

## A Paradigm Shift in the Utilization of Therapeutic Plasmapheresis in Clinical Practice

Kiproff DD<sup>1\*</sup>, Hofmann JC<sup>2</sup>, Rohe R<sup>3</sup>, Morato X<sup>4</sup> and Mehdipour M<sup>5</sup>

<sup>1</sup>Global Apheresis, Inc., 655 Redwood Highway, Ste 370, Mill Valley, CA 94941, Buck Institute on Aging, Novato, CA

<sup>2</sup>Global Apheresis, Inc., 655 Redwood Highway, Ste 370, Mill Valley, CA 94941, California Pacific Medical Center, University of California, San Francisco, CA

<sup>3</sup>Global Apheresis, Inc., 655 Redwood Highway, Ste 370, Mill Valley, CA

<sup>4</sup>Ace Alzheimer's Center, Barcelona, Spain

<sup>5</sup>University of California, Berkeley, CA

### \*Corresponding author:

Dobri Dobrev Kiproff,  
Global Apheresis, Inc., 655 Redwood Highway,  
Ste 370, Mill Valley, CA 94941, Buck Institute on  
Aging, Novato, CA

Received: 10 Nov 2023

Accepted: 15 Dec 2023

Published: 24 Dec 2023

J Short Name: ACMCR

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### Citation:

Kiproff DD, A Paradigm Shift in the Utilization of Therapeutic Plasmapheresis in Clinical Practice. *Ann Clin Med Case Rep.* 2023; V12(5): 1-7

## 1. Abstract

Therapeutic Plasma Exchange (TPE), frequently referred to as plasmapheresis, is an automated procedure which separates whole blood into plasma and blood cells. The plasma is discarded and replaced with physiologic fluids and returned to the patient along with the blood cells. Theoretically, any disease in which a humoral phase is implicated in the pathogenesis may be at least partially mitigated by removal of the patient's plasma and replacement with physiologic solutions. In clinical practice, TPE is used in a hospital setting, usually as a last resort, to treat autoimmune diseases by removing circulating antibodies and/or immune complexes. Recently, it was demonstrated that TPE has several immunoregulatory properties besides removal of circulating antibodies and immune complexes. Both controlled and uncontrolled clinical studies have demonstrated that TPE is associated with only a few mild adverse reactions and can be performed safely in an outpatient setting.

We report our experience in treating patients with TPE on an outpatient basis with several different medical conditions (Alzheimer's disease, Long Covid, PANDAS) and prophylactically in older individuals for the attenuation of inflammation.

## 2. Introduction

The term plasmapheresis (removal of plasma with or without replacement with physiologic solutions) was first used in 1914 by

Abel, et al, in their paper, "Plasma removal with return of corpuscles," which was an account of their attempt to develop an artificial kidney [1]. Today, TPE is used to treat more than 80 diseases. The American Society for Apheresis (ASFA) *Journal of Clinical Apheresis* (JCA) Special Issue Writing Committee is charged with reviewing, updating, and categorizing indications for the evidence-based use of therapeutic apheresis (TPE) in human disease. In the Ninth Edition, the JCA Special Issue Writing Committee has incorporated systematic review and evidence-based approaches in the grading of evidence and categorization of apheresis indications to make recommendations on the use of apheresis in a wide variety of disease and conditions [2]. Plasmapheresis, or TPE, is one of the four major types of apheresis procedures, which includes Erythrocytapheresis, leukocytapheresis, and thrombocytapheresis. The guidelines are published every three years. The last edition was published in May 2023. Apheresis is a Greek word which means "to take away". TPE is still primarily used to remove pathogenic substances from plasma. However, numerous studies have demonstrated that TPE has more profound effects on the immune system that lead to epigenetic change [3]. Recent studies as well as the observations reported here, demonstrate that TPE, when performed by experienced medical personnel, is a safe procedure [4] and can be performed on an outpatient basis for the treatment of medical conditions for which pharmaceutical options are either not available or do not yield satisfactory results.

### 3. Materials and Methods

TPE was performed using Spectra Optia Apheresis Device (TerumoBCT, Lakewood, CO). Vascular access was obtained via antecubital veins using 18-gauge catheters for access and 20-gauge angiocaths for return. Replacement fluids were 5% Human Albumin and intravenous immunoglobulin (IVIG) (Octapharma, Hoboken, NJ and Grifols, Los Angeles, CA, respectively). One plasma volume was the target for each treatment. Two grams of IVIG were administered after each procedure. Laboratory tests were performed at Quest Diagnostics, Mill Valley, CA, Moleculera, Oklahoma City, OK, and Radiance Diagnostics, Naperville, IL. All TPE treatments were performed in a private, outpatient clinic by experienced and board-certified nurses and physicians.

### 4. Alzheimer’s Disease (AD)

AD is the most common type of dementia. It can seriously affect a person’s ability to carry out daily activities. As many as 5.8 million Americans are living with AD. This number is projected to triple to 14 million by 2060 [5]. AD is the result of the cumulative effect of genetic and various comorbidities accumulated over a lifetime. Advanced age and inflammation play a central role. Therapeutic Plasma Exchange (TPE) with albumin replacement is being investigated as a new therapeutic approach for AD [6]. AD patients’ plasma contains amyloid beta (Aβ) protein bound to circulating albumin as well as highly oxidized and glycated albumin that impairs albumin antioxidant action. It is hypothesized that routine TPE-removal of AD patient’s plasma - containing albumin-bound Aβ- might change the dynamic equilibrium of Aβ between cerebrospinal fluid (CSF) and plasma, which would increase the trans-

port of free Aβ from CSF to plasma. The AMBAR (Alzheimer Management by Albumin Replacement) trial (EudraCT#: 2011-001598-25; Clinical Trials.gov ID: NCT01561053) tested TPE with different replacement doses of albumin, with or without IVIG to correct a possible immunological deficit, in mild-to-moderate AD patients. Recently, results of the primary endpoint of the AMBAR trial have been reported [7]. Results demonstrated that TPE treatment could slow down the progression of cognitive, functional, and global symptoms in AD. Progression of the disease was arrested in 61% of patients with moderately severe AD. Significant neurophysiological (including memory, language, and attention/executive functions), neuropsychiatric (including depression and suicide), and quality of life was observed in patients with mild AD [8]. The adverse reactions observed in the trial were mainly mild and rarely necessitated discontinuation of the TPE procedure. A total of 4709 TPE procedures were performed with adverse reactions occurring in 501 patients (10.6%) [4]. After the results of the AMBAR study were published, AD was included in the 2023 special publication of ASFA’s Clinical Applications of Therapeutic Apheresis, An Evidence-Based Approach [9]. After completion of the AMBAR study, two monoclonal antibodies (Aducanumab and Lecanemab) both targeting Aβ in the brain were approved by the FDA for the treatment of AD [10]. (Table 1) compares the results of the clinical trial that lead to the FDA approval of the two monoclonal antibodies with the results of the AMBAR study. It is worth pointing out that both monoclonal antibodies were associated with significant ARIA (Amyloid Related Imaging Abnormalities) which can cause edema and bleeding in the brain [10].

**Table 1:** AD Treatment Pipeline: Efficacy results of mAbs anti-Ab and AMBAR

Effect size comparison across outcomes - % effect size is largest for AMBAR

Alzheimer’s treatment candidates		N	ADCS-ADL Effect Size	ADAS-Cog Effect Size	CDR-Sb Effect Size	ARIAs
mAb anti-Aβ	Aducanumab ENGAGE	1647	18%	11%	-2%	40%
	Aducanumab EMERGE (10mg/kg)	1638	40%	27%	22%	
	Lecanemab (BAN2401)	1795	37%	26%	27%	12%
MULTI-MoA	AMBAR	347	52%	66%	71%	0%

Efficacy comparative Table elaborated by the authors



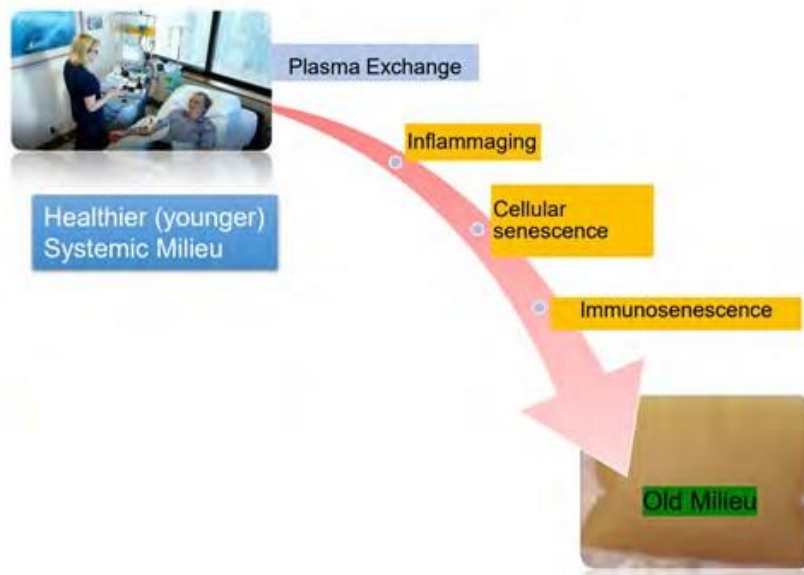
ADCS-ADL: Alzheimer’s Disease Corporative Study-Activities of Daily Living; ADAS-Cog: Alzheimer’s Disease Assessment ScaleCognitive subscale; CDR-Sb: Clinical Dementia Rating-Sum of bones

## 5. Rejuvenation and Biologic Age Reversal

Aging elevates the risk of tissue degeneration and metabolic pathologies, perturbs molecular and cellular homeostasis, and leads to global and multiple loss of organ functions [11]. The United Nations reported that life expectancy for the world's population will reach approximately 77.1 years by 2050, and the number of people above the age of 80 is expected to triple from 143 million in 2019 to 426 million by 2022 [12]. Our aging world is projected to become socio-economically unsustainable. Thus, it becomes essential to better understand the process of aging and to translate experimentally proven rejuvenative strategies to the clinic. Aging is a universal process of physiological and molecular changes that are strongly associated with susceptibility to disease and ultimately death. Chronic inflammatory diseases have been recognized as the most significant cause of death in the world today [13]. More than 50% of all deaths are attributed to chronic inflammatory diseases including ischemic heart disease, stroke, cancer, type 2 diabetes, chronic kidney disease, non-alcoholic fatty liver disease (NAFLD) and autoimmune and neurodegenerative disorders. The biomarkers of inflammation are a predictor of morbidity and mortality in older individuals. Experiments in murine models of parabiosis have demonstrated that heterochronic blood sharing leads to multi-tissue rejuvenation [14]. Blood from an older mouse quickly ages a young mouse, suggesting a potent dominant inhibitory effect of pro-geronic factors over younger ones. This data is

counter to the intuitive idea that young blood and its factors could be injected into older individuals to make them younger, even in the presence of aged tissues and old circulatory milieu. Interestingly, our recent papers highlight broadly positive effects of old plasma dilution on tissue health and regeneration [3]. These studies suggest that simply the removal of pro-geronic factors rapidly and robustly rejuvenated multiple organs in aged mice and improves their cognition. After TPE in older humans, a number of clinical factors improve, and their serum is more supportive of progenitor cell proliferation, suggesting overall rejuvenation in humans, too [3].

An unexpected observation was that TPE not only caused a decrease of certain proteins, but also the increase of others, suggesting a profound regulatory capacity. The proteomics analysis suggests that TPE can influence the three basic physiologic mechanisms which contribute to the aging process; cellular senescence, immunosenescence and systemic chronic inflammation (inflammaging) (Figure 1). In addition, removing age-accumulated factors appears to abrogate their autoinduction. This could indirectly restore rejuvenative factors to more youthful levels, which were otherwise attenuated by the presence of inhibitory proteins. TPE using 5% albumin as a replacement fluid has been suggested as the human model of parabiosis [15]. Currently, a double-blind, placebo-controlled trial is evaluating the possible role of TPE for the attenuation of the aging processes. (Kiprov, et al).



**Figure 1:** Treating The Pathophysiology of Aging

## 6. Cellular Senescence and TPE

Cellular senescence is characterized by cell cycle arrest and activation of a hyper-secretory phenotype (senescence associated secretory phenotype (SASP). TPE effectively removes the pro-inflammatory factors of SASP [16].

## 7. Immuno senescence

Immuno senescence is characterized by phenotypic changes of immunomodulatory cells favoring autoimmunity and chronic inflammation. TPE has an effect of immunoregulatory cells [17].

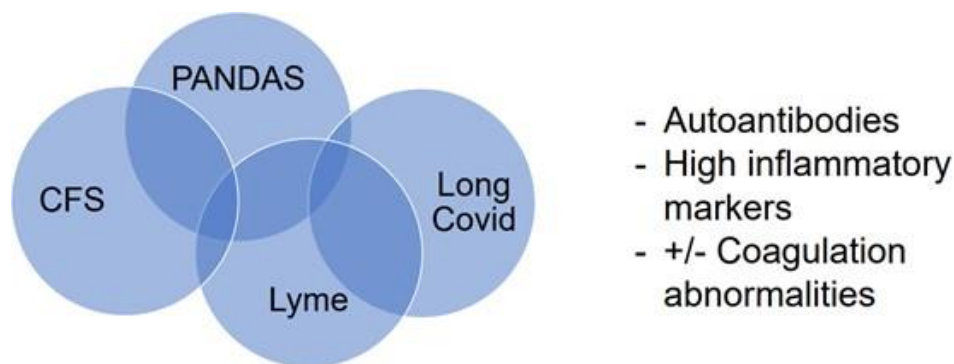
## 8. Systemic Chronic Inflammation (SCI) and TPE

Recent work extrapolates to humans the previous animal studies on blood heterochronicity and establishes a novel direct measurement of biological age. Our results support the hypothesis that, like mice, human aging is driven by age-imposed systemic molecular excess, the attenuation of which reverses biological age. The results on biological age are strongly supported by the data, which demonstrates that rounds of TPE promote a global shift to a younger systemic proteome, including youthfully restored pro-regenerative, anticancer, and apoptotic regulators and a youthful profile of myeloid/lymphoid markers in circulating cells, which have reduced cellular senescence and lowered DNA damage [3].

## 9. Long COVID (Post-acute sequelae of Covid-19, PASC)

Long Covid is a multi-system condition comprised of multiple, severe symptoms following an acute SARS-CoV-2 infection. At least 65 million individuals around the world have Long Covid. Many patients experience dozens of symptoms across multiple organ systems. Several hypotheses for its pathogenesis have been

proposed. Persistent reservoirs of SARS-CoV-2 in tissues and immune dysregulation and autoimmunity being on the top of the list [18]. The triggering of autoimmune conditions by viral infections is well known to the scientific community (Figure 2). Long Covid and Myalgic Encephalopathy/ Chronic Fatigue Syndrome (ME/CFS) share similar symptoms and circulatory neurotransmitter autoantibodies. The incidence of autoimmune disease is significantly increased after Covid-19 infection [19]. TPE is an effective treatment for a multitude of autoimmune conditions [2]. We treated 17 patients with Long Covid. All patients had multiple symptoms. Symptoms either persisted after Covid or occurred shortly after Covid infection. Patients presented for plasmapheresis at 1-24 months after acute Covid infection. All had taken a variety of medications and supplements including Paxlovid, Ivermectin, aspirin, prednisone and Decadron. Six patients had been on Maraviroc and statins as per published protocol. Two patients had HELP apheresis in Germany [20]. Ten of the patients had peripheral neuropathy [21]. Seven of those were biopsy-diagnosed small fiber polyneuropathy (SFP). The others were consistent with chronic inflammatory demyelinating polyneuropathy (CIDP). All patients complained of fatigue especially during exercise, brain fog and psychotic symptoms (anxiety, depression). All patients were tested with the Long Hauler Cytokine panel (Radiance Diagnostics). The panel consists of multiple cytokines and a Long Hauler Index which is calculated by artificial intelligence (AI) algorithms. Fourteen of the patients had elevated Long Hauler Index indicative of severe Long Covid [22]. Patients were also tested for neurotransmitter autoantibodies (Cunningham Panel) (Moleculera).

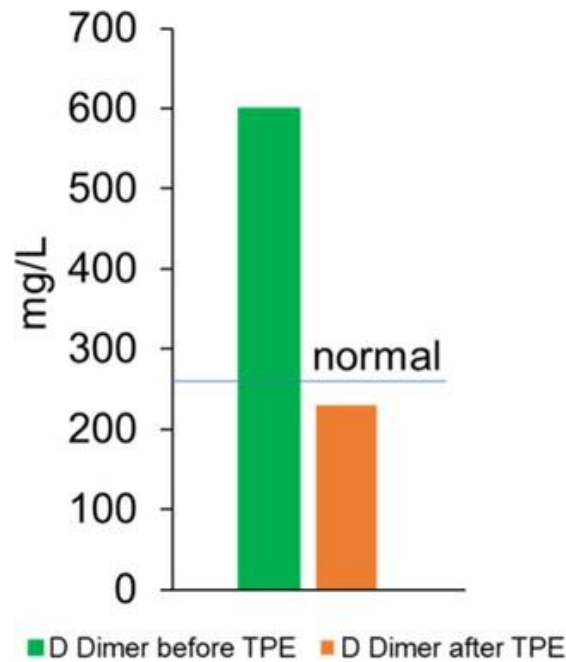


**Figure 2:** Post Infection Immune Dysregulation

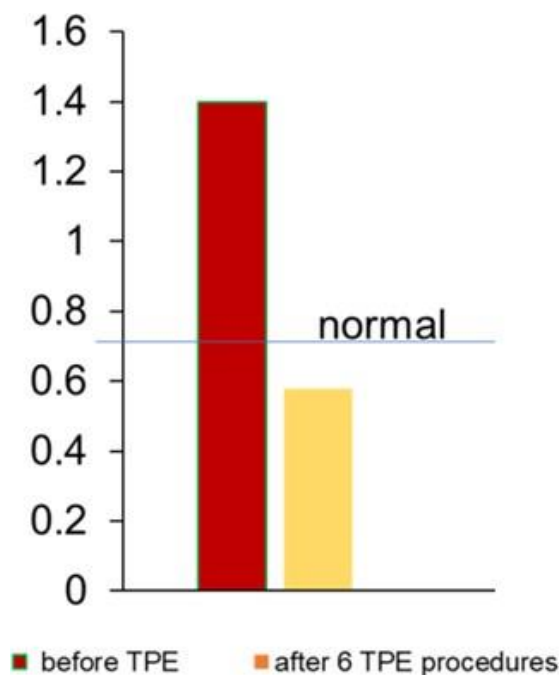
## 10. Results

Eleven (65%) of the 17 patients improved. Peripheral neuropathy improved in all responders, as did fatigue, stamina, and brain fog. However, anxiety, although diminished, persisted in most patients.

The risk of coagulopathy diminished (Figure 3). Blurred vision improved in patients who initially complained of it. The Long Hauler Index normalized in all responders (Figure 4). All responders who failed previous therapies improved in all categories. Neurotransmitter autoantibodies normalized [23].



**Figure 3:** D Dimer changes in a patient with coagulopathy



**Figure 4:** Long Haul Index in a patient with long COVID (Radiance Diagnostics)

**11. Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection (PANDAS)**

PANDAS is another condition that is the result of postinfectious autoimmunity mediated through cross-reactive antibodies produced against molecular “mimics” or epitopes on the GAS cells that resemble host antigens [24]. Removal of these autoantibodies with TPE should result in symptomatic improvement. A double-blind, randomized entry clinical trial compared five one-volume TPE

treatments (n=10) against 2 grams/Kg of IVIG infusions (n=9) or sham IVIG placebo [25]. The obsessive-compulsive symptoms were reduced in 65% in the TPE treatment group versus 42% in the IVIG group and 0% in the placebo group. The clinical improvement was maintained at 12 months indicating the long-lasting effect of TPE. We treated 7 patients with PANDAS over a period of 2 years. Patients were referred for TPE because they had severe symptoms with marked impairment of function at home, at school and with peers, and had not responded to treatment with antibiotics, corticosteroids, and high dose IVIG. In another study of TPE



in 35 severely ill patients with PANDAS, all patients were reported to have at least some benefit from TPE with long-lasting effect of 78% [26]. All patients presented with severe OCD (Obsessive Compulsive Disorder), tics, separation anxiety and sleep difficulties. Two of the patients were suicidal, one of the patients was urine incontinent, and one of the patients refused to eat or drink, requiring daily visits to the emergency room for IV fluid infusions and parenteral feeding. All patients underwent six, one-plasma volume TPE procedures over 2 weeks followed by monthly TPE procedures. All patients continued on high dose IVIG infusions the day after TPE. One of the patients who had mild to moderate symptoms showed a modest improvement. The severely affected patients showed progressive improvement at 6 – 12 months. The suicidal thoughts completely disappeared. The incontinent patient regained full bladder control. The patient who refused to eat and drink slowly, over several months, started to drink and eat and is currently attending college. At 6-12 months, all patients were functional and capable of going to school and college. Improvement of neurotransmitter antibodies was also observed.

## 12. Discussion

Our experience with plasmapheresis in Alzheimer's Disease and PANDAS presented here indicates that this treatment modality is a valuable option for many patients with these conditions. Further, large studies in Alzheimer's Disease are underway. (Ace Alzheimer's Center, Barcelona, Spain). Our observations [27] and the experience of others [28] although limited to small uncontrolled studies, raise the possible role of the use of plasmapheresis in the treatment of Long Covid. Further studies are needed to confirm these preliminary findings.

Although the primary mechanism of action of TPE is the removal of pathogenic substances from plasma, recent scientific advances indicate other possible mechanisms. There is strong evidence that TPE downregulates certain plasma proteins while it upregulates others. It also contributes to immunoregulation by affecting the ratio of T-helper and T-suppressor cells as well as causing changes in B-cells, NK-cells, and neutrophils. These findings are contributing to the use of TPE in more medical conditions, with or without pharmacologic agents. Large controlled clinical studies have demonstrated that TPE is a safe procedure in an outpatient setting when performed by experienced apheresis professionals. In the AMBAR study, we performed more than 4000 TPE procedures, observing adverse reactions, mostly mild, in only 10% of patients. The patients described here received cumulatively 1100 TPE procedures. There was only one, mild allergic reaction to albumin. There are a many medical conditions in addition to the ones described here that are good candidates for outpatient TPE, e.g., CIDP (Chronic Inflammatory Demyelinating Peripheral neuropathy), multiple sclerosis, focal segmental glomerular sclerosis (FSGS), to name a few. Although TPE appears to be an expensive medical procedure, avoiding the considerable cost of hospitaliza-

tion saves a significant amount of money in the overall cost of the medical care of patients suffering from these conditions. Our improved understanding of the mechanism of action of TPE opens the door to the expansion of its application from TPE being used as a "last resort" therapy, performed in an ICU setting, to the treatment of outpatients with many autoimmune diseases that do not respond to medications or experience adverse reactions to them. And the immunomodulatory abilities of TPE enable the possibility for intervention in new conditions, such as Long Covid and inflammaging.

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