

# Spectra Optia<sup>®</sup> Apheresis System: current insights into clinical risks and benefits

Anne Klink  
Silke Rummler

Department of Therapeutic Apheresis,  
Institute of Transfusion Medicine,  
University Hospital Jena, Jena,  
Germany

**Abstract:** The Spectra Optia<sup>®</sup> Apheresis System is an automatic blood component separator used to perform various therapeutic apheresis procedures, cell collection and processing procedures. Users could follow all instructions given by the SPO secure and comfortable. However, there are no formal guidelines for the use of specific apheresis devices in therapeutic apheresis. The focus of this review is the application of this Apheresis System in therapeutic apheresis, and its clinical risks and benefits. Although only few data exist evaluating the use of the Spectra Optia Apheresis System, it can be said that the Spectra Optia device is safe to use and comfortable for both the patients and the operators. The therapeutic procedures like therapeutic plasma exchange, procedures with secondary plasma devices, as well as blood cell depletion procedures can be performed efficiently and precisely using this device. Severe adverse events have not been reported. All published data have shown the clinical benefits, which were more pronounced than the clinical risk. The only disadvantage the system has is the use of citrate, especially in plasma-based procedures, as its optimal use has not been evaluated. For the further evaluation of the Spectra Optia Apheresis System, more clinical outcome data are necessary.

**Keywords:** Spectra Optia<sup>®</sup>, therapeutic apheresis, plasma exchange, secondary plasma device, blood cell depletion, red cell exchange, mononuclear cell collection

## Introduction

Spectra Optia<sup>®</sup> (SPO, Terumo BCT, Lakewood, CO, USA), a new and refined apheresis system that replaced the Cobe Spectra (Cobe; Terumo BCT, Lakewood, CO, USA), is based on the established Trima and Cobe technologies. SPO is now widely used in routine clinical practice as it enables the operators to perform a variety of procedures such as plasma-based and cell-based therapeutic apheresis treatments. For this review, the relevant procedures such as therapeutic plasma exchange (TPE), lipoprotein apheresis (LA), immunoadsorption (IA), depletion of white blood cells (WBC) or platelets, and unstimulated collection of mononuclear cells are listed in Table 1.

However, whether all procedures can be effectively and safely performed still needs to be evaluated. Therefore, we examined recent literature from different databases (PubMed, Medline, and Cochrane Database). Except for those that reported on therapeutic apheresis in children, all publications on therapeutic apheresis procedures were analyzed with respect to their efficacy, clinical risk, and benefits.

## Therapeutic plasma exchange

TPE is used to remove or decrease the level of circulating antibodies, immune complexes, cytokines, abnormal plasma proteins, cholesterol, metabolic waste products, and

Correspondence: Silke Rummler  
Department of Therapeutic Apheresis,  
Institute of Transfusion Medicine,  
University Hospital Jena, AmKlinikum 1,  
Jena D-07747, Germany  
Tel +49 3641 932 5581  
Email [silke.rummler@med.uni-jena.de](mailto:silke.rummler@med.uni-jena.de)

**Table 1** Overview of exchange, depletion and cell collection procedures for cell-based immunotherapy

Procedure	Indications	Mean efficiency
<b>Exchange</b>		
Therapeutic plasma exchange (TPE)	Guillain-Barre syndrome, CIDP, paraproteinemic demyelinating neuropathies, Myasthenia gravis, ANCA-associate rapidly progressive glomerulonephritis, TTP, Good pasture's syndrome, FSGS, symptomatic hyperviscosity in monoclonal gammopathies, AMR in renal transplantation, desensitization LD, AB0i renal transplantation, desensitization, LD	PRE: 83%–92% <sup>8–14</sup> n.t.
Therapeutic plasma exchange single needle access (TPE-SN)		
Secondary plasma devices (SPD)	LA: homozygotes familial hypercholesterolemia	LA: LDL: 57%–59%, Lp(a): 68% <sup>21,22</sup>
• Lipoprotein apheresis (LA)	Rheo: age related macular degeneration, dry	Rheo: no data available
• Rheopheresis (Rheo)	IA: AMR in renal transplantation, desensitization LD,	IA: IgG 61% <sup>22</sup>
• Immunoabsorption (IA)	AB0i renal transplantation, desensitization, LD	
Red blood cell exchange (RBCX)	Sickle cell disease, stroke prophylaxis, iron overload prevention	Reduction of HbS: 51%–56% <sup>25</sup>
<b>Depletion</b>		
White blood cell depletion (WBCD)	Hyperleukocytosis	CE: 47.3% dependent on rebound <sup>37</sup>
Platelet depletion (PLTD)	Thrombocytosis	CE: 50.6% <sup>35</sup>
Red blood cell depletion (RBCD)	Hereditary hemochromatosis, Polycythemia vera	
<b>Unstimulated collection for secondary processing</b>		
Mononuclear cell collection (MNC)	Various cell based immunotherapy	CE: 39%–66% <sup>29,30,34</sup>
Continuous mononuclear cell collection (CMNC)	ECP, DLI	CE: 60%–62% <sup>33,34</sup>

**Note:** The table depicts mean therapeutic efficiency and the most important indications for the procedure regarding the current ASFA guidelines<sup>5</sup>

**Abbreviations:** AB0, incompatible; AB0i, blood group; AMR, antibody mediated rejection; ANCA, antineutrophil cytoplasmic antibody; ASFA, American Society for Apheresis; CE, collection efficiency; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; DLI, donor lymphocyte infusion; ECP, extracorporeal chemo phototherapy; FSGS, focal segmental glomerulosclerosis; LA, lipoprotein apheresis; LD, living donor; Lp(a), lipoprotein (a); PRE, plasma removal efficiency; TTP, thrombotic thrombocytopenic purpura.

plasma-bound toxins and drugs.<sup>1–4</sup> Randomized controlled trials have demonstrated the efficacy of TPE in the treatment of various diseases, including thrombotic thrombocytopenic purpura (TTP), acute inflammatory demyelinating polyradiculoneuropathy, myasthenia gravis, and central nervous system demyelination. TPE is also used to treat many other disorders, though there is a lack of sufficient randomized controlled trials in this regard. More than 100 clinical syndromes and 65 diseases are included in the guidelines of the American Society for Apheresis (ASFA).<sup>5,6</sup> TPE can be performed using either centrifugation-based (cTPE) or filtration-based (mTPE) devices. Physicians in transfusion medicine prefer cTPE, whereas the nephrologists usually use mTPE. Compared to cTPE procedures, the mTPE procedure requires high flow rates to achieve transmembrane pressure, needs a larger vein, and has lower extraction efficiency of 27%–53% (vs 86% in cTPE).<sup>7–9</sup> In addition, mTPE procedures are less effective for higher-molecular weight proteins such as IgM, fibrinogen, and immune complexes.<sup>3,8</sup>

In a recent PubMed search, we found 12 reports on cTPE using SPO.<sup>8–19</sup> In these publications, different data were analyzed. The most important data, such as plasma removal efficiency and utilization of citrate, are listed in Table 2.

Due to the high fraction of removed plasma, it is feasible to use a double peripheral venous access and, if necessary, a single needle method. Peripheral venous access was used in the range from 30% to 60% by the operators.<sup>8,11,12</sup>

During TPE, no serious adverse events (AEs) have been declared.<sup>8</sup> The TPE procedures are safe and well-tolerated, with AEs occurring in ~5%–7% of cases. These AEs generally include reactions to replacement fluid or to citrate and hypotension. Three vasovagal events are mentioned.<sup>14,15</sup> Various amounts of anticoagulant acid citrate dextrose solution A (ACD-A), 5.7%–31.3% of the total consumption, or 1.7% ± 0.7% of the inlet blood volume were returned to the patient during TPE procedures.<sup>10,13</sup> Therefore, with the prophylactic use of 10% calcium gluconate, only signs of mild symptomatic hypocalcemia were observed with the same prevalence of 1.2% as analyzed in an earlier study.<sup>7</sup> By using a low ACD-A infusion rate of 0.8 mL ACD-A/min/L total blood volume, the estimated drop in ionized calcium would not exceed more than 10%–15%.<sup>20</sup>

In some cases, patients cannot tolerate ACD-A; here, ACD-A can be economized by adding heparin. In the section of plasma-based therapeutic apheresis with secondary plasma device (SPD), 2 regimens are demonstrated.<sup>21,22</sup> It should be

**Table 2** Summary of published TPE data regarding efficacy with SPO apheresis device

Authors	Number of patients treated	Total number of procedures performed	Mean ACD-A in mL/min used	Mean platelet loss in %	Mean PRE in %	Time to exchange 1L plasma/min
Kes et al 2016 <sup>8</sup>	27	27	6.58	10.5	83	24.5±6.5
Puppe and Kingdon 2014 <sup>17</sup>	3	25	4.69 <sup>b</sup>	n.t.	n.t.	28±4
Hafer et al 2016 <sup>9</sup>	20	20	5.38	7.0	84	33 (38.1–30.8) <sup>a</sup>
Tormey et al 2010 <sup>14</sup>	20	40	5.69	1.0	87	n.t.
Cid et al 2014 <sup>11</sup>	7	44	5.97	n.t.	83	n.t.
Lambert et al 2011 <sup>13</sup>	16	16	6.61	1.6	83	n.t.
Hequet et al 2014 <sup>12</sup>	20	31	5.08	3.4	87	n.t.
Kim et al 2015 <sup>10</sup>	121	389	3.11	1.6	92	n.t.
Perotti et al 2008 <sup>15</sup>	14	30	n.t.	1.1	86	n.t.

**Notes:** PRE is the volume of plasma that can be removed per volume of plasma that is processed with a specific apheresis device; <sup>a</sup>calculated based on 30 mL/min (26.25–32.50 mL/min) processed plasma volume; <sup>b</sup>calculated based on total blood volume=70mL/kg body weight for male patients and 65mL for female patients.

**Abbreviations:** TBV, total blood volume; TPE, therapeutic plasma exchange; PRE, plasma removal efficiency; SPO, Spectra Optia®; ACD-A, anticoagulant citrate dextrose solution A.

noted that platelet loss in plasma exchange treatments with SPO is not uniformly presented in the literature. Kes et al described a relatively high platelet loss (Table 2) when using a high inlet flow rate greater than 80 mL/min.<sup>8</sup> The results of Tormey et al indicated that the platelet loss can be as low as 1% with moderate inlet flow rates of about 54 mL/min.<sup>14</sup> In particular, SPO plasma exchange might reduce the risk of significant platelet loss in patients suffering from TTP.<sup>19</sup> Clotting or bleeding events in SPO treatment are not found in the literature. Unlike the mTPE, these procedures are associated with AEs, especially clotting and filter replacement, in up to 25% of all procedures.<sup>17</sup>

Regarding the clinical outcome, and IgG reduction of TPE treatment using SPO, only 4 reports were available.<sup>8,9,16,17</sup> Hafer et al. showed the reduction of mean IgG from 5.88g/L (3.42–8.84g/L) baseline to 1.89g/L (1.21–3.52g/L) when exchanging the patients plasma volume 1.2 times in one TPE procedure.<sup>9</sup> In TPE, it is difficult to calculate the removal efficiency of IgG by using fresh frozen plasma as replacement fluid. When albumin was the replacement fluid of choice, the IgG removal efficiency was 72%.<sup>8</sup> One patient, with severe atopic dermatitis, was treated successfully. The mean reduction rate of immunoglobulin E was 29%.<sup>16</sup> TPE performed with SPO due to severe hypertriglyceridemia rapidly reduced the level of serum triglyceride.<sup>18</sup> Autoantibodies associated with crescentic glomerulonephritis and small vessel vasculitis were removed efficiently.<sup>17</sup>

Our own data showed that 9 out of 102 TPE procedures ended prematurely due to technical problems and AEs. Of the 9 cases, 4 cases were due to venous problems, 2 were due to hypotension, and 1 case each was due to vomiting,

hypertension, and citrate reaction. Mild self-limiting or AEs with minor corrective activities occurred in 17% cases.

## Plasma-based therapeutic apheresis with SPD

Specific plasma purification methods such as lipoprotein apheresis (LA) or immunoabsorption (IA) have been developed for selective removal of purported pathological substances. If TPE fails, IA may be an alternative in patients with life-threatening autoimmune diseases or during acute humoral transplant rejection episodes.<sup>38,39</sup> Due to the superior efficacy of the other selective removal systems in cholesterol removal, TPE is less commonly used. Referring to the current ASFA guidelines of 2016,<sup>5</sup> indications for procedures with SPD are listed in Table 1. In a recent PubMed search, only 2 reports regarding SPD were found.<sup>21,22</sup> Handschel et al described a new protocol for LA with SPO.<sup>21</sup> For LA, the authors used dextran sulfate-adsorption cellulose (Kaneka, Osaka, Japan) or the IA method (Pocard, Moscow, Russia) in combination with the ADA-sorb® devices (Medicap, Ulrichstein, Germany). A total of 9 patients were treated with familial hypercholesterolemia. A modified anticoagulation regime with the additional use of heparin in LA was used. In a follow-up, the authors analyzed additional 20 procedures with an optimized whole blood: ACD-A ratio of 20:1 if 10.000 IE heparin was in the ACD-A bag and achieved a total cholesterol reduction of 59% ± 7%. With this regime, 2 episodes of clumping or granularity of buffy coat in the connector were registered. AEs like citrate toxicity were rare due to prophylactic intravenous calcium infusion of 0.026 mmol/min.<sup>26</sup>

Rummler et al used the pore size filter technology with Monet<sup>®</sup> (Fresenius Medical Care, Homburg, Germany) or Evaflux<sup>™</sup> (Kawasumi, Tokyo, Japan) for LA and the adsorption matrix sepharose with coated staphylococcal protein A, Immunosorba<sup>®</sup> (Fresenius Medical Care), for IA.<sup>22</sup> They also worked with the ADAorb<sup>®</sup> device (Medicap). The anticoagulation regime in LA was realized with ACD-A alone (ratio of whole blood: ACD-A, 12:1). In IA, the ACD-A ratio was 15:1, and 1.000 IE/h heparin was additionally administered. Therefore, the citrate utilization was 0.17 mL/mL processed plasma in LA and 0.14 mL/mL processed plasma in IA. The authors analyzed 73 LA in 4 patients. On average, the LDL cholesterol was reduced by 57% (37%–64%), and the lipoprotein (a) levels were significantly reduced by 68% (45%–76%) within 1 session of LA. The LA was found to be safe and effective. No cardiac events or rejection episodes were observed. Nine severely ill patients with different indications for IA (eg, antibody positive neurological diseases, acute humoral rejection after heart transplantation or renal transplantation, idiopathic dilated cardiomyopathy and connective tissue disease) received a total of 76 IA treatments. The circulation amount of IgG was reduced from a mean initial value of 6.6 g/L (1.09–21.0 g/L) to 2.61 g/L (0.33–14.7 g/L).

In total, 97% of all SPD treatments were completed as intended. The reasons for premature finish of the procedures were AEs like breast pain, severe hypotension and venous access problems; the latter AE was rare in occurrence. Citrate toxicity was not seen. The dosage of prophylactic intravenous calcium gluconate administered was 0.029 mmol/min (0–0.047 mmol/min) in LA and 0.033 mmol/min (0–0.052 mmol/min) in IA.<sup>22</sup>

## Red blood cell exchange (RBCX) and/or RBC depletion (RBCD)

RBCX and/or RBCD can be performed within 1 procedure. In the first step, the erythrocytes can be depleted isovolemically, and in the second step, the erythrocytes can be exchanged. Both procedures can be chosen to run independently. The RBCX was established to perform RBCX in sickle cell disease (Table 1). For this purpose, studies were conducted that examined the effectiveness and safety of the procedure. The equivalence of the technical performance with the parameters hemoglobin S (HbS) after treatment, fraction of cells remaining (FCR), procedure duration, processed blood and anticoagulant volumes and the consumption of the RBC units have been confirmed.<sup>23–26</sup>

The RBCD/RBCX protocol in SPO and the isovolemic hemodilution/RBCX protocol in Cobe are comparable.<sup>23,24</sup> No significant differences were found in HbS, hematocrit, FCR, and platelet counts. Interestingly, RBCD performed with SPO requires significantly less normal saline replacement volume and rinse back volumes ( $P < 0.001$ ). However, a longer process time is to be noted in the SPO.<sup>24</sup> An effective reduction of HbS was confirmed by Daniel et al within a single erythrocyte exchange, the initial HbS levels were reduced from 73%–85% to 22%–29%.<sup>25</sup>

The main objective in SPO RBCX was to confirm that the predicted FCR of the patient at the end of the procedure reflects the actual FCR, measured in % HbS. The mean ratio of actual FCR/predicted FCRp was 0.90 (95% CI, 0.86–0.94) within the predefined acceptable range of 0.75–1.25.

The safety profile of RBCD/RBCX in 60 patients examined by Quirolo et al remained effective without severe AEs and unexpected adverse side effects.<sup>26</sup> However, hypotension in RBCD/RBCX procedures with SPO occurred more often in 7% cases vs 1.8% cases in Cobe.

Erythrocyte depletion is mentioned as a method of removing iron in patients with hereditary hemochromatosis. For this purpose, a small study was published where a mean blood volume of  $857.3 \pm 22.3$  mL with a short middle treatment period of  $12.0 \pm 0.4$  min was processed, and the mean hematocrit per session was lowered by ~6%. Iron of  $405.2 \pm 23.2$  mg per procedure was removed.<sup>27</sup>

## Collection of mononuclear cells (MNC)

For the collection of MNC, 2 different options are available. The MNC procedure performs several accumulation phases and collection phases in succession. Here, a high centrifugal force is exerted to achieve an optimal packing factor (default is 20) for the anticoagulated blood to enter the separation channel. The automatic interface management (AIM) system regulates the plasma pump flow rate to control the concentration of cells flowing through the collection port. The collection pump transfers the MNC and platelets from the regulatory chamber to the second chamber where the platelets are selectively removed by elutriation and returned to the patient. Optimal interface positioning is to be set via the collection preference according to the desired product target cell yield and erythrocyte content.<sup>30,34</sup>

The second option is the continuous MNC (CMNC) procedure in which the patient's blood is pumped into the tubing set and the centrifuge rotates to achieve the default packing factor of 4.5 on a slightly larger volume separation channel

with a less minor interface layer. The AIM system regulates the plasma pump flow rate to control the concentration of cells flowing through the collection port, depending on the collection preference. If cells are detected by the AIM system, the collection hose valve moves to the collection position, and the collection pump pushes the MNC into the collection bag. The platelets are suspended in the plasma layer and are returned directly to the patient without the need for a secondary separation chamber.<sup>34</sup>

Indications for the MNC and the CMNC procedures are identical in principle. Examples of the clinical application are the offline method of extracorporeal photopheresis (ECP), collection of autologous peripheral blood stem cells, and further novel immunotherapies such as immature dendritic cell processing or chimeric antigen receptor-modified T-cell therapy. Two of the most common indications are the apheresis of allogeneic peripheral blood stem cells and donor lymphocytes, which will not be further discussed here. All these approaches require a reliable collection of MNC with a defined composition of cell populations. In the database analysis with PubMed and Medline, MNCs were identified for apheresis with the SPO in 28 studies between June 2011 and December 2017.

## Extracorporeal photopheresis

ECP is an established cell therapy for the treatment of cutaneous T cell lymphoma, graft vs host disease, and organ rejection after organ transplantation.<sup>28</sup> Several studies have been performed on the apheresis of MNCs comparing the efficiency of the SPO with its precursor Cobe and other apheresis devices (Table 3). These showed high-quality MNC collection with low platelet and erythrocyte contamination.<sup>29–31</sup> In

unstimulated collection procedures for secondary processing of patient's safety, including a short collection time and a small product volume, is of importance since patients received a series of procedures. Regarding secondary processing, the product hematocrit is more critical as the MNC cell count.<sup>30</sup> Unfortunately, the prediction of the MNC cell count is difficult due to each patient's own particularity. The study by Del Fante et al showed that the use of the SPO MNC procedure can help achieve an average 10% lower product volume with possible benefit for subsequent irradiation and lower fluid load with low body weight.<sup>29</sup>

An interesting strategy to reduce the ACD-consumption is the ramping from initial 1:12 to 1:20 in MNC procedures described by Del Fante et al. The operator modulated the ACD-A ratio considering the platelet count, coagulation status, and comorbidities.<sup>29</sup> An adequate anticoagulation to maintain the adherence platelet function is essential if the differentiation of dendritic cells in ECP occurs through transient engagement of monocytes with device-adherent activated platelets and their ligands.<sup>32</sup> To what extent the anticoagulation regime in ECP may influence the clinical outcome is unknown. For ECP, no WBC threshold is defined. Nevertheless, up to  $1.0 \times 10^{10}$  total lymphocytes with a high purity seems possible to be collected within 1 procedure.<sup>29,30,33,34</sup> The importance of the product purity is described only for patients with an indication for ECP due to lung involvements after transplantation.<sup>29</sup>

Punzel et al compared the MNC procedure with the CMNC procedure in the setting of collection lymphocytes for donor lymphocytes infusion.<sup>34</sup> It was observed that the CMNC procedure takes a shorter processing time and a lower product volume but a higher hematocrit and platelet count in

**Table 3** MNC collection in unstimulated patients for secondary processing to perform offline ECP or for donor lymphocyte infusion

	Unstimulated MNC				Unstimulated CMNC			
	Number of treated patients	Number of procedures	ACD-A utilization in mL/min	Mean collection efficiency in %	Patient	Number of procedures	ACD-A utilization in mL/min	Mean collection efficiency in %
<b>ECP</b>								
Schulz, 2014 <sup>30</sup>	3	54	4.5	57 <sup>b</sup>				
Brosig, 2016 <sup>33</sup>					7	12	n.t.	60 <sup>c</sup>
Del Fante, 2013 <sup>29</sup>	39	63	4.4	39 <sup>c</sup>				
<b>DLI</b>								
Punzel, 2017 <sup>34</sup>	18	18	4.5 <sup>a</sup>	66 <sup>c</sup> 64 <sup>b</sup>	17	17	4.2 <sup>a</sup>	62 <sup>c</sup> 60 <sup>b</sup>
Schulz, 2014 <sup>30</sup>	16	16	5.3	59 <sup>b</sup> 63 <sup>c</sup>				

**Notes:** <sup>a</sup>mixed anticoagulation with 5 IU Heparin/mL ACD-A; <sup>b</sup>CE for lymphocytes (CE- is based on the mean pre- and postapheresis target cell count); <sup>c</sup>CE for MNC.

**Abbreviations:** ACD-A, anticoagulant citrate dextrose solution A; CE, Collection Efficiency; CMNC, continuous mononuclear cell collection; DLI, donor lymphocyte infusion; ECP, extracorporeal photopheresis; MNC, mononuclear cells; nt, not tested; SPO, Spectra Optia®; TPE, therapeutic plasma exchange.

the product. With lower centrifugal forces using a packing factor of 4.0 instead of 4.5 in CMNC, it is feasible to reduce the platelet contamination in cellular product while keeping all target cells at the same yield.<sup>34</sup> Nevertheless, we do not prefer the use of CMNC procedure in the offline ECP setting because a significantly higher hematocrit in the product can hinder the further processing with UVA illumination. The CMNC with the small product volume, shorter procedure time, and thrombocyte savings may be the preferred setting for the collection of peripheral blood stem cells.

An important contribution was made by Brosig et al with their analysis of online and offline ECP methods.<sup>33</sup> All offline ECP procedures showed higher WBC count than online ECP with significant superiority in MNC collection efficiency (CE 54% vs 15%). Side effects were not observed in any ECP methods tested. For the offline methods, calcium was substituted as needed by the anticoagulant with ACD-A, thus effectively preventing the most common side effect.<sup>33</sup>

The report on the preparation of mini buffy coat for adult patients who cannot receive either an online ECP or an offline ECP seems interesting. Whole blood separation with the bone marrow processing program from the SPO apheresis system in 1 group achieved a higher lymphocyte yield than the standard mini buffy coat preparation method with the fully automated separator device Compomat G4. This technique, which has been tested in healthy whole blood donors, should be further investigated in a clinical setting.<sup>27</sup>

With regard to AEs, only mild hypocalcemia in MNC collection for ECP has been reported. The occurrence of mild hypocalcemia was reported by study groups of Del Fante et al and Schulz et al<sup>29,30</sup>

## White blood cell depletion (WBCD) and platelet depletion (PLTD)

For the depletion of WBCs, different procedures performing with SPO are available. It is feasible to use the granulocyte collection (PMN) procedure as well as the WBCD procedure. There are no substantial differences between the 2 methods; only the default settings are different. The set to be used is the SPO-intermediate density layer-Set (IDL-Set). This set is particularly developed to collect a large amount of WBCs or platelets in a short time period. Clinical manifestation of leukostasis due to hyperleukocytosis in acute lymphoblastic (ALL) or acute myeloid leukemia (AML) could motivate the physicians to perform leukocytapheresis procedures. Depletion of WBCs in symptomatic AML with WBC count  $>100 \times 10^9/L$  or ALL with WBC count  $>400 \times 10^9/L$  is recommended regarding the guidelines of the ASFA as category II

grade 1b.<sup>5</sup> In a PubMed search, we found only 3 reports related to WBCD or PLTD with SPO.<sup>30,35,36</sup>

Performance of WBCD with SPO was first described by Schulz et al.<sup>30</sup> They treated 5 patients with leukostasis due to AML and performed a total of 8 PMN treatments. Double total blood volumes, a product equivalent to one-fifth of total blood volume or no more than 300 mins, were processed. ACD-A was used for anticoagulation in a ratio of 12:1 (whole blood: ACD-A). Depending on the clinical situation, the ratio was adapted. It is important to note that, under normal operating conditions, the extracorporeal volume of the IDL-Set does not exceed 253 mL. Under alarm conditions, the extracorporeal volume may increase up to 297 mL. Therefore, it is simple to overcome the allowed extracorporeal volume limit. Nevertheless, beside mild hypocalcemia, no AEs, including hypotonia, were observed.<sup>30,36</sup> A collection efficiency of  $47.3\% \pm 7.4\%$  and platelet attrition of  $32.8\% \pm 2.8\%$  was achieved, but the authors conceded that a highly variable number (up to 50% of leukemic cells) was mobilized into the bloodstream during leukocytapheresis. Despite a low decrease in the WBC count (22%), Cline et al described a high volume of cells collected,  $3.51 \times 10^{10}$  WBC per volume of blood processed using the PMN procedure.<sup>36</sup>

In the Apheresis Unit of Transfusion Medicine at the University Hospital Jena, we treated 7 patients with hyperleukocytosis; of them, 6 cases were due to AML and 1 case was with ALL. We exclusively used the WBCD procedure. The WBC count was reduced by an average of 27% (5%–55%) compared with the baseline. All WBCD procedures were completed as intended. Despite a high extracorporeal volume at the end of the WBCD, there were no AEs.

Only 1 case of PLTD in a pregnant woman at 35 weeks of gestation was reported.<sup>35</sup> Five thrombocytapheresis procedures were performed within 2 weeks. A mean of  $1.3 \pm 0.3$  total blood volume was processed, and the collection efficiency was  $50.6\% \pm 2.6\%$  while preserving leukocyte level. No AEs and no further pregnancy complications were documented.

## Conclusion

There are few available data regarding the clinical risks and benefits of apheresis treatments with SPO. All published data showed clinical benefits, which were more pronounced than the clinical risks. The SPO in TPE works efficiently and achieves high plasma extraction rates even with low inlet flow. The TPE procedures are safe and well tolerated, with AEs occurring in 5%–7% of cases.<sup>14,15</sup> The AEs generally include reactions to replacement fluid, to citrate, and hypotension. Platelet loss when using moderate inlet flow rates is no

longer a clinical risk even in patients who suffer from TTP. The evaluation of the published clinical outcome data were adduced in efficient removal of pathological substances like IgG-autoantibodies, and triglycerides.

SPO SPD-LA treatments achieved a removal efficiency of lipoproteins like LDL cholesterol and lipoprotein up to 59% and 64%, respectively, compared with baseline.<sup>21,22</sup> Particularly, no cardiac events were observed. In SPO SPD-IA, there are almost no published clinical outcome data. However, the described IgG reduction seems to be satisfactory. To date, in plasma-based procedures, the optimal use of citrate has not been evaluated. The use of ACD-A in TPE differs among the apheresis centers from 3.11 mL/min to 6.61 mL/min. Nevertheless, bleeding or clotting was not observed.<sup>8–14,17</sup>

The procedures PLTD, PMN, and WBCD are suitable for fast blood cell depletions. The evaluation of the collection efficiency is difficult, because of the mobilization of WBCs in the blood stream within WBCD or PMN procedures. Furthermore, these procedures often exceed the allowed extracorporeal volume limit. Nonetheless, no severe AEs were observed.<sup>30,36</sup> The described PLTD procedures were able to reduce the platelet in a pregnant woman with thrombocytopenia without AEs.<sup>35</sup>

RBCD/RBCX protocols in SPO are comparable with the isovolemic hemodilution RBCX protocol in Cobe Spectra.<sup>23</sup> No significant differences were found. SPO-MNC procedures in unstimulated patients showed high-quality MNC collection with low platelet and erythrocyte contamination, and 10% lower product volume with possible benefit for subsequent illumination in ECP. Unfortunately, the collection efficiency values are not comparable. The apheresis centers used different calculation formulas.<sup>29,30,33,34</sup> In cell-based SPO procedures, the citrate anticoagulation differs slightly between the apheresis centers. Mild AEs are reported. In general, for further evaluation of the SPO, more clinical outcome data are required.

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## Disclosure

Silke Rummeler works as an in-country reviewer for Terumo BCT, Inc. The authors report no other conflicts of interest in this work.

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