PLASMAPHERESIS – IMPACT ON SHORT TERM DONOR HEALTH

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Chair of the CoE CD-P-TS:s working party Plasma Supply Management (TS093) 2017-2019

(Conflict s of interest: Nothing to declare)

IMPACT ON SHORT TERM DONOR HEALTH

Summary of a

- literature & hemovigilance report review
- congress presentations
- data from TS093 Survey 2017

"Classic" donor complications, donor adverse events

- vasovagal reactions, local complications, citrate reactions

POLITIS C ET AL. IHN-NETWORK DATABASE (ISTARE) HEMOVIGILANCE DATA 2006 – 2012

(VOX SANG. 2016)

VoxSanguinis
The International Journal of Transfusion Medicine
Vox Sanguinis (2016) 111, 409–417

DOI: 10.1111/vox.12447

ORIGINAL PAPER

The International Haemovigilance Network Database for the Surveillance of Adverse Reactions and Events in Donors and Recipients of Blood Components: technical issues and results

C. Politis,[1] J. C. Wiersum,[2] C. Richardson,[3] P. Robillard,[4] J. Jorgensen,[5] P. Renaudier,[6] J.-C. Faber[7] & E. M. Wood[8]
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Vasovagal reactions represented 83% of total reported complications related to whole blood donations and 57% of those relating to apheresis procedures. Rates for whole blood donations and aphaeresis procedures separately were calculated on data available for only 47 of 66 annual reports.

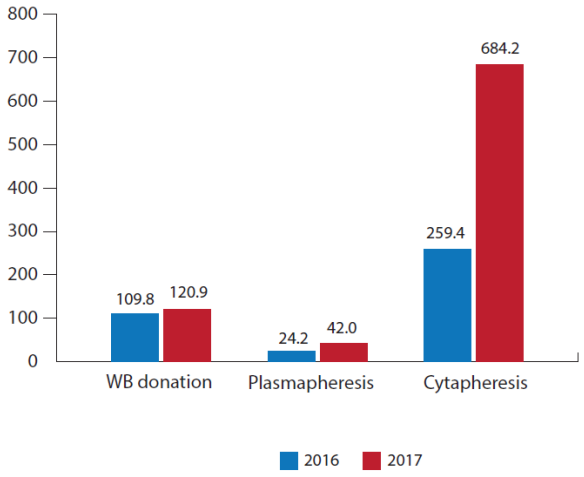
The rate of severe complications with local symptoms related to whole blood donation was 3.2 per 100 000 and 8.2 for apheresis. Thus, the risk of a severe localized complication was nearly three times higher after apheresis than after whole blood donations. Figure 3 demonstrates

→ Very limited information concerning plasma donations

NATIONAL HEMOVIGILANCE DATA - PEI, GERMANY

- Most recent www-published report 2017
- Only serious adverse reactions reported
- (By the ISBT definition: *life-threatening or leading to hospitalisation, incapacity, chronic morbidity or death).*
- 75% of reactions: vasovagal reactions

Figure 4.13 a: Rates of confirmed donor SAR per 1 million donations referring to the number of donations from the reporting BE from 2016–2017. Cytaphereses include thrombocytaphereses, granulocytaphereses, and erythrocytaphereses.



- Serious Adverse Reactions; Number in Cytapheresis > in WB > in Plasmapheresis (2017: 0,42 / 10 000)

- https://www.pei.de/EN/medicine-safety/haemovigilance/haemovigilance-reports/reports-node.html

NATIONAL HEMOVIGILANCE DATA - AUSTRALIA

- Most recent www-published report 2015-2016 (0.56 million plasmapheresis donations), covering all types of DAE:s

Table 40 Adverse event reaction rate by procedure, 2011-12 to 2015-16 (per 10,000 donations)

Procedure	2011–12	2012–13	2013–14	2014-15	2015-16
Whole Blood	271	319	333	352	361
All apheresis procedures	118	152	217	217	252
Plasmapheresis	98	124	163	182	216
Plateletpheresis	302	480	947	655	778
Total procedures	226	257	286	295	311

- All DAE; 216 / 10 000, Serious DAE 6/ 10 000

2. *Plasmapheresis* – The rate of vasovagal reactions in plasma donors is significantly lower than in whole blood or platelet donors. The increase in donation reactions in plasmapheresis donors is attributable to an increase in the number of brief vasovagal reactions not associated with loss of consciousness or injury, and to an increase in the number of citrate reactions reported. This increase reflects changes in the make up of the plasmapheresis donor panel with an increase in the proportion of new and female donors.

→ Informative review, useful data /report format also for Europe

https://www.blood.gov.au/system/files/Donor-Haem-Report-15-16-v14.pdf

SCHULZKI T ET AL. A PROSPECTIVE MULTICENTRE STUDY ON THE SAFETY OF LONG-TERM INTENSIVE PLASMAPHERESIS IN DONORS (SIPLA). VOX SANG. 2006 AUG; 91(2):162-73.

Table 1 Categorization of adverse events and dropouts

Adverse events		Dropout categories		
Severity	Temporal relation to plasmapheresis	Socioeconomic	Medical reasons unrelated to plasmapheresis	Medical reasons related to plasmapheresis
Grade 1 Medical intervention not necessary	Category 1 No temporal relation	1. Lack of time/work schedule conflicts	1. Medical diseases	1. Low IgG
			2. Surgery, accidents, injuries	2. Low TSP
	Category 2	2. Moving from the area		
Grade 2 Monitoring and minimum medical intervention	Unexpected side-effect, no temporal relation		3. Malaise, disturbed well-being	3. Low Hb/Hct
		3. Others		
	Category 3	unsatisfactory compensation; do not need money; too much time to get to the center; difficulty getting transport or child care; discomfort/pain; problems with personnel; concerned about my health; taking a break; friends advised me to stop; piercing; tattooing	4. Pregnancy	4. Others venipuncture-related complications; citrate reactions; nausea, vomiting; dizziness; hypotensive, etc.
Grade 3 Major medical intervention or hospitalization	Cannot be ruled out		5. Diagnostic endoscopy	
	Category 4 Probable or certain		6. Laboratory findings not related to plasmapheresis ALAT elevation; low or high mean cell volume, red cell count, platelet count or leukocyte count; false positive anti-HIV, anti-HCV or HBsAg	
Grade 4 Life-threatening				
Grade 5				

We noticed only five severe clinical adverse events grade 3 that were causally related to plasmapheresis. These were four venipuncture adverse events and one metacarpal fracture after dizziness and fall. No case of severe collapse temporally related to plasmapheresis was observed. Adverse events grades 1 or 2 possibly or probably related to plasma donation comprised palpable haematomas and/or bleeding from venipuncture sites, citrate reactions, nausea and/or vomiting and dizziness and were observed in 132 of 304 836 donations (0·04% of donations). All 132 donors involved

*21 plasma centres, 3783 donors, 304 836 donations
*switched from a moderate to an intensive plasmapheresis programme
*observation 3-year period
*All DAE 4,4 / 10 000, severe 0,16 / 1000

→ Low rate of DAE?

CROCCO I ET AL: ADVERSE REACTIONS IN BLOOD AND APHERESIS DONORS: EXPERIENCE FROM TWO ITALIAN TRANSFUSION CENTRES.

BLOOD TRANSFUS 2009;7:35-38.

- 38 647 Plasma donations
- Only VVR rate specific for plasma donations given (16 / 10 000)

Table I - Adverse reactions occurring during apheresis donations

Adverse reactions	Donations (n = 240,596)*				
	Homologous WBD (n = 183,855)	Autologous WBD (n = 6,669)	Plasmapheresis (n = 38,647)	Plateletpheresis (n = 2,641)	Multicomponent (n = 8,784)
Vasovagal reactions					
Total	346 (0.19%)	16 (0.24%)	63 (0.16%)	18 (0.68%)	43 (0.24%)
Citrate toxicity					
Total	- -	- -	189 (0.38%)**	189 (0.38%)**	189 (0.38%)**
Severe adverse events	6 (0.003%)	3 (0.04%)	- -	- -	1 (0.01%)

Abbreviations: WBD, whole blood donations. Results are expressed as number (percentage). *Donations during the period January 2002 – December 2006. **Pooled incidence (all apheresis procedures = 50,072).

- Total DAE rate for plasma donations missing
- Local reactions not reported

DIEKAMP U ET AL. DONOR HEMOVIGILANCE DURING PREPARATORY PLASMAPHERESIS. MED HEMOTHER. 2014 APR; 41(2):123-33.

N = 1 107 846 donations
All adverse events 655 / 10 000, BUT without technical 195 / 10 000
Severe reactions 6,2 / 10 000

Adverse events observed:
1.4% local
0.55% systemic
4.6% technical – not reported / not existing in other DAE reporting systems

Conclusions: Technical UEs were common with PPP. UEs accompanied first and second donations significantly more frequently than for subsequent donations.

Technical UEs
- Blood counts out of limits
- Donor compliance
- Incomplete RBC return
- Lipemia
- Machine failure
- Operator error
- Disposable defective
- Repeat venipuncture[a]
- Venous access

→ "New" reaction category needed?

BURKHARDT T ET AL. DONOR VIGILANCE DATA OF A BLOOD TRANSFUSION SERVICE: A MULTICENTER ANALYSIS.

TRANSFUS APHER SCI. 2015. DOI: 10.1016/J.TRANSCI.2015.03.014

- N=342 293 donations

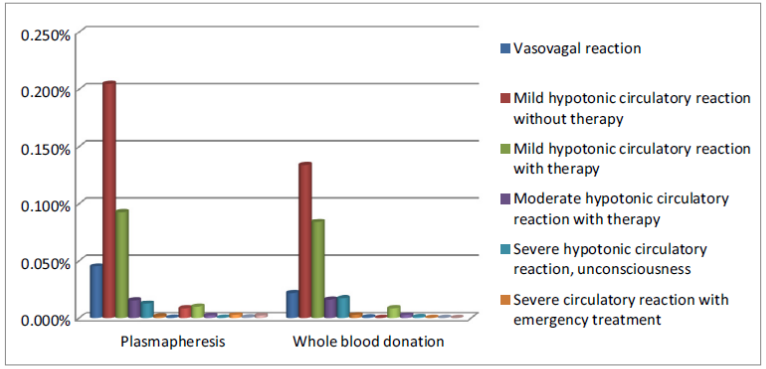


Fig. 2. Circulatory and systemic adverse events in repeat plasmapheresis and whole blood donors. For the sake of clarity only data of the 'top 6' reactions are showed in the legend.

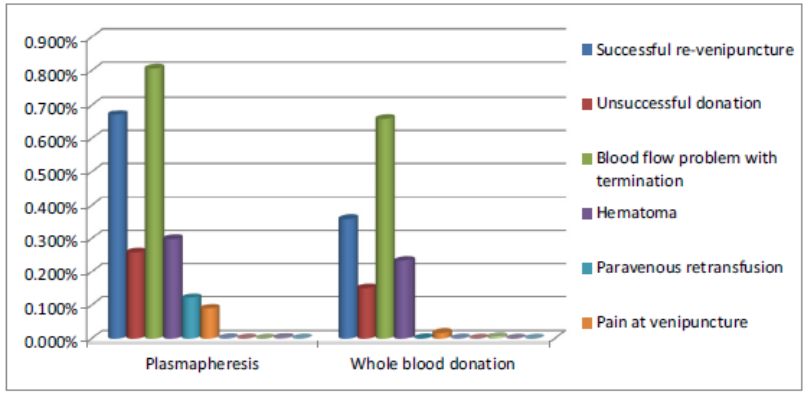


Fig. 3. Comparison of venipuncture induced adverse events in repeated plasmapheresis and whole blood donors. For the sake of clarity only data of the 'top 6' venipuncture induced adverse events are shown in the legend.

Plasmapheresis vs. WB donations: higher number of mild DAE:s ?
(Differences in the age distribution in the donor populations!)

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THOMAS BURKHARDT,
EDQM & EU PLASMA SYMPOSIUM 2019

- 2011-2017

2 068 233 WB donations

851 861 Plasma donations

DRK-Blutspendedienst Nord-Ost gemeinnützige GmbH
Berlin I Brandenburg I Hamburg I Sachsen I Schleswig-Holstein

Deutsches Rotes Kreuz

Important donation conditions for this evaluation

- Selection of plasma volume depending on body weight
- No saline compensation
- Request for fluid intake before and during donation
- Use of equipment from Fresenius/Fenwal (A200) and Haemonetics (PCS2 and MCS+)
- Definition of the adverse events according to the "Standards for Surveillance of Complications Related to Blood Donation (Rev. 2014)"

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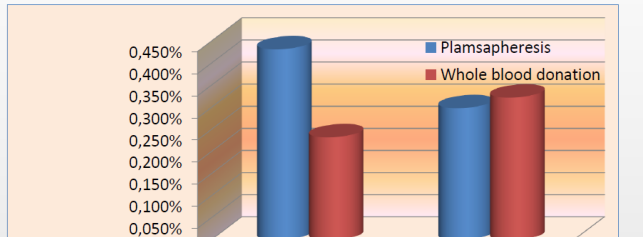
Overview of adverse reactions to whole blood and plasma donations (multiple donors)



	venipuncture-related side effects	Systemic (Vasovagal) adverse reactions
Plamsapheresis	0,432%	0,299%
Whole blood donation	0,233%	0,323%

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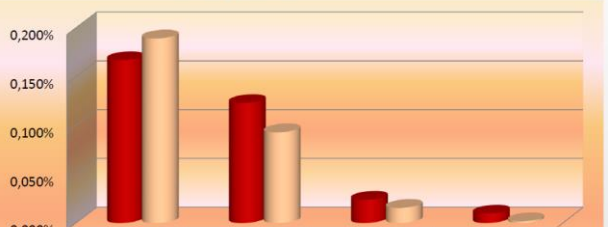
Frequency and severity of vasovagal reactions in whooleblood donation and plasmapheresis



	mild VVR without therapie and LOC	VVR with therapie/ without LOC	VVR with LOC <60 seconds	VVR with LOC >60 seconds
whole blood donations	0,167%	0,123%	0,024%	0,010%
plasma donations	0,189%	0,093%	0,015%	0,002%

Castrén, IPFA&EBA Jan 2020

THOMAS BURKHARDT,
EDQM & EU PLASMA SYMPOSIUM 2019

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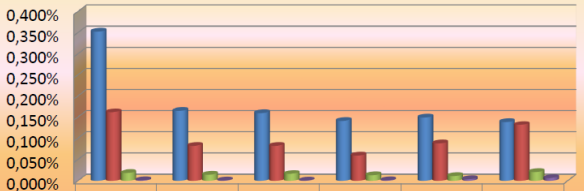
vasovagal reactions in plasma donation depending on age?



	<24 years	25-34 y	35-44y	45-54y	55-64y	> 65y
mild Vasovagale reaction without LOC/without intervention	0,353%	0,165%	0,160%	0,142%	0,150%	0,139%
mild vasovagal reaction without LOC/ with symptomatic therapy or medication	0,162%	0,083%	0,083%	0,060%	0,088%	0,132%
Vasovagale reaction with LOC < 60 sec	0,019%	0,015%	0,017%	0,014%	0,011%	0,021%
Vasovagale reaction with LOC > 60 sec	0,001%	0,001%	0,001%	0,001%	0,004%	0,007%

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Grading Severity of Plasma donor adverse events

- it would be a good idea to introduce a uniform system for assessing the severity of an adverse reaction
- The severity of a side effect can often only be assessed retrospectively.
- this measure could allow a better assessment of adverse reactions that occur

MARY GUSTAFSON; EDQM & EU SYMPOSIUM 2019

PPTA Plasma Protein Therapeutics Association

Pilot Data Analysis

- Assess performance of the Standard by reviewing operational data
- Obtain a snapshot of events recorded over a 3-month period post-implementation
  - 01 March – 31 May 2016
  - Only DAE that occurred during or post donation were evaluated
- 6 companies participated in the pilot study
- Nearly 7.6 million donations were collected; ~79% of industry
- 15,300+ DAE were recorded

PPTA Plasma Protein Therapeutics Association

Top 6 DAE

Rank	Classification	% of DAE	Rate per 10,000 donations
1	Hypotensive: Prefaint, No LOC (Moderate)	57.3%	11.98
2	Local Injury Related to Phlebotomy: Hematoma/Bruise (Complicated)	18.2%	3.81
3	Hypotensive: LOC (brief)	9.0%	1.88
4	Hypotensive: Severe (with or without LOC)	3.2%	0.66
5	Local Injury Related to Phlebotomy: Nerve Irritation	3.2%	0.66
6	Citrate Reaction: Moderate	3.1%	0.65
All others		4.3%	1.29
	TOTAL	100%	20.93
	TOTAL DAE: 15,300+		

KIESSIG S ET AL; POSTER IN ISBT 2013

SIPLA II

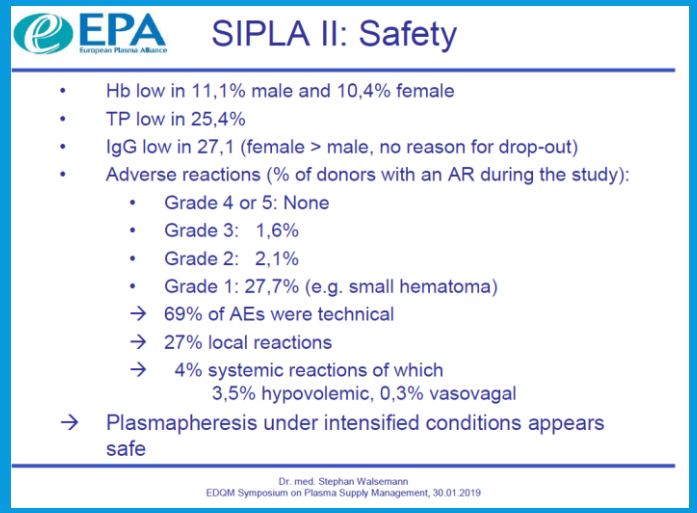
Haema. Blutspendedienst

First results from the Study on Intensive Plasmapheresis II (SIPLA II)

S.T. Kiessig[1], S. Teichmann[1], S. Schneider[3], T. Ouarrak[3], K.P. Krause[1], H. Storch[4], P. Hellstern[2]

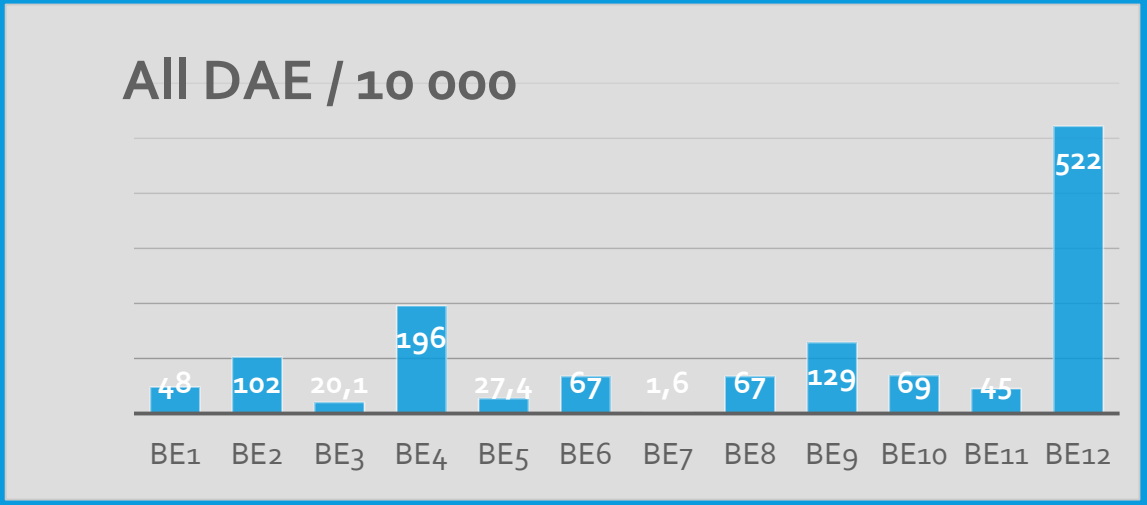
	Total	Male	Female
Safety Parameters			
Total Number of unexpected Events (UE) in all Donations	4,187	2,202 (52.6%)	1,985 (47.4%)
Participants with at Least one UE	1,231	672 (54.6%)	559 (45.4%)
Systemic Reactions per all Donations [%]	4.2% (172/4,129)	2.3% (49/2,166)	6.3% (123/1,963)
Hypovoleamic Reactions [% of all UE]	3.5% (146/4,129)	1.6% (34/2,166)	5.7% (112/1,963)
Vasovagal Reactions [% of all UE]	0.3% (12/4,129)	0.4% (8/2,166)	0.2% (4/1,963)
Local Reactions [% of all UE]	27.2% (1,125/4,129)	25.3% (549/2,166)	29.3% (576/1,963)
Technical Problems [% of all UE]	68.6% (2,832/4,129)	72.4% (1,568/2,166)	64.4% (1,264/1,963)
Severity Grade 1 [% of all UE]	27.7% (1,144/4,129)	25.0% (542/2,166)	30.7% (602/1,963)
Severity Grade 2 [% of all UE]	2.1% (86/4,129)	1.7% (36/2,166)	2.5% (50/1,963)
Severity Grade 3 [% of all UE]	1.6% (67/4,129)	0.9% (20/2,166)	2.4% (47/1,963)
Severity Grade 4 [% of all UE]	0	0	0
Severity Grade 5 [% of all UE]	0	0	0

*65 118 Donations
*All DAE 185 / 10 000
*Severe DAE 9,4 / 10 000



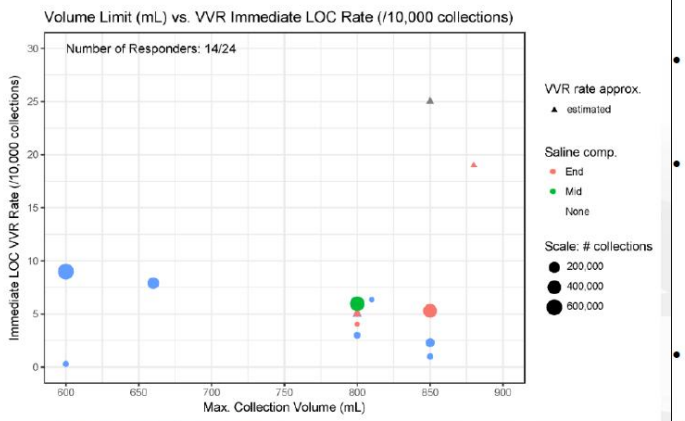
COE CD-P-TS:S WORKING PARTY "PLASMA SUPPLY MANAGEMENT (TS093)" - SURVEY 2017

- Safe and sustainable plasmapheresis – survey of current practices
- The total n responders collecting PfP by apheresis:24
- Dataset covered 2 888 390 plasma donations



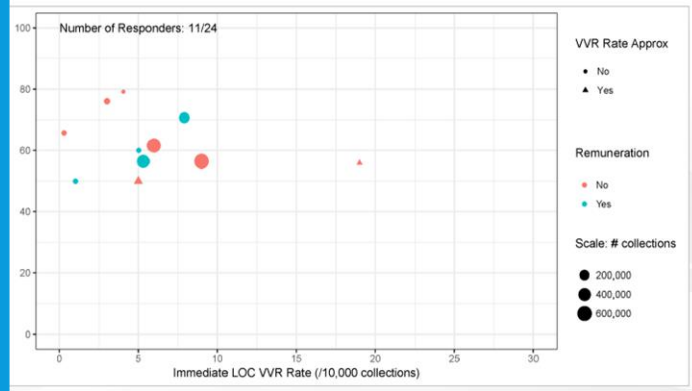
PLASMA SUPPLY MANAGEMENT WORKING PARTY - SURVEY 2017
(J.PINK; EDQM & EU PLASMA SYMPOSIUM 2019)

Maximum collection volume per procedure versus immediate LOC rate (per 10,000 collections)



- LOC rate mainly < 10 / 10,000 collections
- Small trend towards reduced LOC rate with larger collection volume
- Likely due to differences in operating model, donor demographics (% of new, female) and perhaps apheresis platform (smaller ECV)
- Saline compensation unrelated
- 850mL are all remunerated

Retention rate versus immediate LOC rate (per 10,000 collections)



- Retention rate banded in the range of 50%-80%.
- Not correlated with LOC rates, saline compensation or remuneration.
- Caution - small data sample size, variation in reporting

Abstract Submission

Blood donation

Blood collection incl. apheresis

ISBTBasel-712

INSIGHTS IN SAFETY AND RETENTION RATES OF DONOR VS COLLECTION VOLUME; RESULTS FROM AN INTERNATIONAL SURVEY OF PLASMAPHERESIS PRACTICES

J. Castrén[1], S. Wright[2], R. Norda[3], G. Rautmann[4], J. Pink[2]

Castrén, IPFA&EBA Jan 2020

SUMMARY TABLE

Year	Author		n		All Adverse Reactions	Severe / Serious
					per 10 000 donations	
2006	Schulzki	Germany	304 836		**4,5**	0,16
2013	Poster/ Kiessig	Germany	65 118		**185**	9,4
2014	Diekamp	Germany	1 107 846		**195**	6,2
2015	Burkhardt	Germany	335 832	repeat	**101**	
			6 461	1st time	**796**	
2016	Hemovig. report	Australia	560 000		**216**	4
2017	Hemovig. report	Germany				0,40
2019	Presentation/ Gustafson	USA	7 600 000		**20,9**	0,66

CONCLUSIONS

- Figures in plasma donor adverse reactions - lot of variation -> difficult to compare (lack of universal categorizing and codes)
  - in overall:
    - plasmadonors have less DAE:s than WB donors and PLT donors
    - female donors have more DAE:s than male donors
    - young, small size persons and first time donors are "high risk donors" for vasovagal reactions
    - sever ereactions are very rare

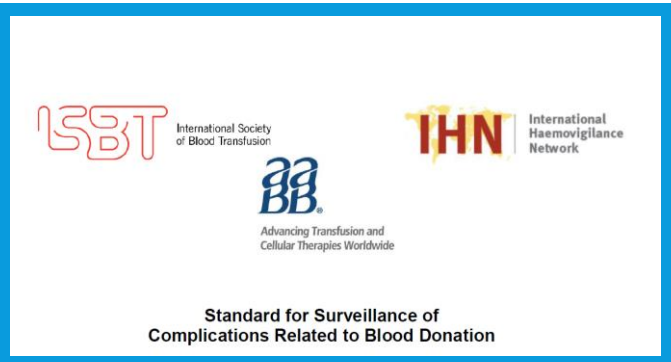
    - "local complications" OR "vasovagal reactions" the most common adverse reaction category??

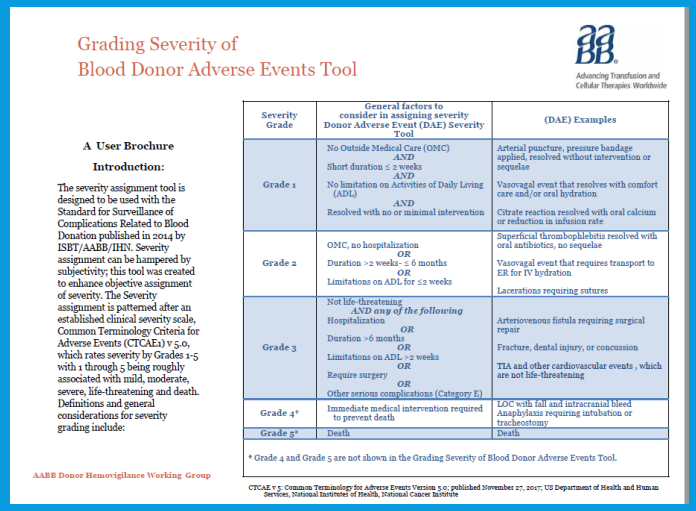
➢ Need for more publications concerning adverse reactions in plasma donors

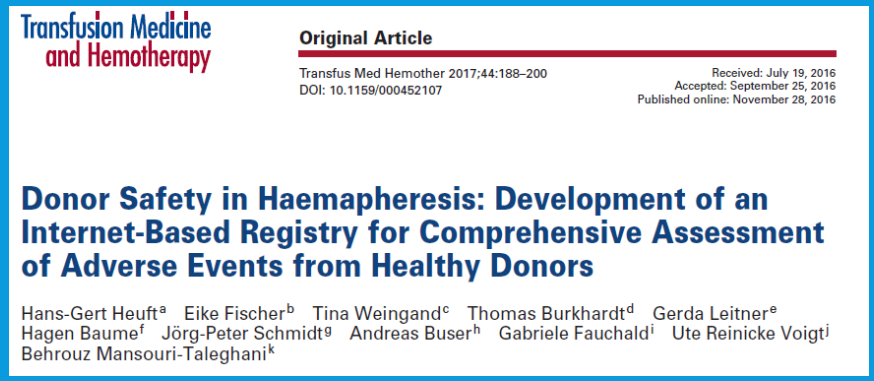
➢ Need for hemovigilance data (donor vigilance) which covers plasma donors – and donation related aspects spesific in plasmapheresesis

➢ there are already some existing solutions ...☺

EXISTING SOLUTIONS







Conclusions

An on-line electronic platform for comprehensive assessment and centre-specific automated evaluation of AEs in haemaphereses has been developed and proved to be stable and safe over a period of 4 years.

Keywords: Adverse reactions, Haemapheresis, Haemovigilance, Plasmapheresis, Plateletpheresis, Stem cell collection, Donor safety, Adverse events

Thank You

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