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The Italian registry of therapeutic apheresis in SISTRA: Year of activity 2022

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ABSTRACT

Therapeutic apheresis refers to a group of extracorporeal blood processing procedures used in the treatment of a variety of systemic diseases. These complex procedures are burdened by adverse reactions related to both procedures and underlying medical conditions.

Given the importance of centralizing the collection and the analysis of information on therapeutic apheresis, the Italian National Blood Center (NBC), at the request of the Italian Scientific Society of Hemapheresis and Cell Manipulation (SIdEM), implemented the Italian Registry of Therapeutic Apheresis (IRTA) including it in the Information System of Transfusion Services (SISTRA), coordinated by the NBC.

In 2022, a total of 34,702 therapeutic apheresis procedures was carried out in 8,781 patients, including paediatric patients, with an average of 3.9 procedures per patient. The 2022 IRTA data indicate that the patient with hematological and/or neurological disorders mainly turns to the apheresis centers. These results confirm the IRTA data from years 2020 and 2021. In the hematological field, the apheresis centers supply hematopoietic stem cells collection for autologous transplantation as well as mononuclear cell collection for extracorporeal photopheresis. With regard to the neurological field, myasthenia, chronic inflammatory demyelinating polyneuropathy and Guillain-Barré syndrome along with other neurological pathologies related to immune disorders are the most treated.

In conclusion, this manuscript presents 2022 activity data of IRTA providing institutions and scientific societies with a wide range of information including type and number of therapeutic procedures, adverse events and patients' outcome.

1. Introduction

Therapeutic apheresis is an extracorporeal treatment used to remove cells or substances from the blood as well as to administer the selected cells or plasma constituents. Since 1999, thanks to the commitment of the Italian Scientific Society of Hemapheresis and Cell Manipulation (SIdEM), the Italian Registry of Therapeutic Apheresis (IRTA) collects and analyzes information on therapeutic apheresis in Italy. However, given that data management requires significant investments, especially for software updates, and most of the apheresis procedures are performed within the transfusion services, the IRTA was included in the information system of the transfusion services (SISTRA), which collects data on all transfusion activity and whose activity is coordinated by the Italian National Blood Center (NBC) [1]. The previous operating years of IRTA, i.e. 2019, 2020 and 2021, were previously reported [2,3]. 2022 IRTA data are presented in this manuscript.

2. Material and methods

IRTA, "Italian Registry of Therapeutic Apheresis", is a section of SISTRA. Types of procedures registered and the concerning diseases are identified by a specific code generated by SISTRA. Participation in data

Abbreviations: NBC, the Italian National Blood Center; SIdEM, the Italian Scientific Society of Hemapheresis and Cell Manipulation; SISTRA, the Information System of Transfusion Services; IRTA, the Italian Registry of Therapeutic Apheresis.

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collection is voluntary and participants enter data annually. The cumulative annual data are entered into IRTA by blood transfusion services, from January to April of the following year the survey.

Emergency procedures include photopheresis procedures foreseen in the treatment of cellular rejection of solid organ transplants, in particular liver and lung transplants. To date, the autologous collection of peripheral stem cells falls under emergencies in the case of pediatric patients, as already reported in the literature [4]: if rejection or mobilization occurs when the apheresis centers are not operational, these proceed according to emergency protocols.

In this paper we report therapeutic apheresis procedures from IRTA 2022 describing number of treated patients, emergency procedures, adverse events to therapeutic procedures, disciplines in which the procedures were used, patients's outcome after treatment. A descriptive analysis of the collected data has been performed. Patients' outcome rates have been calculated as percentage of all examined patients.

3. Results

One hundred thirty-eight therapeutic apheresis centers are registered in SISTRA, 103 (75 %) entered their data. The result is in line with expectations.

In 2022, of all procedures performed therapeutic plasma exchange accounted for 38,9 % (+3.03 % vs. 2021), extracorporeal photopheresis 26,4 % (+ 1.4 % vs 2021), erythrocyte exchanges 6,8 % (+8.4 % vs. 2021), erythro-apheresis 9,8 % (+ 3.6 % vs. 2021), autologous hematopoietic stem cells collections 12,1 % (+18.7 % vs. 2021), and lipoprotein removal procedures 1,7 % (−11.1 % vs 2021) (Table 1).

Among the selective procedures, cascade filtration procedures accounted for 1.6 % (−28.6 % vs. 2021), plasma-adsorption procedures 0.2 % (−70.8 % vs 2021) and immunoadsorption procedures 0.1 % (−43.6 % vs. 2021) (Table 1).

Adverse events occurred in 894 procedures, 2.6 % of the total procedures (−17.5 % vs 2021). The most of them were mild and predominantly referred to hypocalcemia (88.4 % of all adverse events), while severe adverse events constituted only 0.4 % of all adverse events and occurred during therapeutic plasma exchange (3 events) and peripheral stem cell collection (1 event). (Table 2).

Table 3 shows the number of hematopoietic stem cell collection, cytoapheresis and photopheresis procedures. The collection of autologous peripheral blood hematopoietic stem cells was carried out in 2,738 patients (+13.5 % vs 2021), with an average of 1.4 procedures per patient, indicating the good timing of the collection and the efficiency of cell separators. Our data confirm that the pheripheral blood is the major source of hematophoietic stem cells finalized to the autologous transplantation in myeloma and lymphoma patients. Notably, erythrocyte exchange applies mainly to sickle cell disease whereas erythro-apheresis applies to polycythemia/erythrocytosis. Extracorporeal photopheresis is mainly used in the treatment of GvHD, in organ transplant rejection and cutaneous T-cell lymphoma. Its use in autoimmune diseases is still limited, with only 19 patients treated and 196 procedures (Table 3).

As reported in the reference guidelines of the American Society of Apheresis (ASFA, 2023) [5], the specialty areas of application of therapeutic apheresis are numerous. The 2022 Italian data show that the apheresis procedures were mainly used in haematology with 10,858 procedures (−0.8 % vs. 2021) in 2,404 patients (+24.3 % vs 2021), followed by neurology, with 6,982 procedures (+16.9 % vs 2021) in 1, 074 patients (+23.3 % vs 2021), and solid organ transplantation with 1, 978 procedures (−16.5 % vs 2021) in 228 patients (−25 % vs 2021) (Table 4).

In haematology, most of the treated patients had polycythemia vera

Table 2
Adverse events to therapeutic apheresis procedures.

Therapeutic procedure	Mild *	Moderate **	Severe ***
1 - Therapeutic plasma exchange	445	75	3
2 - Cascade filtration	13	1	0
3 - Plasma adsorption (physical, chemical)	0	0	0
4 - IgG / IgE Immunoadsorption	0	0	0
5 - Extracorporeal photopheresis (online)	17	0	0
6 – Extracorporeal photopheresis (off line)	55	13	0
7 - Lipoprotein apheresis	38	1	0
8 - Lymphoplasmapheresis	0	0	0
9 - Cytoreductive leukapheresis	0	1	0
10 - Granulocyte-monocytoapheresis	33	0	0
11 - Therapeutic platelet apheresis	2	0	0
12 - Erythrocyte exchange	24	1	0
13 - Erythro-apheresis	7	0	0
14 - Haematopoietic Stem Cell Collection (HSCC-autotransplant)	154	7	1
15 - Other	3	0	0
Total	**791**	**99**	**4**

* **Mild**: hypocalcemic symptoms, blood circuit clotting, hematoma at puncture site, insufficient blood flow rate.

** **Moderate**: allergic/hypersensitivity reactions, digestive disorders, nausea/vomiting, fever and chills, general discomfort.

*** **Severe**: cardiovascular collapse, vaso vagal reaction/fainting, hemolysis, arrhythmias, use of resuscitation maneuvers.

Table 1
Therapeutic apheresis procedures and number of treated patients, including paediatric patients and emergency procedures.

Therapeutic procedure	Procedures (including emergency procedures) (n)	Patients (including paediatric patients) (n)	Paediatric patients (n)	Emergency procedures (n)
1 – Therapeutic plasma exchange	13,485	2,357	60	1,389
2 - Cascade filtration	569	93	0	0
3 - Plasma adsorption (physical, chemical)	70	7	1	0
4 - IgG / IgE Immunoadsorption	43	7	0	0
5 – Extracorporeal photopheresis (online)	3,532	214	10	2
6 – Extracorporeal photopheresis (off line)	5,635	735	37	12
7 - Lipoprotein apheresis	584	45	6	0
8 - Lymphoplasmapheresis	0	0	0	0
9 - Cytoreductive leukapheresis	75	39	2	29
10 - Granulocyte-monocyte-apheresis	242	33	0	0
11 - Therapeutic platelet apheresis	21	17	0	12
12 - Erythrocyte exchange	2,389	454	80	99
13 - Erythro-apheresis	3,418	1,530	1	72
14 – Autologous Stem Cell Collection	4,212	2,922	148	95
15 - Other	427	328	59	3
Total	**34,702**	**8,781**	**404**	**1,713**

Table 3
Haematopoietic Stem Cell collection (HSCC), Cytoapheresis and Photopheresis: number of procedures and number of patients by disorders.

HSC Collection	Procedures (n)	Patients (n)
700* - Multiple myeloma	2,095	1,316
701* - Lymphoma	1,337	1,052
702* - Acute leukaemia (Autograft/Back up)	137	101
703* - Neuroblastoma	81	62
704* - Other solid tumour	183	139
799* - Other	101	68
Total	**3,934**	**2,738**
Cytoapheresis	**Procedures (n)**	**Patients (n)**
710* - Sickle Cell Disease (Erythrocyte Exchange)	1,739	335
711* - Malaria (Erythrocyte Exchange)	0	0
712* - Polycythaemia / Erythrocytosis (Erythro-apheresis)	2,187	914
713* -Acute Myeloid Leukemia (AML) (cytoreductive leukapheresis)	26	19
714* - Acute lymphoblastic Leukemia (ALL) (cytoreductive leukapheresis)	7	4
799* - Other	83	24
Total	**4,042**	**1,296**
Photopheresis	**Procedures (n)**	**Patients (n)**
720* - GVHD-Graft versus Host Disease	5,599	419
721* - Rejection of solid organ	1,609	156
722* - Cutaneous T lymphoma / Sezary syndrome	693	57
723* - Autoimmune diseases	196	19
799* - Other	30	2
Total	**8,127**	**653**

* The number refers to an internal code generated by SISTRA.

Table 4
Specialty areas of therapeutic apheresis use, number of patients and procedures.

	Procedures (n)	Patients (n)
Haematology	10,858	2,404
Neurology	6,982	1,074
Solid Organ Transplant	1,978	228
Rheumatology	869	142
Dermatology	793	69
Metabolism	774	79
Nephrology	656	35
Gastrointestinal System	307	87
Other	67	33

(erythro-apheresis, category I, grade recommendation 1B according to the 2023 ASFA Guidelines) (+51 % vs 2021) followed by GvHD (15.5 % vs 2021) (ECP, category II, grade 1B), Sickle Cell Disease, non-Acute (+14.6 % vs 2021) (RBC exchange, category I, II and III, grade 1 A, 2 A and 2B), and Thrombotic thrombocytopaenic purpura (TPE, category I, grade 1 A) (+9.2 % vs 2021) (Table 5). Only in approximately 1 % of hematological patients the clinical indication included category III, grade of recommendation 2 C, confirming the high level of appropriateness; also the patients treated for haematological diseases, not included in the ASFA Guidelines, do not exceed 1 %.

The 1,227 patients (+51.3 % vs 2021) with polycythemia vera underwent 2,810 procedures (average 2.29 procedures/patient). A favorable response was observed in 98.8 % of evaluated patients.

The largest number of procedures was performed for the treatment of GvHD, with 3,858 in 300 patients and an average of 13 procedures/patient. We evaluated 245 patients and found that 12.6 % of those achieved the remission of the clinical picture (Table 5).

Therapeutic apheresis also was a widely used therapy in thrombotic thrombocytopenic purpura with 1,625 procedures in 220 patients and an average of 7.3 procedures/patient. The outcome, available for 166 of these patients, was 95.2 % of positive responses with 72.8 % remissions of the clinical picture and 22.4 % improvements.

The response to the treatment of inherited haemochromatosis was equally positive. Out of 114 patients treated whose outcome was reported, 100 % had a positive response.

The overall outcome for the haematological disorders was available for 1,542 patients (64.1 %) with 323 remissions of the clinical picture (20.9 %) and 1,133 improvements (73.4 %) (Table 5).

In neurology (Table 6), we observed that myasthenia (2,808 treatments, +22.2 % vs 2021), chronic inflammatory demyelinating polyneuropathy (CIDP) (1,419 treatments, +3.7 % vs 2021) and Guillain-Barré syndrome (GBS) (1,182 treatments, +72 % vs 2021) are the most frequent diseases where therapeutic apheresis was used. From the analysis of the available outcome data, the best response was for GBS (85.8 %), followed by myasthenia (85.6 %) and CIDP (67.8 %). These are pathologies for which the indication for apheresis has a high level of appropriateness; in fact, only in approximately 2 % of neurological treated patients the ASFA indication fell into category III, grade 2 C; among these the most represented disease is Stiff Man Syndrome. In almost 5 % of patients the diagnosis is not included within the ASFA 2023 Guidelines probably because the neurological field still presents many pathologies with immunological pathogenesis which are still being studied.

The results considered as a whole were also positive. In fact an improvement or remission of the clinical picture was obtained in 79 % of the evaluated patients, most of whose were on maintenance therapy or recovering from disease flares. The outcome was available for 900 patients (83 % of total) (+25 % vs 2021): of these, 118 are in remission of the clinical picture (13 % of total) (+23 % vs 2021) and 594 experience improvement (66 % of total) (+37 % vs 2021).

In rheumatology (Table 7), 37 patients had vasculitis and were treated with 245 procedures (7 procedures/patient) (+7 % vs 2021). Most of these patients experienced an improvement (74 %) or stabilization of the clinical picture (23 %).

The second most represented pathology is ANCA-associated glomerulonephritis, included in the new ASFA guidelines as Mycroscopic polyangiitis and Granulomatosis with polyangiitis. One hundred seventy-five procedures in 33 patients were reported with an average of 5.3 treatments per patient. Nineteen out of 30 patients (63 %) had a positive outcome. Approximately 7 % of the treated patients had a pathology not covered by the ASFA Guidelines.

Good results were observed in patients with cryoglobulinemia, with 141 procedures in 29 patients and an average of 4.9 treatments per patient. Improvement of the clinical picture was obtained in 85 % of cases.

On the whole, the outcome was available for 127 patients (89 %) with only 2 remissions of the clinical picture and 92 improvements (72 %).

In the field of organ transplantation (Table 8), in 2022, 1,978 treatments were performed in 228 patients, with 8.6 procedures per patient. The largest number of treatments was in patients with lung transplant-bronchiolitis obliterative syndrome (BOS) (15.2 procedures/patient), heart transplant-recurrent rejection, (9.9 procedures/patient), and ABO compatible kidney transplant-Ab mediated rejection (5.6 procedures per patient). The therapeutic apheresis as supportive therapy in solid organ transplantation is still not supported by an adequate number of randomized controlled studies, and many experimental aspects remain under discussion. In the ASFA 2023 Guidelines there are still numerous indications in category III, with a low grade of recommendation: the increased number of treated cases will help to confirm the results obtained so far.

Among the kidney transplant recipients, 13 were ABO-incompatible and required 68 procedures. Recurrent heart rejection was the indication for 32 patients, who underwent 318 treatments. Prophylaxis of heart transplant rejection was performed in 7 patients, who underwent 138 treatments. Desensitization for HLA or ABO antibodies involved patients scheduled for kidney (186 procedures per 35 patients), heart (48 procedures per 5 patients) and lung (1 procedures per 1 patient)

Table 5
Haematological disorders: number of procedures, number of treated patients, number of patients at first diagnosis and patients' outcome.

Haematology	Procedures (n)	Patients (n)	Patients at first diagnosis (n)	Patients' outcome			
				Remission	Improved	Unchanged	Worsened
17 - Systemic amyloidosis	2	2	0	0	0	2	0
18 - Autoimmune haemolytic anaemia- Cold agglutinin disease	19	8	5	2	2	2	0
19 - Coagulation factors inhibitors	0	0	0	0	0	0	0
20 - Myeloma - acute renal failure	0	0	0	0	0	0	0
21 - GVHD-Graft versus Host Disease	3,858	300	100	31	172	24	18
22 - ABO-incompatible haematopoietic stem cell transplantation	81	35	12	10	6	0	0
23 - Transplantation-haematopoietic stem cells, anti-HLA antibodies	76	23	12	7	9	1	0
24 - Haemophagocytic syndromes	11	2	2	0	0	1	1
25 - Thrombocytopaenia / thrombosis induced by heparin	1	1	1	0	1	0	0
26 - Immunological thrombocytopaenias	0	0	0	0	0	0	0
27 - Hyperviscosity in hipergammaglobulinaemia	114	48	26	2	30	7	0
28 - Polycythaemia vera-Erythrocytosis	2,810	1,227	146	89	516	6	1
29 - Post-transfusion purpura	0	0	0	0	0	0	0
30 - Red Cell Immunization, D-antigen-Prevention and treatment	0	0	0	0	0	0	0
31 - Anti-D immunization in pregnancy	51	5	2	0	3	0	0
32 - Acute Sickle Cell Disease	132	83	25	21	54	0	0
33 - Sickle Cell Disease, non-Acute Sickle Cell Disease	1,571	270	14	23	162	7	0
34 - Thrombocytosis	21	16	11	0	16	0	0
35 - Thrombotic, coagulation-mediated microangiopathy	28	6	1	0	1	0	0
36 - Thrombotic, complement-mediated microangiopathy	12	2	2	0	2	0	0
37 - Thrombotic microangiopathy associated with drugs	0	0	0	0	0	0	0
38 - Thrombotic microangiopathy associated with infection	0	0	0	0	0	0	0
39 - Post-TMO thrombotic microangiopathy	49	6	3	0	4	1	0
40 - Thrombotic thrombocytopaenic purpura, TTP	1,625	220	82	121	37	4	4
41 - Malaria	0	0	0	0	0	0	0
42 - Babesiosi	11	7	1	5	2	0	0
43 - Erythropoietic porphyria	10	1	0	0	1	0	0
44 - Hereditary haemochromatosis	304	119	30	11	103	0	0
992 - Other	72	23	14	1	12	6	1
Total	**10,858**	**2,404**	**489**	**323**	**1,133**	**61**	**25**

Table 6
Neurological pathologies: number of procedures, number of treated patients, number of patients at first diagnosis and patients' outcome.

Neurology	Procedures (n)	Patients (n)	Patients at first diagnosis (n)	Patients' outcome			
				Remission	Improved	Unchanged	Worsened
1 - Acute disseminated encephalitis	115	28	13	1	9	6	1
2 - CIDP - Chronic inflammatory demyelinated polyneuropathy	1,419	198	67	12	106	51	5
3 - Chronic focal Rasmussen encephalitis	0	0	0	0	0	0	0
4 - Guillain-Barré syndrome (GBS)	1,182	226	152	36	109	18	6
5 - Complex regional pain syndrome	3	1	1	0	0	1	0
6 - Lambert-Eaton syndrome	69	5	1	0	3	0	0
7 - Multiple Sclerosis	354	60	25	1	45	8	0
8 - Myasthenia Gravis	2,808	376	123	51	222	37	9
9 - Neuromyelitis optica	312	62	39	6	35	6	1
10 - NMDAR- antibodies encephalitis	106	18	13	1	11	5	0
11 - Paraneoplastic neurological syndromes	36	9	6	0	0	8	0
12 - Paraproteinemic demyelinating neuropathies	115	17	2	2	12	2	1
13 - PANDAS, Paediatric Neuropsychiatric Post-Streptococcal Syndrome	38	7	5	1	5	1	0
14 - Progressive multifocal leukoencephalopathy (PML) associated with natalizumab	0	0	0	0	0	0	0
15 - VG-potassium channel (VGKC) antibody related Diseases	4	1	1	0	1	0	0
16 - Stiff person syndrome	99	14	6	3	9	1	1
991 - Other	322	52	26	4	27	17	3
Total	**6,982**	**1,074**	**480**	**118**	**594**	**161**	**27**

transplantation.

The overall outcome of the apheresis treatment is available for 165 patients (72 %): 120 out of 165 (73 %), showed a remission of the clinical picture (5 %) or its improvement (68 %).

Overall, as regards the 4 considered clinical specialties (Table 9), 2,734 assessable patients showed a positive response (87 %), consisting in the remission of the clinical picture or improvement respectively in 16.4 % and 70.6 % of the patients. Only 2.4 % of patients worsened, an effect attributed to the worsening of the disease.

4. Discussion

This is the third report from the Italian Registry of Therapeutic Apheresis (IRTA) carried out within the Italian transfusion system and referred to the 2022 activity data. The data from 2019, 2020 and 2021 was the subject of previous publications [2,3]. Apheresis procedures increased from 23,657 in 2019 (pre-pandemic year) to 34,702 in 2022. Haematology is the discipline that mainly addresses apheresis centers due to the growing demand of haematopoietic stem cell collection for autologous transplantation as well as extracorporeal photopheresis, a second line therapeutic approach in post-transplant Graft versus Host

Table 7
Rheumatological pathologies: number of procedures, number of treated patients, number of patients at first diagnosis and patients' outcome.

Rheumatology	Procedures (n)	Patients (n)	Patients at first diagnosis (n)	Patients' outcome			
				Remission	Improved	Unchanged	Worsened
46 - ANCA-associated glomerulonephritis	175	33	15	0	19	9	2
48 - Cryoglobulinemia	141	29	11	1	22	3	0
49 - Schonlein-Henoch purpura	8	1	1	0	0	0	1
50 - Vasculitis	245	37	12	0	26	8	1
51 - Cardiac neonatal lupus	0	0	0	0	0	0	0
52 - Catastrophic Antiphospholipid-Acute Syndrome	44	11	7	1	4	2	1
53 - Scleroderma	105	11	4	0	8	0	1
54 - Systemic lupus erythematosus	52	10	4	0	7	1	1
994 - Other	99	10	3	0	6	3	0
Total	**869**	**142**	**57**	**2**	**92**	**26**	**7**

Table 8
Solid organ transplant: number of procedures, number of treated patients, number of patients at first diagnosis and patients' outcome.

Solid organ transplant	Procedures (n)	Patients (n)	Patients at first diagnosis (n)	Patients' outcome			
				Remission	Improved	Unchanged	Worsened
77 - Heart Transplant-Recurrent Rejection	318	32	1	0	11	1	0
78 - Heart transplant - Prophylaxis of rejection	138	7	2	0	2	0	0
79 - Heart Transplant-Desensitization	48	5	0	0	0	1	0
80 - Heart Transplant-Ab-mediated Rejection	53	8	6	0	3	2	1
81 - Liver Transplant, ABO Desensitization (Living Donor)	0	0	0	0	0	0	0
82 - Liver transplant, ABO Desensitization (deceased donor)	0	0	0	0	0	0	0
83 - Liver transplant, Ab Rejection (ABO / HLA)	42	12	8	1	6	3	0
84 - Lung Transplant-BOS	776	51	5	1	23	17	5
85 - Lung Transplant-Ab-Mediated Rejection	62	8	5	1	3	4	0
86 - Lung Transplant-Desensitisation	1	1	0	0	1	0	0
87 - ABO compatible kidney transplant - Ab mediated rejection	294	52	37	2	42	5	0
88 - ABO compatible kidney transplant - Desensitization, living donor	91	18	12	0	12	3	0
89 - ABO compatible kidney transplant - Desensitization, deceased donor	27	4	2	0	2	1	1
90 - ABO Incompatible kidney transplant - Desensitization, living donor	68	13	6	3	4	0	0
91 - ABO Incompatible Kidney Transplant-Ab mediated Rejection	60	17	2	0	3	1	0
990 - Other	0	0	0	0	0	0	0
Total	**1,978**	**228**	**86**	**8**	**112**	**38**	**7**

Table 9
Patients' outcome and number of assessable patients.

	Patients' outcome				
Specialty	Assessable patients (n)	Remission	Improved	Unchanged	Worsened
Haematology	1,542	323	1,133	61	25
Neurology	900	118	594	161	27
Rheumatology	165	8	112	38	7
Solid organ transplant	127	2	92	26	7
Total	**2,734**	**451**	**1,931**	**286**	**66**
% outcome	100.00	16.50	70.63	10.46	2.41

disease (GVHD). Remaining in the haematological field, the 2022 data also show that the demand of apheresis procedures for patients with thrombotic thrombocytopenic purpura is stable as well as the use of erythrocyte exchange in the treatment of sickle cell disease. Instead, the use of apheresis procedures for the treatment of polycythemia vera is growing. Previous studies [6,7] report how the use of erythro-apheresis, as a replacement for therapeutic phlebotomy, in patients suffering from polycythemia or haemochromatosis, allows for better control of haematocrit, a reduction in hospital admissions and a better quality of life. Recently, even in Italy, numerous therapeutic apheresis centers are using erythro-apheresis to replace therapeutic phlebotomy. A further support in this direction could come from cost saving: the first results of a cost analysis carried out by the Italian Society of Haemapheresis and Cellular Manipulation (SIdEM) would foster this change. Notably the item "Other" in Table 1 includes as many as 317 lymphocytoapheresis procedures for CAR-T therapy. In 2021, 18 CAR-T authorized centers resulted active throughout Italy.

In the neurological field, data are in line with those of the pre-pandemic year (2019). Myasthenia, chronic inflammatory demyelinating polyneuropathy and Guillain-Barré syndrome are the diseases in which apheresis procedures are mostly used. Their use for neurological pathologies related to immune system disorders is stable.

Compared to the pre-pandemic year 2019, the use of therapeutic apheresis in organ transplantation is also increasing in relation to the possibility of overcoming the immunological barrier of HLA incompatibility and ABO incompatibility, especially for kidney transplantation. The use of apheresis remains stable in rheumatology, a medical specialty in which the use of therapeutic apheresis is reserved to clinical cases that do not respond to pharmacological treatment.

Therefore, it confirms the immunomodulatory capacity of therapeutic apheresis in diseases or pathological conditions in which the immunological response is involved, whether autoimmune response in

neuropathies and rheumatological diseases, or alloimmune in solid organ transplants. Therapeutic apheresis performs an action similar to non-specific immunoglobulins, whose availability recently is no longer adequate for the progressively growing demand. For this reason, in diseases where a switch off or a modulation of an abnormal immunological response is advisable, therapeutic apheresis, when applicable, allows to keep the use of immunoglobulins in the second line. In the last 3 years, in correspondence with the pandemia, a reduced availability of immunoglobulins, that are largely used as therapeutic strategy in some neurological and rheumatological pathologies for their immunomodulatory effect [8,9], was registered globally. As far as the Italian situation, the reduced availability of immunoglobulins, a plasma-derived medicinal product dependent from donor plasma, might have contributed to the increased use of apheresis procedures in 2022 [10,11,12].

Regarding the adverse effects of apheresis procedures, our study confirms that therapeutic apheresis is a safe procedure with an extremely limited number of severe adverse events. The greatest number of adverse events occurred during therapeutic plasma exchange, which on the other hand is the most frequent treatment (37.3 % of the total): in almost all the cases mild adverse events are attributable to hypocalcemia. To this regard, it should be noted that all the centers adopt measures for the prompt treatment of symptoms and in many transfusional centers the administration of Ca^{2+} by a continuous infusion pump is used to prevent symptoms. Likewise, for each patient and each procedure, clinical parameters are verified: weight, haematocrit, plasmatic volume, flow rate, extracorporeal volume. SIdEM over the years has also paid great attention to the training of professional involved, progressively improving the safety of procedures. With regard to efficacy, data from this study show that therapeutic apheresis is associated with a general improvement of clinical conditions.

As regards as the compliance with the ASFA Guidelines, it is confirmed that the level of appropriateness of the therapy is very high: there is still a percentage of diseases not included in the consolidated indications; however, many years of experience suggest that apheresis therapy has been, and still is, a valid support in numerous diseases when pharmacological alternatives are not available or not indicated.

Regarding the management of the activity, it has been observed that some regions have concentrated therapeutic apheresis procedures in the main hospitals which therefore perform many procedures/year; to the contrary, in other regions, the activity is spread over the territory with many hospitals performing few procedures. Of the total number of centers that have joined the IRTA, 4 hospitals carried out more than 1,500 procedures/year, most of the hospitals carried out a number of procedures between 101 and 500 procedures/year, and other hospitals which carried out less than 100 procedures/year. In some of these only erythro-apheresis procedures were performed.

In conclusion, the IRTA supplies a wide variety of information including efficacy data to the National Health Service, the regional health authorities and the scientific community, helping to stimulate inter-center benchmarking and improve clinical practices.

CRediT authorship contribution statement

Liviana Catalano: Conceptualization, Methodology, Software validation, Writing. **Giustina De Silvestro:** Conceptualization, Methodology, Software validation, Writing. **Giuseppe Marano:** Conceptualization, Methodology, Software validation, Writing. **Simonetta Pupella:** Conceptualization, Methodology, Software validation, Writing. **Vanessa Piccinini:** Data curation. **Angelo Ostuni:** Supervision. **Vincenzo De Angelis:** Supervision.

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