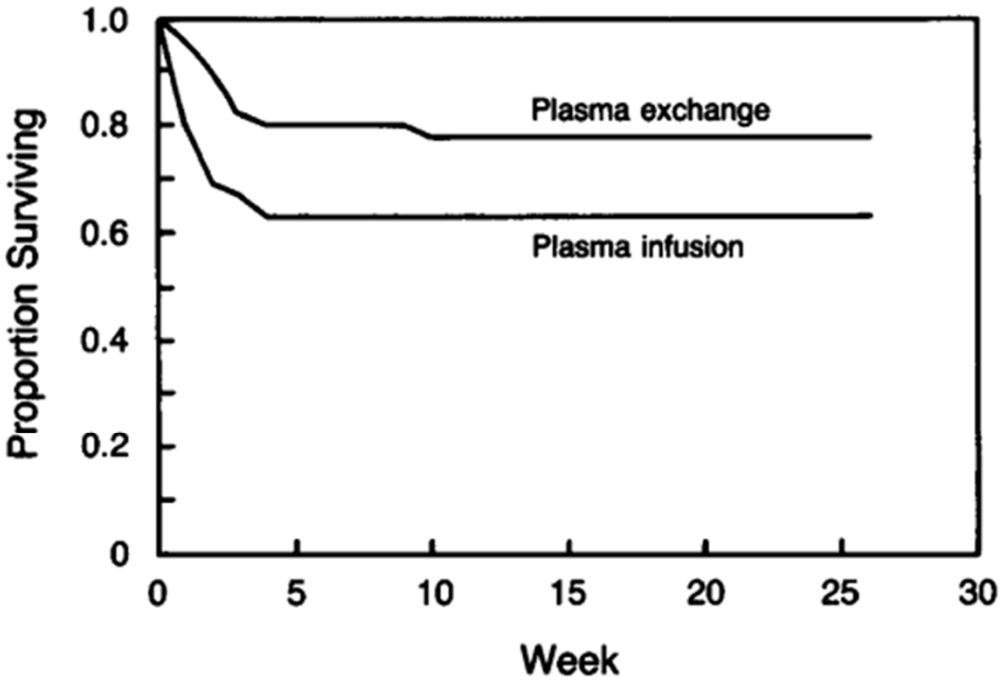



Figure 1. Survival of Patients with Thrombotic Thrombocytopenic Purpura.

The survival curves differ significantly (P = 0.036 by the Breslow–Gehan test).

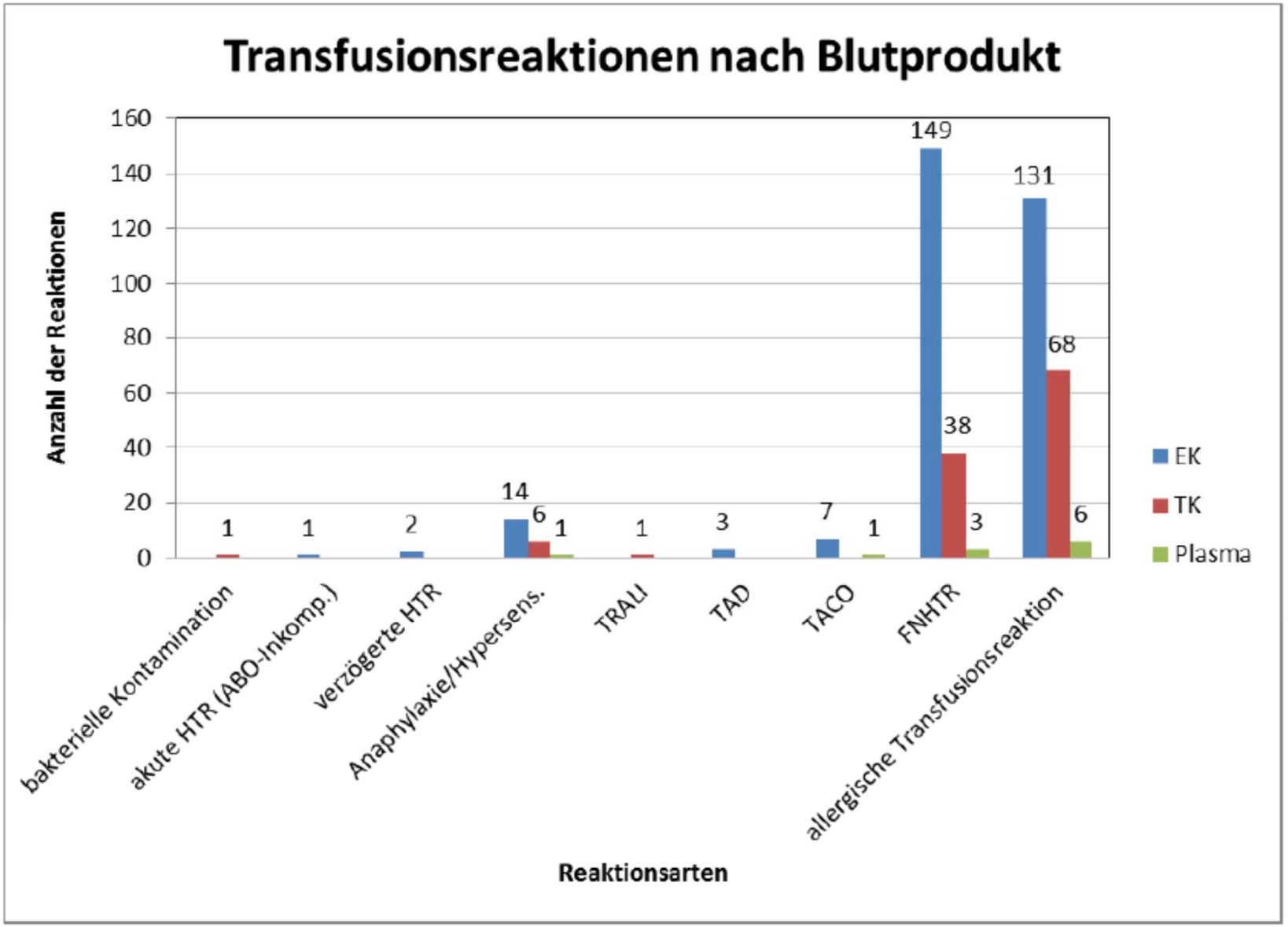
Br J Haematol. 2003 Jun;121(5):778-85.

**Venous thromboembolism associated with the management of acute thrombotic thrombocytopenic purpura.**

Yarranton H, Cohen H, Pavord SR, Benjamin S, Hagger D, Machin SJ.
Haemostasis Research Unit, Department of Haematology, University College London, UK. hyarranton@hotmail.com

## Abstract

Venous thromboembolism (VTE) is not a feature of thrombotic thrombocytopenic purpura (TTP), but there has been a recent report of VTE in association with plasma exchange (PEX) treatment for TTP using the solvent detergent (SD) plasma, PLAS+SD. We reviewed the occurrence of VTE in 68 consecutive patients with TTP (25 men, 43 women). Eight documented VTE events [six deep venous thromboses (DVTs), three pulmonary emboli] were identified in seven patients (all female) during PEX therapy. All six DVTs were associated with central lines at the site of thrombosis. Other known precipitating factors included pregnancy, immobility, obesity and factor V Leiden heterozygosity. VTE occurred at a mean of 53 d following the first PEX. The European SD plasma, Octaplas was the last plasma to be used in PEX prior to the VTE in 7/8 events. **This is the first report of VTE following Octaplas infusion**. VTE is a multifactorial disease and, although several known precipitating factors were present in all patients in this study, the use of large volumes of SD plasma in PEX may be an additional risk factor. We recommend prevention of VTE with graduated elastic compression stockings (class I) at diagnosis and prophylactic low-molecular-weight heparin once the platelet count rises above 50 x 10(9)/l.




personel communication BASG Mrs. Friedl: no Octaplas™ was involved in anaphylaxie / TACO

# THERAPEUTIC USE OF FFP

# Indications for the use of Plasma

- Supportiv transfusion in case of massive transfusions to stabilize the hemostatic function (=> ROTEM)
- Exchangetransfusions, Priming of medical systems (ECMO)
- Bleeding from Vitamin K deficiency
- DIC
- Congenital bleeding disorder where no factor concentrates are available

An approach to clinical reasoning for plasma transfusion

# Patient with deranged coagulation

| | |
|---|---|
| Bleeding | Going to have an invasive procedure |
| Give FFP | Give FFP |
| Coagulation corrects | Coagulation corrects |
| Bleeding stops, uncertain effects on other cloncal outcomes, such as mortality | Bleeding prevented, uncertain effects in other clinical outcomes, such as mortality |

J Anesth
DOI 10.1007/s00540-012-1400-z

CLINICAL REPORT

# Thromboelastometry during intraoperative transfusion of fresh frozen plasma in pediatric neurosurgery

**Teemu Luostarinen · Marja Silvasti-Lundell · Tatjana Medeiros · Rossana Romani · Juha Hernesniemi · Tomi Niemi**

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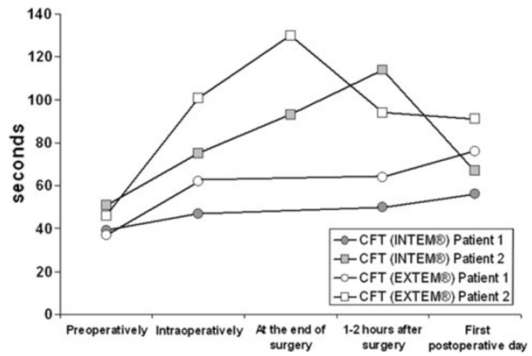


**Fig. 1** Clot formation time (*CFT*) in Intem® (normal reference range, 30–110 s) and Extem (34–159 s) analyses

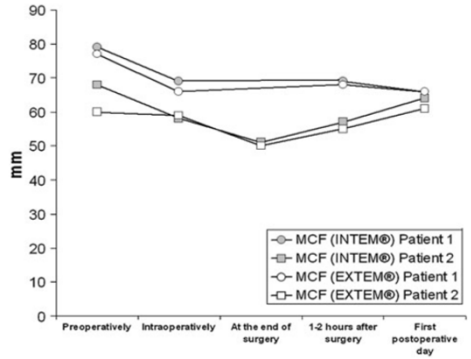


**Fig. 2** Maximum clot firmness (*MCF*) in Intem® (normal reference range, 50–72 mm) and Extem (50–72 mm) analyses

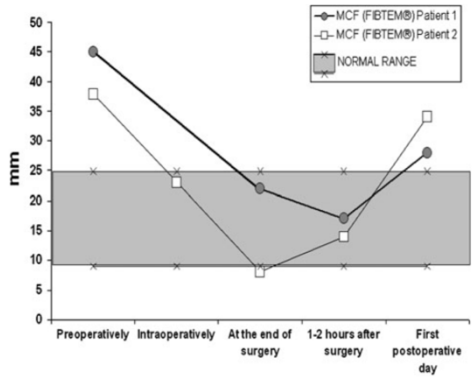


**Fig. 3** Maximum clot firmness (*MCF*) in Fibtem® analysis

J Anesth
DOI 10.1007/s00540-012-1400-z

CLINICAL REPORT

**Thromboelastometry during intraoperative transfusion of fresh frozen plasma in pediatric neurosurgery**

Teemu Luostarinen · Marja Silvasti-Lundell · Tatjana Medeiros · Rossana Romani · Juha Hernesniemi · Tomi Niemi

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- By using FFP instead of large amounts of crystalloids and colloids when major blood loss is expected, blood coagulation is probably less likely to be impaired.
- Our results indicate, however, that the capacity of FFP to correct fibrinogen deficit is limited.

# The use of fresh-frozen plasma in England: high levels of inappropriate use in adults and children

*Simon J. Stanworth, John Grant-Casey, Derek Lowe, Mike Laffan, Helen New, Mike F. Murphy, and Shubha Allard*

**TRANSFUSION** 2011;51:62-70.

- Every hospital was ask to collect data on 40 consecutive different patients recieving FFP transfusions within a 3-month period.
- 114/4696 (2.3%) patients were 1 to 15 years old
  - 38/114 (33%) on PICU
  - 40/114 (35%) on operating room or recovery
  - 55/114 (48%) for non bleeding indications (INR 1.6 (1.2-1.8)) INR reduction 0.1
  - FFP dose: 12 ml/kg (25/104 recieving less than 10 ml/kg)
  - 18/114 (16%) no documented INR or PT before
  - 27/114 (27%) no documented INR or PT after
- 220/4686 (4.4%) patients were < 1 year old
  - 176/220 (80%) on NIC
  - 31/220 (14%) on operating room or recovery
  - 136/220 (62%) for non bleeding indications (INR 1.7 (1.3-2.2)) INR reduction 0.2
  - FFP dose: 14ml/kg (41/202 recieving less than 10 ml/kg)
  - 18/114 (16%) no documented INR or PT before
  - 27/114 (27%) no documented INR or PT after

# Who transfuses what in pediatric wards?

- 1607 blood products were delivered to 233 children
  - 806 pRBC
  - 670 platelet concentrates
  - 131 plasma units
- 68.2% oncohematological ward
- 15.4% intensive care unit
- 10.2% surgery

Navarro C. Arch Pediatr. 2011;1154-61

CHAPTER 20

# The Bleeding Child: Congenital and Acquired Disorders

BRIAN M. WICKLUND, MD, CM, MPH

*Handbook of Pediatric Transfusion Medicine*
*2004*



TABLE 20.6 Rare Hereditary Coagulation Factor Deficiencies

| Factor Deficiency | Bleeding Symptoms (Homozygous Patients) | Treatment | Comments |
|---|---|---|---|
| Factor XI (hemophilia C) | Mild to moderate: epistaxis, easy bruising, bleed postdental or surgical procedures, menorrhagia | 15–20 mL/kg FFP load, 7.5–10 mL/kg every 12–24 hours. (Factor XI concentrate available in Europe) | Maintain 40% to 60% factor level for hemostasis. Antifibrinolytics for dental procedures. |
| Factor XIII | Moderate to severe: umbilical stump bleeds, ICH, SQ, or muscle hematomas, bleeding postdental or surgical procedures | 5–10 mL/kg FFP every 3–4 weeks. (Factor XIII concentrate available) | Prophylactic infusions to prevent bleeding. Antifibrinolytics for dental procedures. |
| Factor VII | Severe: umbilical stump, cephalohematomas, ICH, mucocutaneous bleeding, hemarthrosis, GI bleeding, menorrhagia, bleed postdental or surgical procedures, bleeding postpartum | 10–15 mL/kg FFP every 4–6 hours. rFVIIa for severe hemorrhage or surgery. | rFVIIa dosing 20–30 μg/kg/dose, lower than in inhibitor therapy. Vitamin K therapy of no benefit. |
| Factor X | Moderate to severe: hemarthrosis, deep hematomas, menorrhagia, bleeding postsurgical procedure or trauma, neonatal ICH | 20 mL/kg FFP load, 6 mL/kg every 12 hours for minor bleeding episodes. Prothrombin complex concentrates for surgery | Estrogens may help in reducing bleeding. |
| Factor V | Mild to moderately severe: epistaxis, hematomas, postsurgical or trauma, menorrhagia, postpartum, neonatal ICH, GI, and GU | 20 mL/kg FFP load, 6 mL/kg every 12 hours. May need platelet transfusions in severe bleeding. | Hemarthrosis or deep muscle bleeds are rare. |
| Factor II (prothrombin) | Mild to moderate: epistaxis, hematomas, GI bleeding, menorrhagia, postsurgical or trauma, postpartum | 10–20 mL/kg FFP load, 3 mL/kg every 12–24 hours. Prothrombin complex concentrates | Hemarthrosis are rare. 60 hour half-life, retreatment rarely needed. |
| Afibrinogenemia | Severe: ecchymosis, GI bleeding, hemarthrosis, bleeding postsurgery, posttrauma, or with dental procedures, severe menorrhagia, neonatal ICH, recurrent abortions, abruptio placenta | 4 bags/10 kg (max dose 10 bags). Cryoprecipitate every other to every fourth day. (Fibrinogen concentrate available in Europe.) | Frequent problems with fetal loss in affected females. Consider prophylactic infusions every 3–4 days. |
| Hypofibrinogenemia | Mild: menorrhagia, postsurgical or posttraumatic, recurrent abortions, placental abruption | 4 bags/10 kg (max dose 10 bags). Cryoprecipitate every other to every fourth day. (Fibrinogen concentrate available in Europe.) | Prophylaxis based on severity of bleeding symptoms. |
| Dysfibrinogenemia | Asymptomatic to mild: epistaxis, menorrhagia, bleeding postsurgical or posttrauma | 4 bags/10 kg (max dose 10 bags) Cryoprecipitate every other to every fourth day. (Fibrinogen concentrate available in Europe.) | If fibrinogen activity is >50 mg/dL, fewer bleeding problems. |
| Alpha 2-Antiplasmin | Severe: umbilical cord stump, hemarthrosis, hematomas, epistaxis, posttraumatic, postsurgical or dental procedures, menorrhagia | Antifibrinolytics-epsilon aminocaproic acid or tranexamic acid | Differentiate from hemophilia |
| PAI-1 | Severe: hemarthrosis, hematomas, menorrhagia, easy bruising, severe postsurgical or posttraumatic bleeding | Antifibrinolytics-epsilon aminocaproic acid or tranexamic acid | Differentiate from hemophilia |

FFP = Fresh frozen plasma; ICH = intracranial hemorrhage; SQ = subcutaneous; rFVIIa = recombinant factor VIIa; GI = gastrointestinal; GU = genitourinary; PAI-1 = plasminogen activator inhibitor-1.

## Indication for Transfusion of FFP in children

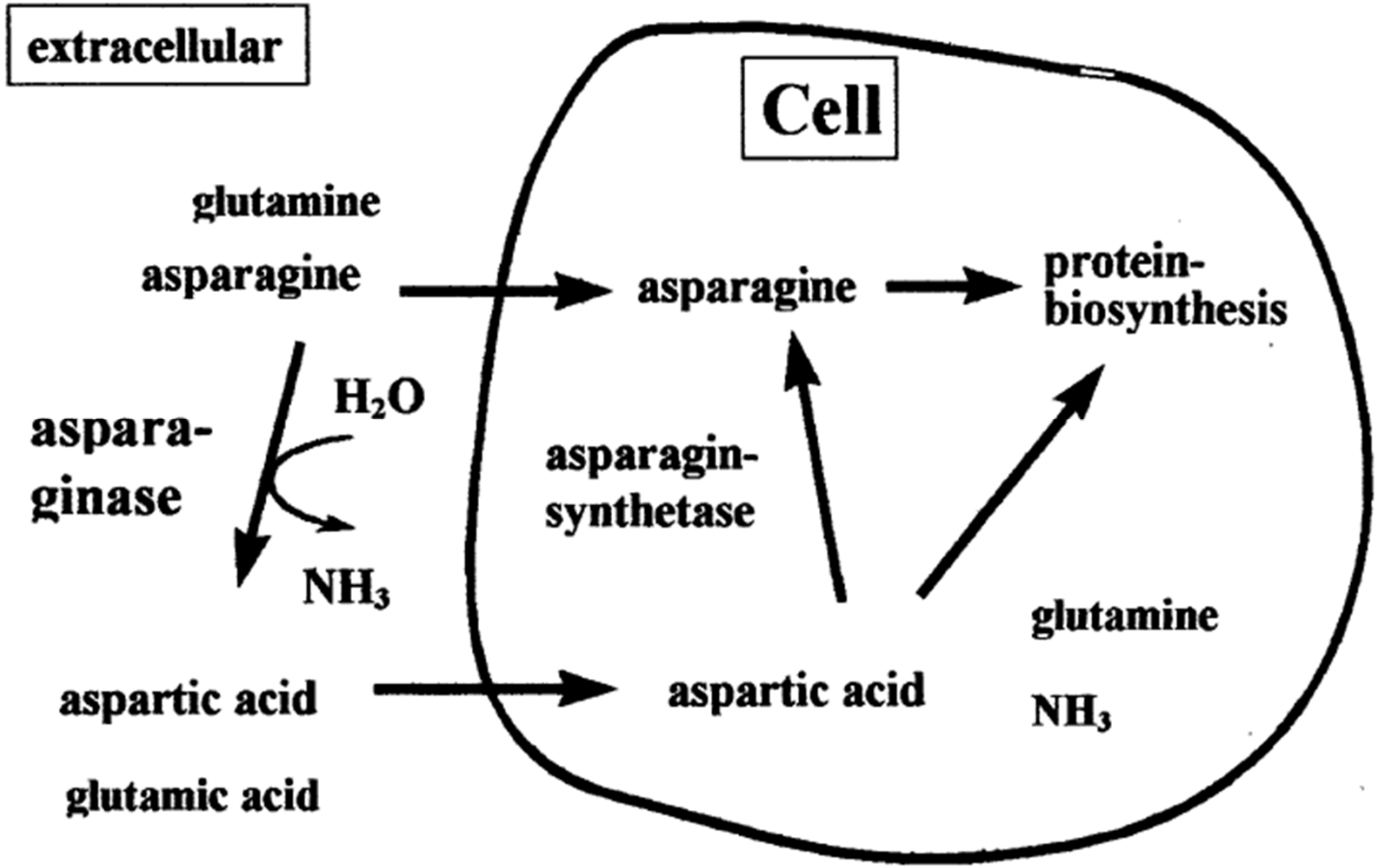
- Emergency treatment of an acute bleeding disorder
- Liver transplantation
- Dissiminated intravascular coagulopathy
- Massive transfusion and coagulopathy of dilution
- Severe coagulation factor deficiency and bleeding
- Severe coagulation factor deficiency and planned invasive procedure
- ATIII, Protein C, Protein S substitution
- Plasma exchange in TTP
- Plasma exchange in Guillain-Barre-Syndrom
- Total blood exchange transfusions


Ebell, Salama Transfusionsmedizin in Pädiatrische Hämatologie und Onkologie Springer Verlag Heidelberg 2006, Editor H.Gadner, C.Niemeyer, G. Gaedicke, J.Ritter

# L-Asparaginase induced Coagulopathy

- In 1953 when Kidd first observed that lymphomas in rat ans mice regressed after treatment with guinea pig serum the discovery of Apsaraginase started.
- Asparaginase was identified as a potential chemotherapeutic agent, and in 1961 when it was isolated as the antilymphoma component of guinea pig serum.
- In the 70-tes the agent was successfully introduced in the induction treatment of childhood ALL
- Since today three different pharmaceutical formulation are available:
  - Erwinia™ (Erwinia chrysanthemi derived)
  - Crasnitin™(E.Coli derived)
  - Pegylated asparaginase (Oncospar™)

# L-Asparaginase induced Coagulopathy




Leukemic blasts need asparagine, normal cells not

# L-Asparaginase induced Coagulopathy

Toxicity of different asparaginase preparations in the treatment of newly diagnosed childhood acute lymphoblastic leukemia

| Toxicities | Asselin et al. [4] | | ALL–BFM[a] | | Eden et al. [53] | | Oettgen et al. [119] |
|---|---|---|---|---|---|---|---|
| | *E. coli* $n=79$ (%) | PEG $n=88$ (%) | Medac© $n=32$ (%) | Crasnitin© $n=30$ (%) | *E. coli* $n=275$ (%) | Erwinase© $n=483$ (%) | *E. coli* (%) |
| Allergic | 14 (17.7) | 12 (13.6) | 8 (25.0) | 19 (63.3) | 1 (0.4) | 1 (0.2) | MD |
| Pancreatitis | 7 (8.8) | 5 (5.7) | 0 (0.0) | 0 (0.0) | 5 (1.8) | 0 (0.0) | MD |
| Liver | 0 (0.0) | 1 (1.1) | 3 (9.4) | 2 (6.7) | 8 (2.9) | 4[b] (0.8) | 56/121 (46.0) |
| Diabetes | | MD | 5 (15.6) | 0 (0.0) | 4 (1.5) | 1 (0.2) | 0 (0.0) |
| Coagulopathy | 0 (0.0) | 1 (1.1) | 1 (3.1) | 0 (0.0) | 12 (4.4) | 16 (3.3) | MD |
| Stroke/seizure | 0 (0.0) | 2 (2.3) | 4 (12.5) | 1 (3.3) | 12 (4.4) | 10 (2.1) | 48/147 (33.0) |
| Cardiovascular | | MD | 0 (0.0) | 2 (6.7) | | MD | MD |
| Other | 9 (11.4) | 4 (4.5) | 0 (0.0) | 0 (0.0) | | MD | MD |
| Total | 30 (37.9) | 25 (28.3) | 21 (65.6) | 24 (80.0) | 42 (15.3) | 32 (6.6) | |

[a] Unpublished data from paediatric patients, treated between July 1992 and March 1995 according to the ALL–BFM protocol.
[b] According to the information of the authors documentation not complete.
MD, missing data.

Thrombosis (mostly CNS thrombosis) are related to other thrombotic risk factors like Factor V Leiden, inserted central venous catheter a.s.o.

U.Nowak-Göttl Blood Coagul Fibrinolysis 1995:761-4; U.Nowak-Göttl Fibrinolysis 1994:761-4

A. Attarbaschi
G. Mann
M. Kronberger
V. Witt
H. Gadner
M. Dworzak

# Effects of Dose-Reduced Medac® L-Asparaginase on Coagulation in Trial ALL-BFM 2000

*Gerinnungsveränderungen unter Dosis-reduzierter Medac® L-Asparaginase in der Studie ALL-BFM 2000*

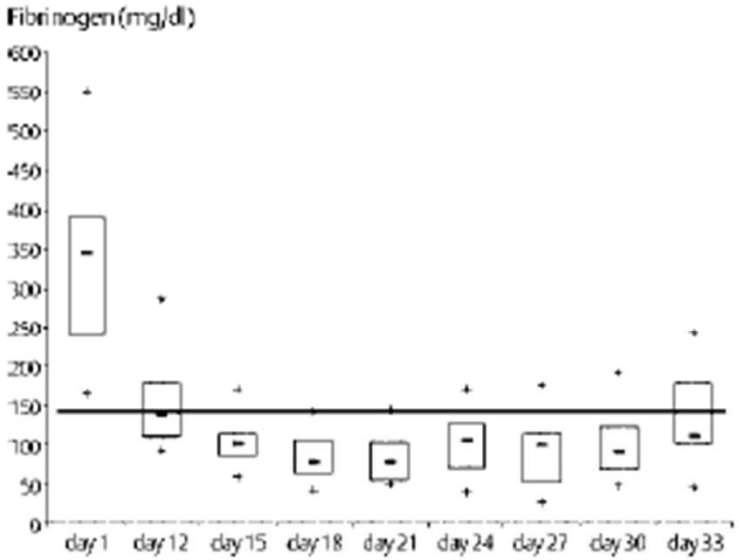



Fig. 1 Changes of the fibrinogen level (mg/dl) according to the days of L-ASP administration in induction therapy. The short line within the box represents the median and the bottom and top edges represent the 25th and 75th percentiles. The minimum and maximum values in the sample are indicated with a '+' sign. The bold line signifies the lower normal range of fibrinogen.

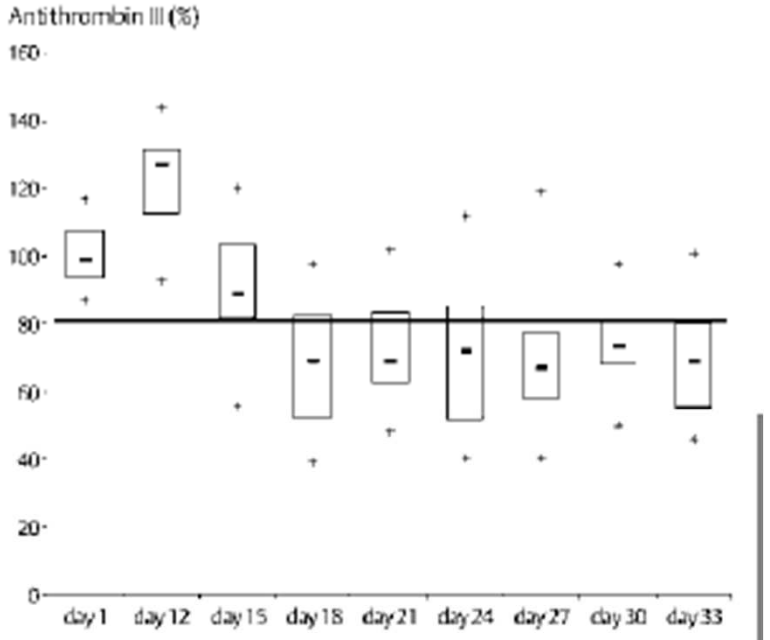



Fig. 2 Changes of the AT III level (%) according to the days of L-ASP administration in induction therapy. The short line within the box represents the median and the bottom and top edges represent the 25th and 75th percentiles. The minimum and maximum values in the sample are indicated with a '+' sign. The bold line signifies the lower normal range of AT III.

Attarbaschi A Effects of Dose-Reduced ... Klin Pädiatr 2003; 215: 321 – 326

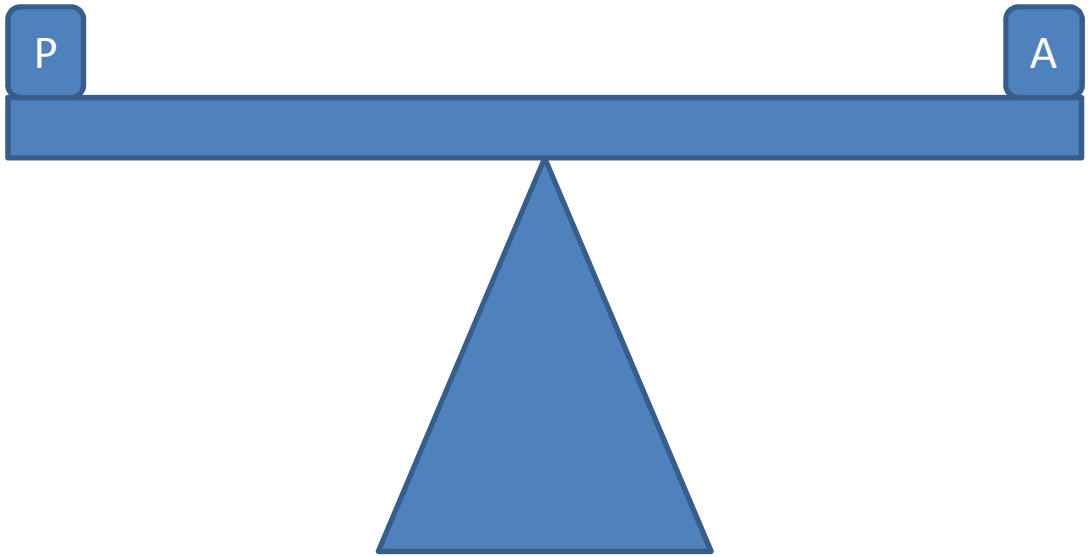
# L-Asparaginase induced Coagulopathy

- Impairment of protein synthesis
- Changes in coagulation factor function

➢ Haemorrhage

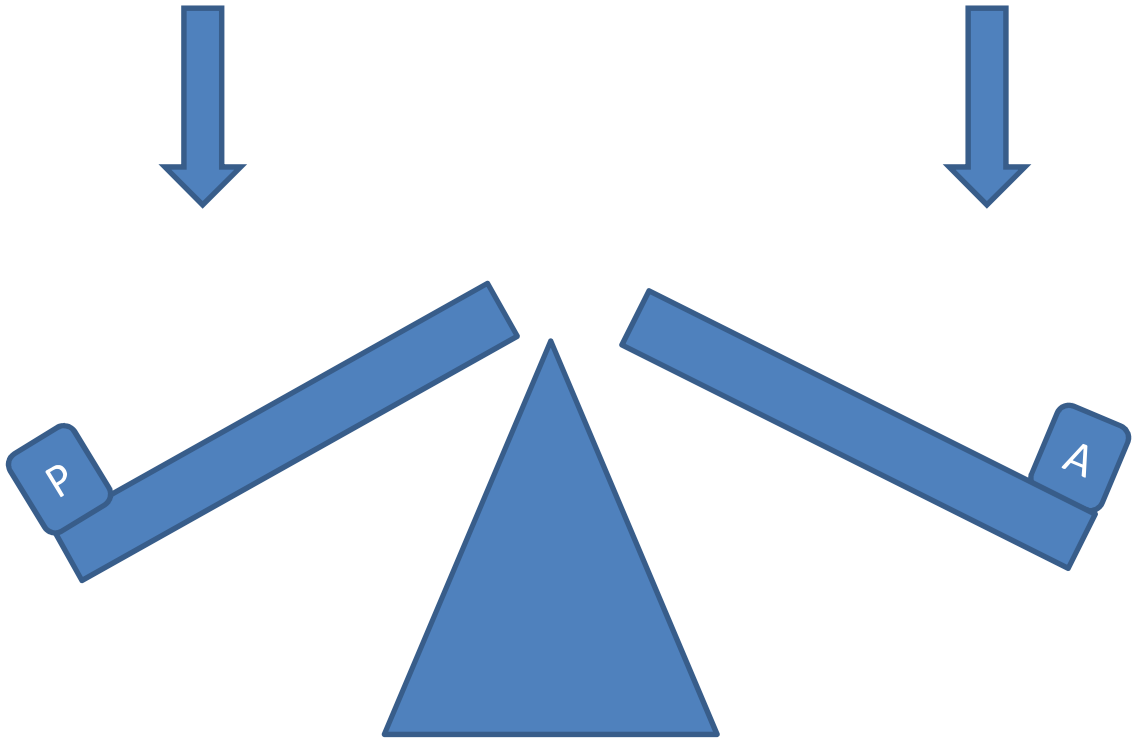
➢ Thrombosis

# L-Asparaginase induced Coagulopathy




P = procoagulatory factors; A = anticoagulatory factors

# L-Asparaginase induced Coagulopathy

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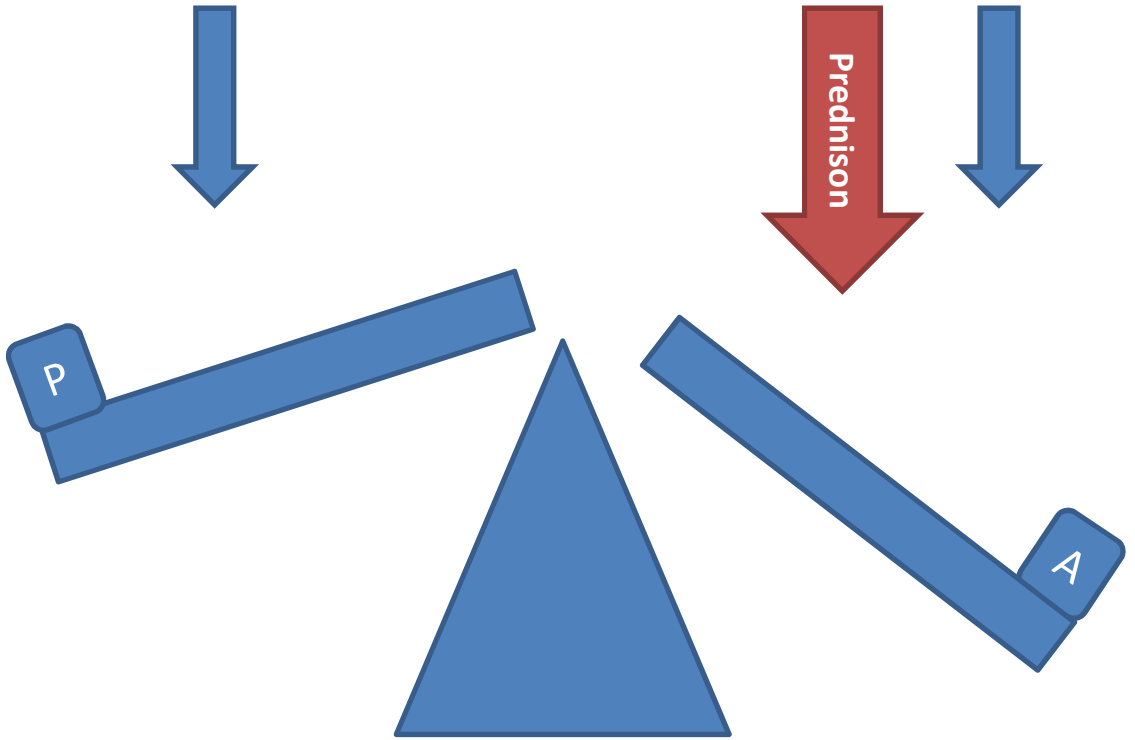
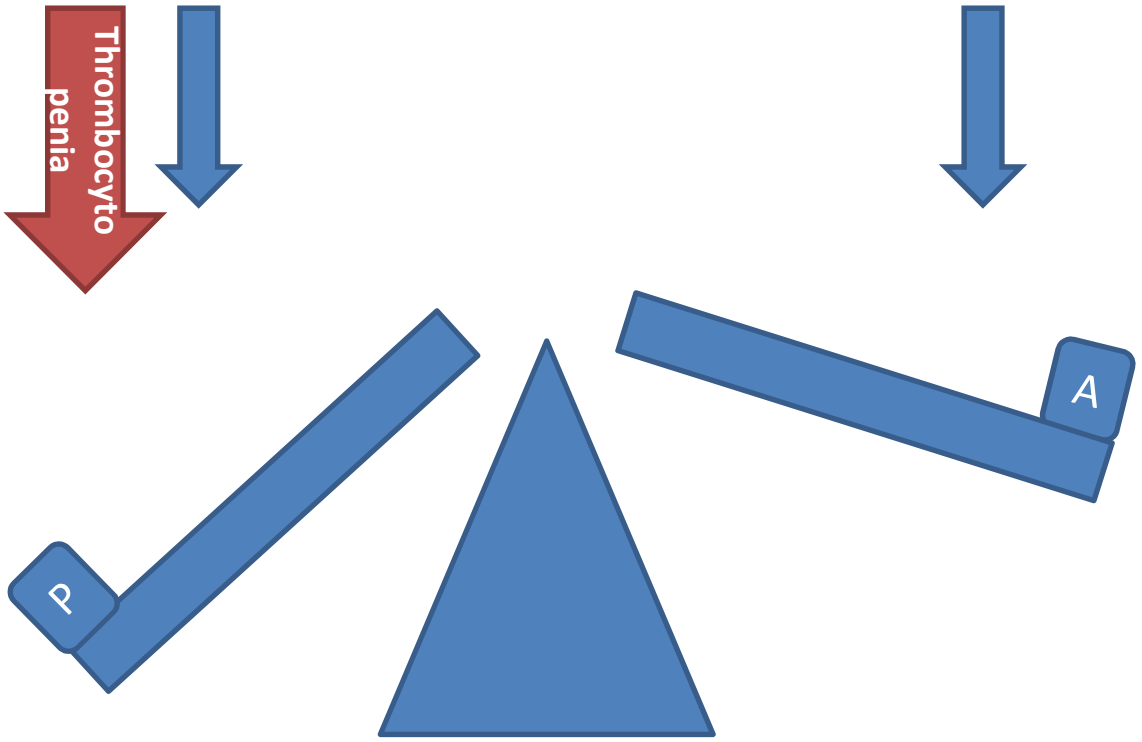
# L-Asparaginase induced Coagulopathy




P = procoagulatory factors; A = anticoagulatory factors

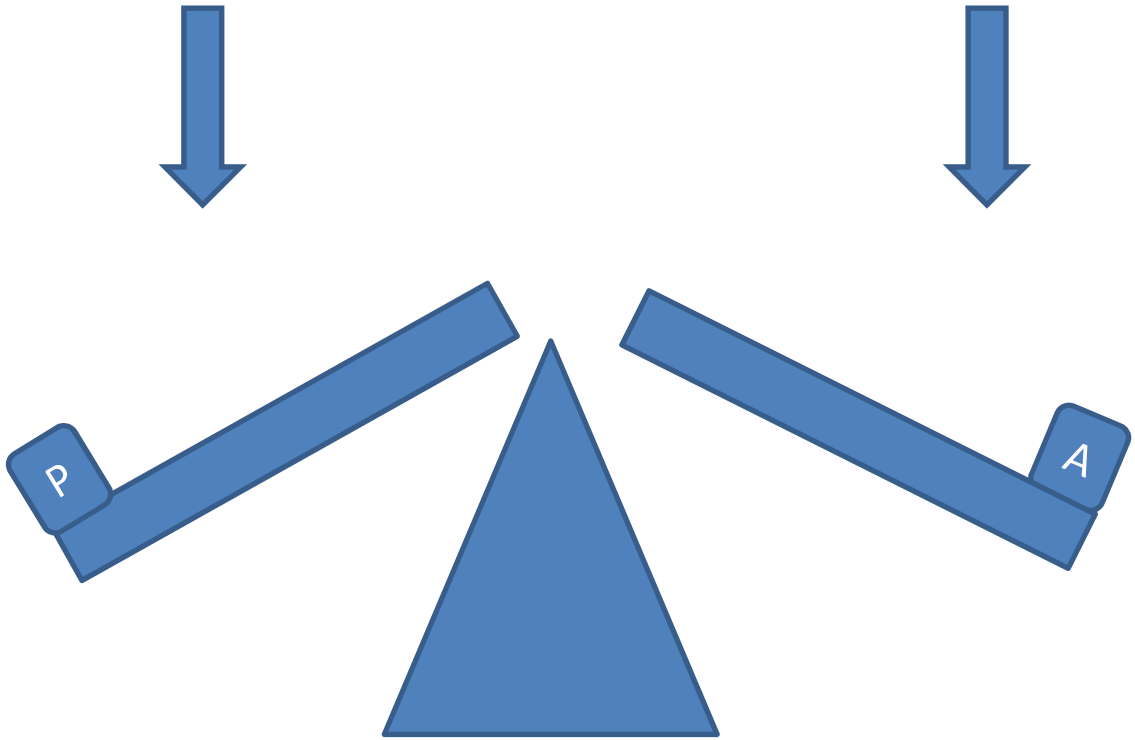
# L-Asparaginase induced Coagulopathy




P = procoagulatory factors; A = anticoagulatory factors

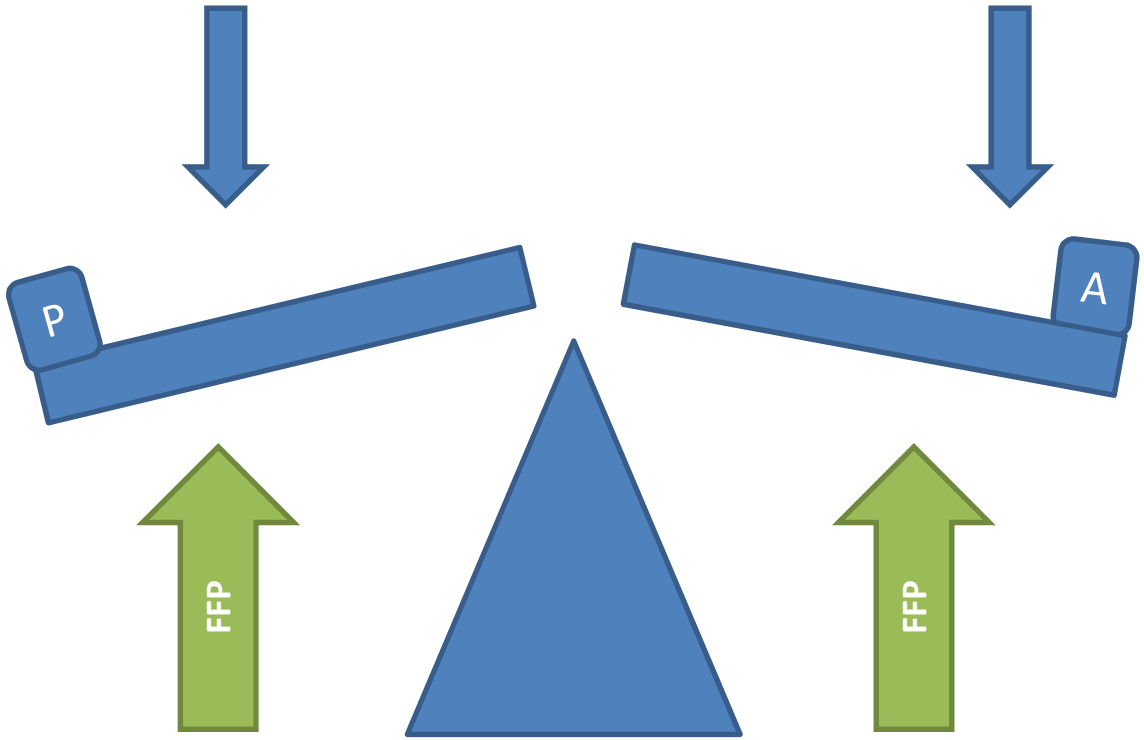
How to prevent
How to treat

# L-Asparaginase induced Coagulopathy



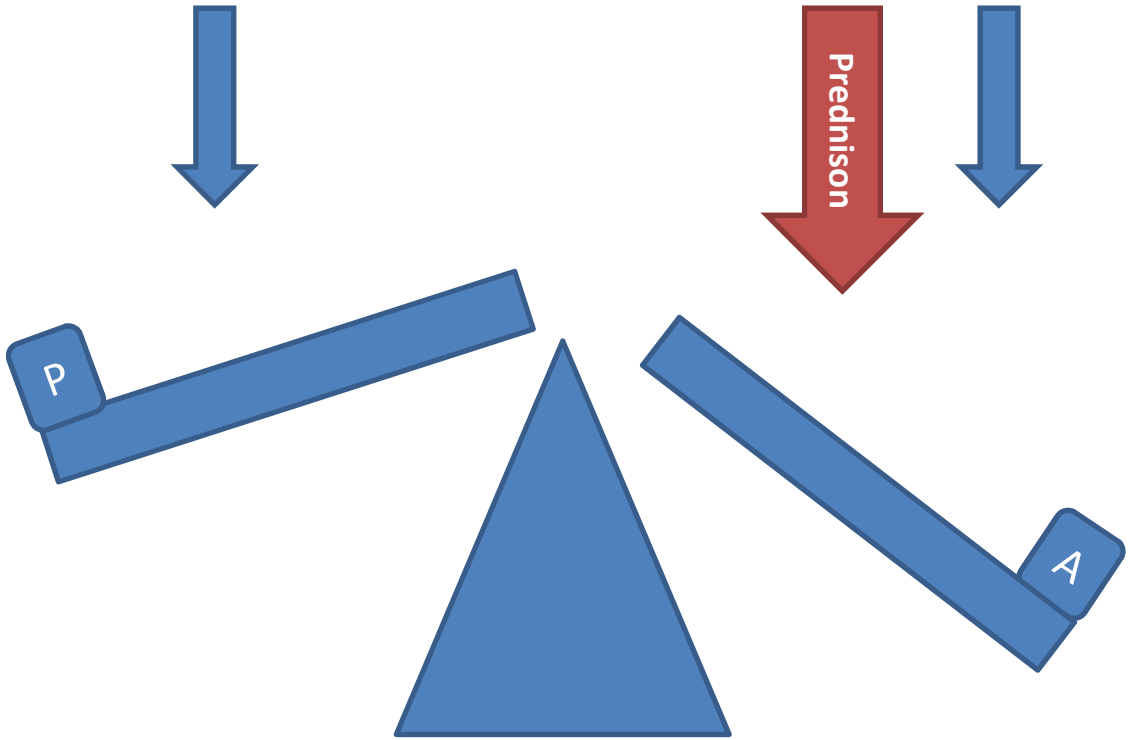

P = procoagulatory factors; A = anticoagulatory factors

# L-Asparaginase induced Coagulopathy



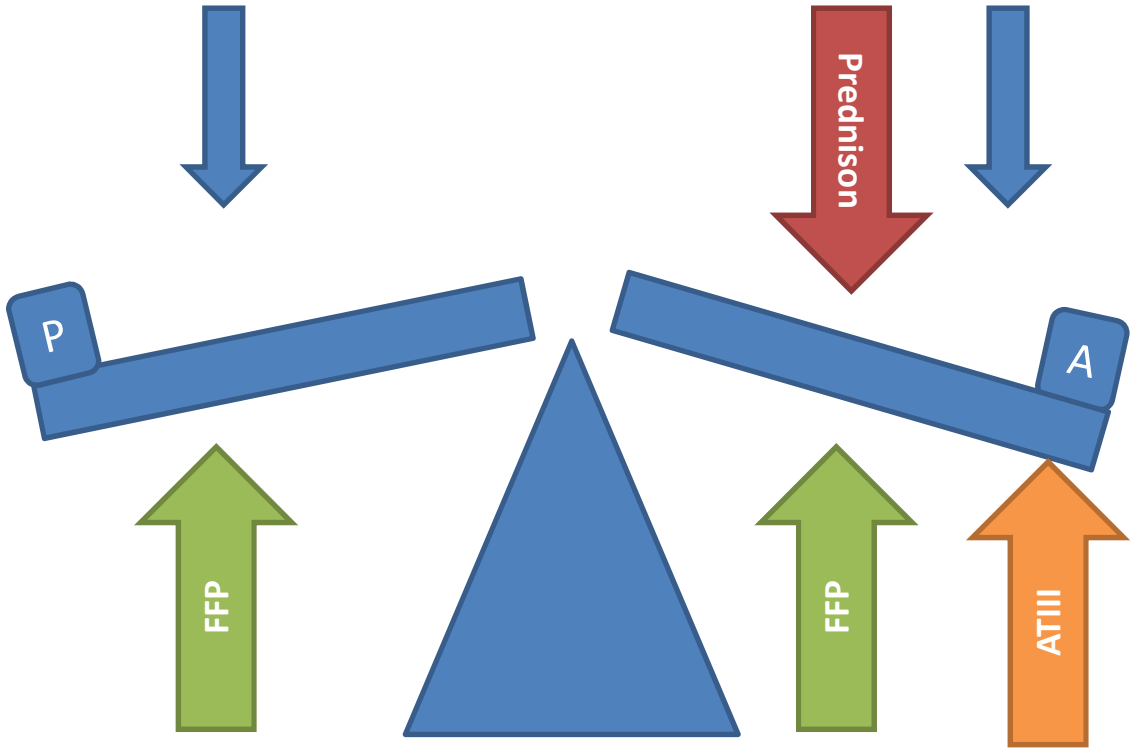

P = procoagulatory factors; A = anticoagulatory factors

# L-Asparaginase induced Coagulopathy



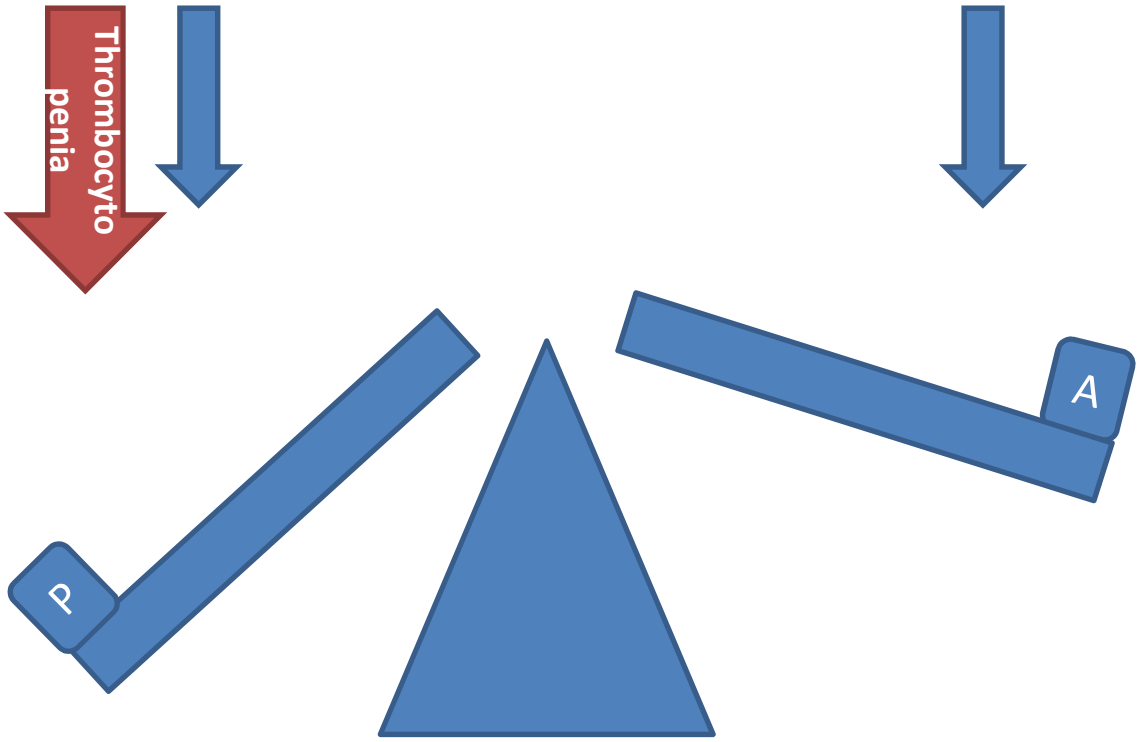

P = procoagulatory factors; A = anticoagulatory factors

# L-Asparaginase induced Coagulopathy



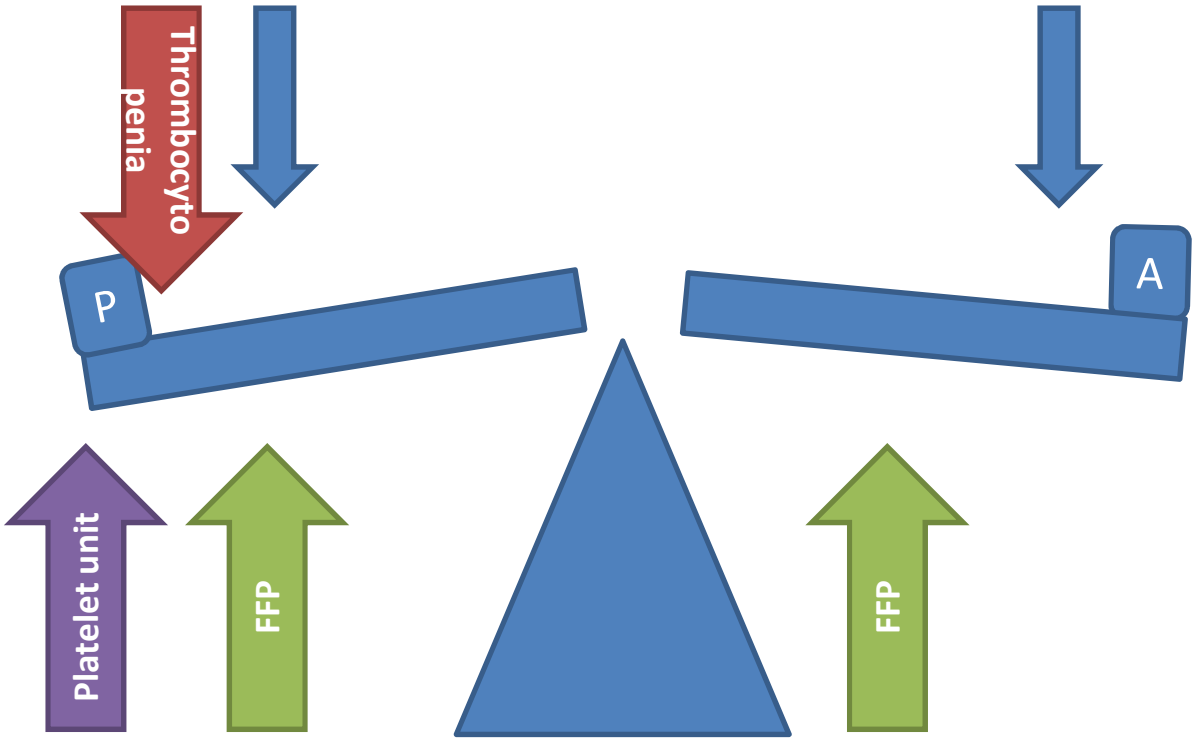

P = procoagulatory factors; A = anticoagulatory factors

# L-Asparaginase induced Coagulopathy




P = procoagulatory factors; A = anticoagulatory factors

# L-Asparaginase induced Coagulopathy




P = procoagulatory factors; A = anticoagulatory factors

# Treatment guideline St. Anna Kinderspital

| | ATIII (%) | Fbg (mg/dl) | PTZ (%) |
|---|---|---|---|
| Normal (APCR > 2,0) | ≤50 | ≤50 (*) | ≤50 |
| APCR > 1,5 bis 2,0 | ≤60 | ≤50 | ≤50 |
| APCR <=1,5 | ≤70 | ≤50 | ≤50 |
| Action | ATIII | Octaplas | Vit.K |

# results from 4 patients with ALL and L-Asparaginase induced coagulopathy in BFM induction therapy treated with Octaplas™ and Kybernin™

| | Before | After | |
|---|---|---|---|
| PT | 40 (35 – 60) | 65 (60 – 85) | [%] |
| Fibrinogen | 62 (48 – 78) | 98 (67 – 120) | [mg/dl] |
| ATIII | 52 (40 – 58) | 75 (65 – 85) | [%] |
| D-Dimer | 2.9 (1.0 – 8.5) | 2.6 (1.0 – 7.6) | |

Laboratory results in morning where used as before and results from the 12h to the next day as after

*short report*
*Haematologica 1995; 80:451-453*

# INEFFICACY OF FRESH FROZEN PLASMA IN THE TREATMENT OF L-ASPARAGINASE-INDUCED COAGULATION FACTOR DEFICIENCIES DURING ALL INDUCTION THERAPY

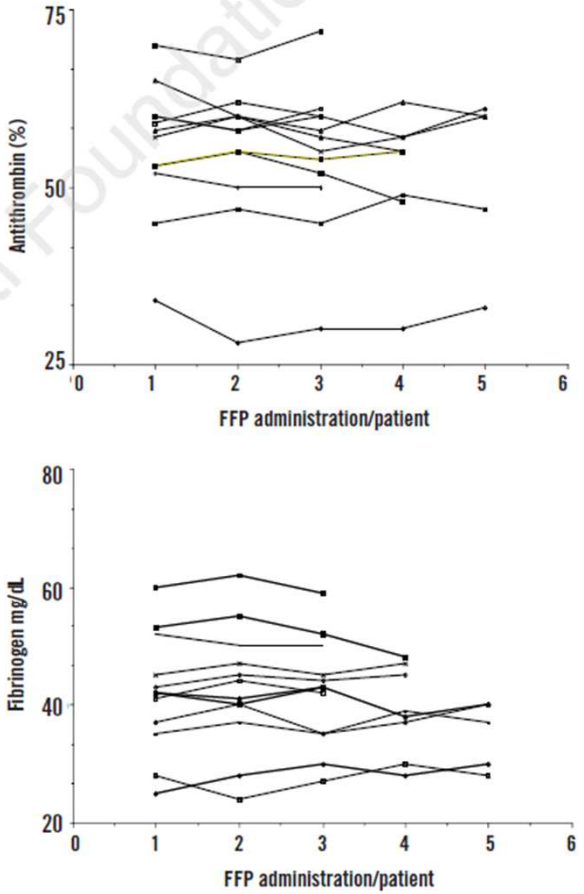
*Ulrike Nowak-Göttl, Bertha Rath, Martha Binder, Jörg-Ullrich Hassel, Johannes Wolff, Stefanie Husemann, Jörg Ritter*

*Center of Pediatric Hematology and Oncology, University Hospital Münster, Germany*

ABSTRACT

**A prospective longitudinal study was conducted to determine whether single-donor fresh frozen plasma (FFP) substitution was able to influence L-asparaginase-associated hypoproteinemia. Within a 36-month period, 20 of 42 children with ALL received a total of 42 prophylactic FFP doses at a median of 10 (5-20) mL/kg when fibrinogen levels decreased to < 60 mg/dL and thrombin time was lengthened. Laboratory monitoring before, during and after FFP substitution showed no short-term improvements and demonstrated only a minimal increase in fibrinogen and $\alpha_2$-antiplasmin. Plasma levels of antithrombin and plasminogen remained unchanged. Furthermore, administration of FFP had no influence on thrombin generation, the plasmin/$\alpha_2$-antiplasmin complex or enhanced D-dimer formation.**

*Key words: fresh frozen plasma, fibrinogen, antithrombin, thrombin generation, D-dimer formation*




Single center study, small patient number (42 children), single donor plasma used, dose 10 ml/kg bw (5-20 ml/kg bw), no bleeding occurred, no comparison to the „non“ treated group.

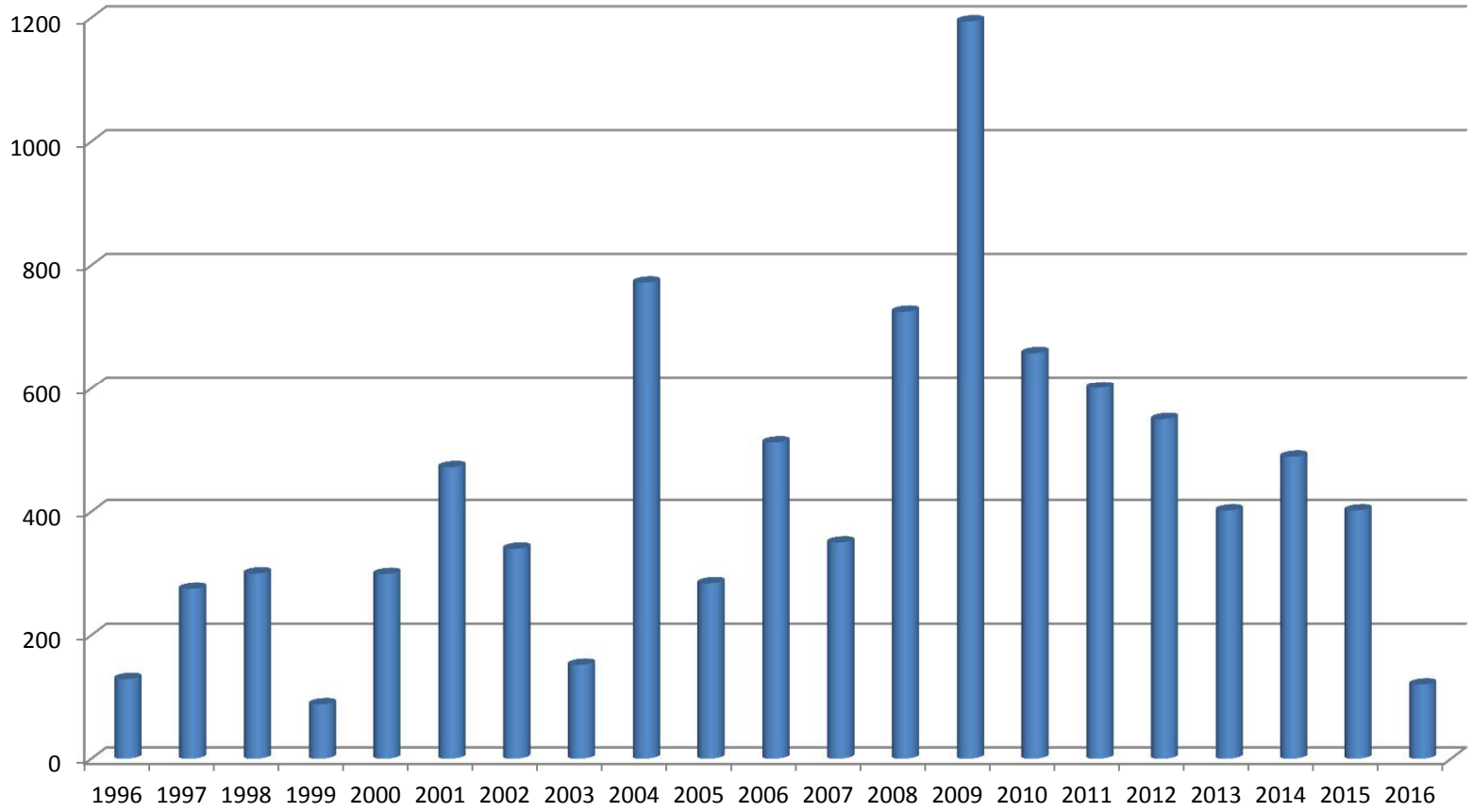
# Bleeding complications

- Without thrombocytopenia or infection or secondary not seen in our institution during the last 10 years

# Thrombotic complications

- Thrombosis of CNS sinus venosus seen in treated an non treated patients (statistics under working process)
- Further risk factor (not studied) like CVC, Factor V Leiden a.s.o. in nearly 40% of the patients

# Octaplas™ transfused in the St. Anna Kinderspital

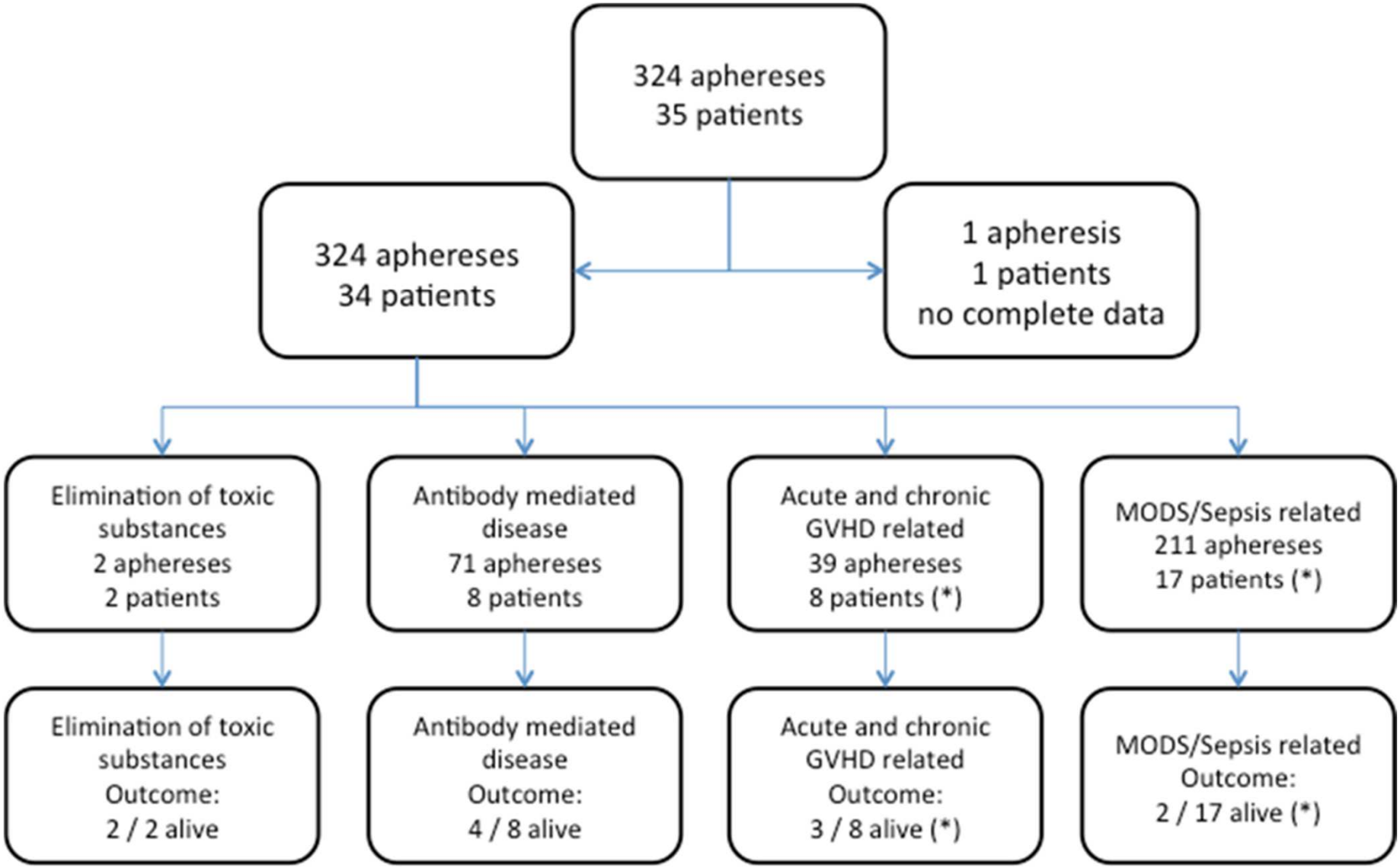


# Use of TPE in the St. Anna Kinderspital

- From 1996 to 2016 8116 units of Octaplas™ were transfused
- Main indications:
  - Coagulopathie
    - After chemotherapy (L-ASP + Corticoids)
    - Unknown reason
    - Hepatopathy
    - Sepsis / DIC
    - Bleeding
  - Total plasma exchange

# TPE at St. Anna Kinderspital

- Median age 13.8 y (0.94 – 22.7)
- Median bw 40 kg (9.9 – 80)
- In median 6 TPE per patient (1 – 40)
- In median 1940 ml plasma exchange (372 – 5270)
- In median 48.2 ml/kg plasma exchange (13 – 99)
- In median 10 Octaplas™ (2 – 19)
- 70% of all transfused Octaplas™


324 aphereses
35 patients
324 aphereses
34 patients
1 apheresis
1 patients
no complete data
Elimination of toxic substances
2 aphereses
2 patients
Antibody mediated disease
71 aphereses
8 patients
Acute and chronic GVHD related
39 aphereses
8 patients (*)
MODS/Sepsis related
211 aphereses
17 patients (*)
Elimination of toxic substances
Outcome:
2 / 2 alive
Antibody mediated disease
Outcome:
4 / 8 alive
Acute and chronic GVHD related
Outcome:
3 / 8 alive (*)
MODS/Sepsis related
Outcome:
2 / 17 alive (*)

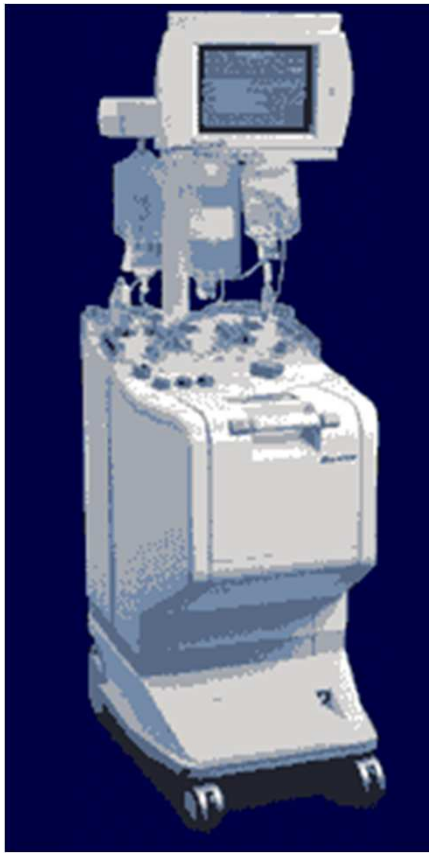
# TPE at St. Anna Kinderspital

- Indications
  - TTP
  - Myasthenia gravis
  - Opsoklonus Myoklonus Syndrom
  - Sepsis
  - SIRS
  - ITP
  - MTX-Intoxication
  - Hyper IgE
  - Dysproteinemia
  - AIHA
  - Autoimmune disease
  - Rhabdomyolysis

# Cell separators

Cobe spectra™

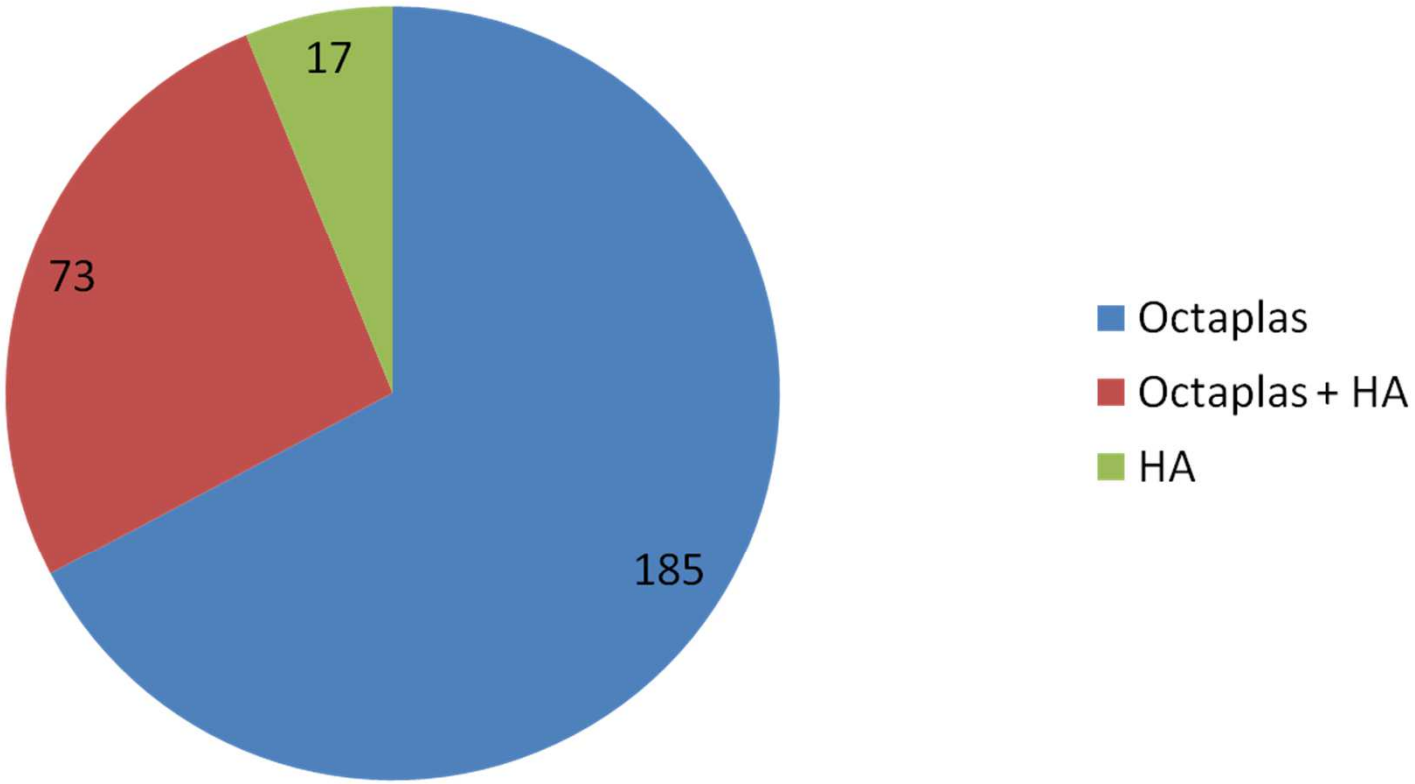

OPTIA™



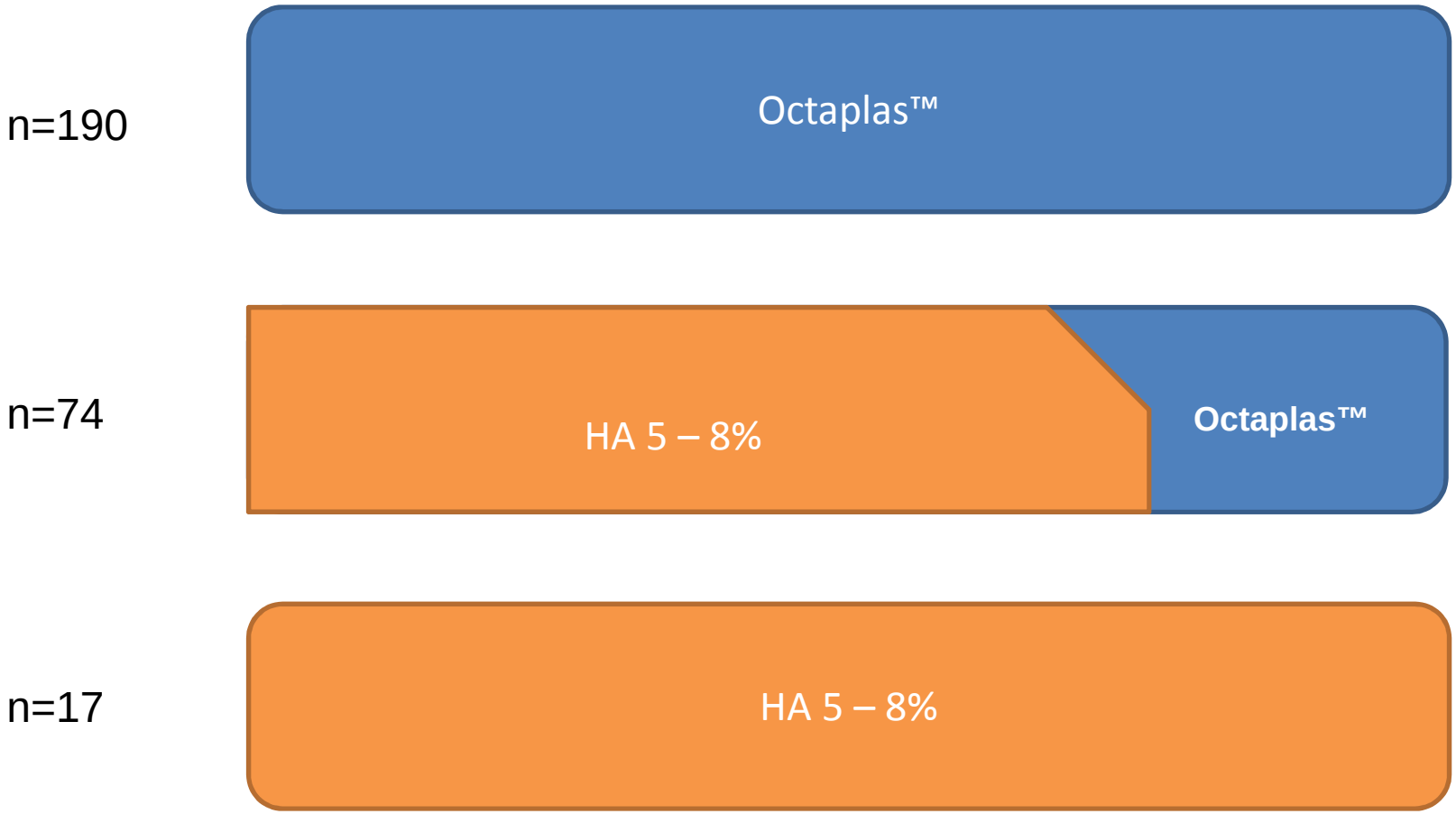
AMICUS™

Life18™

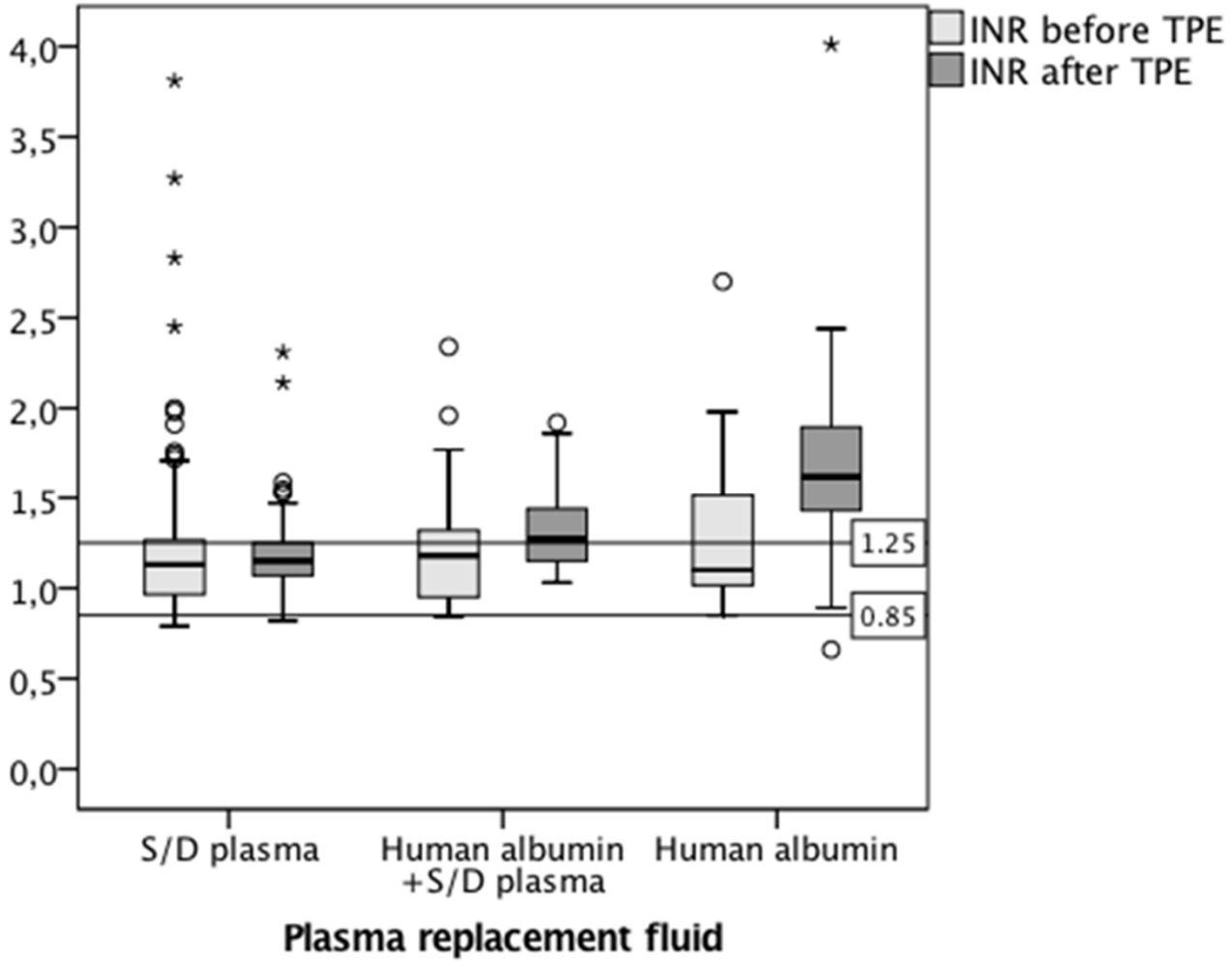
# Plasma exchange fluid used



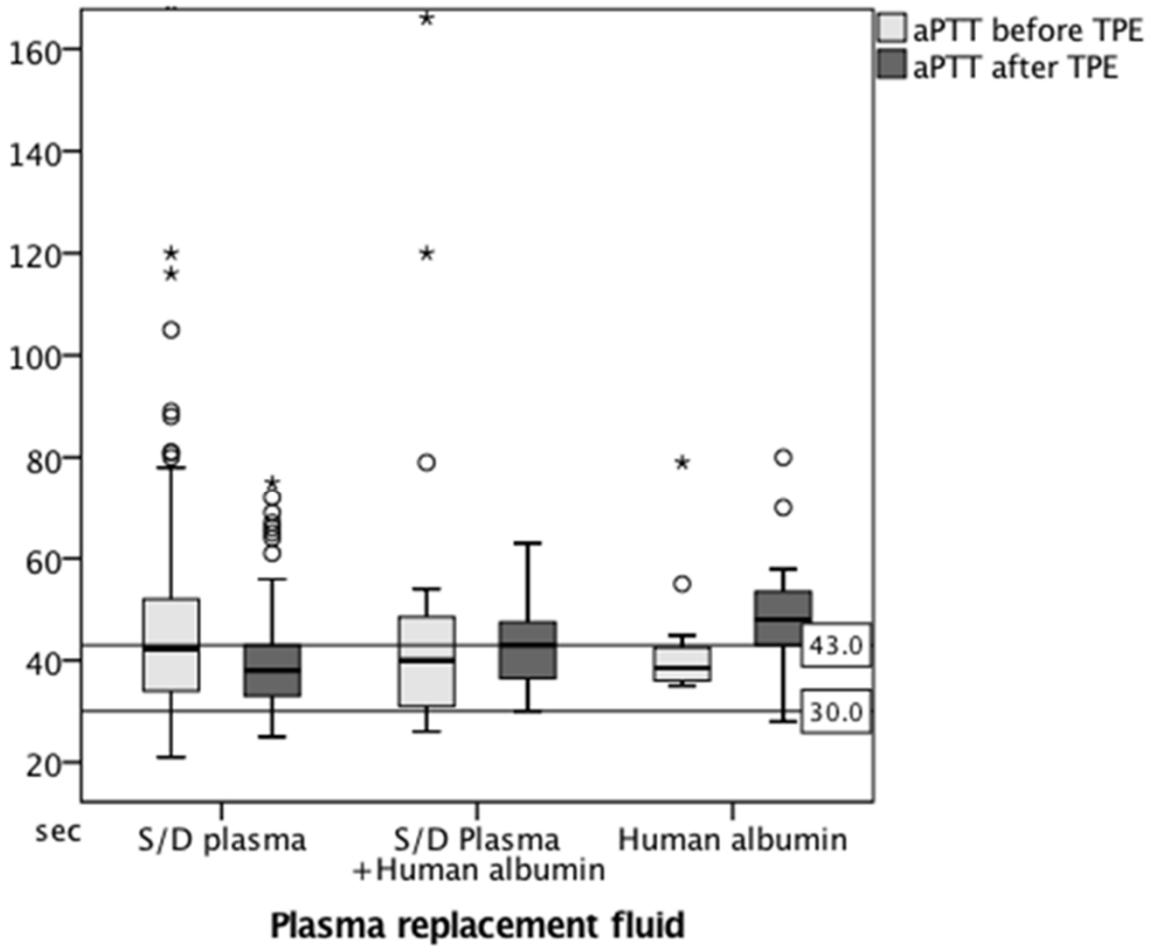
# Handling of plasma exchange fluid



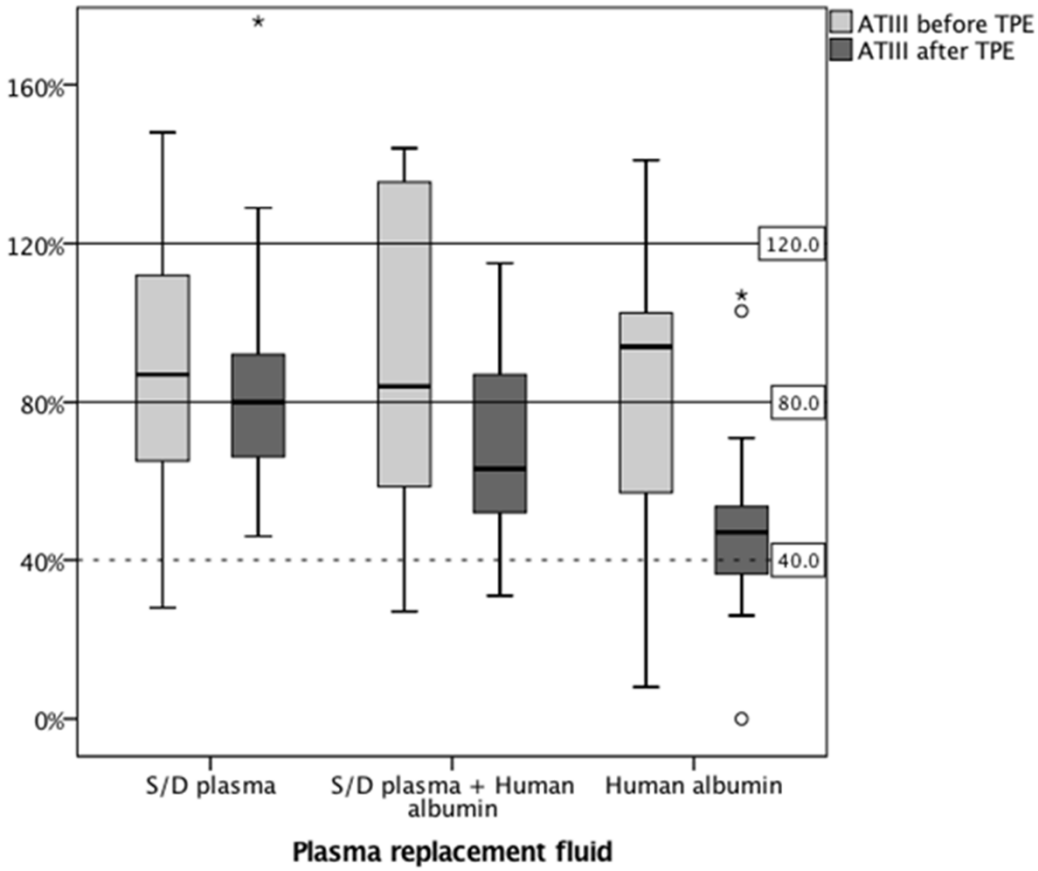
# INR pre and post



# aPTT pre and post



# ATIII pre and post



# Side effects

- Side effects in conventional transfusion episodes
  - No reported severe adverse effects
- Side effects in TPE
  - 1 edema, itching (first TPE, change to HA 5% as exchange fluid)
  - 1 catheter occlusion (Hickman catheter)

# conclusions

- TPE with Octaplas™ in children and young adults is save
- TPE with HA leads to a dilution coagulopathy in contrast to TPE with Octaplas™ only and Octaplas™ in combination with HA
- Octaplas™ could be used in combination with HA to avoid dilution coagulopathy after TPE
- The efficiency for treatment of the L-Asparaginase induced coagulopathy is under a prospective study protocol

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Transplantation and the American Society of Transplant Surgeons

doi: 10.1111/j.1600-6143.2010.03228.x

Brief Communication

# Successful Isolated Liver Transplantation in a Child with Atypical Hemolytic Uremic Syndrome and a Mutation in Complement Factor H

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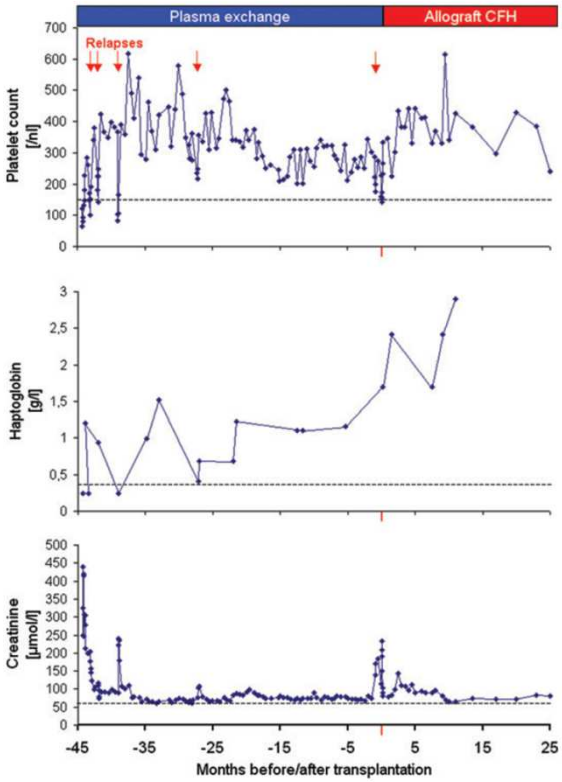
[a] *Liver Unit,* [b] *Department of Paediatric Nephrology, Birmingham Children's Hospital NHS Foundation Trust, Birmingham, UK*
[c] *Institute of Human Genetics, Newcastle University, International Centre for Life, Newcastle upon Tyne, UK*
[d] *University Hospital Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Mindelsohn Way, Birmingham, UK*
* *Corresponding author: Wolfram Haller, wolfram.haller@rch.org.au*

**A male infant was diagnosed with atypical hemolytic uremic syndrome (aHUS) at the age of 5.5 months. Sequencing of the gene (*CFH*) encoding complement factor H revealed a heterozygous mutation (c.3644G>A, p.Arg1215Gln). Despite maintenance plasmapheresis he developed recurrent episodes of aHUS and vascular access complications while maintaining stable renal function. At the age of 5 years he received an isolated split liver graft following a previously established protocol using pretransplant plasma exchange (PE) and intratransplant plasma infusion. Graft function, renal function and disease remission are preserved 2 years after transplantation. Preemptive liver transplantation prior to the development of end stage renal disease is a valuable option in the management of aHUS associated with *CFH* mutations.**

*Immediately after admission alternate day hemodialysis and PE were commenced with an initial exchange volume of ca. 90 mL/kg Octaplas with each session. The change to plasma infusions (60 mL/kg/week) 2 weeks later was followed by a relapse 1 month after first presentation*




| Relapse | | Maintenance PE after relapse | |
|---|---|---|---|
| Age (months) | Trigger | Volume (mL/kg) | Frequency (times per week) |
| 6.5 | Plasma infusions started 3 weeks prerelapse | 45 | 3 |
| 8 | URTI, CVL change 5 days before | 45 | 3 |
| 11 | No obvious cause | 63 | 3 |
| 22 | CVL sepsis (CONS), PE reduced from 63 to 45 mL/kg twice weekly 1 week before | 63 | 3 |
| 61 | CVL sepsis (CONS) | 60 | 3 |

CVL, central venous line; CONS, coagulase-negative *Staphylococcus aureus*; URTI, upper respiratory tract infection.



*Haller American Journal of Transplantation 2010*