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Plasma exchange therapy in the critically ill patient: A Narrative Review.

Tomas Rodríguez-Yánez [ID] [1], Amilkar Almanza [ID] [1, 2], Diana Borre-Naranjo [ID] [3], Carmelo Dueñas-Castell [ID] [4], Rodrigo Daza-Arnedo [ID] [5], Jorge Rico-Fontalvo [ID] [5,6].

1. Departamento de Medicina Interna, Medicina Crítica y Cuidados Intensivos, Clínica Gestión Salus y la Nuestra, Cartagena-Colombia.
2. Servicio de Medicina Interna, Grupo de Investigaación GRICIO, Cartagena-Colombia.
3. Departamento de Medicina Crítica y Cuidado Intensivo, Hospital Serena del Mar, Cartagena-Colombia.
4. Departamento de posgrado de Medicina Crítica y Cuidados Intensivos, Universidad de Cartagena, Colombia.
5. Asociación Colombiana de Nefrología e Hipertensión, Bogotá-Colombia.
6. Institución Prestadora de Servicios de Salud Nephromedicall, Medellín-Colombia.

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Abstract

Introducción: Plasmapheresis has been used with different levels of evidence in neurology, nephrology, and rheumatology. Management guidelines have evolved with the development of randomized clinical trials; However, the low prevalence of some conditions that can potentially benefit from this intervention is a limitation.

Objective of the review: This article is a narrative review that reviews the basic principles of plasma exchange therapy, establishes the levels of evidence, and identifies entities that may benefit from this treatment.

Essential points of the review:

In category I, the conditions are established where the therapy is first-line; in category II, plasmapheresis is the second treatment option; in category III, the optimal role has yet to be established; and in category IV, it is an ineffective treatment.

Among the category I renal indications are Goodpasture syndrome with diffuse alveolar hemorrhage, recurrent focal and segmental glomerulosclerosis in kidney transplant, vasculitis associated with ANCA, rapidly progressive, ABO incompatible kidney transplant.

Conclusion: Due to the lack of clinical studies, some pathologies remain with indications category II to IV. Due to the low prevalence and incidence in intensive care, the collective work of the scientific community is needed.

Keywords:

Plasma exchange, plasmapheresis, intensive care, clinical practice guidelines.

* Corresponding author

Email: Jorge Rico-Fontalvo < jorgericof@yahoo.com >/Address: IPS Nephromedicall. Race 43 #2934. Office 8. La Candelaria, Medellín, Antioquía, Colombia. CP 050012. Tel [57] 604-2329993.

Plasma exchange therapy is used in several life-threatening pathological conditions or debilitating diseases as adjuvant treatment or for the management of complementary therapies [1]. Plasmapheresis is derived from a Greek word that means removal by force. This technique was used for the first time in 1914 in an animal model case report and was described as an extracorporeal blood purification technique [2, 3]. In the 1970s, it was used to treat various medical conditions, and it was not until 1990 that a consensus on the main indications developed [3].

With different levels of evidence, plasma exchange has been used in treating various diseases, especially in neurology, hematology, nephrology, and rheumatology [4]. Management guidelines have evolved with the development of randomized clinical trials (RCTs) of greater methodological rigor; however, the low prevalence of some conditions that can potentially benefit from this intervention has limited the development of extensive studies to guide the precise scenarios for its use. This review is necessary because, in many of our countries in Latin America, nephrologists provide support for carrying out this therapy in critically ill patients.

Basic principles of plasma exchange therapy

Plasma exchange therapy is a procedure that consists of extracting a specific volume of plasma to remove higher molecular weight particles and pathogens and reduce circulating immune complexes (for example, IgG in myasthenia gravis (MG) and IgM in Waldestrom macroglobulinemia). To improve effectiveness, the substance to be extracted should ideally be identified to have its molecular weight, volume of distribution, and half-life; it is essential to be clear that the degree of removal of the particles is separate from the improvement of symptoms [5, 6].

The exact mechanisms by which plasma exchange generates its effects include eliminating pathogenic mediators found in the plasma, including autoantibodies, complement components, and cytokines [6]. The characteristics of the replacement fluid will depend on the type of disease.

The goal of plasma exchange depends mainly on the disease. Sometimes, the objective may be to reduce IgM levels to minimize plasma viscosity; in other pathologies, such as myasthenia gravis, the aim will be to achieve rapid clinical stabilization by eliminating acetylcholine receptor antibodies. In Guillain–Barré syndrome (GBS), the goal is to improve muscle strength and decrease the need for mechanical ventilation due to an ineffective muscle response in the intercostal muscles [6].

The most frequent scenarios in intensive care where plasma exchange therapy is valuable and essential are known. Neurological, hematological, and renal disease indications stand out; see Table 1 and Table 2.

Indications

In 2019, the American Society for Apheresis (ASFA) published the graded guidelines for therapeutic apheresis, and the previous categories for them will be maintained, as described in Table 3 [4]. Table 4 describes the indications and categories of the main pathological conditions that require plasma exchange in intensive care.

Main conditions requiring plasma exchange in intensive care

Guillain–Barré syndrome (GBS)

Guillain–Barré syndrome (GBS) is a common cause of flaccid paralysis worldwide [9]. This entity corresponds to an immune-mediated polyradiculoneuropathy of variable presentation, in which an autoimmune injury compromises the myelin of the peripheral nerves, usually preceded by an acute infectious or immune process [9, 10].

The treatment of GBS varies according to the clinical stage. Current recommendations suggest using intravenous immunoglobulin (IVIG) and plasma exchange. These have demonstrated similar effectiveness and improved functional outcomes with accelerated recovery without impacting disease progression or preventing extensive nerve damage. These treatments have comparable safety profiles and are associated with few adverse effects [9].

A meta-analysis of 6 RCTs with moderate-quality evidence in 649 participants compared plasma exchange therapy with supportive treatment. It was found that plasma exchange therapy was associated with a significant improvement in the recovery of patients in the intervention groups without an increase in adverse events or mortality [11]. Regarding the number of plasma exchange sessions, five is the most common indication in clinical practice [12]. The sequential use of IVIG therapy and plasma exchange is not recommended, with little support in this regard [13].

Consequently, and with the available evidence, the ASFA 2019 guidelines recommend using plasmapheresis in patients with severe Guillain–Barré syndrome, that is, those who may require mechanical ventilation with a level of evidence of 1-A [4].

Myasthenia gravis

Myasthenia gravis (MG) is a neuromuscular junction disorder characterized by the presence of autoantibodies against acetylcholine receptors (AChRs), muscle-specific kinase (MuSK), or lipoprotein-related protein 4 (LPR4) [14]. In 2019, the ASFA recommended plasma exchange in the acute phase of MG as a first-line treatment (Category I) with a grade IB recommendation with high-quality evidence and second-line therapy in chronic MG (Category II) with a 2B grade of recommendation with moderate quality. The rationale for using plasma exchange in MG is the rapid depletion of pathogenic

antibodies present in the plasma and, consequently, at the neuromuscular junction [4].

Plasma exchange therapy is indicated during different disease phases, including the myasthenic crisis, in the perioperative period for thymectomy, or as adjuvant therapy to immunotherapy [15]. Initially, immunomodulatory therapies were used to treat the crisis or acute phase of MG, mainly IVIG and plasma exchange therapy [15]. These strategies help manage acute exacerbations of the disease, but they have limitations in controlling chronic symptoms [14]. A recent systematic review and meta-analysis revealed that treating patients with immune-mediated MG with mycophenolate and immunoglobulin or plasma exchange is associated with positive outcomes [16].

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDIP)

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired autoimmune disorder of peripheral nerve and nerve root function in which there is an inflammatory response mediated by macrophages that involves more significant proximal segments than distal segments; these inflammatory infiltrates are adjacent to myelinated fibers [17].

A systematic review addressing the treatment of CIDP, including the use of steroids, IVIG, and plasma exchange therapy [18], found, with moderate quality evidence, that twice-weekly plasma exchange therapy produced short-term improvement in terms of disability compared with placebo. Regarding the rate of complications, information derived from observational studies revealed adverse events related to vascular access, the use of citrate, and hemodynamic changes in 3 to 17% of plasma exchange procedures [18].

Table 1. Considerations of plasma exchange therapy in neurological diseases

Disease	Replacement volume	Replacement fluid	Frequency
Autoimmune encephalitis	1–1.5 VP	Albumin	Interdiary
Multiple sclerosis	1–1.5 VP	Albumin	5-7 plasma exchanges for 14 days
Optic nueromyelitis	1–1.5 VP	Albumin	Daily or interday Every day or every other day
Polyradiculopathy demyelinating inflammatory chronicle .	1–1.5 VP	Albumin	2–3 times a week until improvement, then taper
Myasthenia gravis	1–1.5 VP	Albumin	Every day or every other day

PV: plasma volume.

Table 2. Considerations of plasma exchange therapy in hematological diseases [6].

Disease	Replacement volume	Replacement fluid	Frequency
Hyperviscosity syndrome (Hypergammaglobulinemia, Waldenstrom macroglobulinemia)	1–1.5 VP	Albumin or albumen/SS.	Daily until symptoms disappear (1 to 3 RP)
Syndrome antiphospholipid catastrophic	1–1.5 VP	Plasma (+/- albumin)	Daily or Interdaily until clinical response
Thrombocytopenic purpura thrombotic	1-1.5 VP	Plasma	Daily until platelet count is > 150x 10 9/l, Normalization of LDH. Hemolysis improvement
Vasculitis with diffuse alveolar hemorrhage - ANCA	1–1.5 VP	Plasma	Daily or Interdaily until the disease is controlled.
Complement-mediated thrombotic microangiopathy (atypical hemolytic uremic syndrome)	1–1.5 VP	Plasma	Daily until PTT is ruled out and biological therapy is started.
Autoimmune hemolytic anemia	1–1.5 VP	Albumin	Daily until the disease is controlled.

SS: Saline solution. PV: Plasma Volume.

Table 3. Categories of indications for plasmapheresis

I	Disorders for which apheresis is accepted as first-line treatment either as a stand-alone primary treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as a second line either as a stand-alone treatment or in conjunction with another mode of treatment.
III	The optimal role of apheresis therapy has not been established, decision making must be individualized.
IV	Disorders in which published evidence suggests that apheresis is ineffective or may be harmful.

Consequently, based on information from previous studies, the ASFA guidelines, updated in 2019, recommend three first-line therapies for CIDP: corticosteroids, IV immunoglobulin (IVIG), and plasma exchange. The initial treatment selection is based on availability, costs, and the possibility of starting early to prevent axonal degeneration and, thus, disability [4].

The CIDP management guidelines recommend the use of corticosteroids as first-line therapy and the alternative of using immunomodulatory therapy based on IVIG. This alternative is plasma exchange therapy. The working group of the European Guidelines strongly recommends plasma exchange therapy, suggesting an initial treatment of 5 exchanges over two weeks; after this stage, the exchange interval should be individualized [19].

Multiple sclerosis

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system. In MS, destruction of the myeloma sheath occurs with axonal degeneration and the death of neuronal cells [20].

An observational study involving 140 patients with steroid-refractory recurrent multiple sclerosis and neuromyelitis optica evaluated plasma exchange and immunoadsorption (IA). No significant differences were found regarding side effects (3.9% vs 3.6%, P = .96) or response rates (P = 0.65). From this work, it is essential to note that younger age and earlier initiation of apheresis were associated with a better response rate [21].

The 2019 guideline update, the ASFA recommends plasma exchange for treating acute exacerbations and relapses in category II level 1A patients. It has also been used in patients treated with natalizumab who develop progressive multifocal encephalopathy [4].

Hematological and renal

Thrombotic microangiopathy

Thrombotic microangiopathy (TMA) is a clinical syndrome characterized by the presence of microangiopathic hemolytic anemia (low hemoglobin, high reticulocytes, low haptoglobin, elevated lactic dehydrogenase (LDH), with detectable schistocytes in peripheral blood, and a negative Coombs test), peripheral thrombocytopenia (platelets <150,000/mm3 or decrease >30% from baseline) and injury to one or more organs in the absence of alternative diagnoses, mainly disseminated intravascular coagulation and antibody-mediated hemolytic anemia (normal fibrinogen levels, prothrombin time in the normal range) [22].

ASFA-derived indications for 2019 include category I thrombotic thrombocytopenic purpura, ticoplinide-associated thrombotic microangiopathy, factor H antibody complement-mediated thrombotic microangiopathy, category III clopidogrel-associated thrombotic microangiopathy, coagulation-mediated thrombotic microangiopathy (THBD, DGKE mutation, and PLG) complement-mediated thrombotic microangiopathy (complement mutation factor gene), sepsis-associated thrombotic microangiopathy, atypical uremic syndrome, category IV, and gemcitabine/kinine-associated thrombotic microangiopathy [4]. Some of these indications should be reviewed at length in Table 4.

Thrombotic thrombocytopenic purpura (TTP)

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening hematological disorder [23]. This condition may be caused by a severe inherited deficiency of plasma ADAMTS13 activity resulting from the ADAMTS13 mutation, termed inherited or congenital (<5% of cases). However, more frequently, TTP is acquired due to the presence of autoantibodies that inhibit the plasma activity of ADAMTS13, referred to as immune-mediated TTP (iTTP) (95% of cases) [24].

Patients with TTP present with thrombocytopenia, microangiopathic hemolytic anemia, and varying degrees of organ dysfunction or damage. Treatment of patients with immune-mediated TTP is based on therapeutic plasma exchange with corticosteroids, rituximab, and caplacizumab. Triple therapy (TPE, caplacizumab, and immunosuppressants) constitutes the standard of care for patients with confirmed or probable PTA [24]. Factors associated with treatment failure include delays in the initiation of plasma exchange, severely altered levels of consciousness, coma, and elevated creatinine levels [13].

An early clinical trial, which included 102 patients with TTP, randomized patients to receive plasma exchange therapy or infusion with fresh frozen plasma. Plasma exchange therapy reduced mortality (dead 2 vs 8, $P = 0.035$). In this work, plasma exchange improved short-term mortality, six-month mortality, and platelet count [25].

Daily plasma exchange therapy eliminates autoantibodies against ADAMTS13 while replacing the loss or inhibition of the ADAMTS13 enzyme from the exchange fluid's donor plasma [24]. Immunomodulatory treatment, which includes the early use of monoclonal antibodies such as rituximab or caplacizumab, can enhance the benefits of plasma exchange [24].

Hemolytic uremic syndrome (HUS)

The clinical characteristic of hemolytic uremic syndrome (HUS) is the triad of hemolytic anemia, thrombocytopenia, and renal failure. The leading cause in children is secondary toxin-mediated infection caused by *Escherichia coli* O157:H7, which causes severe episodes of diarrhea. In contrast, this infection is mainly related to genetic factors in adults. HUS can be divided into typical and atypical HUS [26]. The difference between PTT and SHUA lies in the ADAMTS13 plasma activity test. When plasma ADAMTS13 activity is greater than 10 IU/dL, the diagnosis of HUS should be considered after reasonable exercise to exclude secondary causes of TMA [24].

Table 4. Indications for plasmapheresis and category.

DISEASE	INDICATIONS	CATEGORY
Neurological		
Acute disseminated encephalitis	Refractory to corticosteroids	II
Guillain Barre syndrome	Primary treatment	I
Myasthenia gravis		
Chronic inflammatory demyelinating polyradiculoneuropathy		I
Multiple sclerosis		
methyl -D aspartate receptor antibodies		I
Syndromes for neurological neoplastics		III
Acquired chronic demyelinating polyneuropathies	IgG/IgA/IgM	I
Multiple sclerosis		
Optic nueromyelitis		
Eaton-Lambert syndrome		II
Hamatological		
Acute sickle cell anemia	Cerebral ischemia acute chest syndrome	I II
Nonacute sickle cell anemia	Prophylaxis of cerebral ischemia/Pregnancy Vaso-occlusive crisis	I II
Thrombocytosis	Symptomatic	II
Thrombotic microangiopathy	Mutation THBD, DGKE, PLG	III
Drug-associated thrombotic microangiopathy	Ticlopidine Clopidogrel	I III
Complement-associated thrombotic microangiopathy	Factor H antibody	I
thrombocytopenic purpura		I
Severe autoimmune hemolytic anemia	Severe agglutination	II
Severe antiphospholipid syndrome		I
Heparin-induced thrombocytopenia	Thrombosis	III
immune thrombocytopenia	Refractory to handling	III
Hyperviscosity in hypergammaglobulinemia	symptomatic	I
T-cell lymphoma .	Erythrodermic	II
Kidney		
Goodpasture syndrome	Diffuse alveolar hemorrhage	I
Focal segmental glomerulosclerosis	Recurrent in kidney transplant	I
IgA nephropathy	Half Moon	III
ANCA associated vasculitis	MPA/GPA/RLV: RPGN, Cr ≥ 5.7	I
Other vasculitis	Hepatitis B polyarteritis nodosa	II
Miscellaneous		
Patient with severe COVID-19	severe COVID	
Sepsis and multiple organ failure		III
Thyroid storm		II
Acute liver failure		I-III
Systemic amyloidosis	Related to dialysis	II
Hereditary hemochromatosis		I
Heart transplant	Cellular rejection Rejection prophylaxis	II II
Liver transplant	Living donor ABO desensitization	I
Lung transplant	Bronchiolitis obliterans syndrome	II
ABO compatible kidney transplant	Antibody-mediated rejection Living donor desensitization	I I
ABO incompatible kidney transplant	Living donor desensitization Antibody-mediated rejection	I II
Thyroid storm		II
HELLP syndrome	Postpartum Before birth	III IV
Versus host disease	Acute	II
Toxic epidermal necrolysis	Refractory	III
Familial hypercholesterolemia	homozygous	I
Pancreatitis due to hypertriglyceridemia	Severe	III
Inflammatory bowel disease	Ulcerative colitis	III
Hereditary hemochromatosis		I

All presentations of HUSs share endothelial lesions that lead to TMA. In the case of typical HUS, it is secondary to *Escherichia coli* O157:H7 infections. Other related etiologies include *Streptococcus pneumoniae* infections. In this variant of HUS, the benefit of plasma exchange is uncertain, with some experiences being reported in series and isolated case reports. In a multicenter, retrospective, case-control study of 23 hospitals in northern Germany with a population of 298 patients with typical HUS [27], no clear benefit was found from using plasma exchange alone or in combination with steroids. Some benefits were associated with the use of the antibiotic and monoclonal antibody eculizumab [24]. The evidence for plasma exchange therapy in patients with typical HUS is limited; according to the ASFA 2019 recommendations, HUS is classified as category IV [4].

Atypical HUS (aHUS) is a rare disease resulting from deregulating the alternative complement pathway on the cell surface, resulting in endothelial dysfunction [28, 29]. Patients with aHUS benefit from complement-oriented therapeutic indications, which include eculizumab and anti-C5 monoclonal antibodies. In this case, plasma exchange eliminates sizeable molecular weight substances, such as harmful factor H antibodies, in plasma. The effectiveness of plasma exchange in clinical trials has yet to be established. Its use is likely to eliminate active growth factors, which, in theory, would be beneficial. The ASFA in 2013 included aHUS as category II, and the 2019 update included aHUS as category III and category I when mediated by the H antibody [4].

Catastrophic antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an autoimmune disease with cardinal manifestations, including thrombotic events and recurrent abortions. This systemic disease is associated with cytopenias, cognitive dysfunction, heart valve disease, kidney failure, and skin ulcers. Patients with APS present circulating antiphospholipid antibodies, including anticardiolipin immunoglobulin (Ig)G or IgM, anti-B2 glycoprotein (anti-b2GPI) IgG or IgM, or lupus anticoagulant, which must also remain detectable in controls on a long-term basis [30].

On the other hand, catastrophic antiphospholipid syndrome (CAPS) is a subentity associated with severe acute pancreatitis (SAP) that threatens life, resulting in multiple organ dysfunction and a mortality rate of approximately 50%. The pathophysiological mechanisms involve the presence of thrombosis due to the presence of autoantibodies that cause platelet activation and endothelial dysfunction [31].

The optimal therapy for this condition is unknown, and different alternatives have been proposed, including plasma exchange therapy, which has shown some usefulness [32]. Because it is rare, formal clinical trials are limited; consequently, the available evidence is derived from case series and observational studies [33].

Plasma exchange has proven helpful in different types of microangiopathy. The role of antiphospholipid antibodies in the pathogenesis of cASF raises the possibility of using plasma exchange therapy as a potential therapeutic option for cASF. A retrospective analysis of a series of 250 patients, with a recovery rate of 56%, estimated that the survival rate of patients treated with combined therapy with anticoagulants, corticosteroids, and plasma exchange was 77.8%, followed by that of patients treated with anticoagulants, corticosteroids, plasma exchange and the possibility of adding IVIG, with a survival rate of 69% [34]. In another case series involving 21 patients with cAPS who received standard treatment associated with plasma exchange, 16 patients achieved complete remission, and 3 achieved partial remission [32].

In a multicenter observational study that evaluated the admission of patients with APS to intensive care, within the therapeutic indications, the use of systemic anticoagulation was the only factor associated with a reduction in mortality, with an HR of 0.1 (95% CI [0.03-0.3], P <0.0001). Double therapy (corticosteroids + anticoagulant, 0.2 [0.07-0.6]; P = 0.005), which is associated with an improvement in survival in patients with definite/probable catastrophic APS, would be directed primarily by the benefits derived from the use of systemic anticoagulation. Regarding triple therapy (corticosteroids + anticoagulant + IV immunoglobulins or plasma exchange immunoglobulins or plasma exchange: HR 0.3, 95% CI [0.1-1.1]; P = 0.07), a trend toward improvement in survival was observed, suggesting that there would be a subpopulation of patients with CAPS who would potentially benefit more significantly from this therapy [35].

Finally, in most reported cases, fresh frozen plasma has been used as plasma exchange fluid in a low albumin proportion. The benefits of plasma would be related to the contribution of antithrombotic factors, which would benefit the patient [36]. Plasma exchange could also be a rescue therapy in patients who fail initial treatment with steroids, anticoagulation agents, and IVIG [31]. The evidence regarding the use of plasma exchange therapy in CAPS is limited and, in many cases, indirect; its use is suggested according to the availability and local experience of the treating physicians until more rigorous methodological studies are available to clarify its indications.

Multiple myeloma

In patients with multiple myeloma (MM), plasma exchange therapy is generally considered for patients with hyperviscosity syndrome, neuropathy, or high concentrations of free light chains to prevent kidney injury associated with their deposition [37]. The latter is frequent, occurring in approximately 30% of these patients with some degree of compromise in renal function, and a nonnegligible number of patients will end up receiving renal replacement therapy [37].

Among the most frequent causes of acute kidney injury in patients with MM is the excessive production of monoclonal light chains with nephrotoxic effects, as these elements precipitate at the level of the distal renal and collecting tubules. Adequate treatment accompanied by supportive measures is associated with reversing renal involvement in 25% to 58% of patients [38]. Reducing light chain concentrations in patients with MM is associated with recovery and improvement in renal function [39]. A retrospective study, which analyzed 24 months of follow-up of patients with MM and acute kidney injury treated with plasma exchange therapy and chemotherapy or bortezomib, showed a reduction in light chain concentrations and an

increase in survival compared to those treated alone with bortezomib [38]. However, the availability of increasingly effective and accessible strategies for the treatment of patients with MM has limited their use within the first lines of treatment, especially for patients with hyperviscosity syndrome. In summary, more studies are required in this regard [37].

Rapidly progressive glomerulonephritis

Rapidly progressive glomerulonephritis (RPGN) corresponds to a set of clinical entities characterized by deterioration in kidney function that evolves in a matter of days to weeks, which, if it follows its natural course, leads to end-stage renal failure in most patients.

Within this group of diseases, patients with IgA nephropathy (IgAN), including Henoch-Schönlein purpura nephritis (HSP), who present with RPGN, have a poor prognosis despite receiving aggressive immunosuppressive treatment. The usefulness of plasma exchange therapy is questioned. A recently published systematic review, which included 29 reports and 9 case series in which 3 to 18 sessions of plasma exchange therapy were used, revealed that the response rate was variable but generally between 40 and 70% according to the group of patients evaluated. However, they are low-quality observational studies. Clinical trials are also needed that offer the possibility of establishing precise plasma exchange therapy protocols for this group of patients [40].

Consequently, additional studies are necessary to clarify protocols and indications for renal replacement therapies in patients with PRGN.

Miscellaneous

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis

Vasculitis is a heterogeneous group of diseases with an autoimmune substrate. The category of ANCA-associated vasculitis includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and granulomatosis eosinophilia with polyangiitis (EGPA) [41].

First-line treatment strategies for MPA and GPA after diagnosis and evaluation of organ involvement include the use of glucocorticoids and cyclophosphamide as standard therapies for inducing remission. Other alternatives, depending on the severity and state of the disease, include monoclonal antibodies such as rituximab, methotrexate, or mycophenolate mofetil, the latter in the absence of organ dysfunction or minimal renal involvement [41]. Plasma exchange is an alternative for patients with severe renal involvement and a high probability of adverse events.

In 2007, a randomized clinical trial of 137 patients who evaluated the use of plasma exchange therapy against high doses of methylprednisolone in patients with ANCA-associated vasculitis and severe renal impairment (creatinine >5.8 mg/dL) was conducted. At three months of follow-up, 33 (49%) of the 67 patients who were treated with IV methylprednisolone and 48 (69%) of the 70 patients who were treated with plasmapheresis were alive and without dialysis treatment (the 95% confidence interval for the difference was 18 to 35%; P = 0.02). However, there were no differences in survival or adverse effects [42].

A subsequent meta-analysis included nine clinical studies with a population of 387 patients. An RR of 0.80 was identified for end-stage renal disease or death in patients treated with plasma exchange compared with patients treated with standard therapy (95% CI, 0.65-0.99; P = 0.04). A statistically significant difference in protection against end-stage renal disease was 0.64 (95% CI, 0.47-0.88; P = 0.006), while a significant difference in mortality was 1.01 (95% CI, 0.71-1.4; P = 0.9) [43]. the PEXIVAS study, rethinking this therapeutic indication.

In the PEXIVAS study, a randomized clinical trial with a two-by-two factorial design evaluated the use of plasma exchange therapy and two oral glucocorticoid regimens in patients with severe ANCA-associated vasculitis, defined as an estimated glomerular filtration rate of <50 mL./minute/1.73 m² body surface or diffuse alveolar hemorrhage. There were 100/352 patients (28.4%) in the intervention group and 109/352 patients (31.06%) in the control group, with a hazard ratio of 0.86 (95% CI 0.65 to 1.13; P=0.27). No differences were found in the presence of end-stage renal disease (27.9% vs. 25.5%) between the intervention and control groups. In general, plasma exchange therapy did not offer additional benefits compared to glucocorticoid-based therapy; additionally, the low-dose regimen was shown to be non-inferior to conventional treatments [44].

The recommendations of the primary management guidelines have been updated according to the results of the PEXIVAS study. The updates to the ASFA guidelines, considering biopsy-proven RPGN with acute glomerular inflammation and fibrinoid necrosis, crescents, minimal fibrosis (chronic damage), and a fulminant clinical course (Cr ≥5.7 mg/dL or DAH), suggest the immediate initiation of multimodal immunosuppression, which includes plasma exchange therapy to prevent irreversible changes [45].

On the other hand, the recommendations of the American College of Rheumatology (ACR)/Vasculitis Foundation do not recommend the use of plasma exchange for all patients with active glomerulonephritis, favoring its use in the treatment of patients with a greater risk of progression to disease end-stage renal disease (ESRD) [46]. Currently, the role of plasma exchange therapy in patients with ANCA-associated vasculitis is controversial and is becoming increasingly precise.

Acute liver failure

Acute liver failure (ALF) corresponds to an acute episode of liver dysfunction. NAFLD is a clinical condition characterized by an abnormality in liver function blood tests in an individual without underlying chronic liver disease. The most common causes are paracetamol toxicity and viral hepatitis; other causes include the ingestion of toxins, hepatotoxic drugs, autoimmune hepatitis, and sepsis, among others. It is associated with high mortality, between 50-90%, due to alterations such as hepatic encephalopathy and severe coagulopathy [47, 48].

Initial evidence for the use of plasma exchange in patients with liver failure has been derived from case series and cohort studies [49]. Work with greater methodological rigor began in 2016 [50]. This intervention has been shown to reduce the levels of inflammatory cytokines and improve the hemodynamic profile and transplant-free survival time in patients with ALF [49].

During this stage, a prospective, randomized, controlled, multicenter study assigned 182 patients with ALF to receive standard medical therapy (90 patients) versus standard medical therapy plus high-volume plasma exchange (HVP) (92 patients). Within the study population, standard medical treatment plus HVP was associated with in-hospital survival of 58.7% versus 47.8% in the standard treatment group. Additionally, HVP was associated with increased transplant-free survival time (HR 0.56; 95% CI 0.36 – 0.86; P =0.0083). These benefits are related to attenuating the innate immune response and improving multiorgan dysfunction [51].

A retrospective analysis of 32 ALF patients awaiting liver transplantation was recently published [52]. In this work, an improvement after HVP was demonstrated, which included coagulopathy (INR, 4.46 [2.32-6.02] vs. 1.48 [1.33-1.76], P < 0.05), total bilirubin (22.6 [9.1-26.4] vs 8.9 [5.6-11.3], P < 0.05), alanine aminotransferase (506 [341-1963] vs 120 [88-315], P <0.05), and ammonium levels (130.6 [123.7-143.8] vs 98.2 [84.2-116.5], P <0.05). Survival improvement was also achieved in the intervention group (94% vs 69%, P =0.068). Overall, this therapeutic strategy was associated with favorable outcomes [52].

Regarding the support for the use of plasma exchange therapy in patients with ALF, significantly elevated levels of cytokines (TNF-alpha, IL-10, IL-2, IL-4, and IFN-Y) have been reported compared to those in healthy subjects. These can be purified using plasmapheresis, in addition to the benefits already mentioned in improving the hemodynamic profile [49]. On the other hand, the required plasma exchange volume is generally between 1.0 and 1.5 times the patient's estimated plasma volume [49].

According to the management guidelines published by the ASFA in 2019, HVP has been recommended as a first-line treatment for ALF and fulminant Wilson's disease [4]. As a first measure in the case of ALF, the use of daily HVP is recommended, and the possibility of daily treatment is evaluated until liver transplantation or liver recovery is recommended [49]. For patients with fulminant Wilson's disease, the recommendation is daily plasma exchange until transplantation or liver recovery [4, 49]. These recommendations have been endorsed in previously published guidelines, although they are less specific than those developed by the ASFA guidelines [48, 53].

Sepsis and multiple organ dysfunction

Sepsis and septic shock are conditions associated with high morbidity and mortality in critically ill patients. Therefore, identifying strategies aimed at reducing the impact of multiple organ dysfunction and mortality is desirable. Among these alternatives, extracorporeal blood purification techniques have been evaluated, with different levels of evidence about cytokine clearance, vasopressor-sparing effects, and mortality reduction [54]. Blood purification modalities include high-volume hemofiltration/dialysis with or without high-cutoff filters as well as hemoabsorption techniques (including CytoSorb and polymyxin-B filters), as well as plasma exchange, the latter offering the possibility of replacing the protective factors and those consumed by the individual [54].

A meta-analysis that included 37 clinical trials with a population of 2,499 patients evaluated the impact of different extracorporeal blood purification therapies. Very low-quality evidence suggested a reduction in mortality associated with plasma exchange therapy (relative risk = 0.63 [95% CI, 0.42 to 0.96], P = 0.03, very low certainty of the evidence). These studies underscore the need to carry out studies with greater methodological rigor aimed at identifying the inflammatory phenotypes of sepsis, which could benefit from these therapies [55].

However, a recently published meta-analysis with different blood purification techniques identified 38 RCTs with 2729 patients. This work included a few patients requiring plasma exchange therapy (n=106). The available information does not suggest benefits from this type of therapy in patients with sepsis [56].

The ASFA recommendation for 2019 in patients with sepsis and multiple organ failure for plasmapheresis is category III [4]. Currently, we do not have clinical trials with adequate methodology to evaluate the real impact of this type of therapy in patients with sepsis and septic shock.

HELLP

Hemolytic anemia, elevated liver enzymes, and low platelet count (HELLP) syndrome is a clinical condition that occurs in pregnant and postpartum women, generally between 27 and 36 weeks of pregnancy, but can develop up to 6 weeks after delivery. It is characterized by microangiopathic hemolytic anemia, increased liver enzyme levels, and thrombocytopenia [57– 59]. It is believed to be caused by endothelial cell injury, vasospasm, platelet activation, altered prostacyclin/thromboxane balance, and decreased release of endothelium-derived relaxing factor [60, 61].

HELLP syndrome has historically been considered a severe complication of preeclampsia, the treatment of which consists of immediate stabilization of the pregnant woman with anticonvulsant prophylaxis with magnesium sulfate, reduction of blood pressure with antihypertensive medications, controlled volume expansion, in addition to control of coagulation disorders, and immediate delivery in cases of severe preeclampsia [62].

For this reason, treatment for HELLP syndrome is similar to that used for the management of severe preeclampsia [59, 63, 64]. Plasma exchange therapy is a therapeutic alternative for patients who have not responded to postpartum treatment and supportive therapy within 24 to 72 hours of diagnosis. This procedure can replace a patient's plasma with plasma from a donor and remove harmful particles from the blood circulation [65, 66].

There are no randomized controlled trials of plasma exchange in this setting; the evidence is derived from case reports.

Conclusions

Plasma exchange therapy is a procedure used as an adjuvant treatment to other therapies for various pathological conditions, many of which are life-threatening. We are making progress in understanding the indications for its use, which are given by the level of evidence that clinical studies have supported this therapy. Patients in critical care are an essential part of their indications, which may be due to various pathological conditions, primarily neurological, hematological, renal, and other diseases. It is necessary to become familiar with this therapy, and we hope to grow with more evidence, given that in several pathologies, there needs to be more information available.

Abbreviations

ACR (American College of Rheumatology).
ASFA (American Society for Apheresis).
RCTs (randomized clinical trials).
ALF (acute liver failure).
MG (Myasthenia Gravis).
IgM (Immunoglobulin M).
TMA (thrombotic microangiopathy).
MM (multiple myeloma).
Thrombotic thrombocytopenic purpura (TTP).
Guillain–Barré syndrome (GBS).
APS (antiphospholipid syndrome).
Hemolytic uremic syndrome (HUS)

Supplementary information

The supplementary materials have yet to be provided.

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Contributions of authors

Tomas Rodríguez-Yánez, Conceptualization, Methodology, Writing – Original draft.
Amilkar Almanza: Conceptualization, methodology, Writing – Original draft.
Diana Borre-Naranjo: Conceptualization, visualization, validation, writing-review and editing, formal analysis.
Carmelo Dueñas-Castell: Conceptualization, visualization, validation, writing-review and editing, formal analysis.
Rodrigo Daza-Arnedo: Conceptualization, project administration, supervision, validation, visualization, writing – review and editing.
Jorge Rico-Fontalvo: Conceptualization, project administration, supervision, validation, visualization, writing – review and editing.
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The authors declare no conflicts of interest.

Author information

-**Tomas Rodríguez-Yánez,** Internal medicine, critical medicine and intensive care, Health management clinic and La Nuestra. Cartagena. Colombia.

ORCID https://orcid.org/0000-0001-9251-9376

-**Amilkar Almanza,** Internal medicine, critical medicine and intensive care, Health management clinic and La Nuestra. Cartagena. Colombia. Internist. GRICIO research group. Cartagena. Colombia.

ORCID https://orcid.org/0000-0002-0222-2403

-**Diana Borre-Naranjo,** Intensivist. Coordinator of the Critical Medicine and Intensive Care Department at the Serena del Mar Hospital, Cartagena. Colombia.

ORCID https://orcid.org/0000-0003-0329-8909

-**Carmelo Dueñas-Castell,** Pulmonologist Intensivist, Postgraduate Coordinator of Critical Medicine and Intensive Care, University of Cartagena, Colombia.

ORCID https://orcid.org/0000-0001-5699-8904

-**Rodrigo Daza-Arnedo,** Nephrologist. Colombian Association of Nephrology and HTA. Bogota. Colombia.

ORCID https://orcid.org/0000-0002-6295-4972

-**Jorge Rico-Fontalvo.** Nephrologist. Colombian Association of Nephrology and HTA. Bogota. Colombia. Nephrologist. IPS Nephromedicall. Medellin. Colombia.

ORCID https://orcid.org/0000-0002-2852-1241

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