

# The Italian Registry for Therapeutic Apheresis. A Report From the Apheresis Study Group of the Italian Society of Nephrology

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on Behalf of the Apheresis Study Group of the Italian Society of Nephrology

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Many clinical indications and different technical issues have been reported on therapeutic apheresis: much criticism has also been recorded in several instances, mainly due to the lack of large clinical trials to validate collected data. A Registry where all the available data can be organized and analyzed therefore becomes a priority for all the professionals involved in apheresis. The purpose of this report is to describe the data submitted from 1994 to 2004 from 15,285 treatments on 1,477 patients from 44 Centers, including mainly, but not exclusively, Nephrological Units, collected by the Apheresis Study Group of the Italian Society of Nephrology in 15 Italian regions. Plasma exchange accounted for 56.2% of the procedures, and of these 50.4% were performed by filtration. Plasma treatment was used in 40.1% of procedures, namely with Protein A immunoabsorption (14.6%), LDL-Cholesterol dextran sulfate adsorption (9.7%), and semiselective cascade or double filtration (12.6%). Cell apheresis, limited to photopheresis, was used in 0.85% of cases, and whole blood treatment (direct adsorption lipoprotein, and molecular adsorption recirculating system) in 2.7%. The procedures analyzed here account for less than 20% of estimated therapeutic apheresis performed in Italy, according to the national survey of activity performed for year 2000 by the Italian Apheresis Society. Notwithstanding that the data are largely incomplete, they are sufficiently informative for a definite trend: plasma treatment with filtration on fractionation filters and adsorption must be used as often as possible, instead of plasma exchange, thus obtaining the most selective removals. *J. Clin. Apheresis* 20: 101–106, 2005 © 2005 Wiley-Liss, Inc.

**Key words:** therapeutic apheresis; apheresis registry; plasma treatment; plasma exchange; Italy

## INTRODUCTION

For more than 10 years, data collection of therapeutic apheresis procedures has been one of the goals of the Apheresis Study Group of the Italian Society of Nephrology, a small task force, which published the "Guidelines for Therapeutic Apheresis in Nephrology" in 1999 [1], and primarily considered the establishment of a Registry as a safety and quality issue.

Therapeutic apheresis has been indicated in several diseases in many different clinical fields, from neurology to dermatology, from organ transplantation to metabolic errors, from hematology to nephrology. Data collection of the single procedures is cumbersome, and requires nowadays a large database with a well-organized staff: it is therefore still limited, and largely based on personal interest and initiative. Moreover, most of the time, productive apheresis largely overcomes therapeutic apheresis, and little is

known about therapeutic procedures practised, especially including technical issues, local distribution, and/or regional clusters in diseases, together with incidence and pattern of adverse events. The establishment of a Registry, where all the available data can be organized and analyzed, therefore, becomes a priority for all the professionals involved in apheresis [2–5].

Nephrologists have been very interested in therapeutic apheresis, partly due to their attitude towards

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TABLE I. Therapeutic Apheresis Registry 1994–2004

Top five most Frequently treated diseases		Female	Male	Total
Guillain Barré syndrome	Neurology	67	100	167
Cryoglobulinemia	Systemic vasculitis	72	51	123
Myasthenia gravis	Neurology	62	44	106
Systemic lupus	Systemic vasculitis	77	13	90
TTP	Hematology	40	35	75

extracorporeal blood treatments, and partly due to the fact that they faced kidney diseases for which there was a strong indication for plasma removal and substitution. Later, plasma treatment instead of plasma exchange was introduced and, again, intensive care specialists and nephrologists were equipped with filtration techniques, due to their experience with hemodialysis and hemofiltration, and cascade techniques with plasma fractionation were introduced. More recently, whole blood treatment, like hemoperfusion or hemoabsorption, has been developed on a larger clinical basis, and once again the procedure is much like hemodialysis, thus focusing the strong interest of the nephrological community.

The Apheresis Group of the Italian Society of Nephrology started to collect data on apheresis in 1994, mainly in Nephrological Units in Italy, but since the beginning, the Group has addressed its efforts in the collection and analysis of therapeutic apheresis procedures of all kinds, performed also in other Centers and for the treatment of non-nephrological diseases. Following the initial experience during 1994–1999, data collection was performed by a standardized questionnaire that was subsequently modified and improved on an electronic basis. The Registry is now Internet based; the website is [www. aferesi.it](http://www. aferesi.it) and it is coordinated by Stefano Passalacqua, MD ([passalacqua@ aferesi.it](mailto:passalacqua@ aferesi.it)).

The Registry is open, and the participation of other Scientific Societies is appreciated. A continuous collaboration throughout the years has been maintained with SIDE, the Italian Society for Apheresis, which has recently published data of a national survey of apheresis in Italy [6]. The data presented by SIDE were provided by 102 Apheresis Units from 19 Italian regions, and included techniques, devices, clinical indications, and adverse effects of about 165,000 apheresis procedures performed in Italian Blood Banks and Apheresis Units during one year, with a very large prevalence (90.8%) of productive apheresis.

## RESULTS

The Registry is now automatically updated, and the last release was April 24, 2004. The data of 15,285 procedures have been recorded from 1994 to 2004 by

44 operating Units in 15 Italian regions, mainly nephrology, but also lipid clinics, neurology and intensive care units. Therapeutic, non-productive apheresis procedures have been recorded and analyzed. Although mainly Nephrological Units are at present recorded in the Registry, apheresis procedures were performed for the treatment of many different clinical conditions, not only nephrological indications, including, among others, immunologic, metabolic, and neurologic diseases.

Therapeutic apheresis procedures were performed by means of plasma exchange (PE) through centrifugation or filtration, plasma treatment (TP), which included different filtration, fractionation and adsorption devices, cell apheresis limited to photo-apheresis (CA), and whole blood treatment on adsorbent columns (TS) for selective removals (i.e., LDL-cholesterol, bilirubin).

Vascular access for apheresis was obtained through artero-venous fistula in 13.4%, central venous catheters in 10.45%, and through a variable combination of peripheral veins in all other cases. Anticoagulation was performed with heparin in 82%, a combination of heparin and citrate in 9.7%, and with citrate only in 4.9%.

No side effects were reported in 97.08% of procedures. The reported side effects were mild in the vast majority of cases, mainly linked with hypotension, citrate toxicity, and blood access-related problems. There were 5 deaths recorded, corresponding to 0.03%; 4 patients were treated with PE and 1 with TP.

A total number of 1,477 patients were enrolled, 741 males and 736 females, each of whom received on average 10.5 procedures. The procedures were separated into groups of treatment, according to the kind of procedure and to timing: a group of treatment was performed with the same technique, was never longer than one year, and the time that elapsed between one procedure and the other did not exceed 35 days. A total of 2,132 groups of treatment was recorded, 593 of these in vasculitis and systemic diseases, 497 in neurologic, 330 in hematologic, and 249 in nephrologic diseases.

The five most frequent diseases treated by apheresis respectively were, as reported in Table I, Guillain Barré syndrome in 167 cases, cryoglobulinemia in

**TABLE II. Therapeutic Apheresis Registry 1994–2004\***

Disease	PE	TP	CA	TS	Total
Hypercholesterolemia	51	1,398	0	122	1,571
Systemic lupus erythematosus	1,041	502	0	0	1,543
Cryoglobulinemia	436	1,046	0	0	1,482
Guillain Barré syndrome	763	80	0	0	841
Myasthenia gravis	527	147	0	0	674
Focal segmental glomerulosclerosis	310	338	10	0	658
Glomerulonephritis (unspecified)	327	235	0	0	607
Vasculitis	435	170	0	0	605
TTP	568	11	0	0	579
Chronic demyelinating polyneuropathy	201	345	0	0	546
Myeloma	457	14	0	0	471
Macroglobulinemia	222	191	0	0	413
Rheumatoid arthritis	335	62	0	0	397
Wegener granulomatosis	232	137	0	0	369

\*PE: plasma exchange; TP: plasma treatment; CA: cell apheresis; TS: whole blood treatment.

**TABLE III. Therapeutic Apheresis Registry 1994–2004**

Techniques and procedures distribution	Treatments	
	No.	%
Plasma exchange		
Centrifugation	837	5.48
Filtration	7,709	50.44
Complete system	30	0.2
Other	24	0.16
Total	8,600	56.26
Plasma treatment		
Dextran sulfate LDL adsorption	1,496	9.79
Phenylalanin adsorption	100	0.65
Resins adsorption	91	0.6
Tryptophan adsorption	74	0.48
Cascade filtration	1,933	12.65
Heparin-induced extracorporeal LDL adsorption (HELP)	9	0.06
Protein A immunoadsorption	2,233	14.61
Sheep anti-IgG immunoadsorption (THERASORB Life 18)	3	0.02
Other	203	1.33
Total	6,142	40.18
Cell apheresis		
Photopheresis	130	0.85
Other	0	0
Whole blood treatment		
Dextran sulfate LDL adsorption (DX21)	5	0.03
Direct adsorption lipoprotein (DALI)	274	1.79
Molecular adsorption recirculating system (MARS)	134	0.88
Other	0	0
Total	413	2.7
Total treatments	15,285	100

123, myasthenia gravis in 106, SLE in 90, and TTP in 75, without any regional prevalence or distribution of the diseases. The largest number of procedures was reported for the treatment of familial hypercholesterolemia, chronically repeated in 152 patients with 1,571 procedures, followed by SLE in 237 patients with 1,543 procedures, cryoglobulinemia in 175 cases with 1,482 procedures, Guillain Barré syndrome in 179 with 841 procedures, and myasthenia gravis in 140 with 674 procedures (Table II).

PE accounted for 56.26% of the procedures, and, out of these, 50.44% were performed by filtration. TP was used in 40.18% of cases, namely with Protein A immunoadsorption (14.61%), LDL-cholesterol dextran sulfate adsorption (9.79%), and semiselective cascade filtration or double filtration (12.65%). CA, namely photopheresis for acute graft rejection, has been used in a small number of cases, and accounts for 0.85%, and TS (direct adsorption lipoprotein and molecular adsorption recirculating system) for 2.7%

**Table IV. Clinical Outcome of the Most Frequently Treated Diseases\***

Disease	Patients (no.)	Clinical remission (%)	Improved (%)	Unchanged (%)	Worsened (%)
Guillain Barré syndrome	167	30.2	52.8	13.2	3.8
Cryoglobulinemia	123	<b>2.6</b>	68.8	20.4	8.3
Myasthenia gravis	106	4.8	82.4	12.0	<b>0.8</b>
Systemic lupus erythematosus	90	15.1	38.7	43.1	3.1
TTP	75	33.3	45.8	13.9	7.0
Multiple myeloma	70	2.7	58.7	37.3	1.3
Hyperbilirubinemia	54	18.5	68.5	<b>9.2</b>	3.7
Vasculitis	40	4.0	58.0	34.0	4.0
Liver disease	36	10.0	55.0	20.0	15.0
Kidney graft rejection	35	43.3	<b>33.3</b>	16.7	6.7

\*The lowest percentage value for every column of outcome is in bold.

of procedures (Table III). The procedures performed by TP, CA, and TS did not require any substitution fluid. Human albumin solutions 3–5% in saline were used most of the time as substitution reinfusion in PE procedures, with the only exception of TTP where plasma was exchanged with fresh-frozen plasma.

Clinical outcome was reported in the Registry as (1) clinical remission, (2) improved, (3) unchanged, (4) worsened. Taking into account the groups of treatment separated according to large pathologies, a clinical remission and/or improvement was reported in 363 out of 458 groups of treatments in neurological diseases (79.2%), 202/284 hematological (71.1%), 134/217 nephrological (61.7%), 336/539 vasculitis and systemic diseases (62.3%), and 115/165 metabolic diseases (69.6%).

The performances and results for the main diseases treated with apheresis are summarized in Table IV, where the lowest percentage of outcome for every category is in boldface.

## DISCUSSION

The Registry was conceived within the Italian Society of Nephrology as a means to collect as many data as possible of the nephrologic activity in the small area of macromolecular plasma treatment [6]. It soon became evident that often Nephrologists, partly due to a personal interest or ability in extracorporeal treatments, partly due to local necessity, are called to treat non-nephrologic diseases. Moreover, other experts in Neurology, Immunology, Intensive Care, or Metabolic Diseases started therapeutic apheresis on their own, and later shared their experience with specialists in other fields. Initially, through the collaboration with the Italian Apheresis Society (SIDE), which mainly reported data from Apheresis Units and Blood Banks, and whose interdisciplinary character is well recognized, the idea of a common apheresis registry was undertaken, but it had to be postponed, due to the differences in the collection of data [7].

An overview of the Registry is useful to point out that therapeutic apheresis procedures are largely distributed within nephrologic and non-nephrologic units all over Italy (nearly all the Italian regions are represented), although data are certainly underestimated, and that neurological diseases, namely Guillain Barré syndrome and myasthenia gravis, are still within the top five treated diseases. Cryoglobulinemia and SLE, not necessarily accompanied by nephropathy, are the other most treated diseases together with TTP.

An interesting feature of the Registry, which is especially focused on therapy, is represented by the very large proportion of plasma treatment procedures, namely double filtration, plasma or whole blood adsorption and immunoabsorption, instead of plasma substitution by traditional plasma exchange, that indicates the preference for plasma treatment instead of plasma substitution. Great importance is, therefore, attributed to plasma treatment and to the minimization or avoidance of substitution fluids. In this respect, the pilot experience of immunoabsorption in neurologic diseases [8] and of plasma detoxification in liver failure is important to be recognized [9], along with a protocol to assess the role of therapeutic apheresis in recurrent focal segmental glomerulosclerosis [10, 11]. Another field of interest is the treatment of severe hypercholesterolemia, which a 10-year survey reveals to be the current most treated disease. The Registry collects over 1,500 procedures, with a very small number of plasma exchanges, and a variety of selective procedures of LDL-apheresis that all proved to be safe and suitable for long-term treatment [12, 13].

As regards blood access and the choice of anticoagulation, a nephrologic bias has to be considered, since over 13% of patients had an arteriovenous fistula, and heparin was by far the most used anticoagulant, not only with plasma filtration, but also with other techniques, including plasma separation by centrifugation and plasma treatment by adsorption,

## Apheresis Study Group Registry: Participating Centers

Participant	Center	Departement	City
Giusti Bruna Pia	Osp. S.D. Donato	Nefrol. e Dialisi	Arezzo
Mauro Ragaiolo	Osp. C.G. Mazzoni	Nefrol. e Dialisi	Ascoli Piceno
Tommaso De Palo	Osp. Giovanni XXIII	Nefrol. e Dialisi Pediatrica	Bari
Carlo Manno	Consorziale-Policlinico	Nefrol. e Dialisi Pediatrica	Bari
Alfonso Ramunni	Policlinico Di Bari	Nefrol. e Dialisi	Bari
Riccardo Losappio	Osp. Umberto I	Nefrol. e Dialisi	Barletta
Sonia Pasquali	Policlinico S. Orsola Malpighi	Nefrol. e Dialisi	Bologna
Felice Fortina	Osp. SS. Trinita	Nefrol. e Dialisi	Borgomanero
Antonio Barracca	Osp. Brotzu	Nefrol. e Dialisi	Cagliari
Salvatore Alba	Osp. Cardarelli	Nefrol. e Dialisi	Campobasso
Gabriele Liuzzo	Osp. Tomaselli	Nefrol. e Dialisi	Catania
Lorenzo Di Liberato	Osp. SS. Annunziata	Nefrol. e Dialisi	Chieti
Augusto Di Silva	Osp. Di Formia	Nefrol. e Dialisi	Formia
Franco Scaccia	Osp. Umberto I	Nefrol. e Dialisi	Frosinone
Giancarlo Marinangeli	Osp. Civile	Nefrol. e Dialisi	Giulianova
Riccardo Giusti	Osp. Campo Di Marte	Nefrol. e Dialisi	Lucca
Pierpaolo Toffoletto	Osp. Umberto I	Nefrol. e Dialisi	Mestre
Carlo Antozzi	1 <sup>st</sup> Naz. Neurol C. Besta	Neurologia	Milano
Ghil Busnach	Osp. Niguarda Ca' Granda	Nefrol e Dialisi	Milano
Giuseppe Pastore	Osp. S. Giacomo	Nefrol e Dialisi	Monopoli
Carlo De Pascale	Osp. D. Cotugno	Nefrol. e Dialisi	Napoli
Dario Zazzaro	Osp. G.B. Grassi	Nefrol. e Dialisi	Ostia
Luciangela Calvisi	Osp. A. Segni	Nefrol e Dialisi	Ozieri
Poisetti Pier Giorgio	Osp. Civile	Nefrol. e Dialisi	Piacenza
Rodolfo Puccini	Osp. S. Chiara	Nefrol Dialisi Trapianto	Pisa
Maurizio Ciccarelli	Osp. Reggio Calabria	Nefrol. e Dialisi	Reggio Calabria
Michele Ferrannini	Policlinico Tor Vergata	Nefrol. e Dialisi	Roma
Carlo Meloni	Osp. S. Eugenio	Nefrol. E Dialisi	Roma
Gilnardo Novelli	Università La Sapienza	II Patologia Chirurgica	Roma
Stefano Passalacqua	C.I. Columbus U.C.S.C.	Nefrol. e Dialisi	Roma
Renzo Pretagostini	Policlinico Umberto I	Nefrol. Dialisi Trapianto	Roma
Elios Russo Gaspare	Policlinico Umberto I	Nefrol E Dialisi	Roma
Cladio Stefanutti	Università La Sapienza	Ambulatorio Aferesi	Roma
Luigi Moriconi	Osp. Valdarno Inferiore	Nefrol. e Dialisi	S. Miniato
Maria Cossu	Osp. SS Annunziata	Nefrol. e Dialisi	Sassari
Giulio Monaci	Policlinico Le Scotte	Nefrol Trapianto	Siena
Alberto Scatizzi	Osp. SS. Annunziata	Nefrol. e Dialisi	Taranto
Roberto Laudati	Osp. Oirm S. Anna	Centro Trasfusionale	Torino
Massimo Milan	Osp. G. Bosco	Immunoematologia	Torino
Dario Roccatello	Osp. G. Bosco	Cento Cmid Leinaudi	Torino
Antonio Niccolini	Osp. S. Chiara	Nefrol. e Dialisi	Trento
Cristina Maresca Maria	Osp. S. Maria Dei Battuti	Nefrol. e Dialisi	Treviso
Mietta Meroni	Osp. Di Vimercate	Nefrol. e Dialisi	Vimercate
Sandro Feriozzi	Osp. Grande Degli Infermi	Nefrol. e Dialisi	Viterbo

where a mixture of citrate and heparin was generally employed.

Therapeutic apheresis-related side effects are few, usually mild, although more common than in productive apheresis [7]. It has to be pointed out, however, that the loss of 5 patients, with a gross mortality of 0.03%, was reported in cases treated with PE in 4 cases, and with TP in 1 case, and this overview may confirm that plasma processing is generally safe and well tolerated by patients.

Notwithstanding being largely incomplete, the analysis of data collected in the Registry is sufficiently informative for at least two kinds of considerations: (1) the number of therapeutic apheresis procedures performed is certainly underestimated either in Blood

Banks or in other Apheresis Centers, but it appears to be employed in many different clinical conditions in a quite homogeneous way all over the country, and (2) in our data, it appears that a definite trend to employ plasma treatments with different techniques, from cascade filtration to whole blood adsorption, can be recognized in order to achieve as often as possible the most selective plasma removal.

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