Arbeitsgemeinschaft
Plasmapherese e. V.

20 years of intensified plasmapheresis

Experiences and challenges

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How it all began

Until the late 19-eighties the collection of plasma was carried out manually, i.e.

- Several units of whole blood were collected from several voluntary donors and spun down in big floor standing centrifuges. After separation of cells and plasma, the cells were reinfused to the donor.
- This procedure was repeated until the required amount of plasma (usually 400-500 mL) had been collected from a donor.
- The main donor risk, except for the known risks for whole blood donation, was the reinfusion of the wrong red cells to the „neighbour“ donor

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Automated pheresis

- In the late 19-eighties the automated plasma collection by apheresis became possible, leading to a significant increase in collected plasma .

- In those days the demand for plasma derived products was mainly driven by Factor VIII used for the treatment of haemophiliacs. The other proteins collected such as immunoglobulins and albumin were rather by products of the plasma pools.

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The new equipment

With the arrival of the new machines, new requirements for donor safety had to be developed.

- How much plasma should be collected at a time ?
- What should the interval between 2 donations be ?
- Should there be an annual limit ?
- Should there be limits for Total Protein or other proteins ?
- Should donor suitability criteria other than for whole blood donors be laid down ?

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Situation in Germany

- In Germany, collection of blood and blood products, is not and has never been limited to State or Red Cross organisations. It can also be carried out by e.g. hospital based blood banks or private institutions.

- After the HIV/AIDS scandals in the early nineties, the so called „Transfusion Act“ was passed.

- Together with the Drug Law this new Act enforces collection of blood and blood products under highly regulated conditions.

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ARGE Plasmapheresis

In 1997 the so called „working group“ (ARGE) Plasmapheresis was founded. The objective of this organisation is:

- the procurement of high quality, safe plasma derived products under economically viable conditions,
- the support of growing knowledge about donor suitability and donor safety in plasma by collecting and collating scientific data and background information,
- cooperation with scientific organisations and regulating authorities in order to improve the awareness of the differences of plasma collection compared to whole blood and the special requirements regarding donor and product issues

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Development of Regulations in Germany

1991 TP on every donation, IgG every 15th donation
Donation volume 650 mL plus anticoagulant

1997 ARGE Plasmapheresis was founded and 520 000 L source plasma collected

1999 The ARGE started the SIPLA study

2003 The ARGE multi -center SIPLA study was completed

⇒ The importance of IgG as the lead protein regarding donor safety (as well as product quality)as well as differentiated collection volumes were recognised

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Development of Regulations in Germany

=> Subsequently 2005 IgG and TP have to be tested at every fifth donation

=> 2010 a body weight dependent collection volume (with anticoagulant included for practical reasons) in 3 steps of 650, 750 and 850 mL is introduced.

Potentially 45 donations per year, (changed to 60 donations per year in 2018)

2016 > 2.2 mio L plasma collected

self sufficiency reached except for anti-D HI plasma

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What is the recipe ?

- IgG levels are highly variable from donor to donor. They depend on gender, age, childhood exposure to antigens, immunisations, recent infections suffered, individual factors and most strongly on ethnicity
- We see IgG‘s of first time plasma donors from 0 to 28 g/L.
- Persons with an IgG of < 6 g/L or above 19 g/L as a first time are sent for further investigation.
- TP is always tested in combination with IgG to see the complete picture and observe the donor‘s protein metabolism over a longer period of time.
- Both proteins are always tested from the product (anticoagulated plasma) and reconverted to serum values with a validated conversion factor . We so avoid unneccessary blood sampling

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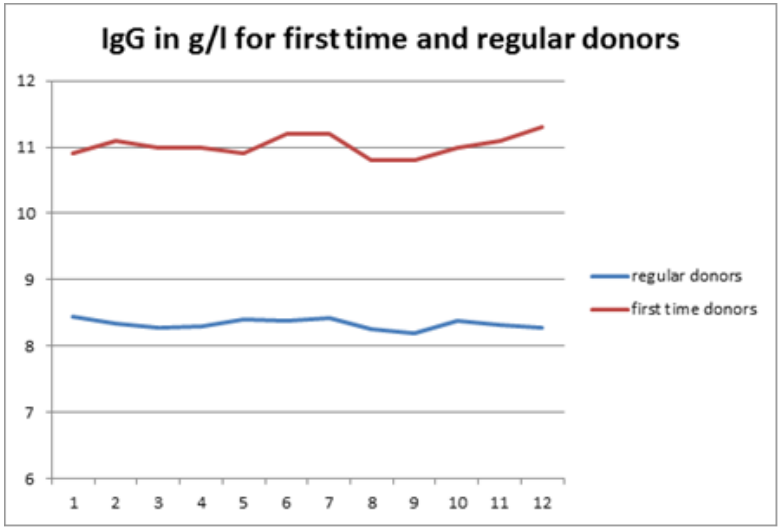
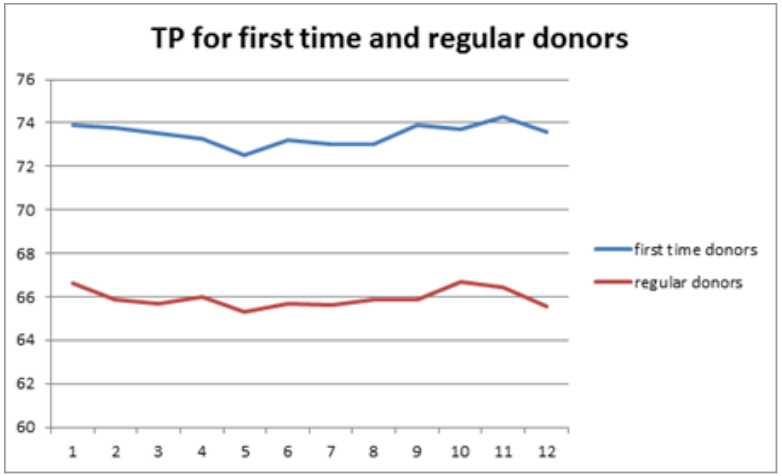
The Art of Keeping donors above IgG levels of 6 g/L

IgG levels drop by 2-3 g/L with regular donation and take approx. 2 to 3 weeks to recover to original levels.

TP drops by approx 8 g/L with regular donation

Recovery rate to original levels varies significantly and needs individual donation patterns





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The Art of Keeping donors above IgG levels of 6 g/L

Therefore, in order to achieve sufficient quantities to meet the demand, plasma collectors developed a system to guide donors regarding their donation frequency.

1) Manual, according to donor‘s last IgG
2) With a fixed donation interval, according to donor‘s last IgG
3) With an electronic system, that increases IgG/ TP testing frequency, when levels drop, and reduces donation frequency accordingly, to avoid dropping IgG < 6 or TP < 60 g/L.

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Donation frequency management systems

There are advantages and disadvantages to all systems:

- Manual systems: time consuming, too much room for individual decisions by different doctors and frequency being changed at every visit, loss of potential plasma
- Algorithm system: might be unflexible, donor is in a fixed donation pattern, loss of potential plasma
- Electronic system: needs to be programmed in the donor software, but is the ideal system to guide donors and doctors.

Donors may have an electronic access to a „traffic light“ system. When the light is „green“ there IgG level is acceptable and they are ready to donate again. Unneccessary (unsuccesful), frustrating visits to the plasma center can so be avoided. Very few deferral due to low protein, Plasma donations optimised

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Donation frequency

As a result of guiding and individualising donors‘ donation frequency,
(and of course personal reasons) numbers of donations vary greatly:

Average number of donations per year

- 1 - 5 34 %
- 6-10 16 %
- 11-20 18 %
- 21-30 12 %
- 31-45 17%
- >45 3 %

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Individualised Plasma donation

With any of the systems collectors get a good overview over that specific donor‘s protein recovery rate and can act accordingly and reduce donation frequency, if necessary or encourage higher donation frequency, if protein levels are very high.

We achieve higher donation frequencies than with a rigid 2 week interval and still maintain donor safety and adequate plasma protein levels.

We have collected data on millions of plasma donors over the last 20 years, and have seen an enormance variance in protein loss and recovery among individual donors.

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Individualised Plasma donation

- We therefore pledge for an individualised plasma donation system according to that individual donor‘s protein recovery rate.
- Accordingly regulatory maximum number of donations or a maximum donation volume per year, are completely arbitrary, be it 24, 33, 45, 60 or 104.
- These requirements should all be waived and replaced by a mandatory IgG / TP monitoring system.
- Likewise annual volume limitations are senseless. Plasma donation is not an issue of „volumes“ .We collect proteins, with IgG as the most sought after being the most important one for an increasing number of therapies.

- Achieving as many donations as possible for that specific donor‘s protein recovery rate with as little deferrals for low IgG as possible and keeping him longterm healthy and happy as a donor, is the only way to a suffcient plasma supply on an national, European or international level

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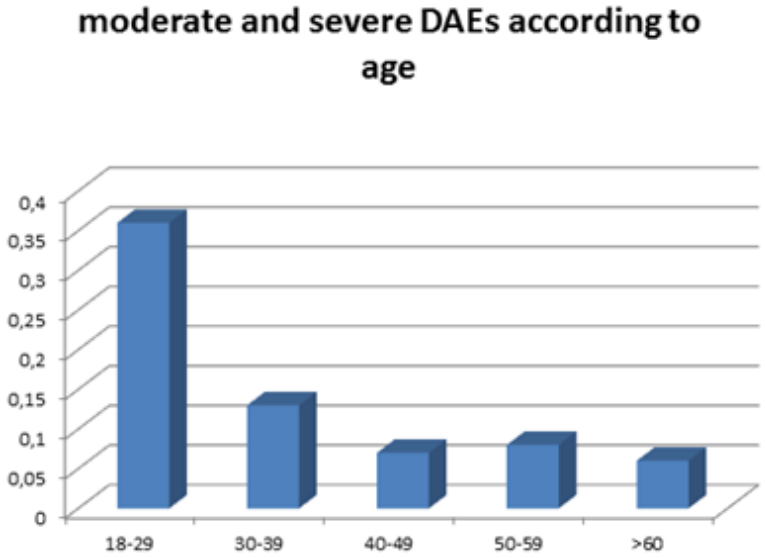
Individualised Plasma donation

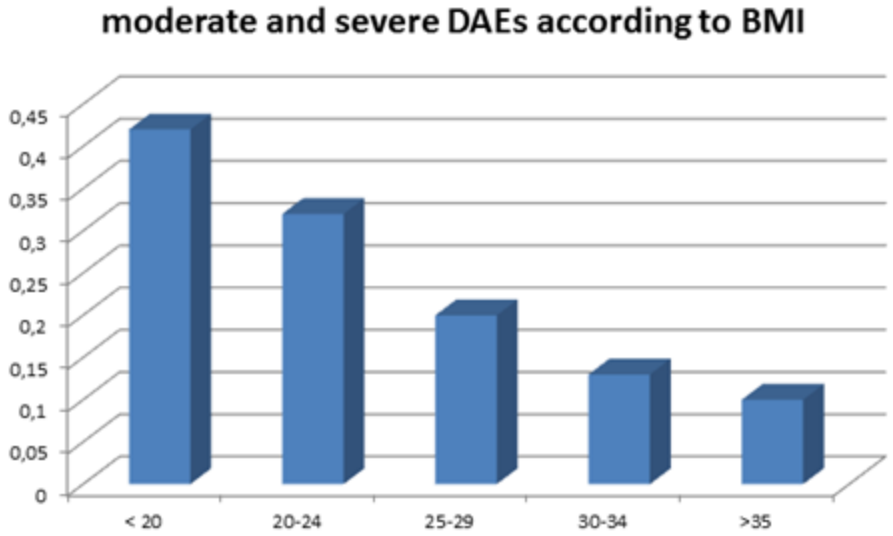
Donation volume

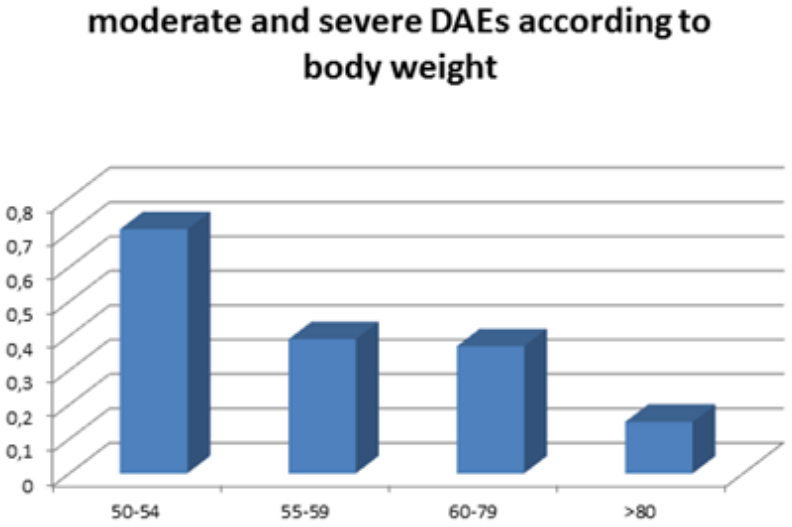
Likewise, the actual donation volume should be individualised.

Currently donors are categorised in 3 different donation volume categories only based on body weight.

However we know, that many other factors like age or BMI play an important role







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Individualised Plasma donation

Our data show that high collection volumens are generally tolerated very well, far better than collection in the lower weight groups

However the volumes are arbitrary and a weight increase of 2 kg (e.g. after Christmas) may put a donor in the next higher category, which he is not used to and does not tolerate well.

We need a new generation of plasma collection machines, where other factors determining a „healthy individualised“ donation, like e.g. a calculated max. ECV and BMI are also taken into account

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Individualised Plasma donation

With that new machine generation, our donor software could calculate an individual mamimum donation volume safe for that specific donor on that specific day.

We would have less donor incidents due to donors in wrong volume groups and a higher return rate of donors

This would again add to the „healthy individualised donation“ idea with a maximum output of plasma.

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Challenges for the future

- The demand for plasma for the manufacturing of immunoglobulins is increasing every year and requires a joint effort of all countries to significantly increase plasma collection
- The ARGE Plasmapheresis members have collected and published a large number of data over the last 20 years in order to improve donor selection and donor safety. (see publication list attached)
- However we are still lacking sufficient information on issues like e.g. max ECV, long term effect of regular plasma donations on the bone metabolism, potential harm of plasticisers.

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Challenges for the future

There are still a lot of challenges to further optimise safe donations for happy patients !!

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References collated by first ARGE Chairman Prof. H. Storch

- Schulzki, T et al. 2006 (*I a) demonstrated in the SIPLA-Study with a long term intensive plasmapheresis program of 650-850 ml up to 60 times/year the donor safety, if monitoring of the donor with TP and IgG is established.
- Diekamp, U. et al. 2014 (*II a) has shown that adverse events (AE) during plasmapheresis are more often technical and accompanied significantly with the first and second donation than for subsequently donations.

- The donor vigilance data, collected by Burkhardt, T. et al. (*II a) for plasma donations according the German Guidelines to the manufacture of blood and blood components showed clearly the safe plasmapheresis with low incidence of AE. First time donors and female gender were associated with higher incidence of AE compared with repeat donations.

- Positive effects of plasmapheresis on hypertension in 666 donors with donations of 625 ml-800 ml (excluding citrate) were demonstrated by Rosa-Bray et al.
- 2015(*I b), when the donation interval was less than 14 days.

- St. Kiessig has given a presentation on this PMWSG-Meeting, dealing with saline and AE considering the exchange volume during the plasmapheresis. Based on this data (Literature see 2.2.4) he suggested to give saline infusion for rinsing the disposable tubing in order to limit the loss of erythrocytes but not during the plasmapheresis procedure, because its reduced the yield of plasma proteins using for fractionation.

- All these topics deliver strong data to individualize the donation frequency, intervals and donation/ year based on the control of TP and IgG.

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References collated by first ARGE Chairman Prof. H. Storch

- Burgin et al.1992 (*II a) analyzed 127 new and 124 established donors over a five-month period and highlighted need for regular testing of total protein(TP) and IgG in regular plasma donors.
- Ciszewski et al. 1993 (*II a) accepted a weekly donation interval after a control of (TP), IgG, IgA and IgM in a 6-month study.
- Lewis et al. 1994 (*II a). Comparison of plasma donors with 69-74 donations/year showed many with TP and IgG lower than the accepted limits, increased B-cells and decreased NK -and suppressor-T cells.
- Hellstern et al. 2001(*II a) Plasma collected, using intensive plasmapheresis, contains lower levels of IgG compared with moderate plasmapheresis and lower Factor V and FVII if slow freezing is used instead of rapid plasma freezing.
- Jansson et al. 2003 (*I b) demonstrated in a moderate plasmapheresis collection program no significant changes in the protein patterns and no increase in adverse effects.
- Tran-Mi, B. et al. 2004 (*II a) demonstrated that intensive plasmapheresis with up to 45 Liter/annum is safe. The donors did not develop impaired immunity, iron store depletion or an increased cardiovascular risk.