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Review

Adverse events in apheresis: An update of the WAA registry data

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ABSTRACT

Apheresis with different procedures and devices are used for a variety of indications that may have different adverse events (AEs). The aim of this study was to clarify the extent and possible reasons of various side effects based on data from a multinational registry.

The WAA-apheresis registry data focus on adverse events in a total of 50846 procedures in 7142 patients (42% women). AEs were graded as mild, moderate (need for medication), severe (interruption due to the AE) or death (due to AE).

More AEs occurred during the first procedures versus subsequent (8.4 and 5.5%, respectively). AEs were mild in 2.4% (due to access 54%, device 7%, hypotension 15%, tingling 8%), moderate in 3% (tingling 58%, urticaria 15%, hypotension 10%, nausea 3%), and severe in 0.4% of procedures (syncope/hypotension 32%, urticaria 17%, chills/fever 8%, arrhythmia/asystole 4.5%, nausea/vomiting 4%).

Hypotension was most common if albumin was used as the replacement fluid, and urticaria when plasma was used. Arrhythmia occurred to similar extents when using plasma or albumin as replacement. In 64% of procedures with bronchospasm, plasma was part of the replacement fluid used.

Severe AEs are rare. Although most reactions are mild and moderate, several side effects may be critical for the patient. We present side effects in relation to the procedures and suggest that safety is increased by regular vital sign measurements, cardiac monitoring and by having emergency equipment nearby.

Contents

1. Introduction

Therapeutic apheresis has been widely used since 1975 when Lockwood et al. published the survival benefits of treating patients with Goodpasture syndrome with immunosuppression and apheresis [1]. The procedure used was a plasmafiltration technique for removal of antibodies. Since then, the number of techniques [2] as well as the indications [3] has increased.

When the number of patients increased, it was possible to perform controlled studies in several of the diseases. Thus, it became possible to clarify the usefulness of the therapy for various diseases, and to develop guidelines such as those of the American Society for Apheresis [3–6]. Still, clarity and local strategies vary. To ensure increased safety and efficacy, national quality assessment registries were developed in Canada [7,8], France [9–11], and some other countries such as Italy [12–14], Sweden [15,16], Korea [17], the Czech Republic [18] and Germany [19,20]. For a broader comparison, a rheopheresis registry has been established [21] as well as a more general apheresis registry on behalf of the World Apheresis Association [22,23]. Several international cross sectional surveys have been performed by Malchesky et al. [24–26].

The Canadian Apheresis Group (CAG) has combined their registry activities with randomized multicenter studies resulting in an important milestone showing the beneficial effects using apheresis in the treatment of thrombotic thrombocytopenic purpura [27]. Further CAG studies included investigations about replacement fluids [28,29], plasma exchange for immune thrombocytopenic purpura [30], multiple sclerosis [31] and myeloma cast nephropathy [32].

Since the extent of side effects during apheresis occurs at a rate of approximately 5% [22], the number of cases with various adverse events (AEs) of various grades is rather low even in larger centers. Using data from larger registries enables a more accurate estimate of AEs, while controlled studies are important to clarify indications. To be able to

Table 1
Grading of adverse events (AEs) based on patient experience and outcome.

Grading	Measures and consequences
1. Mild	Tolerated without medication
2. Moderate	Need of medication due to AE
3. Severe	Interruption due to AE
4. Death	Due to AE

compare the extent of AEs between centers and methods, it is also important to use similar criteria.

The aim of this study was to investigate the extent of various severe side effects that occur during apheresis so that the risks for the patients and precautions to be taken can be clarified.

2. Material and methods

The study included all data entered by the apheresis centers that participated in the WAA apheresis registry (www.waa-registry.org). The data for procedures were entered consecutively and prospectively regarding variables such as type of procedure, type of replacement fluid, and type and grade of AEs (Table 1, Appendix). When analyzing data, a total of 50,846 procedures had been registered for 7,142 patients (57% men 43% women). The median age was 55 years (range 0–94 years). Data for AEs were missing in 5.9% of the procedures (n = 2990 of the first treatments). Data were also missing for other variables, thereby reducing the numbers available for analyses for various reasons. The specific analysis of apheresis registry AEs data was approved by the local ethics committee (D number: 2011-113-31M and 2012-311-32M).

The definition of grades of AEs are given in Table 1. Hypotension was defined as a drop in systolic blood pressure of more than 40 mmHg or below 90 mmHg. Plasma exchange (PE) was performed with replacement with of liquid stored plasma (LSP), fresh frozen plasma (FFP), cryoprecipitate poor plasma (CPP), solvent detergent plasma – Octaplas® and Octaplas LG®, and hydroxyethyl starch (HES).

Statistical analyses were performed using the Student's T-test, Mantel–Haenszel chi square test, and for smaller numbers the Fisher exact test. Correlation analyses were performed with the Spearman test and the Pearson test for univariate comparison and linear regression analysis. In the multivariate analysis, the grade of AE was designed as the dependent factor entering the variables plasma, albumin, age, gender and calcium *intravenously* as prophylaxis and centers in the model. A two-tailed p-value of less than 0.05 was considered as significant. SPSS 19 software was used as well as open access Epi-info 7 (http://wwwn.cdc.gov/epiinfo).

3. Results

The various main groups of diseases treated by apheresis are shown in Table 2.

Data regarding an AE was given for 47,856 procedures. In 2,760 procedures AEs as well as a specific grading were reported (Table 3). So far, no death due to the apheresis treatment was reported. In 0.3% of procedures, the patient suffered from more than one AE (Table 3). The grade of AE related to the most common groups of diseases treated is given in Table 4. The three most common groups were those treated for endocrine and metabolic (hyperlipidemia contributed to the main part of those procedures), neurologic and malignant diseases (mainly treated by cytapheresis).

Table 2
Distribution of 7,102 patients in field of diagnoses groups according to the ICD-10 code system (clear diagnosis missing in 40 patients).

Field of diagnoses	Total N	% of all
Malignancy	2,950	41.8
Neurology	990	14.0
Hematology	681	9.6
Transplantation & donors	576	8.2
Rheumatology	501	7.1
Endocrinology	446	6.3
Organ rejection	278	3.9
Ophthalmology	146	2.1
Gastro intestinal	130	1.8
Muscular disease	112	1.6
Nephrology	81	1.1
Myocardial disease	79	1.1
Dermatology	52	0.7
Infectious disease	40	0.6
Other groups	40	0.6

3.1. Mild and moderate adverse events

Mild and moderate AEs were mainly due to access problems, such as the need for reinsertion of a puncture needle

Table 3
Distribution (numbers) of the severity of adverse events, first up to the third at the same occasion (% in parentheses). In case of multiple adverse events during an apheresis procedure, the most severe is listed first, followed by the second most severe and then the third.

Adverse event (AE)	First AE	Second AE	Third AE
Mild	1,154 (2.4)	34 (0.1)	5 (0.0)
Moderate	1,438 (3.0)	81 (0.2)	10 (0.0)
Severe	168 (0.35)	13 (0.0	4 (0.0)
Total AE	2,760 (5.8)	128 (0.3)	19 (0.05)

Table 4
Distribution of all procedures in the most common groups of diagnoses according to the ICD-10 code, and related to the extent of various grades of adverse event (AE). Reference is the value achieved for all procedures (total).

Field of diagnoses	% of all proc.	Mild AE	Moderate AE	Severe AE
Endocrinology	32.0	3.7^{aaa}	1.8^{bbb}	0.2^{bb}
Neurology	17.0	1.9^{bb}	2.2^{bbb}	0.4
Malignancy	14.7	1.1^{bbb}	4.9^{aaa}	0.2
Rheumatology	10.1	2.0	5.3^{aaa}	0.6^{aa}
Hematology	8.0	2.0	3.8^{aa}	0.4
Organ rejection	7.1	0.5^{bbb}	0.8^{bbb}	0.2
Gastro intestinal	2.5	5.7^{aaa}	1.8^{b}	0.3
Transplantation & donors	2.1	2.2	5.3^{aaa}	0.4
Ophthalmology	1.6	2.2	3.9	0.4
Nephrology	1.3	1.5	3.9	1.0^{a}
Total N = 47856 (reference)	100	2.4	3.0	0.3

More than reference: $^{aaa}p < 0.001$; $^{aa}p < 0.01$; $^{a}p < 0.05$; Less than reference: $^{bbb}p < 0.001$; $^{bb}p < 0.01$; $^{b}p < 0.05$.

Table 5
Most common findings of mild specified AE/10,000 procedures.

Symptom, reason	AE/10,000
Access problems	130
Hypotension	36
Tingling	19
Device problems	17
Urticaria	12
Nausea/vomiting	12
Hematoma at puncture site	10
Hypertension	5
Flush	2
Phlebitis	2
Shivering, fever	2
Arrhythmia	1
Back pain	1
Vertigo	1

at a peripheral site or a local hematoma (Table 5). Moderate AEs were mainly experienced as tingling sensations (Table 6).

3.2. Severe adverse events

The interruption of apheresis due to severe adverse symptoms was registered in 168 procedures (Table 7).

3.3. Change of AEs over time

The evolution in number and grade of AEs over the years is illustrated in Fig. 1. The incidence of mild and severe events decreased over time (mild: r = –0.64, p = 0.036; severe AEs r = –0.86, p = 0.001, Spearman's test) while the moderate AEs remained constant.

In general, there was an increased risk for AEs during the first apheresis procedure compared to the subsequent ones (8.9% vs 6.1%, p < 0.001, RR 1.4, CI 1.3–1.6). When multiple symptoms appeared during an apheresis procedure, the risk for severe AEs was increased. Women had a greater risk for AE than men both during the first (p < 0.001, RR 1.4, CI 1.2–1.7) and the following procedures (p < 0.001, RR 1.5, CI 1.3–1.6).

There was a weak correlation (r < 0.1, p < 0.001) between the severity of AEs and both the volume processed and the volume of replacement fluid (not identical with volume processed).

Table 6
Most common findings of moderate specified AEs/10,000 procedures.

Symptom, reason	AEs
Tingling	174
Urticaria	45
Hypotension	30
Nausea	9
Technical problems	6
Hypertension	6
Chills and fever	6
Flush	5

Table 7
Severe adverse events (primary reason in 168 procedures) resulting in interruption of apheresis given as specified AEs/10,000 procedures.

Symptom, reason	AEs
Hypotension, syncope	11
Urticaria	6
Fever, chills	3
Nausea, vomit	2
Access problem	2
Flush	2
Tingling, stitching	2
Arrhythmia	2
Bronchospasm	1
Quincke edema	1
Technical problem	0.8
Abdominal pain	0.8
Back pain	0.8
Epilepsy	0.6
Hypertension	0.4
Spasm	0.4
Asystolia	0.2
TRALI chest pain	0.2
Anaphylaxis	0.2
Gastro intestinal bleeding	0.2
Wrong plasma	0.2
Adverse event to drug	0.2
Chest pain	0.2
Anxiety + hyperventilation	0.2

3.4. Type of procedure

Therapeutic apheresis procedures using filtration had more AEs then those performed with a centrifugation technique (11% versus 6%, p-value <0.0001, OR 1.8, CI: 1.5–2.3). Significant differences were valid for mild, moderate and severe AEs (Table 8). The differences in AE between other procedures and plasma exchange with centrifugation technique are given in Table 8. In some groups, only a few treatments were done, which did not allow statistical comparison.

3.5. Anticoagulation

Information on anticoagulation together with the presence or absence of AEs was registered in 44,154 procedures (Table 9). Comparison of various anticoagulation methods used indicated that procedures with heparin compared to those using acid citrate dextrose, solution A (ACD-A, approximately 2.1% citrate) or solution B (ACD-B, approximately 1.2% citrate) had more mild (RR 1.97, CI 1.70–2.30) and less moderate (RR 0.30, CI 0.23, –0.40) or less severe AEs (RR 0.47, CI 0.26–0.88). When the combination of ACD-A and heparin was used compared to ACD-A or B there were more moderate (RR 1.74, CI 1.52–1.99), but less severe AEs (RR 0.30, CI 0.22–0.40). Procedures with citrate phosphate dextrose (CPD) versus ACD-A or ACD-B showed less mild AEs (RR 0.64, C 0.46–0.88), but more moderate side effects (RR 1.96, CI 1.67–2.30, Table 9).

3.6. Access

AEs were also analyzed in relation to the access using 'peripheral vein to peripheral vein' as the reference

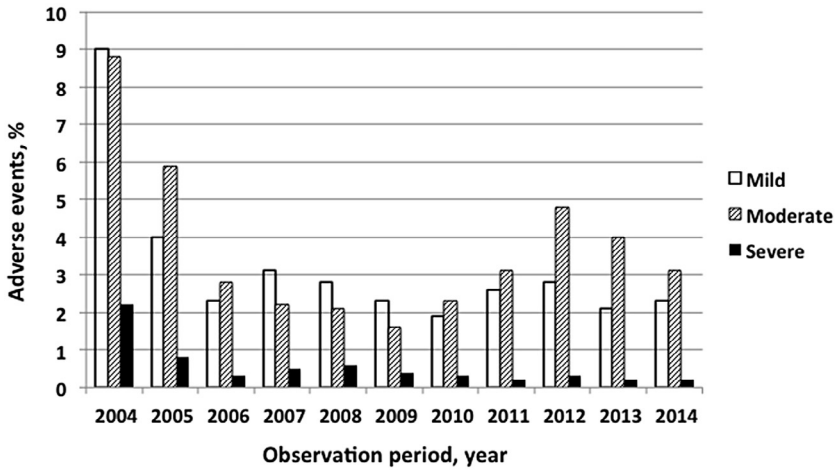

Fig. 1. Distribution (in %) of mild (open), moderate (hatched) and severe (filled) adverse events over the observation period from 2004 to 2014.

(Table 10). Procedures performed when a central access was used were related to more severe AEs. Access problems were mainly present when using peripheral veins, but also with an AV-fistula and AV-graft (Table 11).

3.7. Donor vs. patient apheresis, collection of cells for cellular therapy

Table 12A includes data of adverse events of those procedures registered for autologous versus allogeneic collection. Donor apheresis was performed as cytapheresis for peripheral leukocyte and stem cell collections (n = 620 donors, 56% men) in 1,684 occasions. The mean age was 46 years (±14, range 3–74 years). The grade of adverse events is shown in Table 12A. There were more mild AEs during allogenic procedures ($p < 0.001$, RR 3.2, CI 2.3–4.4), more moderate AEs during autologous procedures ($p = 0.006$, RR 1.4, CI 1.1–1.9), and there was no difference for severe AEs.

Seventy percent of the mild AEs were due to problems with access. The various other symptoms are given in Table 12B.

Table 8
Percentage of adverse events (AE) graded as mild, moderate and severe in 44,856 procedures compared to reference (plasma exchange by centrifugation).

Apheresis procedure used	Grade of AE			Total	% of total apheresis
	Mild	Moderate	Severe	N =	
PEx, centrifugation (reference)	1.6	3.8	0.7	15,948	36
PEx, filtration	2.9^{aaa}	6.6^{aaa}	1.0^{a}	994	2
Cell collection, allo PBSC	4.3^{aaa}	3.9	0.2	1,652	4
Cell collection, auto PBSC	1.2	6.8^{aaa}	0.1	3,096	7
Leukapheresis, centrifugation	1.8	4.5	0.4^{bb}	1,569	3
Erythrapheresis	1.4	0.4^{bbb}	0.0^{bbb}	1,345	3
LDL-apheresis	4.4^{aaa}	0.4^{bbb}	0.1^{bb}	4,804	11
LDL-apheresis, adsorption	4.0^{aaa}	2.6^{bbb}	0.1^{bbb}	5,834	13
LDL-apheresis, filtration	5.6^{aa}	0.8^{bbb}	0.1	2,063	5
LDL-apheresis, precipitation	8.1^{aa}	0.0	0.0	74	0
LDL-apheresis, other	0.0	0.0	0.0	1	0
Protein A adsorber	4.8^{aa}	2.8	1.1^{aaa}	1,074	2
Cascade filtration	0.3^{bb}	8.9^{aaa}	0.1^{bbb}	757	2
ECP	0.9^{bb}	1.5^{bbb}	0.0^{a}	3,199	7
Leukapheresis, filtr./adsorption	0.5	4.4^{a}	0.0	205	0
Leukapheresis, Nikisso column	6.3	0.0	0.0	16	0
Leukapheresis, Otsuka column	0.0	0.8^{b}	0.0^{b}	242	1
Rheopheresis	5.9^{aa}	2.1	0.3	388	1
Liver detoxification	0.0	6.7	0.0	15	0
Lp(a) adsorption	1.5	0.0^{bb}	0.0^{bb}	204	0
IgG adsorption, Sheep ab	3.3^{aa}	1.5^{bb}	0.2^{bb}	614	1
ABO mismatch adsorption	1.2	5.1	0.0	671	1
Adsorption, other	13.0^{aa}	2.2	0.0	46	0
Total	2.6	3.2	0.4	44,856	

PEx = plasma exchange; PBSC = peripheral blood stem cell collection; ECP = extra corporeal photopheresis therapy; more than reference: $^{aaa}p < 0.001$; $^{aa}p < 0.01$; $^{a}p < 0.05$; less than reference: $^{bbb}p < 0.001$; $^{bb}p < 0.01$; $^{b}p < 0.05$.

Table 9
Distribution of adverse events in relation to anticoagulation used. Statistical comparison was performed with acid citrate dextrose solution A (ACD-A) or solution B (ACD-B) as reference related to the other options containing more than 150 procedures.

	Mild	Moderate	Severe	Total N
ACD-A or ACD-B (reference)	2.4	3.0	0.4	30,605
Heparin (standard)	4.8[aaa]	0.9[bbb]	0.2[b]	5,572
ACD + heparin	2.1	5.3[aaa]	0.2[b]	4,915
CPD. citrate	1.5[bb]	6.0[aaa]	0.3	2,659
Low molecular weight heparin (LMWH)	2.9	3.5	0.6	170
Hespan and citrate	0.0	0.0	0.0	57
ACD + LMWH	6.5	2.2	2.2	48
Heparin + ACD-A	4.4	4.4	4.4	45
Macrodex and NaCitrate	0.0	0.0	0.0	37
No anticoagulation	5.6	0.0	0.0	18
Heparin + CPD	0.0	0.0	0.0	3
CPD + heparin	0.0	0.0	0.0	1
Heparin + LMWH	0.0	0.0	0.0	1
Other	0.0	0.0	0.0	23
Total	2.6	3.2	0.4	44,154

More than reference: [aaa]$p < 0.001$; less than reference: [bbb]$p < 0.001$; [bb]$p < 0.01$; [b]$p < 0.05$.

3.8. Colloid replacement fluids

The data of adverse events when using replacements fluids are shown in Tables 13 and 14A–C. Albumin and plasma were the main replacement fluids given during a plasma exchange (PE). For albumin, a 4% solution was most frequently used (54%) followed by a 5% solution (38%). When plasma was used as replacement fluid, fresh frozen plasma was most common (FFP; 69%) and then liquid stored plasma (25%). Cryoprecipiate poor plasma was more rarely used (4%) as was Octaplas® (2%) and Octaplas LG® (0.2%). Hydroxyethyl starch (HES) was used in 1.5% of procedures that were given replacement. When HES was used, it was as part of the replacement during PE by centrifugation (66%)

Table 10
Distribution of accesses in relation to severity of adverse events. Statistical comparison of accesses with more than 200 procedures to peripheral vein to vein in relation to grade of AE.

	Mild	Moderate	Severe	Total N	% of total
Peripheral vein to vein (reference)	2.6	3.3	0.2	18,380	64.3
Femoral vein, double lumen	1.0[bbb]	3.3	0.3[aa]	2,395	8.4
Jugular vein, double lumen	1.9[b]	3.8	0.4[a]	3,132	11.0
Subclavian vein, double lumen	0.9[bbb]	4.2[a]	0.4	2,726	9.5
AV fistula	3.1	1.3[bbb]	0.1	1,112	3.9
AV graft	4.8	2.7	0.0	146	0.5
Artery to artery	0.0	0.0	0.0	5	0.0
Other	0.7	1.3	0.0	153	0.5
Hemoport	0.0	0.0	0.0	109	0.4
Femoral vein to peripheral	2.3	4.5	0.0	44	0.2
Jugular vein to peripheral	0.0	5.1	0.9	117	0.4
Subclavian vein to peripheral	0.0	4.8	0.0	63	0.2
Artery to vein	0.5	7.4[aa]	0.9	215	0.8

More than reference: [aa]$p < 0.01$; [a]$p < 0.05$; Less than reference: [bbb]$p < 0.001$; [b]$p < 0.05$.

Table 11
Distribution of 10 most common adverse events (episodes/10,000 procedures) in relation to access (Information from a total of 31,426 procedures).

	Peripheral vein to vein	Femoral vein[a]	Jugular vein[a]	Subclavian vein[a]	AV fistula	AV graft	Artery to vein	Total AEs N
Tingling	242	203	162	294	30	102	221	697
Access problem	148	36	11	18	148	204	44	346
Hypotension/syncope	58	52	81	36	66	0	0	182
Urticaria	37	40	126	98	22	51	310	171
Technical problems	12	4	37	7	44	51	0	48
Bleeding, hematoma	17	0	0	4	0	102	0	37
Nausea/vomit	9	16	20	11	0	0	44	33
Fever/chills	5	16	11	15	0	0	44	24
Hypertension	4	36	8	4	0	0	44	24
Flush	2	8	17	7	7	0	0	16

[a] Double lumen catheter for access.

Table 12
(A) Adverse events (in %) in donor procedures versus patients (leukapheresis procedures); (B) various symptoms of adverse events in donor apheresis given as AEs/10,000 procedures (AEs/10E4).

(A) None	Mild	Moderate	Severe	AE total	Total N
Patients (reference)	1.3	5.9	0.2	7.4	4,836
Donors	4.3[aaa]	3.9[bb]	0.2	8.4	1,684

(B) Donor apheresis

Grade of AE	Symptoms	AEs/10E4
Moderate	Tingling, stitching	536
Mild	Hypotension	67
Mild	Tingling, stitching	42
Mild	Access hematoma	25
Moderate	Nausea/vomiting	25
Moderate	Headache	25
Moderate	Hypotension	25
Mild	Vertigo	17
Severe	Fasciculations	17
Mild	Hypertension	8
Mild	Phlebitis	8
Mild	Nausea/vomiting	8
Moderate	Flush	8
Moderate	Vertigo	8
Moderate	Chills/fever	8
Severe	Anxiety & hyperventilation	8
Severe	Hypotension	8

More than reference: [aaa]$p < 0.001$; less than reference: [bb]$p < 0.01$.

or filtration (8%) and during cell apheresis (32%). In 26% of these, HES was the only replacement fluid.

Among the severe AEs, hypotension and syncope were most common, which was especially noted when albumin was used as a replacement (48% if albumin only, 6% if albumin and plasma, 12% if only plasma). In 30% of the patients with hypotension, neither plasma nor albumin was used. Urticaria was more often related to the use of plasma (76%). Compared to apheresis procedures with saline only, analyses showed that the risk for urticaria was increased when apheresis was performed with replacement of plasma ($p < 0.001$, RR 89, CI 28.4–278) or albumin during the procedure ($p < 0.01$, RR 4.72, CI 1.39–16.02), and also when the combination of albumin and plasma ($p < 0.001$, RR 91,CI 29.0–288) was used. When comparing plasma versus albumin, the risk for urticaria was higher with plasma ($p < 0.001$, RR 18.9, CI 11.6–30.7).

Bronchospasm occurred in 11 procedures. Seven of these were during PE with centrifugation using FFP as replacement in six and Octoplas® in one. In four procedures, no replacement was used (autologous stem cell collection in 2, extra corporeal photopheresis and protein A adsorption in one each).

The incidence of AEs did not differ when plasma only was used compared with the combination of plasma and albumin. There was no significant difference in regard to the presence of urticaria or bronchospasm between FFP versus Octaplas®. Arrhythmia or asystolia was present to a similar extent if plasma (3/6404) or albumin (4/11365) was used.

Comparison between genders revealed that women experienced more mild ($p = 0.03$, RR 1.57, CI 1.04–2.38) and moderate ($p < 0.001$, RR 2.0, CI 1.51–2.69) AEs than men when neither albumin nor plasma was used during the apheresis. Women experienced more moderate AEs than

Table 13
Adverse events (%) graded as mild, moderate and severe in relation to main type of albumin, plasma or hydroxyethyl starch (HES) used as replacement fluid during plasma exchange with centrifugation.

Replacement	N	Mild	Moderate	Severe
Other than albumin (reference)	12,134	1.4	4.3	0.6
Albumin 3.5%	484	0.2[bbb]	2.9[b]	0.6
Albumin 4%	6,353	1.3	2.7[bbb]	0.7
Albumin 5%	4,441	2.1[aaa]	3.6	0.5
Albumin 20%, diluted	379	2.5	1.0[bbb]	1.5
Other than plasma (reference)	10,287	1.3	1.8	0.5
Liquid stores plasma	1,717	2.4[aaa]	5.9[aaa]	1.3[aaa]
Fresh frozen plasma	4,824	1.3	6.0[aaa]	0.7[a]
Cryoprecipitate poor plasma	282	2.8[aaa]	5.3[aaa]	0.7
Octaplas®	155	5.2[aaa]	1.9	1.3
Octaplas LG®	16	0	0	0
Other than HES (reference)	19,671	1.4	3.4	0.6
HES	328	0.0	0.0[bb]	0.0

More than reference: [aaa]$p < 0.001$; [a]$p < 0.05$; less than reference: [bbb]$p < 0.001$; [bb]$p < 0.01$; [b]$p < 0.05$.

Table 14
(A) Severe AE/10,000 procedures with main substitution using either plasma or albumin as replacement for plasma exchange with centrifugation technique; (B) moderate AE/10,000 procedures with main substitution using either plasma or albumin as replacement for plasma exchange with centrifugation technique; (C) mild AE/10,000 procedures with main substitution using either plasma or albumin as replacement for plasma exchange with centrifugation technique.

	Plasma	Albumin
(A) Severe grade AE in %		
Urticaria, conjunctivitis	25	12
Chills and fever	16	9
Hypotension, syncope	11	25
Flush	5	1
Bronchospasm	5	2
Tingling, stitching	4	2
Epilepsy	4	0
Quincke edema	4	1
Arrhythmia	3	1
Hypertension	1	0
Asystolia, cardiac arrest	1	1
Phlebitis	1	2
Abdominal pain	1	1
ABO incompatibility	1	0
Access problems	1	2
Technical failure	0	2
(B) Moderate grade AE in %		
Urticaria, conjunctivitis	236	69
Tingling, stitching	209	91
Hypotension	32	69
Chills and fever	30	9
Flush	17	9
Hypertension	17	3
Quincke edema	9	2
Nausea and/or vomiting	9	8
Back pain related to apheresis	5	5
Phlebitis	4	3
Abdominal pain	2	4
Vertigo	2	1
Fatigue	2	0
Serum reaction	2	1
Bronchospasm	1	0
Hemolysis (visualized or measured)	1	1
Pruritus	1	0
Palpation	1	0
Epistaxis	1	0
Dyspnea	1	1
Access problems	0	13
Access-hematoma	0	3
Drug related AE	0	1
Myocardial insufficiency	0	1
Anaphylactic shock	0	1
Late complication, other	0	1
Access-hematoma, prolonged bleeding	0	1
Technical failure	0	0
(C) Mild grade AE in %		
Urticaria, conjunctivitis	65	13
Tingling, stitching	32	27
Access problems	25	33
Technical failure	9	7
Chills and fever	6	4
Access-hematoma	6	13
Late hepatitis C (within 4 months after apheresis)	6	0
Nausea and/or vomiting	5	7
Flush	5	3
Back pain related to apheresis	5	3
Hypotension	2	46
Bronchospasm	2	0
Vertigo	1	1
Arrhythmia	1	1
Phlebitis	0	2
Hypertension	0	1
Abdominal pain	0	1
Headache	0	1
Access-hematoma, prolonged bleeding afterwards	0	1

men when albumin was used as replacement ($p < 0.001$, RR 1.21, CI 1.25–1.83), but not when used in combination with plasma or when plasma was the only option. There was no difference between the various concentrations of albumin replacement used and AEs between genders. There was no difference in the use of calcium prophylaxis between the genders in the various situations given above.

HES was used as replacement fluid in some procedures and for this, no AEs were registered (Table 13).

3.9. Calcium given intravenously as prophylaxis

Patients who received intravenous calcium as prophylaxis (Ca) experienced more AEs than those not using calcium (Table 15). This difference was valid for mild ($p = 0.003$, RR 1.35, CI 1.11–1.64), moderate ($p < 0.001$, RR 1.92 CI 1.69–2.19) or severe AEs ($p < 0.001$, RR 1.82 CI 1.29–2.57). The substitution of Ca varied between treatments such as for PE by centrifugation when initially 24% of the patients received Ca (Fig. 2A) versus 8% of those treated by filtration (Fig. 2B); for some cell collection and immunoadsorption techniques more than 90% received Ca. In the sub-analysis a negative outcome for Ca-prophylaxis was valid for therapeutic apheresis with centrifugation and filtration procedures, while there were no differences for LDL-apheresis. Analysis of the various symptoms showed that for mild AEs, Ca prophylaxis had been used more frequently when tingling ($p < 0.002$, RR 1.8 CI 1.12–2.93), nausea and vomiting ($p < 0.001$, RR 6.1 CI 2.4–15.7) or urticaria ($p = 0.006$, RR 2.01 CI 1.2–3.5) were reported, while there were fewer reports of hypotension ($p = 0.004$, RR 0.35 CI 0.17–0.73). When comparing PE by centrifugation with all other apheresis procedures tingling was more prominent for mild and moderate AEs when using Ca with other procedures than PE by centrifugation (RR > 2.9). Mild hypotension was less common for PE by centrifugation when Ca was used while for moderate and severe hypotension as AE, there was no difference if Ca-prophylaxis was used or not.

For moderate AEs there was a negative effect of Ca for tingling, nausea and vomiting, urticaria and flushing. No difference was seen for hypotension.

Severe AEs were more frequently registered when Ca was used. The significant findings were for chills/fever ($p = 0.0036$, RR 6.90 CI 1.87–25.5) and urticaria ($p = 0.038$, RR 2.49 CI 1.14–5.46).

In a multivariate analysis using the grade of AE as the dependent factor there was an increased risk for AE with plasma, older age, female gender and Ca ($p < 0.001$ for all

Table 15
Distribution of grade of adverse events (AE) (in %) and use of calcium prophylaxis or No prophylaxis (reference). Data presented for 26,036 procedures.

	No prophylaxis	Ca-prophylaxis
Non AE %	95.4	92.2
Mild	1.4	1.9[aa]
Moderate	2.7	5.2[aaa]
Severe	0.4	0.7[aaa]

More than reference: [aaa]$p < 0.001$; [aa]$p < 0.01$.

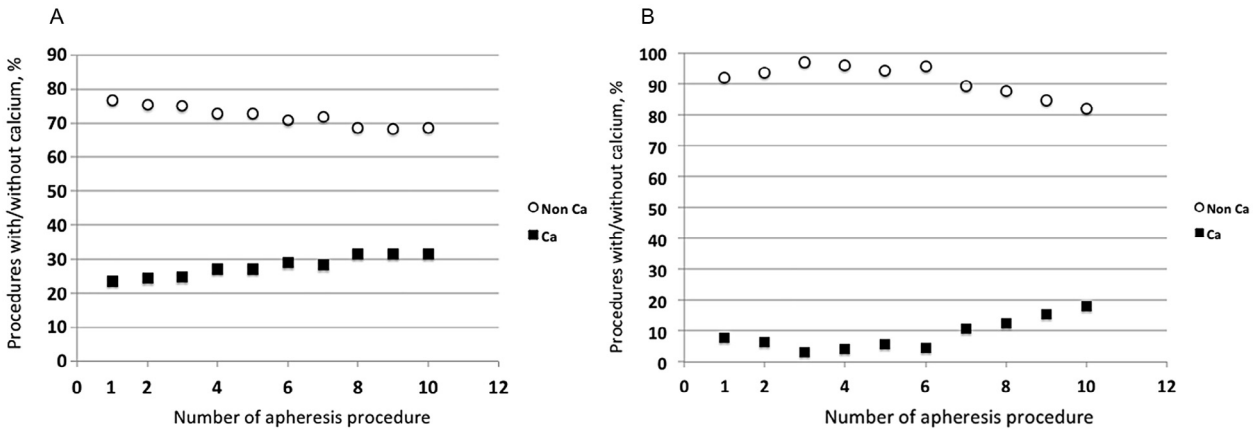

Fig. 2. (A) Percentage of procedures with (filled squares) or without (open circles) calcium prophylaxis intravenously during plasma exchange with centrifugation. (B) Percentage of procedures with (filled squares) or without (open circles) calcium prophylaxis intravenously during plasma exchange with filtration.

variables) while albumin and center effect were not significant in the model.

Tables 16–18 lists the most occurring symptoms (excluding access and technical problems) for frequently used procedures. Patients treated by leukocytapheresis using columns or filters, for e.g., ulcerative colitis, complained of tingling (moderate grade, 86%) and abdominal pain (moderate grade, 14%). Patients treated with sheep antibody immunoadsorption complained of nausea or vomiting (mild grade, 43%), tingling (moderate grade, 26%) and chills/fever (mild, 13%).

4. Discussion

Data prospectively collected within the WAA registry over the years show that the incidence of mild and severe AEs has decreased. The reduction in mild AEs may be due to various preventive measures. Another reason may be that centers entering data over time become less prone to register mild AEs. However, more than 50% of the mild AEs were due to access problems and among accesses the highest incidence of mild AEs was related to vein to vein access and to patients that had an arterio-venous fistula or graft.

The reduction in severe AEs over time is probably related to an increased awareness of side effects and the staff being more alert to prevent progression into severe AEs.

Previous studies have reported death caused by apheresis in 0.05% of treatments [33]. Although there was no evident death due to the apheresis in more than 50,000 procedures in this registry, severe AEs occurred in 4 of 1000 procedures. This included patients with asystole that were resuscitated and others with severe arrhythmia. Patients at higher risk for AE are those getting their first apheresis treatment procedure. This might be due to the fact that the patients are less familiar with the first treatment, but may also be due to more awareness of the staff to AEs if the patient reacted during the first procedure. Such awareness can be increased if the patient's history indicates tendencies for allergic reactions. An increased risk is also present, due to activation of the bradykinin system, when a patient is treated with angiotensin converting enzyme inhibitors in combination with apheresis using polysulphone filters. The blood membrane interaction thereby is increased [34].

The present study showed that plasma exchange and the use of liquid stored plasma as replacement fluid could explain a higher incidence of AE's. These data confirmed previous reports [22,35] that side effects were more common in women than men. Further investigation of liquid plasma, stored at 2–6 °C for up to 42 days, showed an early (<14 days of storage) cold-induced contact activation with loss of C1 INH-function. This was observed in plasma from female donors [36]. The extent of activation of the complement system was further investigated during prolonged storage of plasma at 2–6 °C [37]. Different alterations caused by storage of plasma are difficult to evaluate clinically. Morbidity in terms of AEs may differ [16], but short-term mortality seems to be unaffected [37]. The increased vulnerability in female patients undergoing therapeutic apheresis remains to be further explored.

As was noted previously [22], PE using filtration technique resulted in almost double the number of AEs than PE with centrifugation technique. Although it is known that the complement system is activated more by filtration procedures [38], it is possible that experience of the center is at play in this observation. An experienced center that performs many aphereses may buy a centrifuge, whereas a center that performs apheresis occasionally uses membranes.

The present study also shows that the extent of AEs also differs in relation to what type of disease the patient has. Therefore, most severe AEs were noted for patients suffering from nephrological and rheumatological diseases and least for those who were treated for hypercholesterolemia by LDL apheresis. The data cannot clarify if this is due to the underlying condition or to various medications such as the use of angiotensin converting enzyme inhibitors, other antihypertensives, or hypovolemia due to diuretics. However, differences in AEs between specific diagnoses were also previously reported in a more extended analysis [39]. But these differences may, to some extent, also be due to the

Table 16
Main symptoms (AEs/10,000 procedures) that may be expected to appear with plasma exchange procedures.

Grade of AE	Symptoms	AEs
Plasma exchange, centrifugation		
Moderate	Tingling	99
Moderate	Urticaria, conjunctivitis	68
Moderate	Chills, fever	42
Mild	Chills, fever	10
Mild	Urticaria, conjunctivitis	8
Mild	Tingling	8
Moderate	Chills, fever	8
Moderate	Hypertension	8
Moderate	Flush	8
Moderate	Nausea/vomiting	4
Moderate	Back pain	4
Moderate	Quincke edema	4
Severe	Chills, fever	3
Mild	Access hematoma	3
Mild	Nausea/vomiting	2
Mild	Flush	2
Mild	Chills, fever	2
Severe	Urticaria, conjunctivitis	1
Severe	Chills, fever	1
Severe	Tingling	1
Severe	Flush	1
Moderate	Phlebitis	<1
Moderate	Abdominal pain	<1
Moderate	Access hematoma	<1
Severe	Bronchospasm	<1
Mild	Back pain	<1
Severe	Epilepsy	<1
Severe	Arrhythmia	<1
Severe	Quincke edema	<1
Mild	Hypertension	<1
Plasma exchange, filtration		
Moderate	Urticaria, conjunctivitis	305
Moderate	Flush	46
Moderate	Chills, fever	33
Mild	Urticaria, conjunctivitis	29
Moderate	Nausea/vomiting	20
Mild	Late hepatitis C	15
Moderate	Hypertension	13
Mild	Tingling	9
Moderate	Hemolysis	7
Moderate	Arrhythmia	7
Moderate	Back pain	7
Moderate	Abdominal pain	7
Mild	Chills, fever	6
Severe	Chills, fever	3
Mild	Hemolysis	3
Mild	Arrhythmia	3
Mild	Back pain	3
Mild	Access hematoma	3
Severe	Urticaria, conjunctivitis	3
Severe	Hypertension	1
Severe	Back pain	1
Severe	Nausea/vomiting	1
Severe	Flush	1

different types of procedures used for various diagnoses, such as for patients on LDL apheresis that have a lower risk for severe AEs than patients on other apheresis procedures.

There was also a difference in the incidence of AEs related to various anticoagulation methods used. This may be due to citrate leading to hypocalcemia on one hand and interactions with the heparin molecule on the other hand. Notably, heparin induced thrombocytopenia was only suspected in one case. Thereby the use of heparin showed less moderate and severe AEs than ACD-A and B. The use of CPD indicated more moderate AEs than heparin. Maybe these differences are due to the citrate load and metabolism or a secondary change of electrolytes, such as reduced ionized calcium, magnesium, and potassium, that can be noted during citrate administration [34,35,40–43]. There may also be retention of citrate if the load is larger [44], and in those with kidney failure and hemodialysis, there is increased diffusible calcium to 80% of the total calcium and induced substantial dialytic loss of calcium as well as a prolonged half life of citrate [45].

Severe AEs were more frequent with femoral and jugular than with peripheral vein access. This may be due to a difference in the diagnoses treated and the type of procedure performed. Therefore, patients with a need for higher blood flow (e.g. also on acute hemodialysis) or with a prolonged treatment series (e.g. more severe condition) may more often need a central access. A central access, especially a jugular vein catheter positioned within the right atrium of the heart, may also influence the sinus node and cardiac rhythm to a greater extent due to a higher and more localized concentration and effect of citrate either directly or on the level of ionized ions.

There were significantly more mild, but less moderate AEs in donors than in patients who performed cell apheresis. The mild component may be due to the fact that a donor would be more alert to mild side effects than a patient that has to be treated for a severe disease, and probably accept more symptoms before complaining.

During PE replacement, the fluid used was mainly albumin (4% or 5%) and FFP. The AE panorama varied significantly for the different replacement fluids. Hypotension was a greater risk when using albumin while urticaria was the predominant AE for plasma replacement.

Mild AEs were mainly due to access problems, such as a need for replacement of a puncture needle at a peripheral site or a local hematoma. Hypotension and tingling were symptoms that were most frequent in mild AEs. Notably, in some of these procedures, arrhythmia was detected although no medical measures were necessary.

Moderate AEs were mainly experienced as a tingling sensation. It is not obvious that these symptoms were related to hypocalcemia since the group who were prescribed calcium as prophylaxis more often suffered from these symptoms. Other reasons for tingling during the apheresis procedure could be hypomagnesemia and hyperventilation, for example.

Severe AEs were mainly due to hypotension. Since hypotension was more common when albumin only was used as replacement, a reason may be a too low colloid osmotic pressure and refilling of the intravascular volume. The analyses do not clarify if replacement volumes with albumin were sufficient to correct for this. In general, a replacement ratio of 1:1 with a 5% albumin solution should compensate for colloid osmotic pressure drop. But, patients with e.g., a neurological disease, may have a reduced ability for compensatory vasoconstriction. In 30% of the patients with hypotension, neither plasma nor albumin was used. A plausible explanation would be that even if the fluid chosen is adequate in its colloid osmotic concentration, it is important to refill the volume to at least a 1:1 extent, and

Table 17
Main symptoms (AEs/10,000 procedures) that may be expected to appear with cellapheresis and LDL-apheresis procedures.

Cellapheresis			LDL-apheresis		
Grade of AE	Symptoms	AEs	Grade	Symptoms	AEs
Moderate	Tingling	343	Mild	Chills, fever	108
Moderate	Nausea/vomiting	23	Moderate	Tingling	59
Mild	Tingling	9	Mild	Access hematoma	26
Moderate	Chills, fever	9	Moderate	Chills, fever	13
Moderate	Drug AE	5	Mild	Hypertension	13
Mild	Nausea/vomiting	4	Mild	Nausea/vomiting	9
Mild	Vertigo	1	Mild	Abdominal pain	4
Mild	Chills, fever	1	Mild	Phlebitis	4
Mild	Arrhythmia	1	Mild	Flush	4
Mild	Access hematoma	1	Mild	Tingling	4
Moderate	Hypertension	<5	Mild	Back pain	4
Moderate	Back pain	<5	Mild	Vertigo	4
Moderate	Allergic reaction, other	<5	Mild	Allergic reaction, other	4
Moderate	Tachycardia	<5	Mild	Hemolysis	4
Moderate	Chills, fever	<5	Moderate	Abdominal pain	3
Moderate	Bronchospasm	<5	Moderate	Hypertension	1
Severe	Tingling	<1	Mild	Headache	<4
Severe	Chills, fever	<1	Severe	Back pain	<1
Severe	Anxiety, hyperventilation	<1	Severe	Abdominal pain	<1
Severe	Arrhythmia	<1	Moderate	Nausea/vomiting	<1
Severe	Urticaria, conjunctivitis	<1	Severe	Nausea/vomiting	<1
Severe	Bronchospasm	<1	Severe	Chills, fever	<1
Mild	Angina pectoris	<1	Moderate	Chills, fever	<1
Mild	Fatigue	<1	Moderate	Angina pectoris	<1

also adjust the replacement timely with the removal. Otherwise, the refilling volumes may be too small and given too late to prevent hypotension.

The second most frequent severe AE was urticaria. Plasma as replacement fluid was more often related to episodes of urticaria. Arrhythmia was rare and there was no evident difference in risk to suffer from arrhythmia if plasma or albumin was used as replacement fluid. Bronchospasm appeared also in other apheresis procedures (not using colloids as replacement fluid) than plasma exchange. In the latter, all of them had received plasma as replacement.

Calcium/magnesium prophylaxis has been shown to reduce the extent of adverse events in previous reports [33–35,42,46,47]. However, the number of procedures in those reported studies were limited, and in some of them, the grading of the AE was vague.

Our present data show that procedures performed when calcium was given intravenously as prophylaxis resulted in more AEs for all grades. In a sub-analysis the negative outcome for calcium prophylaxis was valid for therapeutic apheresis with centrifugation and filtration procedures, while there were no differences for LDL-apheresis.

When analyzing the various symptoms, for mild, moderate and severe AEs, a negative relation with calcium prophylaxis was even valid for the least expected symptoms such as tingling, nausea, vomiting and urticaria. However, we cannot discriminate if, in some procedures, the calcium administration was given as treatment due to side effects, but registered as prophylaxis. One beneficial effect of calcium prophylaxis may be the finding of fewer episodes of mild hypotension while moderate hypotension did not differ between the groups with or without calcium prophylaxis. Since comparison was made with those not receiving any calcium at all, the reason could not be due to a too low dose and thereby lack of general effect. A longitudinal investigation showed that there was only a limited tendency to increase the use of calcium prophylaxis over the number of procedures.

The negative effect of calcium prophylaxis seen for chills/fever and urticaria may be due to an effect of calcium activating the acute phase reacting systems, including the complement and the clotting system. An increased tendency of clotting in the venous bubble trap has been noted when calcium was infused there (personal communication). This is also in agreement with the physiological function of the calcium ion.

In a multivariance analysis using the grade of AE as the dependent factor, there was an increased risk for AE by being older, being female, using plasma as replacement and with I.V. calcium as prophylaxis.

Whether the negative effect of calcium as prophylaxis is due to negative selection of patients that are more prone to side effects is not clarified in this study. However, in general, the use of calcium prophylaxis seemed to be more a habit of the center and related to the treatment procedure than a selective effect. The data entered in this study do not discriminate between continuous or intermittent infusion of calcium. There might be a better preventive effect using a continuous infusion according to a previous report by Weinstein [40]. Notable is that the number of treatments in their study was limited. Although they saw no benefit to oral supplementation [40], such benefit was found by Sassi et al. [48]. In another study, calcium chloride was more effective than calcium gluconate in maintaining calcium levels [35,49]. In those studies, the symptoms of paraesthesia were significantly reduced by calcium. In addition, the infusion of citrate during apheresis procedures may result in a prolongation of the QT-time and thereby increased risk for

Table 18
Main symptoms (AEs/10,000 procedures) that may be expected to appear with immunoadsorption, extracorporeal photopheresis and apheresis in conjunction with AB incompatible donor transplantation procedures.

Grade of AE	Symptoms	AEs
Immunoadsorption, protein A		
Mild	Hypertension	66
Moderate	Tingling	36
Mild	Tingling	33
Mild	Phlebitis	16
Mild	Nausea/vomiting	16
Moderate	Pruritis, generalized	14
Moderate	Urticaria, conjunctivitis	14
Moderate	Nausea/vomiting	9
Moderate	Hypoglycemia	9
Mild	Flush	8
Mild	Vertigo	8
Mild	Chills, fever	8
Mild	Access hematoma	8
Moderate	Hypertension	5
Moderate	Angina pectoris	5
Moderate	Flush	5
Moderate	Chills, fever	5
Severe	Nausea/vomiting	4
Severe	Arrhythmia	2
Severe	Flush	2
Severe	Chills, fever	2
Severe	Quincke edema	2
Severe	Anaphylaxis	2
Severe	Bronchospasm	2
Extracorporeal photopheresis		
Moderate	Tingling	114
Mild	Tingling	4
Mild	Chills, fever	4
Moderate	Chills, fever	2
Mild	Arrhythmia	1
Mild	Phlebitis	1
Mild	Chills, fever	1
Mild	Bronchospasm	1
Mild	Access hematoma	1
Severe	Intestinal bleeding	<1
A/B-immunoadsorption		
Moderate	Urticaria, conjunctivitis	207
Moderate	Pruritis, generalized	91
Moderate	Tingling	45
Moderate	Hypertension	45
Moderate	Nausea/vomiting	30
Moderate	Abdominal pain	15
Moderate	Flush	15
Moderate	Chills, fever	15
Mild	Tingling	4
Mild	Chills, fever	4
Mild	Urticaria, conjunctivitis	4

arrhythmia [50]. This risk may be greater if the patient has a central dialysis catheter and if calcium is given intermittently. The change in other electrolytes such as magnesium and potassium may further interfere in this regard.

However, to more specifically clarify the benefits versus possible disadvantages of substitution of calcium further investigations should be performed. Those studies should also consider other ions and the combination of citrate infused as anticoagulant for the procedure in combination with the amount of additives present in albumin and plasma products replaced with during treatment. The calcium binding effect of albumin as replacement must also be considered, and this effect may also change depending on alterations by effects such as uremia [51].

Although severe AEs are less frequent, they can appear even with techniques and replacement fluids that would normally not be related to such procedures. We therefore suggest the use of regular pulse and blood pressure measurements and careful surveillance, preferably including cardiac monitoring, during apheresis treatment and having emergency equipment nearby.

In conclusion, data from the WAA registry indicate that the diagnosis and treatment procedures as well as the replacement fluid seem to participate in the extent and severity of AEs. Although severe AEs are rare, episodes of especially severe hypotension, bronchospasm, arrhythmia and asystole may be critical for the patient. Further studies must clarify eventual benefits or risks with citrate anticoagulation and calcium prophylaxis by infusion.

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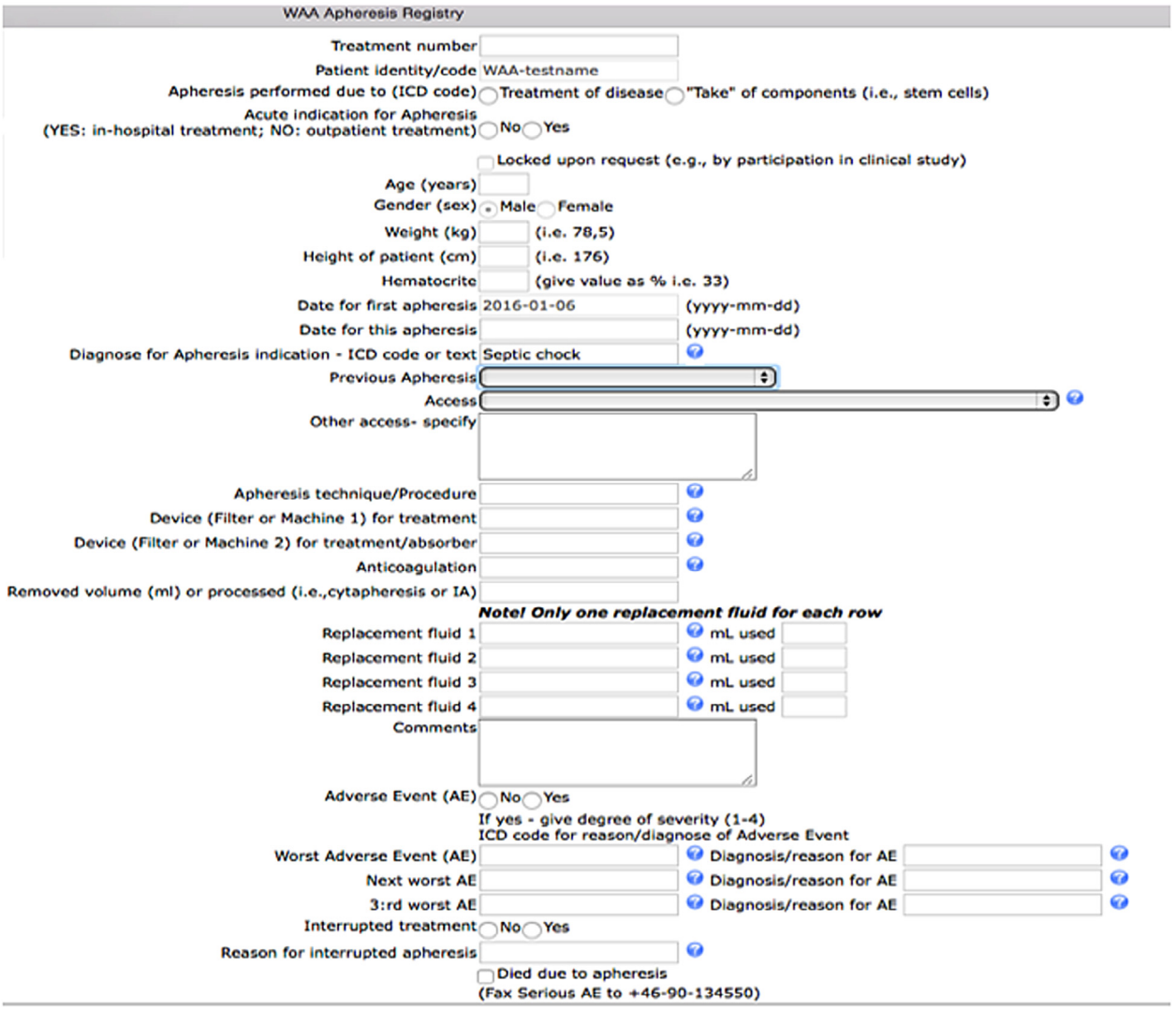
We thank all participating staff that has helped to enter data into the registry and thereby enable an increased awareness of side effects in these various modes of apheresis, thereby supporting the patients in a safer care.

Appendix

Overview of page for variables entered into the registry during each procedure.



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