Transfusion and Apheresis Science xxx (xxxx) xxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

The world apheresis association registry, 2023 update

Hans Vrielink [a], Kaatje Le Poole [a], Bernd Stegmayr [b,*], Jan Kielstein [c], Gösta Berlin [d], Osman Ilhan [e], Guldane Cengiz Seval [e], Heinrich Prophet [f], Astrid Aandahl [g], Dries Deeren [h], Ines Bojanic [i], Milan Blaha [j], Miriam Lanska [j], Zdenka Gasova [k], Zdenka Bhuiyan-Ludvikova [k], Sarka Blahutova [l], Radomira Hrdlickova [l], Judita Audzijoniene [m], Antanas Griskevicius [m], Tanya Glatt [n], Virginia Strineholm [o], Michael Ott [b], Thomas Nilsson [p], Elizabeth Newman [q], Kurt Derfler [r], Volker Witt [s], Fredrik Toss [t]

[a] Unit of Transfusion medicine of Sanquin Blood Supply, Sanquin Blood Supply Foundation in Amsterdam, the Netherlands
[b] Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
[c] Academic Teaching Hospital Braunschweig, Medical Clinic V – Nephrology, Rheumatology, Blood Purification, Germany
[d] Department of Clinical Immunology and Transfusion Medicine, and Department of Biochemical and Clinical Sciences, Linköping University, Linköping, Sweden
[e] Department Haematology, University Hospital, Ankara, Turkey
[f] Nephrocare Rostock GmbH, Rostock, Germany
[g] Dep of Immunology and Transfusion Medicine, Akershus University Hospital, Lorenskog, Norway
[h] AZ Delta, Roeselare, Belgium
[i] Clinical Department of Transfusion Medicine and Transplantation Biology, University Hospital Centre Zagreb, Croatia
[j] IV. Internal Hematological Klinik, Fakultni Nemocnice, Hradec Králové, Czech Republic
[k] Apheresis Department, Institute of Hematology and Blood Transfusion, Prague, Czech Republic
[l] Blood Centre, University Hospital Ostrava, Ostrava, Czech Republic
[m] Therapeutic apheresis unit, Vilnius university hospital Santariskiu clinics, Vilnius, Lithuania
[n] South African National Blood Service, Johannesburg, South Africa
[o] Apheresis Center, University Hospital, Orebro, Sweden
[p] Department of Nephrology, University Hospital, Uppsala, Sweden
[q] Bone Marrow Transplant & Apheresis, Apheresis & Cell Therapies Unit, Concord Repatriation General Hospital, Concord, NSW, Australia
[r] The Institute for the Diagnosis and Therapy of Atherosclerosis and Fat Metabolism Disorders, Athos, Vienna, Austria
[s] St. Anna Kinderspital, University Hospital, Vienna, Austria
[t] Department of Clinical Microbiology, Division of Clinical Immunology, Umeå University, Umeå, Sweden

ARTICLE INFO

Keywords:
Apheresis
Register
Adverse events
Indications
Procedures

ABSTRACT

The WAA apheresis registry contains data on more than 140,000 apheresis procedures conducted in 12 different countries. The aim is to give an update of indications, type and number of procedures and adverse events (AEs).
Material and Methods: The WAA-registry is used for registration of apheresis procedures and is free of charge. The responsible person for a center can apply at the site www.waa-registry.org
Results: Data includes reported AEs from 2012 and various procedures and diagnoses during the years 2018–2022; the latter in total from 27 centers registered a total of 9500 patients (41% women) that began therapeutic apheresis (TA) during the period. A total of 58,355 apheresis procedures were performed. The mean age was 50 years (range 0–94). The most common apheresis procedure was stem cell collection for which multiple myeloma was the most frequent diagnosis (51%). Donor cell collection was done in 14% and plasma exchange (PEX) in 28% of patients; In relation to all performed procedures PEX, using a centrifuge (35%) and LDL-apheresis (20%) were the most common.
The main indication for PEX was TTP (17%). Peripheral veins were used in 56% as the vascular access. The preferred anticoagulant was ACD. AEs occurred in 2.7% of all procedures and were mostly mild (1%) and moderate 1.5% (needed supportive medication) and, only rarely, severe (0.15%).
Conclusion: The data showed a wide range of indications and variability in apheresis procedures with low AE frequency.

* Correspondence to: Umea University, Dept Public Health and Clinical Medicine, Unit Medicine, Umea, Sweden.
E-mail address: bernd.stegmayr@umu.se (B. Stegmayr).

https://doi.org/10.1016/j.transci.2023.103831

Available online 7 October 2023

1. Introduction

Therapeutic apheresis (TA) frequently represents an ancillary or second line treatment option when conventional therapy fails to stop or reverse a disease. Besides TA, apheresis techniques are frequently used to collect sufficient numbers of cells for cellular therapies, e.g. CD34 + cells for hematopoietic stem cell therapy and CD3 + cells as a source for chimeric T-cell antigen receptor (CAR-T) therapies. Since many different techniques and protocols are used it is important to consider the risk-benefit ratio for apheresis procedures at an individual patient level. Larger pools of data may improve knowledge of efficacy and safety. The Canadian and the French national registries were the first developed in 1981 and 1985, respectively, followed by other national registries [1]. To compare information on an international basis, reports were prepared on performances and AEs based on questionnaires that were published by Malchesky et al. [2–5].

Another approach to achieve an international feed-back on indications, outcome data and adverse events (AEs) was initiated in parallel by a group of researchers representing various national registries [6]. Based on their experiences, an electronic registry was established and endorsed by the European Society of Artificial Organs (ESAO), the European Society for Haemapheresis (ESFH) and integrated into the World Apheresis Association (WAA) [7–12].

The WAA register welcomes all apheresis centers to participate. Participation is free of charge and independent from industry. Each center can download their data for internal use or compare it to overall data achieved by merged analysis [7,13–24].

The aim of the present report is to give an update on the WAA registry data as well as a call for study ideas investigating various topics by using WAA data.

2. Material and methods

The WAA registry data is entered at the local center level. Data are checked, and when needed cleaned, for significant outliers or implausible data on a continuous basis by the registry holder.

Table 1
Grading of adverse events (AEs) based on patient complaints, apheresis staff intervention or patient mortality due to the apheresis procedure.

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

Data are collected at different units by initiation of the manager of an apheresis center that accepted to apply and to get access to the registry at the site www.waa-registry.org. Data from centers that entered data on a more regular basis during the latest years participate in this report. To date, more than 140,000 apheresis procedures have been registered. Data were collected at 27 centers from 12 different countries within the frame of the routine apheresis procedures from January 1st 2018 to December 31st 2022, for a total of 5 years. In the present report we update the results of AEs and indications with a focus on recent years.

Based on approved registry criteria, patients are informed of the registry's purpose and function and asked for consent to allow collection of his/her data regarding the treatment procedure and outcome criteria. Analysis of the apheresis registry data was approved by the Umea Ethics Committee (ID number: 2011–113–31 M and 2012–311–32 M).

Procedures subtypes were merged into one group such as for Cell collection/removal including collection (stem cell, mononuclear cells) or removal of various cells, for instance leukocytes/blasts and erythrocytes. Data on desensitization for anti-A, anti-B or both are merged. LDL-apheresis techniques are merged. Not included in the report is platelet depletion (163 procedures).

Figures presented are descriptive in nature and no formal statistical comparisons have been performed. The Spearman correlation test was used to estimate trends in AEs. Apparent differences observed over time or between centers should be interpreted with caution as they may origin from unaccounted confounding.

Symptoms of AEs were monitored, and if reported by the patient or staff, scored based on criteria in Table 1.

3. Results

During the years 2018–2022 in a total of 9500 patients (41% women) 58,355 TA procedures were performed. The number of apheresis procedures registered per year and centers registering their apheresis procedures are shown in Fig. 1.

The mean age of the patients during 2018–2022 was 50 years (range 0–94). Fig. 2 shows the change in mean age and percentage of women over the years. The most common apheresis procedure performed (Table 2) was a cell collection. Among those procedures, stem cell collections in patients suffering from multiple myeloma was most frequent (51%). For those treated with PEX, TTP was the most frequent indication (17%, Table 3).

Table 2 shows the main indications for TA, while new treatment modalities such as IgE adsorption and Lp(a) adsorption are becoming more common.

Per patient PEX by centrifugation was the second most common technique used and the most common TA procedure performed. In 56%

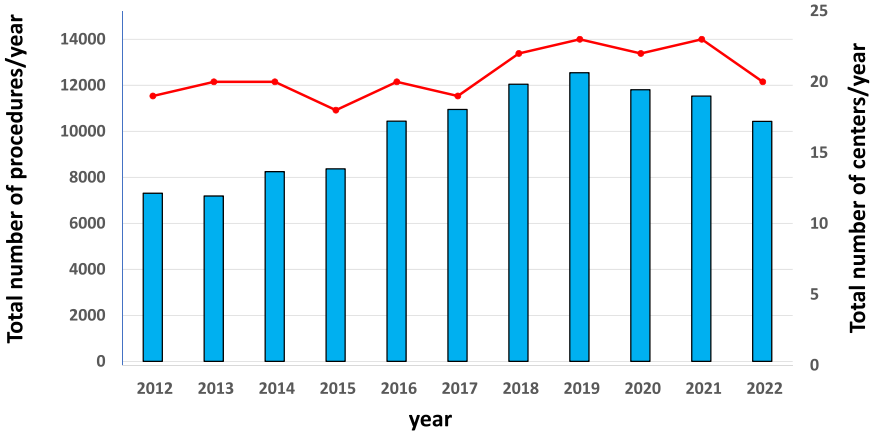

Fig. 1. Numbers of procedures performed and participating centers in the period 2012–2022. Displayed as a line and scale to the right are the number of participating centers with 50 or more procedures/year and bars represent the total numbers of procedures/year with the scale to the left.

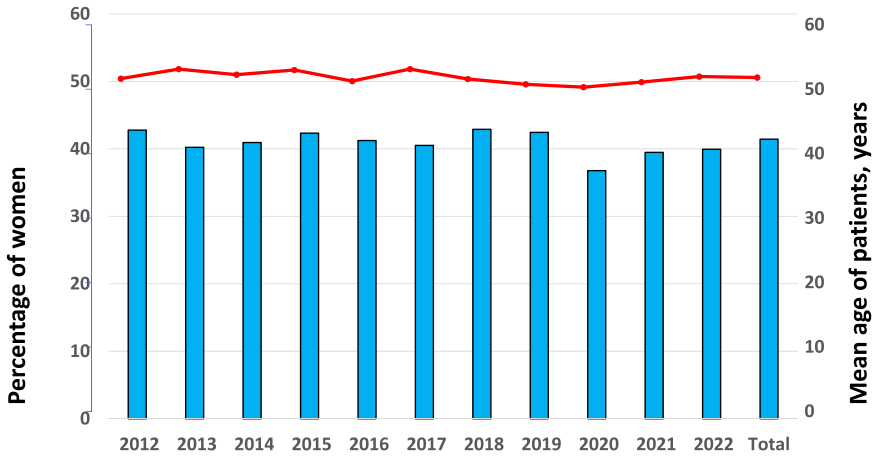

Fig. 2. Mean age of involved patients including the percentage female patients. The bars represent the yearly distribution of percentage of women that received TA (scale left side). The mean age of the patients over the years is shown by a line (right scale).

of the procedures, vascular access via peripheral veins was achieved. The most frequent anticoagulant was acid citrate dextrose (ACD) in various composition.

Fig. 1 shows the distribution of AEs since 2012. The number of adverse events reported seemingly declined between 2012 and 2017. Analyzing for trends, a decreased risk over time was noted by correlation analysis for Mild AE ($p = 0.01$), Moderate ($p = 0.005$), and Severe ($p = 0.005$). Besides this, for the period 2018–2022, the trend appeared stable for Moderate and Severe AEs and worsened for Mild AEs ($p = 0.01$). Table 4 shows the most frequent type of AEs during the latest five years. During that period, in 3% of TA procedures an AE was reported, including technical and access problems. Most frequent were Mild (1.5%) and Moderate (1.4%) (mainly by tingling & pricking, urticaria, hypotension) AEs. Severe AEs occurred only in 0.15% (mainly by urticaria, hypotension, tingling) of all procedures. Table 4 shows the most frequent AEs, excluding access or technical reasons. This ended up in 0.57% Mild AEs, 1.35% Moderate AEs, and 0.12% Severe AEs.

Differences in reported AEs over time, between apheresis methods and between reporting centers are shown in Figs. 3–5. In 140,000 procedures there has been one recorded patient death, potentially linked to the apheresis procedure. This was an elderly man, described in a previous publication [25]. He was treated with TA for TTP and suffered from a fatal myocardial infarction during the apheresis procedure.

Table 2
Differentiation of procedures in relation to patients (n = 9500) performed during the period Jan 2018- Dec 2022.

	All patients		All procedures	
Type of procedure	N	Percentage	N	Percentage
Cell collection/removal	4480	47.2	9456	16.2
PEX, by centrifugation	2648	27.9	20281	34.8
Donor cell collection (allogeneic)	1316	13.9	1674	2.9
ECP	276	2.91	10272	17.6
Leukapheresis	114	1.20	365	0.6
LDL apheresis	94	0.99	11807	20.2
PEX, by filtration	93	0.98	480	0.8
Cascade filtration	90	0.95	1127	1.9
Free light chain filtration	66	0.69	288	0.5
Anti-AB-ab removal	56	0.59	193	0.3
IgE adsorption	54	0.57	370	0.6
Globaffin adsorption	45	0.47	659	1.1
Immune adsorption, other	27	0.28	103	0.18
Protein A absorption	11	0.12	322	0.55
IgG adsorption/ Sheep ab column	11	0.12	605	1.0
Rheopheresis	8	0.08	61	0.10
Lp(a) adsorption	6	0.06	102	0.17
Plasma-Lymphocyte apheresis	1	0.01	15	0.03
CRP-adsorption	1	0.01	2	0.00
Info missing	103	1.08	173	0.30
Total	9500	100	58355	100

Plasma exchange (PEX), extracorporeal photopheresis (ECP), lipoprotein (Lp)

4. Discussion

The present WAA registry report is an update on the internationally collected data from apheresis procedures for various indications and with different methods. Over the years a decline in AEs was noted until 2017. Since then, the frequency of AEs did not change. Since inter-center differences exist as well as indications and other variables, the present trend over time is substance for further investigation. The cause of worsening trends in AEs is important to clarify, such as possible relations to type of procedures and diagnoses. In addition, assessment of possible center effects will enable deepened analyses and interaction. Notable is that there is a variation between centers regarding techniques and side effects as well as in indications and substitution fluids, also shown in previous studies from the WAA registry [5,14–23,26,27].

The aim of the registry is also to collect post apheresis health data, at the last session and at follow up. However, this has only been achieved to a limited extent since numerous apheresis units do not easily get hold of information on outcome data. Such a problem may be present if the responsible physician for the patient at another unit is unable to give feed back to physicians at the apheresis center.

Table 3
Indications for the first therapeutic plasma exchange (PEX) during the 5-year period in a total of 2648 patients receiving TA.

Indications for first treatment	**%**
TTP	17.1
Hematological diseases, mixed	12.5
Myasthenia gravis	7.6
Guillain Barre syndrome	5.4
M. Waldenström	3.7
PR3-ANCA vasculitis	3.3
Multiple sclerosis	3.2
Goodpasture Syndrome	2.8
Multiple myeloma	2.6
Septic shock, GAS	2.4
MPO-ANCA vasculitis	2.3
CIDP	1.7
Myelitis	1.7
Transplant rejection, kidney	1.5
Graft versus host disease	1.5
Desensitization before kidney transplantation	1.1

Thrombotic thrombocytopenic purpura (TTP), Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), Anti-Neutrophilic Cytoplasmic Autoantibodies (ANCA).

Table 4
AE frequency in 54,164 apheresis procedures in the timeframe 2018–2022. Technical and technical vascular access problems were excluded here.

Symptoms	Mild AE% N = 310 (0.6%)	Moderate AE% N = 729 (1.3%)	Severe AE% N = 63 (0.1%)
Urticaria, conjunctivitis	1.9	8.4	25.4
Hypotension	13.2	5.2	23.8
Tingling, pricking	38.7	74.3	11.1
Late complications	1.6	1.0	4.8
Angina pectoris			3.2
Asystolia/Cardiac arrest/			3.2
Nausea and/or vomiting	10.3	3.9	3.2
Back pain related to apheresis	1.6	0.7	3.2
Hypertension	1.6	0.5	3.2
Convulsions, not specified as epilepsy	0.6	0.4	3.2
Bronchospasm	0.3	0.3	3.2
Abdominal pain	2.3	1.2	1.6
Chills and fever	0.6	1.0	1.6
Anaphylactic Shock		0.3	1.6
Vertigo	4.2	0.1	1.6
Transient ischemic attack (TIA)		0.1	1.6
Syncope		0.1	1.6
Vascular access hematoma and prolonged bleeding		0.1	1.6
Arrhythmia	3.2		1.6

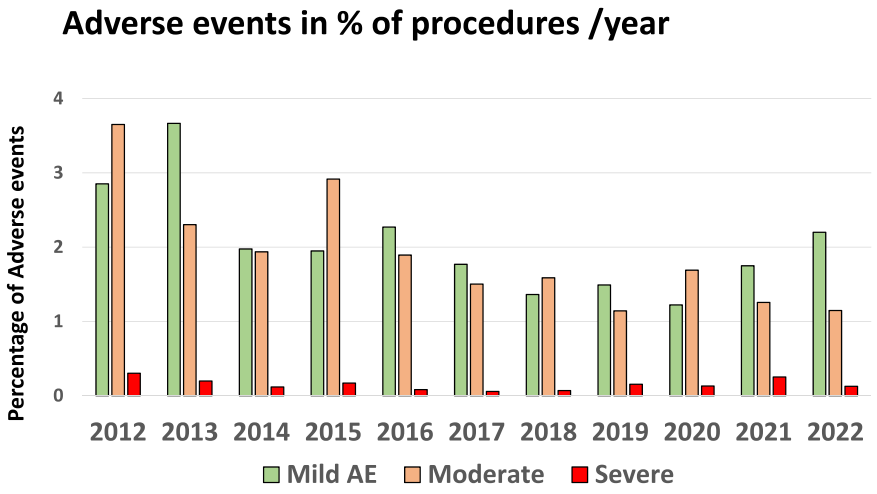

Fig. 3. Numbers and rating of reported adverse events. Distribution in percentage of adverse events present during apheresis procedures performed through the years 2012–2022 graded as Mild, Moderate and Severe.

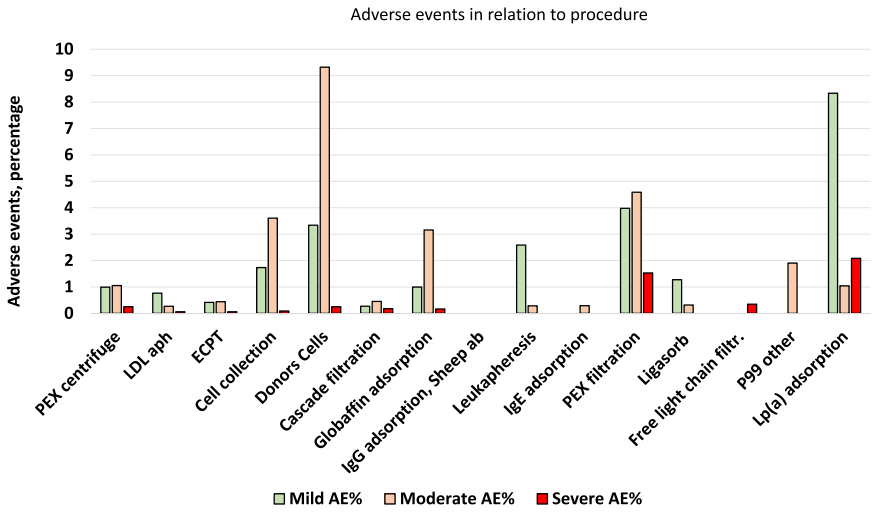

Fig. 4. Adverse events reported in relation to the procedure type. Overall percentage of adverse events in relation to various procedures used for apheresis. Procedures performed through the years 2012–2022 and AE graded as Mild, Moderate and Severe. P99 represents 'other procedures.'.

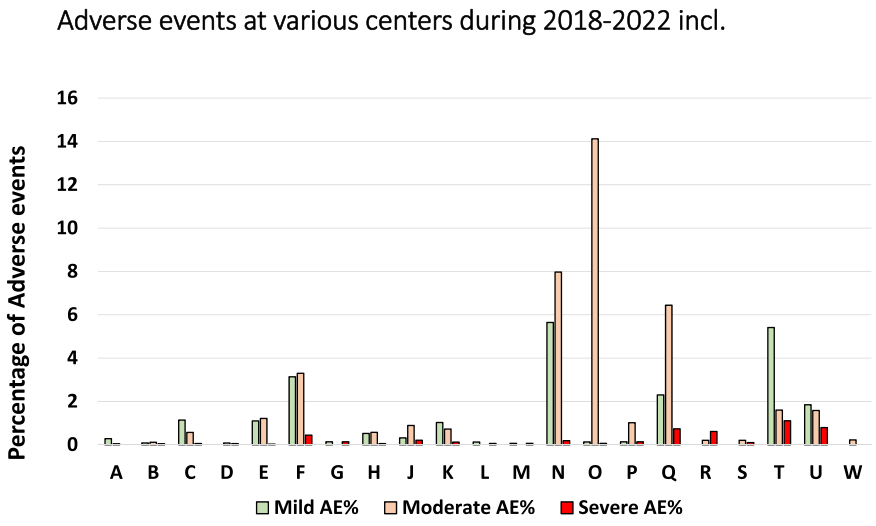

Fig. 5. Adverse events reported by participating centers. Distribution of adverse events at different apheresis centers showing the variation that may exist. Differences may depend on indications, devices, replacement fluid and other variables. Further analyses may help clarify reasons for side effects that may be counteracted. Included are procedures performed through the years 2012–2022 and AE graded as Mild, Moderate and Severe. Centers in alphabetic order based on included procedures with a cut off at 456 procedures (W) for the center with fewest apheresis procedures included.

Still, we could collect some outcome data from the WAA registry regarding more specified diagnoses or procedures [24,28], although additional ethical and practical hurdles may present along the way.

We believe compiling international data enables meaningful comparisons of procedures, settings and time trends and will also serve to improve apheresis care and outcomes in the future. Collecting additional information of patient outcomes is a high priority for the registry going forward.

Funding

The Register Centrum Norr, responsible for coordinating Registers in northern Sweden, at Vasterbotten County Council, Umea, Sweden supported administration of the WAA registry together with the University of Umea IT support unit.

Acknowledgement

We thank all patients that consented to participate in the registry that enables us to improve safety and efficacy of therapeutic apheresis. We also thank all local physicians and nurses as well as other staff that helped collect data for this important purpose.

References

[1] Stegmayr B, Korach JM, Norda R, Rock G, Fadel F. Is there a need for a national or a global apheresis registry? Transfus Apher Sci 2003;29:179–85.
[2] Malchesky PS, Koo AP, Roberson GA, Hadsell AT, Rybicki LA. Apheresis technologies and clinical applications: the 2002 international apheresis registry. Ther Apher Dial 2004;8:124–43.
[3] Malchesky PS, Koo AP, Roberson GA, Hadsell AT, Rybicki LA. International Apheresis R. Apheresis technologies and clinical applications: the 2005 International Apheresis Registry. Ther Apher Dial 2007;11:341–62.
[4] Malchesky PS, Koo AP, Rybicki LA. Apheresis technologies and clinical applications: the 2000 International Apheresis Registry. Ther Apher 2001;5:193–206.
[5] Malchesky PS, Koo AP, Skibinski CI, Hadsell AT, Rybicki LA. Apheresis technologies and clinical applications: the 2007 International Apheresis Registry. Ther Apher Dial 2010;14:52–73.
[6] Rock G., Korach J.M., Ramlow W., Norda R., Stegmayr B. Representatives for development of the WAA registry. Representing the Canadian Apheresis Group, the French Society for Apheresis, the German Lipidapheresis registry in planning, the Swedish Apheresis Group Register. 2001.
[7] Stegmayr B, Ptak J, Wikström B. World Apheresis Registry- First data report. (Abstract 101). J Artif Organs 2004;27:589.
[8] Stegmayr BG, Ivanovich P, Korach JM, Rock G, Norda R, Ramlow W. World Apheresis Registry (Abstract P165). J Artif Organs 2004;27:638.
[9] Stegmayr BG, Rock G. The World Apheresis Association (WAA) registry. WAA Newsl 2004;12:13.
[10] Stegmayr BG, Ivanovich P, Korach JM, Rock G, Norda R, Ramlow W. World apheresis association-world apheresis registry. Transfus Apher Sci 2005;32:205–7.
[11] Stegmayr BG, Ivanovich P, Korach JM, Rock G, Norda R, Ramlow W. World apheresis registry. J Clin Apher 2005.
[12] Stegmayr B, Klingstedt J, Grahn BE, Vinnervik P. The new WAA apheresis registry. Transfus Apher Sci 2006;34:259–62.
[13] Ptak J, Stegmayr B. World apheresis registry and its potential utilization in the Czech Republic. Trans Hemat Dnes 2004;10:118–21.
[14] Stegmayr B, Ptak J, Wikstrom B. World apheresis registry report. Transfus Apher Sci 2007;36:13–6.
[15] Stegmayr B, Ptak J, Wikstrom B, Berlin G, Axelsson CG, Griskevicius A, et al. World apheresis registry 2003-2007 data. Transfus Apher Sci 2008;39:247–54.
[16] Witt V, Stegmayr B, Ptak J, Wikstrom B, Berlin G, Axelsson CG, et al. World apheresis registry data from 2003 to 2007, the pediatric and adolescent side of the registry. Transfus Apher Sci 2008;39:255–60.
[17] Mortzell M, Berlin G, Nilsson T, Axelsson CG, Efvergren M, Audzijoni J, et al. Analyses of data of patients with Thrombotic Microangiopathy in the WAA registry. Transfus Apher Sci 2011;45:125–31.
[18] Stegmayr B, Ptak J, Nilsson T, Berlin G, Mirea V, Axelsson CG, et al. Panorama of adverse events during cytapheresis. Transfus Apher Sci 2013;48:155–6.
[19] Stegmayr B, Mörtzell Henriksson M, et al. Adverse events in apheresis in relation to colloid replacement fluids. Data from the WAA apheresis registry (Abstract). Int J Artif Organs 2015;38:362.
[20] Mortzell Henriksson M, Newman E, Witt V, Derfler K, Leitner G, Eloot S, et al. Adverse events in apheresis: An update of the WAA registry data. Transfus Apher Sci 2016;54:2–15.
[21] Stegmayr B. The World Apheresis Association Registry. Transfus Apher Sci 2017;56:69–70.
[22] Stegmayr B, Mortzell Henriksson M, Newman E, Witt V, Derfler K, Leitner G, et al. Distribution of indications and procedures within the framework of centers participating in the WAA apheresis registry. Transfus Apher Sci 2017;56:71–4.
[23] Toss F, Edgren G, Berlin G, Stegmayr B, Witt V. Does prophylactic calcium in apheresis cause more harm than good? - Centre heterogeneity within the World Apheresis Association Register prevents firm conclusions. Vox Sang 2018;113:632–8.
[24] Mortzell Henriksson M, Weiner M, Sperker W, Berlin G, Segelmark M, Javier Martinez A, et al. Analyses of registry data of patients with anti-GBM and antineutrophil cytoplasmatic antibody-associated (ANCA) vasculitis treated with or without therapeutic apheresis. Transfus Apher Sci 2021;60:103227.
[25] Stegmayr B, Newman E, Witt V, Derfler K, Leitner G, Eloot S, et al. Using the world apheresis association registry helps to improve the treatment quality of therapeutic apheresis. Transfus Med Hemother 2021;48:234–9.
[26] Norda R, Axelsson CG, Axdorph U, Berlin G, Wikstrom B, Stegmayr B. Recognition of intercenter differences may help develop best practice. Ther Apher Dial 2008;12:347–54.
[27] Norda R, Schott U, Berseus O, Akerblom O, Nilsson B, Ekdahl KN, et al. Complement activation products in liquid stored plasma and C3a kinetics after transfusion of autologous plasma. Vox Sang 2012;102:125–33.
[28] Blaha M, Gasova Z, Berlin G, Audzijoniene J, Griskevicius A, Dykes J, et al. Analysis of extracorporeal photopheresis within the frame of the WAA register. Transfus Apher Sci 2021;60:103172.