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Therapeutic Plasmapheresis: Indications and Clinical Outcomes

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Abstract

Therapeutic plasma exchange is a procedure that involves separating plasma from the cellular components. The plasma that is taken out is discarded and swapped with a solution that includes both crystalloid and colloid components or fresh frozen plasma also.[1] Therapeutic plasmapheresis (TP) is used to treat autoimmune diseases, certain poisonings, and any other conditions where there is a need to rapidly eliminate toxins from the bloodstream. The most important part of plasmapheresis is separation plasma and exchange with plasma of donors. The change of action of the immune system is secondary. During the process, large amounts of plasma can be replaced without putting too much strain on the circulation.[2] This review provides us with information about plasmapheresis, comprehensive examination of its methods, indications, and effects within hematological disorders. It explores potential future directions for the development of plasmapheresis, shedding light on emerging trends and innovations in the field. The article provides a brief analysis of the advantages and disadvantages associated with the use of plasmapheresis. It also compares plasmapheresis to commonly employed treatment methods for a specific disease entity.

Keywords: plasmapheresis, therapeutic plasma exchange, TPE, protein disorders, autoimmune disorders, bleeding disorders, thrombotic microangiopathies, TMA

1.Introduction

Therapeutic plasma exchange (TPE), also known as plasmapheresis, is a medical procedure where blood or plasma undergoes separation, extraction, and substitution with a colloidal solution containing albumin and/or donor plasma. The objective is to effectively eliminate a pathological entity. Volumes of plasma, typically ranging from 1 to 1.5 liters, are exchanged to eliminate dysfunctional cells, immune complexes,autoantibodies, cellular byproducts, toxins, parasites or bacteria.[3]

Plasmapheresis is employed in the management of diverse life-threatening and debilitating diseases, serving as a primary treatment method or in conjunction with other therapeutic approaches.[1]

In 2023, the American Society for Apheresis (ASFA) published the ninth edition of scientific evidence regarding the indications for therapeutic apheresis and issued comprehensive guidelines. Seventy-seven diseases and 119 indications for therapeutic plasma exchange were highlighted. The list comprises 20 instances where TPE is designated as a first-line treatment (ASFA category I) and 23 cases where TPE is identified as a second-line treatment (ASFA category II) for various diseases.

Plasmapheresis finds application in a spectrum of medical domains, including neurological disorders, hematological disorders, renal disorders, hepatic disorders, transplantation-associated complications, and other systemic conditions. Specific hematological emergencies necessitate the infusion of plasma and cryoprecipitate to reinstate coagulation factors and normal coagulation function.[4]

The article will discuss the mechanisms, limitations, and complications of therapeutic plasma exchange. It will specifically focus on the indications and treatment effects for certain hematological diseases, including protein disorders, autoimmune disorders, bleeding disorders, and thrombotic microangiopathies, using plasmapheresis.

2. Mechanisms of the Therapeutic Plasma Exchange

Plasma exchange stands as the oldest and most extensively used apheretic technique, owing to its straightforward execution. As a nonselective method, it indiscriminately removes all components of plasma.[2]

In the course of a Therapeutic Plasma Exchange (TPE) session, the patient's blood is collected from either a peripheral or central access site and directed into the apheresis system. Two primary techniques are employed for TPE: centrifugal separation and membrane separation.[4]

In the process of centrifugal therapeutic plasma exchange, a continuous extracorporeal circuit is established, connecting the patient to the centrifuge and then back to the patient. To prevent coagulation, citrate, an anticoagulant, is introduced into the blood flow at a rate of 10-150 ml/min. The centrifugal forces come into play, separating and filtering plasma from the denser components of blood, including white and red cells. Subsequently, a replacement fluid

containing albumin and/or fresh frozen plasma is reintegrated with the blood, and the combined mixture is returned to the patient.

Throughout membrane therapeutic plasma exchange, a continuous extracorporeal circuit is created, connecting the patient to the filter-membrane and subsequently returning to the patient. To prevent clotting and ensure the smooth flow of blood, heparin, serving as an anticoagulant, is introduced into the bloodstream. The membrane's ultrafiltration properties, influenced by the pore size and distribution, play a pivotal role in the separation and filtration of plasma from the denser components of blood, such as white and red cells.

In this process, a replacement fluid, comprising albumin and/or fresh frozen plasma, is meticulously reintegrated with the filtered blood. The amalgamated mixture is then returned to the patient through the extracorporeal circuit.[3]

While the membrane separation technique is quite popular in Japan and Germany, in the United States, it is used less frequently compared to centrifugal plasma exchange, despite gaining some popularity.

Centrifugal plasma separation is commonly used by pathologists, transfusion medicine experts, and nephrologists. On the other hand, the membrane separation of plasma, achieved through a filtration device, bears a strong resemblance to hemofiltration or ultrafiltration carried out with a dialysis machine. Consequently, this method is primarily conducted by nephrologists.

In the intensive care unit (ICU) plasmapheresis plays a pivotal role in fast eliminating harmful antibodies, inflammatory factors from the bloodstream and immune complexes. The challenges include possible worsening of the hemodynamics, electrolyte imbalances, coagulopathies, and infection risks.

The majority of the plasmapheresis methods use albumin replacement to ensure less immunogenicity and enhance overall safety. Specific hematological emergencies necessitate the infusion of plasma and cryoprecipitate to reestablish normal coagulation function by replenishing essential coagulation factors. Some of these examples are thrombotic microangiopathy (TMA) with factor H autoantibody, thrombotic thrombocytopenic purpura (TTP), drug-induced TMA, and diffuse alveolar hemorrhage (DAH) associated with ANCA vasculitis.[4]

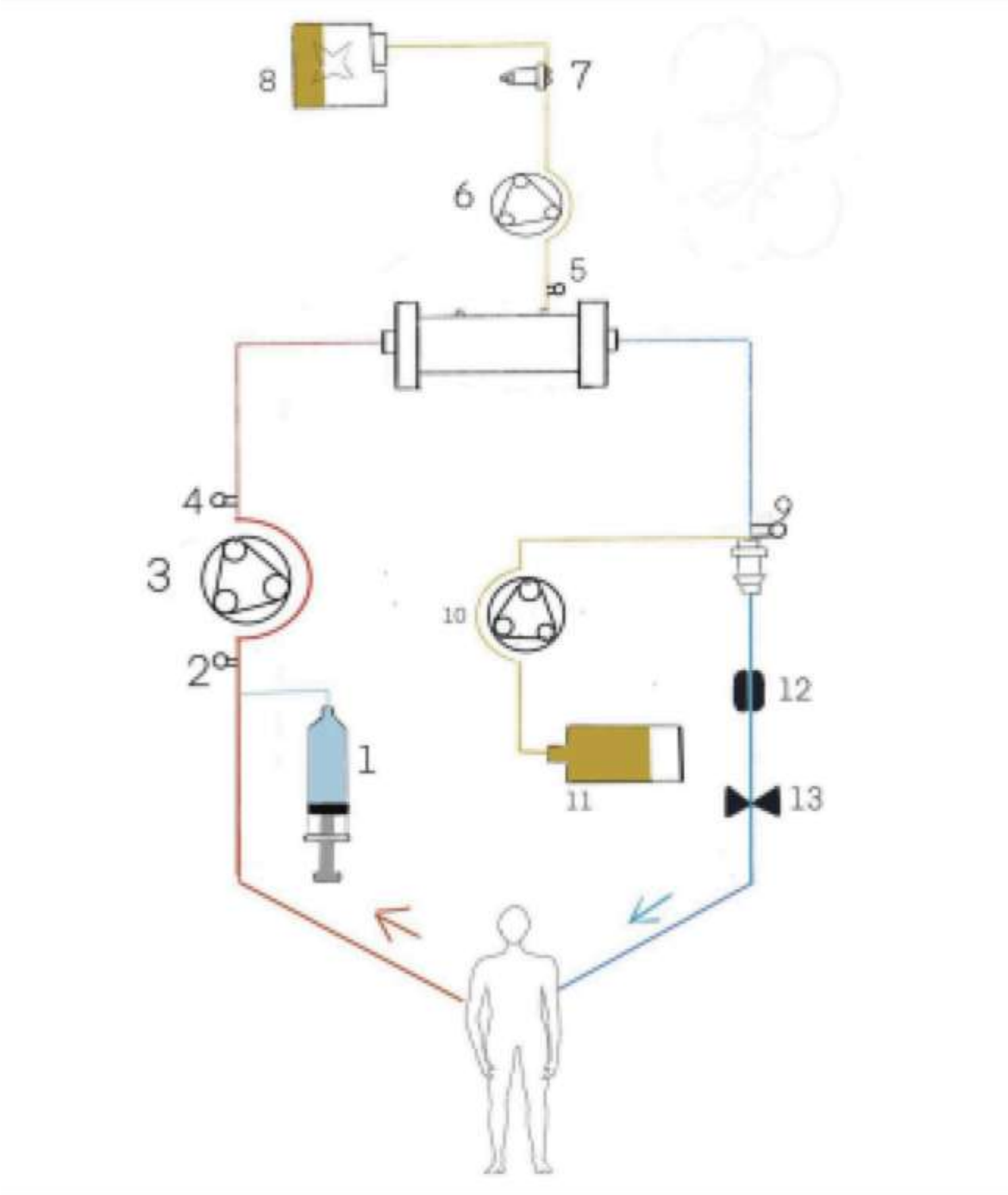

Figure. 1. Mechanisms of the Therapeutic Plasma Exchange scheme:

1. Anticoagulant pump 2. Arterial pressure sensor 3. Blood pump 4. Pro-filter pressure sensor 5. UF pressure sensor 6. UF pump 7. Blood leak detector 8. UF container 9. Venous pressure sensor 10. Replacement pump 11. Replacement bag 12. Air detector 13. Clam

3. Limitations and Complications

Plasmapheresis is adaptable to various settings, including intensive care units, specialized apheresis centers and hospitals. However, executing plasmapheresis in intensive care units presents unique challenges, mainly due to the hemodynamic instability commonly observed in ICU patients.

The type of plasmapheresis impacts the outcome. The effectiveness of plasmapheresis also depends on the expertise of the therapeutic team and the gravity of the treated disease. Plasmapheresis is typically contemplated in critical scenarios, especially when there is a risk of irreversible organ damage or imminent mortality without immediate intervention. Initiating plasmapheresis requires careful consideration of timing. Typically, patients are considered for plasmapheresis after undergoing initial medical treatment that yielded an insufficient response or resulted in worsening symptoms. As a precaution, it is recommended to administer medications after the completion of the plasmapheresis procedure.[3]

Although the incidence of complications from TPE is low, they can occur at various stages, such as due to the primary disease, the dosage of anticoagulants and the choice, the type of replacement fluid, the choice of vascular access and the specific plasmapheresis method used.[5] Patients experiencing hemodynamic instability, septicemia, or those with a history of prior anaphylactic reactions to components like FFP, albumin, or heparin should steer clear of plasmapheresis.[3] Among all patients undergoing TPE, those with anti-NMDA receptor encephalitis have the highest risk of complications.[5] To prevent potential complications, continuous monitoring, and the judicious replacement of fluids and electrolytes are necessary. It is crucial to prevent hypotension during plasmapheresis. Administering FFP or albumin-based fluid is recommended to counteract the filtration of the transfused proteins.

Therapeutic plasma exchange can further cause hypotension or electrolyte imbalance, most notably hypocalcemia and hypokalemia, which may result in cardiac arrhythmias.[4] Another common complication includes thromboembolism,hemorrhage and death from the procedure itself with anaphylactic, allergic or hemolytic reaction, which occurs more likely from plasma or blood transfusion.[3]

Moreover, plasmapheresis, as an invasive procedure, requires a central venous catheter. The possibility of hospital-acquired infections is ever-present.

Plasmapheresis also requires specialized equipment and trained healthcare personnel, which adds to the cost of the procedure.[4]

Table 1. Indications for therapeutic plasmapheresis.

Indications	Plasma exchange type	Category
IMMUNOLOGICAL DISORDERS		
Myasthenia		
Short-term treatment of the acute form	WO, IA	I
Long-term treatment		
Guillain-Barré syndrome	WO, IA	I
Hashimoto's encephalopathy	WO	II
Acute Disseminated Encephalomyelitis	WO	II
METABOLIC DISORDERS		
Familial hypercholesterolemia		
Homozygotes	LA	I
Heterozygotes	LA	II
Homozygotes/Heterozygotes	TPE	II
Acute Liver Failure	TPE-HV	I
	TPE	III
Refsum's Disease	TPE, LA	II
Wilson's Disease	TPE	I
Thyroid storm	TPE	II
Atherosclerosis of the lower extremities	LA	II

Table 2. Indications for therapeutic plasmapheresis (cont.).

TOXICOLOGICAL DISORDERS		
Mushroom poisoning	TPE	II
Drug overdose	TPE	III
Envenomation	TPE	III
AUTOIMMUNE DISORDERS		
Kidney transplantation: ABO blood group incompatibility	TPE, IA	
Desensitization, living donor		I
Humoral rejection		II
Kidney transplantation: ABO blood group compatibility	TPE, IA	
Antibody-dependent rejection		I
Desensitization, living donor		I
Hematopoietic stem cell transplantation: ABO blood group incompatibility	TPE	II
Heart transplantation: desensitization	TPE	II
Liver transplantation: ABO blood group incompatibility (desensitization, living donor)	TPE	I
Catastrophic Antiphospholipid Syndrome (CAPS)	TPE	I
Acquired Hemophilia A (AHA)	TPE, IA	III
Autoimmune Hemolytic Anemia, severe (AIHA)	TPE	
Severe cold agglutinin disease		II
Severe warm autoimmune		III

Table 3. Indications for therapeutic plasmapheresis(cont.).

PROTEIN DISORDERS		
Waldenstrom Macroglobulinemia – Hyperviscosity in hypergammaglobulinemia	TPE	I
Multiple Myeloma – Myeloma cast nephropathy	TPE	II
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	TPE/IA	I
Cryoglobulinemia	TPE/IA	II
THROMBOTIC MICROANGIOPATHIES		
HELLP Syndrome	TPE	
Postpartum		III
Antepartum		IV
Thrombotic Thrombocytopenic Purpura (TTP)	TPE	I
Hemolytic-Uremic Syndrome (HUS)	TPE	II

Note: a) Recommendation Categories: I – Indication where plasma exchange is considered first-line treatment (either alone or in combination with other forms of therapy)., II – Indication where plasma exchange is considered second-line treatment (either alone or in combination with other forms of therapy)., III – Optimum role of apheresis therapy is not established. Decision making should be individualized., IV – Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances., b) Removes macromolecules (including fibrinogen, LDL, α2-macroglobulin, IgM)., c) High-volume., d) Special adsorptive columns for β2-microglobulin removal., ANCA – antineutrophil cytoplasmic antibodies, HBV – hepatitis B virus, IA – immunoadsorption, LA – lipoprotein apheresis, NYHA – New York Heart Association, CNS – central nervous system, TPE – therapeutic plasma exchange, TPE-HV = TPE-high volume.

4. Hematological diseases in which plasmapheresis is used

4.1. PROTEIN DISORDERS:

Waldenstrom Macroglobulinemia (WM)

Waldenström macroglobulinemia (WM) is a type of lymphoplasmacytic lymphoma primarily affecting the bone marrow, characterized by the presence of an immunoglobulin M (IgM)

monoclonal protein, which can vary in size. This condition, classified as a B-cell non-Hodgkin lymphoma, has an estimated annual incidence of 3–4 cases per million individuals, with a higher prevalence among Caucasian males, typically diagnosed between the ages of 65–70. Structurally, IgM molecules are large and have the ability to form pentamers. The excessive presence of IgM monoclonal protein can lead to hyperviscosity syndrome (HVS) [6].

The symptoms of hyperviscosity stem mainly from shear forces causing the rupture of venous channels lacking support. The main signs and symptoms of HVS are bleeding (gingival, mucocutaneous, gastrointestinal), epistaxis. Retinal hemorrhage can occur blurred or loss of vision and diplopia. Other manifestations include congestive heart failure, shortness of breath, renal impairment, and anorexia. Symptoms from the central nervous system are nonspecific as headache, dizziness, fatigue, ataxia, hearing disorders and disturbed consciousness, that's why they need confirmation through serum viscosity measurements [7,8]. Viscosity is quantifiable in absolute units such as centipoise (cP). The standard serum viscosity for a healthy individual is around 1.5 cP [8]. HVS can manifest at various IgM and viscosity levels, and its onset may differ among patients. However, it commonly arises when the viscosity level reaches or exceeds 4.0 cP [10]. Standard current management is therapeutic plasma exchange (TPE) [6,7,8,9]. Early diagnosis plays a very important role in treatment of patients with HVS in WM. It is essential for preventing further advancement of the condition [8]. The fundoscopic examination is one of the best tests, because retinopathy may be detected even in individuals who do not report visual issues [6]. After diagnosis TPE should be conducted immediately, because it promptly relieves the clinical symptoms of hyperviscosity [8,9]. This procedure removes paraproteins from the patient's plasma, while returning all cellular components to the patient [8]. TPE does not affect the underlying malignant process responsible for HVS, that's why systemic immunochemotherapy should be initiated soon after TPE [6]. A single plasma exchange is often adequate to alleviate symptoms and enable the start of systemic treatment [7]. The selection of the regimen often relies on considerations of side effect profiles and the preferences of both the doctor and the patient [8]. Current chemotherapy approaches primarily revolve around rituximab combined with other systemic agents [6,7,8,10]. For first-line treatment, the bendamustine-rituximab (BR) combination is commonly employed [6,7,8,9]. Due to the risk of rituximab-induced IgM flare, it is advisable to add rituximab only when the serum IgM level is below 4,000 mg/dL. Alternative first-line regimens include bortezomib-rituximab-dexamethasone (BDR) and cyclophosphamide-rituximab-dexamethasone (DRC)

[7,8]. Additionally, the ibrutinib-rituximab combination is used due to the ability of ibrutinib to swiftly decrease IgM levels [7,8]. Therapeutic plasma exchange (TPE) has demonstrated effectiveness in treatment of HVS in WM [7,8,9]. It reverses retinopathy and other clinical manifestations of HVS. TPE is also considered a safe procedure, with a low incidence of severe adverse events, estimated at 1.0% based on data from a European registry study involving over 7,000 patients undergoing filtration-based exchange. Since about 75% of IgM is intravascular, usually only one or two sessions of TPE are needed to alleviate hyperviscosity syndrome (HVS) in Waldenström macroglobulinemia (WM). TPE typically results in a reduction of viscosity by 20–30% [8].

Multiple Myeloma (MM)

Multiple myeloma (MM) is a cancerous condition involving abnormal proliferation of plasma cells and the production of monoclonal or excessive free light chains (FLCs, or M proteins) [11,12,13]. MM occurs more frequently in men compared to women, with a prevalence twice as high in African Americans than Caucasians [12]. Typically, MM affects older individuals, with a median diagnosis age of 65 years [12,14]. Potential factors contributing to MM development include obesity, exposure to ionizing radiation, chronic antigen stimulation, genetic predisposition, and environmental factors. The proliferated cells disrupt the bone marrow (BM) microenvironment, leading to excessive production of monoclonal immunoglobulins (Ig), compromised immune function, and heightened osteoclast activity [12]. Renal insufficiency develops in over half of MM patients, and their prognosis depends heavily on the potential reversibility of the renal failure [11,14]. Cast nephropathy (also known as myeloma kidney) and hypercalcemia, often induced by heightened renal tubular filtration of FLCs, is a potentially reversible contributor to renal failure [11]. Management of renal failure in multiple myeloma include general measures, renal replacement therapy, plasmapheresis, high cut-off dialyzer (HCO-HD), chemotherapy, autologous hematopoietic stem cell transplantation (Auto-HSCT), allogenic HSCT and renal transplantation. General measures include avoiding nephrotoxic medications, diuretic medications, aminoglycosides, ACEI, ARI, and intravenous (IV) radiocontrast. For initial correction of severe hypercalcemia calcitonin should be administered. When necessary, hemodialysis or peritoneal dialysis are used as supportive measures [12]. Also, reversible proteasome inhibitors such as bortezomib and immunomodulatory drugs such as thalidomide have proven to be highly effective and are

regarded as protective of kidney function [12]. Regular monitoring of serum free light chains (FLC) levels is strongly advised to evaluate treatment effectiveness. Addressing elevated serum FLCs involves volume expansion with IV saline, and chemotherapy
incorporating a corticosteroids and alkylating agent to reduce M-protein production [12]. Therapeutic plasma exchange (TPE) is used to rapidly lower FLCs, associated with better kidney function and overall survival in MM [12,14]. While a small trial showed no significant differences, a subset of dialysis-dependent patients benefited from TPE. However, a large trial failed to show substantial benefits, leading to debate. Critics question study methodology and endpoints. Despite recommendations against TPE, some studies show benefits, especially when combined with chemotherapy [12]. Intensive TPE may improve outcomes if initiated promptly alongside chemotherapy until FLC levels decrease significantly [12,14].

4.2. AUTOIMMUNE DISORDERS:

Catastrophic Antiphospholipid Syndrome (CAPS)

Antiphospholipid Syndrome (APS) is a acquired hypercoagulable disorder characterized by recurrent venous and/or arterial thrombosis and obstetric complications. This pathology arises from the production of autoantibodies targeting protein-phospholipid complexes, specifically lupus anticoagulant (LA), anti-β2-glycoprotein I (anti-β2GPI), and/or anticardiolipin (aCL). The persistence of these antibodies is discernible through laboratory assessments. Catastrophic Antiphospholipid Syndrome (CAPS) represents an acute and lifethreatening manifestation of APS, marked by simultaneous thrombosis in at least three organ systems within a brief timeframe.[15] Commonly affected are the small vessels of the kidneys, heart, lungs, brain, and skin, leading to critical clinical sequelae such as renal failure, heart failure, myocardial infarction, pulmonary embolism, encephalopathy, stroke, reticular cyanosis, and skin necrosis. Thrombotic events may extend to larger vessels, and the acute phase can induce systemic inflammatory response syndrome (SIRS). The etiology of CAPS remains incompletely elucidated, with genetic factors, including the presence of HLA class II genes and genetic thrombophilia, as well as environmental factors such as infections, cancer, contraceptives, SLE flares and pregnancy, implicated as predisposing factors. [16,17,18] The prevalence of antiphospholipid antibodies in CAPS episodes includes LA (83%), aCL IgG (81%), aCL IgM (49%), anti-β2GPI IgG (78%), and anti-β2GPI IgM (40%). Additional laboratory findings encompass thrombocytopenia (67%) and the presence of schistocytes on peripheral blood smear

(22%).[19] In the therapeutic realm, plasmapheresis is considered a viable intervention, and the detection of specific antibodies assumes pivotal significance in guiding the application of this therapeutic modality. Overall, a comprehensive understanding of the clinical and laboratory facets of CAPS is imperative for accurate diagnosis and judicious management of this critical medical condition. The optimal management of Catastrophic Antiphospholipid Syndrome (CAPS) remains uncertain, given the absence of prospective studies attributable to the condition's low incidence. Nonetheless, the therapeutic approach is guided by three principal objectives: addressing any identifiable precipitating factors, preventing and managing ongoing thrombotic events, and attenuating excessive cytokine production. A recommended therapeutic paradigm involves a triple therapy strategy encompassing anticoagulation, glucocorticosteroids, and therapeutic plasma exchange (TPE) and/or intravenous immunoglobulin (IVIG). The triple therapy approach, as evidenced by data from the CAPS Registry cohort, has demonstrated an independent association with improved survival in CAPS patients. Mortality rates among individuals treated with triple therapy, those receiving components of the triple therapy in alternative combinations, or those without any elements of the prescribed triple therapy were 29%, 41%, and 75%, respectively. Notably, the mortality rate in patients administered triple therapy with both IVIG and TPE mirrored that of individuals receiving triple therapy with either IVIG or TPE alone, suggesting that simultaneous administration of both may not be imperative. In cases of refractory or relapsing CAPS, various alternative therapeutic modalities have been explored, including cyclophosphamide, rituximab, and eculizumab. These adjunctive approaches aim to address persistently challenging cases and enhance treatment efficacy beyond the standard triple therapy regimen. [15] Per the 2023 iteration of the Guidelines for the Use of Apheresis Therapeutics in Clinical Practice, formulated by the American Society of Apheresis (ASFA), TPE is acknowledged as a first-line intervention in CAPS. It is recognized as a viable standalone therapeutic measure or as part of a combination therapy approach (Category I). However, it is essential to note that the strength of this recommendation is categorized as weak, attributed to the predominantly low or very low-quality evidence derived from observational studies or case series (Grade 2C). Consequently, alternative therapeutic strategies may be deemed equally rational in the management of CAPS. [19] TPE prescription: plasma volume: 1-1.5 EPV, frequency: Daily or every other day, replacement fluid: Frozen plasma or frozen plasma/albumin, duration: Minimum of 3 to 5 sessions with longer-term duration based on clinical response. [21,22] The specific mechanism through which TPE

confers therapeutic benefits in CAPS remains elusive. Nevertheless, it is postulated that the ameliorative effects of TPE may be attributed to the removal of antiphospholipid antibodies, cytokines, tumor necrosis factor, and complement components, all of which are likely to play pivotal roles in the pathophysiology of CAPS. [19,20]

Acquired Hemophilia A (AHA)

AHA is a rare autoimmune disorder marked by the production of antibodies targeting coagulation factor VIII (FVIII), resulting in its inhibition and causing a sudden and severe bleeding disorder. The polyclonal autoantibodies associated with AHA typically belong to class G immunoglobulins, predominantly falling into the IgG1 and IgG4 subclasses. The etiology of AHA is often unclear in about half of the cases, while the other half is linked to factors such as pregnancy or the presence of coexisting diseases like hematopoietic or lymphatic system tumors, solid malignant tumors, autoimmune disorders, allergic diseases (including reactions to medications), or infections. [23,24] The development of anti-factor VIII autoantibodies shows a biphasic age distribution, featuring a minor peak in women aged 20–30 years, often associated with postpartum inhibitors, and a more substantial peak in the elderly population. In cases of acquired FVIII deficiency, bleeding manifestations typically impact the skin, muscles, soft tissues, and mucous membranes, contrasting with hemarthroses. The management of AHA involves a dual approach encompassing antihemorrhagic and immunosuppressive strategies.[25] Primary interventions to prevent bleeding include recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (aPCC). In cases of AHA with a low FVIII inhibitor titer and mild bleeding, factor VIII concentrate or desmopressin may be considered. Recombinant porcine factor VIII is also a viable option. To address the inhibition of inhibitor production, various immunosuppressive methods are employed. Prednisone and cyclophosphamide constitute the first-line immunosuppressive regimen.[25] According to data from the European Registry of Acquired Haemophilia, approximately 70% of patients achieve complete remission with this therapeutic approach. Conversely, treatment combining immunoadsorption (IA), intravenous immunoglobulin (IVIG), cyclophosphamide, prednisolone, and FVIII in patients without paraneoplastic syndrome yields a higher complete remission rate of 93%. The optimal role of IA and TPE in the treatment of AHA has not been established. Decision making should be individualized. In the case of IA, the degree of recommendation is weak, due to evidence of medium quality. However, in the case of TPE, we

are dealing with evidence about low or very low quality. IA is more extensively researched than TPE for the extracorporeal elimination of coagulation factor inhibitors. CS and CRs suggest that IA can reduce antibody titers, enhance the response to factor replacement, and mitigate severe bleeding in hemophiliacs with spontaneous inhibitors, although not all patients exhibit a clinical response. Due to its specialized and costly equipment, IA is typically reserved for patients with refractory inhibitors unresponsive to alternative therapies. TPE has been employed to diminish inhibitor levels in individuals with inhibitors to factor VIII and various coagulation factors. However, akin to IA, not all patients demonstrate a positive response to TPE.[19] Limited CS and CRs also discuss the use of TPE to elevate factor levels in patients without inhibitors, especially when a specific factor replacement product is unavailable or when the required volume of simple plasma transfusion exceeds the patient's tolerance.

Autoimmune Hemolytic Anemia, severe (AIHA)

Autoimmune Hemolytic Anemia (AIHA) encompasses disorders where autoantibodies induce intravascular hemolysis through the terminal lytic complex (C5b-C9) or more commonly, extravascular destruction in the spleen via the macrophage-phagocytic system. Patients may manifest symptoms like fatigue, jaundice, and dyspnea, or remain asymptomatic if well-compensated. Laboratory findings include hemolysis (anemia, hyperbilirubinemia, elevated serum LDH) and a positive direct antiglobulin (Coomb's) test (DAT). AIHA classifies into Warm Autoimmune Hemolytic Anemia (WAIHA) and Cold Agglutinin Disease (CAD)/Cold Autoimmune Hemolytic Anemia (CAIHA). WAIHA involves IgG hemolysins optimal at 37°C, associated with idiopathic (30% of cases), secondary (linked to autoimmune diseases, lymphoproliferative disorders, infections, or post-transplantation), and drug-induced causes. In WAIHA, the positive DAT shows anti-IgG and potentially antiC3b. CAD results from IgM autoantibodies reacting optimally at 0-5°C, observed postinfections or in lymphoproliferative disorders. The DAT is positive with anti-C3b only. AIHA severity is influenced by autoantibody characteristics, including titer, avidity to RBC antigens, complement fixation ability, and, for cold autoantibodies, thermal amplitude— representing the highest temperature of antibody reactivity with its antigen. A high thermal amplitude indicates activity within in vivo temperature ranges. [26,27,28] The primary treatment modality for WAIHA involves prednisone at a dosage of 1 mg/kg/day. Prednisone functions by inhibiting antibody production, thereby mitigating Fc receptormediated hemolysis in the spleen. The RAIHA randomized

controlled trial established the effectiveness of prednisone and rituximab as first-line therapy for WAIHA. In cases where corticosteroids and rituximab prove ineffective, splenectomy may be considered. For refractory cases, therapeutic options include IVIG, cyclophosphamide, vincristine, mycophenolate mofetil, azathioprine, sirolimus, and monoclonal antibodies. The efficacy of eculizumab was demonstrated in a single case report. For CAD with severe hemolytic anemia, primary intervention involves the avoidance of cold exposure. Rituximab remains the most effective first-line therapy, although achieving complete and durable remissions is infrequent. In February 2022, the FDA approved Sutimlimab for CAD treatment. Sutimlimab, a humanized IgG4 monoclonal antibody, inhibits the classical complement pathway at C1, thereby preventing complement opsonin deposition and hemolysis. A Scandinavian study demonstrated the effectiveness of bendamustine in combination with rituximab in 32 of 45 CAD patients. Bortezomib is also recognized as effective. In cases of life-threatening hemolysis, emergency interventions such as blood transfusions, eculizumab, extracorporeal column immunoabsorption apheresis, and therapeutic plasma exchange (TPE) may be necessary. Prednisone and splenectomy typically lack effectiveness due to the liver's predominant role in destroying C3b-sensitized red blood cells. Secondary CAD generally responds well to antilymphoma chemotherapy. Ongoing research continues to uncover novel therapies for both Warm and Cold Autoimmune Hemolytic Anemia. TPE is indicated in AIHA for severe cases of CAD and severe WAIHA. For severe CAD, apheresis is acknowledged as a second-line intervention, employed either independently or in conjunction with other therapeutic modalities (category II). However, in severe WAIHA, the optimal role of apheresis therapy remains undetermined, and decisions should be tailored to individual circumstances (category III). In both scenarios, the grade of recommendation is weak, attributed to the limited and of low quality or very low-quality evidence available. [19] TPE is used to eliminate pathogenic immune complexes, activated complement components, and circulating autoantibodies, mainly in patients with fulminant hemolysis unresponsive to red blood cell transfusion or steroids. TPE may temporarily control disease progression until more aggressive immunosuppressive therapies take effect or if treatment fails. While some case reports and series in WAIHA show favorable results with TPE, others report no significant effect. Studies comparing TPE with no TPE in severe WAIHA have found no difference in posttransfusion hemoglobin levels.[27,29] Whole blood exchange (WBE) has been studied in severe cases of AIHA, and TPE may be beneficial in CAD with intravascular IgM autoantibodies.

Improvement in AIHA after TPE is usually temporary and depends on autoantibody characteristics and production rate, requiring concomitant immunosuppressive treatment. [26] Some case reports suggest the success of using TPE as a precursor to treatment with IVIG, cyclophosphamide, or bortezomib.

4.3.THROMBOTIC MICROANGIOPATHIES:

Thrombotic Thrombocytopenic Purpura (TTP)

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy, mainly affecting 30-40 years old women. It is divided into two variants- congenital [Upshaw-Schulman syndrome (USS) or cTTP] caused by ADAMTS13 gene mutation and immune-mediated (iTTP) caused by anti-ADAMTS13 autoantibodies, which procure decreased activity of disintegrin-like metalloprotease and metalloproteinase with thrombospondin type 1 motifs 13. These factors physiologically reduce the size of von Willebrand factor, whereas blood of patients with TTP contains ultralarge multimers of von Willebrand factor (UL-VWFMs). Endothelial cells secrete the UL-VWFMs by shear forces in inhesion of fast blood flow and in small vessels, leading to platelet adhesion and thrombosis. Patients with TTP typically present reduced platelet count and microangiopathic hemolytic anaemia with schistocytes. Although thrombi are present in every tissue, they are uncommon in the liver and lungs, because of low pressure blood circulation. Malfunctions are present mainly in organs with high shear forces such as the pancreas, brain, kidneys and heart. Fever is often the first symptom, followed by other manifestations, such as confusion, headaches, paresis, speech and vision impairment, seizure, abdominal pain, nausea, arrhythmia, ecchymosis and haemorrhages. Nevertheless, haemorrhages of the gastrointestinal or nervous system are not prevalent [30,31]. Treatment of cTTP is based on fresh frozen plasma (FFP) or alternatively intermediate purity factor VIII concentrate (BPL 8Y), rather than therapeutic plasma exchange (TPE) [32], while the treatment of iTTP is based on the use of plasmapheresis conducted as TPE, which is recommended as a core element of therapy. ISTH guidelines are suggested to be followed for thrombotic thrombocytopenic purpura management. The group of patients who suffer a first acute event of iTTP can be treated with TPE and addition of corticosteroids. This recommendation was marked as strong, however the certainty of evidence is very low due to moderate reduction of the mortality rate in life threatening situations, while side effects of short-term corticosteroids use are minor. According to strong recommendation, patients who experience iTTP relapsing

episode, TTPe along with corticosteroids is favoured over TPE alone. Very low certainty of the evidence is associated with serious adverse effects of repeated pulses of high dose corticosteroids. [33]. However, a case study described by Galindo-Calvillo et suggests a possibility of treatment iTTP without TPE. The patient was successfully treated with prednisone and rituximab, due to inability to apply TPE during the COVID-19 pandemic. Moreover, implementation of albumin solution was mentioned from other publications, as an alternative substitution to TPE [34]. Nevertheless, the use of TPE remains a standard procedure with addition of corticosteroids, adding rituximab with caplacizumab for more acute cases. [33] Recent studies favour the usage of caplacizumab to accelerate the clinical response, while rituximab is favoured for recurrent iTTP [35,36].

Hemolytic-Uremic Syndrome (HUS)

Hemolytic-uremic syndrome (HUS) is another microangiopathy in which plasmapheresis is used. Typically HUS manifests with a triad of symptoms, thrombocytopenia, hemolytic anaemia and renal failure, eventually leading to replacement renal therapy in approximately 33% cases. Symptoms of HUS include fever, hypertension, pericardial effusion with tamponade, hemiparesis, encephalopathy, seizures, stupor, cortical blindness, oliguria, diarrhoea, vomiting, jaundice, ecchymosis and oedema. Less frequent symptoms are scotoma, pulmonary hypertension with haemorrhage, decreased vision acuity, diplopia, ocular pain and gangrene. Long term complications comprise end stage renal impairment, hypertension, diabetes and neurological symptoms. The outcome of HUS may vary according to differences in the pathogenesis. Classification of HUS treated with therapeutic plasma exchange (TPE) consists of HUS associated with infection and complement-mediated atypical HUS. Most common HUS associated with infection is Shiga toxin-associated HUS, which affects 90% of HUS cases, mainly younger children. The predominant pathogen is Escherichia coli O157:H7 (STEC HUS), while Escherichia coli serotypes and Shigella dysenteriae are sporadic. It is reported that STEC enteritis leads in 5-15% cases to HUS. Prothrombotic and proinflammatory properties of Shiga-like toxin (Stx) are responsible for the release of ultralarge multimers of von Willebrand factor (UL-VWFMs) by the vascular endothelial cells, causing increased aggregation and adhesion of platelets. Moreover, Stx binds to renal cells leading to cortical necrosis in kidneys, damage of vascular endothelial cells, glomerular endothelial cell swelling and capillary lumen thrombotic occlusions. Streptococcus pneumoniae-associated HUS (pHUS) detected in nearly 0,9-5%,

affects usually children below 2 years old in event of meningitis, pneumonia or sepsis with the mortality rate up to 50%. Neuraminidase is a causative factor for exposing the Thomsen-Freidenreich (T-) antigen by breaking down sialic acid on the cell surface. The pathological mechanism is based on exposing T-antigen on erythrocytes, endothelium and platelets, which is binded by IgM anti-T antibody. Complement-mediated atypical HUS (aHUS) is detected in 5-10% cases of HUS. The pathology of aHUS is the excessive complement cascade due to the cleavage of C3 resulting in increase of C5a and C5b-9 activity, mainly caused by genetic impairment of Factor H. The pathomechanism relies on damage of endothelial cells causing platelets coagulation cascade. Approximately 50% of patients with genetic aetiology have the CFH gene mutation on chromosome 1, encoding regulators of complement activation (RCA). Another factors of aHUS include systemic diseases (antiphospholipid antibody syndrome, systemic lupus erythematous and scleroderma), medical treatment (sirolimus, cancer chemotherapy, calcineurin inhibitors, ionizing radiation, anti-vascular endothelial growth factor agents), metabolic defects (cobalamin defects, methyl malonic aciduria with homocystinuria) [37,38, 39]. Concerning the Shiga toxin-associated HUS, it is argued whether plasma exchange is beneficial. Current treatment methods indicate control of hypertension, fluid resuscitation combined with appropriate electrolyte supply, alternatively antibiotics, eculizumab and TPE. Nevertheless, studies suggest that TPE may improve the neurological condition of patients in severe condition, especially if applied early on (24-48h), although it requires further research. Its role is based on removal of Stxs, prothrombotic factors and proinflammatory cytokines. [40,41,42]. The management of pHUS comprises supportive care as well as extended-spectrum cephalosporin and vancomycin for more severe paediatric cases. Studies show that the use of plasma exchange for pHUS is limited, however, the reduction of neuraminidase, anti-T antigen antibodies and galectin-3 obtained by TPE might be beneficial for the outcome of patients. Xiu-Li Wang et emphasise application of T-antibody-negative plasma as a key to the successful outcome of TPE to prevent further exacerbation, which is important to note, according to the prevalence of T-antibody in donors' blood. Moreover, transfused plasma containing factor H can be advantageous. Additionally, washing of blood with dextran may be helpful to reduce the level of T-antibodies. Eculizumab remains an option for treatment due to its downregulation of excessive complement activity [43,44,45,46]. In aHUS, eculizumab, a monoclonal C5 antibody, persists as first-line treatment concerning its binding affinity to complement protein C5 preventing C5b-C9 concentration increase. Recently ravulizumab was accepted for the therapy

as long-acting C5 monoclonal antibody. TPE remains a secondary choice for aHUS management if eculizumab is inaccessible, due to its incompatible results, owing to various mutations and technique-related complications regarding mainly paediatric patients, although adults respond to lesser extent to TPE [38,47,48]

HELLP

Hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome occurs within 0,2-0,8% pregnancies, with a mortality risk up to 24%, while the perinatal mortality rate is up to 37%, depending on time of the diagnosis, class, acute renal failure or possible infections. Mississippi classification categorises HELLP severity into three groups, from which HELLP I is saddled with the highest risk. This perinatal and maternal life-threatening condition leads to enhanced probability of cardiovascular disease and refers to complications of preeclampsia antepartum, mostly throughout the third trimester, or within 48 hours postpartum. Outcome of HELLP comprises renal failure, disseminated intravascular coagulation (DIC), pulmonary oedema and placental abruption. Main symptoms are upper-right quadrant abdominal pain and malaise, both developed in about 90% of cases, vomiting and nausea. HELLP is a result of endothelial dysfunction causing increased activity of coagulation and complement system. Moreover, increased level of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and D-dimer is detected along with microangiopathic hemolyzed erythrocytes and thrombocytopenia. Clinically, the elevated LDH level is a marker for hemolysis. [49,50 ,51]. TPE is described as effective when conservative therapy is not sufficient or as a method for thrombocytopenia management. Plasma exchange supplies a proper amount of albumin and coagulation factors, moreover it reduces inflammatory cytokines, ammonium, bilirubin, endotoxines, angiotensin and renin, enhancing renal, hepatic and neurological condition. In general, TPE is implemented for patients who do not present the improvement 48-72 hours postpartum. Nevertheless, the procedure of plasmapheresis conducted within 24 hours can drastically enhance the clinical outcome and significantly reduce the mortality of the HELLP I class. Additionally, transfusion of fresh frozen plasma (FFP) is beneficial, preventing DIC outcome. American Society for Apheresis in the eighth edition marks TPE as IV category for treating antepartum HELLP while delivery remains the final management (according to other publications) and III category for postpartum HELLP [50,51,52]. Kojima et al suggest that implementation of TPE should be based on the severity of

symptoms, not solely on the diagnosis [50]. Mortality risk factor, that should be highly considered, based on other articles, is the renal failure, for which the application of TPE is beneficial [51,52].

5. Conclusion

In conclusion, therapeutic plasmapheresis emerges as a promising intervention for various hematological diseases, offering notable benefits alongside a few limitations. This review has highlighted its indications and clinical outcomes, shedding light on its efficacy in conditions such as thrombotic thrombocytopenic purpura (TTP), autoimmune hemolytic anemia (AIHA), and multiple myeloma (MM), among others. The ability of plasmapheresis to rapidly remove pathogenic factors from the blood makes it a valuable adjunctive therapy, particularly in autoimmune and immune-mediated disorders.

Moving forward, several potential directions of development for plasmapheresis warrant exploration. Advancements in technology, such as the development of more efficient and selective filtration systems, could enhance the procedure's efficacy while minimizing associated risks. Additionally, further research is needed to optimize treatment protocols, including the determination of optimal timing, frequency, and duration of plasmapheresis sessions for different hematological conditions.

Despite its advantages, plasmapheresis also presents certain drawbacks. These include the need for specialized equipment and trained personnel, as well as the risk of complications such as hypotension, electrolyte imbalances, and infection. Moreover, its effectiveness may vary depending on the underlying disease pathology and individual patient factors. In comparison to other therapeutic methods in hematological diseases, plasmapheresis offers unique advantages, particularly in cases where rapid removal of circulating pathogenic factors is crucial. Unlike immunosuppressive therapies, plasmapheresis acts directly on the circulating blood components, providing a more targeted approach. However, its role may be complementary to other treatments such as corticosteroids, immunosuppressants, and monoclonal antibodies, depending on the specific disease context.

Therapeutic plasmapheresis holds considerable promise as a therapeutic modality in hematological diseases, offering a targeted approach to the removal of pathogenic factors from the bloodstream. Continued research and technological advancements will further refine its utility and optimize patient outcomes in the future.

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