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The Role of Plasmapheresis in Critical Illness

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Synopsis

In this chapter, we will review the current recommendations from the American Society for Apheresis regarding the use of plasmapheresis in many of the diseases that intensivists commonly encounter in critically ill patients. Recent experience indicates that therapeutic plasma exchange (TPE) may be useful in a wide spectrum of illnesses characterized by microvascular thrombosis, the presence of auto-antibodies, immune activation with dysregulation of immune response, and in some infections.

Keywords

therapeutic plasma exchange; thrombotic microangiopathy; microvascular thrombosis; auto-antibodies; liver failure; hemophagocytic lymphohistiocytosis; rapidly progressive glomerulo nephritis; vasculitides; solid organ transplantation

Introduction

Since antiquity, mankind has hypothesized there are bad substances called “humors” which accumulate in the blood of sick patients and that the removal of these humors would make

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[1]The American Society of Apheresis published a comprehensive evidence-based guideline to aid intensivists in using plasmapheresis as a therapeutic strategy

[2]Plasmapheresis has seen an increase in usage in critically ill patients

[3]Thrombotic microangiopathies, vasculitides, liver failure, ABO incompatible solid organ transplantation, neurologic disorders, renal disorders, and immune dysregulation are some of the disorders that intensivists could consider using plasmapheresis as a therapeutic strategy

patients feel better. Bloodletting, the practice of draining blood from sick patients, has been around since the Egyptians, dating back one thousand years B.C. The practice of bloodletting peaked in the 18th century and evolves with modern technology to this day. Blood has four major components: red blood cells, white blood cells, platelets, and plasma. With modern machinery, blood can be separated into each of these four components. Thus, if a particular blood component is causing harm, it can be selectively removed and replaced with the same blood component from healthy donors.

In this chapter, we will review the current recommendations from the American Society for Apheresis for plasmapheresis in many of the diseases that intensivists commonly encounter in critically ill patients.[1] Apheresis is derived from the Greek word “aphairesis” – to take away. Plasmapheresis is an apheresis procedure that separates and removes the plasma component from a patient. Plasma exchange is when plasmapheresis is followed by replacement with fresh frozen plasma infusion.

Techniques of Separating Plasma from Whole Blood

Plasmapheresis is performed by two fundamentally different techniques: centrifugation or filtration. With centrifugation apheresis, whole blood is spun so that the four major blood components are separated out into layers by their different densities. With filtration plasmapheresis, whole blood passes through a filter to separate the plasma components from the larger cellular components of red blood cells, white blood cells, and platelets. Centrifugation apheresis is commonly performed by blood bankers. A major advantage is that there is no limit on the size of the molecules being removed. Its disadvantage is that it usually requires a consultation to another service such as a blood banker. Filtration plasmapheresis is commonly performed by nephrologists and intensivist. Its major advantage is that a large filter can be easily added to the existing continuous veno-venous hemodialysis circuit without much interruption to patient care. However, a disadvantage is that the size of the molecules removed is limited by the size of the pore of the filter. This is problematic because certain plasma molecules are larger than existing available filters, for example the ultra-large von Willebrand factor multimers can measure up to 12 million daltons.

Plasmapheresis/Plasma Exchange in Critically Ill Patients

In 2010, The American Society for Apheresis (ASFA) published its updated comprehensive “Guideline on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach”.[1] The society divided its recommendations into four categories:

- **Category I**: “Disorder for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment”.
- **Category II**: “Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment”.
- **Category III**: “Optimum role of apheresis therapy is not established. Decision making should be individualized”.
- **Category IV**: “Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. Internal Review Board approval is desirable if apheresis treatment is undertaken in these circumstances”.

This chapter reviews many of the diseases in critically ill patients that plasmapheresis/ therapeutic plasma exchange (TPE) may play a role in the therapeutic strategy.

Thrombotic Microangiopathies

Thrombotic microangiopathies are syndromes associated with disseminated microvascular thrombosis.[2] Clinically, these syndromes manifest as new onset thrombocytopenia and if untreated, will lead to multiple organ failure and death. Thrombotic Thrombocytopenic Purpura (TTP), Hemolytic Uremic Syndrome (HUS), Disseminated Intravascular Coagulation (DIC) and Catastrophic Antiphospholipid Syndrome (CAPS) are different spectrums of thrombotic microangiopathies. The ASFA gives a category I recommendation for plasmapheresis/therapeutic plasma exchange (TPE) in patients with TTP and atypical HUS due to autoantibody to factor H, category II recommendation for TPE in patients with CAPS, and a category III recommendation for TPE in patients with Hematopoietic Stem Cell Transplant – Associated Thrombotic Microangiopathy.[1]

Thrombotic Thrombocytopenic Purpura (TTP)

The classic “pentad” of TTP is composed of: thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, renal failure, and fever. The underlying pathophysiologic process of TTP is the deficiency of ADAMTS-13 (a.k.a. von Willebrand factor (VWF) -cleaving proteinase) leading to uncleaved thrombogenic large and ultra-large VWF.[2] Autopsies on patients who died from TTP demonstrate distinctive VWF- and platelet-rich microthrombi.[3–6] There are two forms of TTP, congenital and acquired. In the congenital form, there is a genetic abnormality in ADAMTS-13.[7] In the acquired form, ADAMTS-13 inhibitors and/or proteolytic inactivators are present in the plasma.[8,9] There is a growing list of ADAMTS-13 inhibitors and proteolytic inactivators including interleukin-6, plasma-free hemoglobin, IgG auto-antibody, Shiga toxin, plasmin, thrombin, and granulocyte elastase.[9–14] TPE has been shown in a large randomized controlled trial to significantly improve survival compared to plasma infusion.[15] The ASFA gives a category I recommendation for TPE in TTP.[1]

TPE is thought to remove the large and ultra-large VWF, remove the ADAMTS-13 inhibitors and proteolytic inactivators, and replenish ADAMTS-13.[2] Because the underlying pathology is the deficiency of ADAMTS-13, the recommended TPE replacement fluid is plasma or plasma with cryoprecipitate removed (i.e. the plasma portion that is depleted with ultra-large VWF and large plasma VWF).

Typical Hemolytic Uremic Syndrome (HUS)

The “triad” of HUS is thrombocytopenia, microangiopathic hemolytic anemia, and renal failure.[2] This syndrome is divided into typical HUS and atypical HUS. Typical HUS, which accounts for 85–90% of all HUS, is commonly associated with infection and diarrhea.[16,17] Shiga toxin-producing Escherichia coli 0157:H7 accounts for the majority of typical HUS with a mortality of <5%. Shiga toxin has been shown *in vitro* to 1) induce ultra-large VWF to be released from endothelium, and 2) inhibit ADAMTS-13, similar to the pathophysiology of TTP. However, clinical association studies have not consistently shown severe ADAMTS-13 deficiency in Escherichia coli 0157:H7-induced HUS.[6] Certain neuramidase producing-bacteria, such as Streptococcus pneumonia, account for a minority of typical HUS and has a higher mortality when compared to that of typical HUS with a mortality rate of 19–50%. Neuramidase has been shown to cleave sialic acid residues from cell surface protein exposing the Thomsen-Freidenreich (T-) antigen. HUS occurs when endogenous IgM directed against the T-antigen binds to the exposed T-antigen on endothelium, red blood cells, and platelets resulting in platelet-rich thrombi formation in the microvasculature. Currently, the ASFA does not recommend TPE (category IV) for typical HUS.[1]

Atypical Hemolytic Uremic Syndrome

In atypical HUS, in addition to the typical "triad" of signs and symptoms, patients have neurologic abnormalities beyond that of the usual "irritability" seen in most children with typical HUS. Investigation into pathophysiology of atypical HUS has identified two different processes, genetic abnormalities or acquired autoantibodies. Currently, it is thought that up to 60% of patients with atypical HUS have genetic abnormalities in the complement pathway.[17] Autoantibodies against factor H have been observed in up to 10% of patients with atypical HUS.[17] In either case, there is uncontrolled activation of the alternative complement pathway, resulting in direct injury to the microvasculature. Atypical HUS has a reported mortality rate of 25%.[17]

The ASFA gives a category I recommendation for TPE in atypical HUS due to autoantibody to factor H. [1] Factor H regulates and inhibits the alternative pathway of the complement pathway. TPE is thought to remove the autoantibody to factor H and normalize complement activities.[18]

The ASFA gives a category II recommendation for TPE in atypical HUS due to complement factor gene mutations.[1] These genes include inhibitors of alternative complement pathways such as factor H, factor I, membrane cofactor protein, complement factor H-related proteins, and C4b binding protein. Gain-of-function mutations for alternative complement pathways also been described such as factor B, and C3.[17]

During the first 24–72 hours of a patient presenting with the "triad" of signs and symptoms, along with neurologic abnormalities, most clinicians are not able to differentiate TTP from atypical HUS, nor differentiate atypical HUS due to autoantibody to factor H from atypical HUS due to complement factor gene mutations. The authors of this chapter recommend consulting nephrology and hematology to send the appropriate ADAMTS-13, VWF and complement studies. In addition, TPE should be initiated until the results of biomarkers can differentiate the diagnoses. Because the underlying pathology is the deficiency of complement H activity, the recommended TPE replacement fluid is either plasma or albumin. The authors of this article recommend plasma as the replacement fluid since it has normal Factor H activity.

Disseminated Intravascular Coagulation (DIC)

DIC is characterized by intravascular activation of coagulation leading to the consumption and exhaustion of coagulation proteins and platelets. Autopsies in patients who died with DIC reveal extensive fibrin deposition in small and mid-size vessels in all organs.[3,4,6,19] One of the proposed mechanisms for DIC is that systemic inflammation, such as occurs in sepsis, activates leukocytes and endothelium. These cells then synthesize, express, and release tissue factor. Tissue factor forms a complex with factor VII leading to the activation of coagulation and the resultant disseminated microvascular thrombosis with fibrin-rich microthrombi.[20] Clinically, these patients present with shock and in a prothrombotic and antifibrinolytic state with subsequent bleeding diathesis. Many case series and observational studies suggest that TPE might have a beneficial effect in DIC.[21–25] TPE is thought to normalize the blood coagulation to homeostasis milieu by removing tissue factor and plasminogen activator inhibitors-type-I, and by replacing antithrombin III, protein C, and coagulation factors. Currently, the ASFA does not have a specific recommendation for TPE in DIC.

However, the ASFA gives a category III recommendation for TPE in Sepsis with Multiorgan Failure.[1] Large trials have documented that sepsis can induce thrombotic microangiopathy, and in particular, sepsis-induced DIC is present in 30–50% of patients with severe sepsis.[19,26] DIC has been shown to be one of the major contributing

mechanisms to multiple organ failure in critically ill patients.[19] Thus, there is a biologic plausibility that the beneficial treatment effect of TPE in Sepsis with Multiorgan Failure could be from reversing DIC.

Thrombocytopenia-Associated Multiple Organ Failure (TAMOF)

Recently, investigators observed that pediatric patients with Thrombocytopenia-Associated Multiple Organ Failure (TAMOF) have thrombotic microangiopathy and that TPE may have a beneficial effect.[25] These investigators reported that pediatric patients with new onset thrombocytopenia defined as platelet counts < 100,000/mm^3 and at least 3 failing organs have a pathophysiologic process similar to that of TTP such as low ADAMTS-13 activities, presence of ultra-large VWF, and high VWF activities. A subset of TAMOF patients also had prolonged prothrombin time suggesting fibrin pathway activation, as in DIC. On autopsies, pediatric TAMOF patients have VWF-rich and platelet-rich microthrombi similar to patients with TTP, and also fibrin-rich microthrombi similar to patients with DIC. In a small single center trial, they reported that TPE had a significant beneficial treatment effect in reducing organ failure score (Pediatric Logistic Organ Dysfunction) and mortality. Of note, all of these patients had concurrent sepsis. Thus, the ASFA category III recommendation for TPE in Sepsis with Multiorgan Failure,[1] as discussed above, encompasses sepsis-induced TAMOF.

A larger multi-center registry of TPE in pediatric TAMOF is in its analysis phase. Hopefully, this registry will shed more light on the treatment effect of TPE for TAMOF. Because the underlying pathology could be in part from deficient coagulation factors due to consumption, the recommended TPE replacement fluid is either plasma or albumin. The authors of this article recommend plasma as the replacement fluid.

Catastrophic Antiphospholipid Syndrome (CAPS)

The underlying pathology in CAPS is an acquired hypercoagulable state due to the presence of antiphospholipid, anticardiolipin, and/or anti-beta 2 glycoprotein I antibodies.[27] The clinical presentation is acute microvascular venous and arterial thrombosis leading to multiple organ failure. Currently, the definition of CAPS includes 1) involvement of at least 3 organs, 2) manifestation in less than one week, 3) confirmed histopathology of small vessel occlusion in one tissue, and 4) presence of antiphospholipid antibodies.[28] This syndrome may be clinically indistinguishable from TTP, HUS, DIC, and TAMOF. For example, overt DIC is present in 20% of patients with CAPS. Biomarkers could help to differentiate between CAPS from TTP, HUS, and DIC.

The ASFA gives a category II recommendation for TPE in CAPS.[1] TPE is thought to remove antiphospholipid antibodies, inflammatory cytokines, and complement, and to replace the deficient coagulation factors.[29–31] The recommended TPE replacement fluid is plasma as it has normal level of coagulation proteases.

Hematopoietic Stem Cell Transplant – Associated Thrombotic Microangiopathy

The causes of thrombotic microangiopathy in hematopoietic stem cell transplant are unclear.[32–35] Endotheliopathy is suggested to be the underlying pathophysiologic process.[36] However, it is postulated that there could be multiple triggers including high-dose conditioning chemotherapy, irradiation, graft-versus-host disease (GVHD), mammalian target of rapamycin (mTOR) and calcineurin inhibitor drugs, and infection. The mainstay of therapy involves treating GVHD, reducing doses of the mTOR and calcineurin inhibitor drugs, and treating infection. ADAMTS-13 activities have been shown to be low normal in these patients. Some patients seem to respond to TPE. Thus, a trial of TPE with a defined

endpoint in selected patients with persistent thrombotic microangiopathy might be considered.[37–39]

The ASFA gives a category III recommendation for TPE in Hematopoietic Stem Cell Transplant – Associated Thrombotic Microangiopathy.[1] The recommended TPE replacement fluid is plasma or plasma with cryoprecipitate removed.

Thrombotic Microangiopathy: Drug-Associated

A number of drugs have been shown to activate platelets and/or cause endotheliopathy. Antiplatelet drugs such as ticlopidine and clopidogrel are members of the thienopyridine class of drugs which inhibit the adenosine diphosphate (ADP) receptor/P2Y12 on platelets. They have been shown to induce TTP-like pathophysiology with low ADAMTS-13 activities and clinical signs of thrombotic microangiopathy in rare cases.[40–42] Calcineurin inhibitors such as cyclosporine and tacrolimus have been reported to induce endotheliopathy progressing to thrombotic microangiopathy.[43–46] Management includes either stopping the offending drug or, if this is not an option, at least reducing the drug intake. TPE is thought to be beneficial similar to its use in acquired TTP.

The ASFA gives a category I recommendation for TPE in ticlopedine or clopidogrel and category III for TPE in cycloporine or tacrolimus-Associated Thrombotic Microangiopathy.[1] The recommended TPE replacement fluid is plasma or plasma with cryoprecipitate removed.

Vasculitides

Catastrophic Antiphospholipid Syndrome (CAPS)

This syndrome is often grouped with vasculitides as it is diagnosed by rheumatologists. However, CAPS is a thrombotic microangiopathy and has significant overlap with TTP, HUS, DIC and TAMOF. Please refer to the above section of Thrombotic Microangiopathies for a review of CAPS.

Systemic Lupus Erythematosus (SLE)

SLE is an autoimmune disorder that causes chronic inflammation due to circulating auto-antibodies, immune complexes and complement deposition. SLE is much more common in women than in men. Clinical symptoms such as malaise, arthritis, rash and fever, are non-specific and often vary from person to person. However, severe progression of disease can occur with involvement of virtually any organ with consequent manifestations such as stroke, renal failure, pulmonary hemorrhage, myocarditis, hemolytic anemia, and pulmonary embolism. Confirmatory tests include the presence of specific anti-nuclear antibodies such as anti-double stranded DNA and anti-Smith antibodies. First line therapy includes anti-inflammatory and immunosuppressive agents. However, when severe SLE presents with cerebritis or pulmonary hemorrhage, TPE is recommended.[47–50]

The ASFA gives a category II recommendation for TPE in severe SLE such as with cerebritis or diffuse alveolar hemorrhage.[1] The ASFA does not recommend TPE (category IV) for SLE-associated nephritis. TPE is thought to remove auto-antibodies, complement, interferon alpha, and immune complexes.[51,52] The recommended TPE replacement fluid is either plasma or albumin.

Liver failure

Wilson's disease in fulminant hepatic failure with hemolysis

Wilson's disease is an autosomal recessive genetic disorder that results in excessive accumulation of copper in the liver, brain, cornea, kidney and heart.[53] The genetic mutation is on the ATP7B gene, which codes for P-type ATPase (cation transport enzyme). This leads to impaired biliary copper excretion and linkage of copper to ceruloplasmin, a copper-carrying protein. As copper continues to accumulate in the liver, patients may present with asymptomatic elevation of liver enzymes, hepatitis, cirrhosis or with fulminant liver failure. These patients may also present with hemolytic anemia due to copper inhibition of red blood cells energy metabolism or direct damage to the cell membrane. When patients with Wilson's disease present with fulminant liver failure, it is thought that a significant amount of copper is released from necrotic hepatocytes. Plasma-free copper then causes rapid destruction of red cells which leads to rapid release of plasma-free hemoglobin. Elevated plasma-free hemoglobin has been shown to cause oxidative stress, nitric oxide depletion, endotheliopathy, microvascular thrombosis, and multiple organ failure. The only definite therapy is liver transplantation. However, without aggressive support, the patient is at risk of succumbing prior to liver transplantation.

The ASFA gives a category I recommendation for TPE in Fulminant Hepatic Failure with Hemolysis.[1] TPE is thought to provide rapid removal of plasma-free copper and hemoglobin.[54–58] The recommended TPE replacement fluid is plasma.

Acute fulminant liver failure

Acute fulminant liver failure has many causes and can develop from previously healthy liver or from chronic liver failure.[59] The liver has four major functions including protein synthesis, toxin clearance, gluconeogenesis/glycolysis, and biliary clearance. When the functions of protein synthesis and toxin clearance are severely compromised, severe clinical deterioration ensues. The liver synthesizes most of the major coagulation proteases. Without these, patients may develop severe coagulopathy and are at high risk of spontaneous hemorrhages, especially in the brain. In addition, patients are also at high risk for developing severe cerebral edema due to accumulation of toxins such as ammonia, endogenous benzodiazepines, and aromatic amino acids etc…[60,61] If there is no spontaneous recovery of liver function, patients will require liver transplantation. Currently, there are no U.S. Food and Drug Administration approved liver-support devices. Clinicians are only able to provide supportive care for these patients such as transfusion of blood products, securing the airway for hepatic coma, providing medical support for increase intracranial pressure, providing hemodynamic support and appropriate antibiotics. These strategies, however, do not address the accumulation of toxins in the plasma. Furthermore, large amount of blood product transfusions and the commonly associated hepato-renal syndrome will inevitably lead to severe fluid overload. TPE is thought to remove the accumulation of toxins in the plasma and to restore coagulation back to its homeostasis milieu without fluid overloading the patients.[60,62–64]

The ASFA gives a category III recommendation for TPE in Acute Liver Failure.[1] The recommended TPE replacement fluid is plasma or mixed plasma and albumin.

Solid Organ Transplantations

ABO Incompatible Solid Organ Transplantation

Due to shortage of available organs and especially ABO-matched organs, ABO incompatible organs are now frequently used in transplantation. During and after an ABO-

incompatible solid organ transplantation, the recipient's natural anti-bodies to the A and/or B antigen on the donated organ will start to cause destruction of the newly grafted organ.[65] This might present as a hyperacute or acute humoral rejection. The mainstay of therapy has been immunosuppression. However, with the adjunct of TPE during the pre-and post-transplantation periods, along with immunosuppression and intravenous immunoglobulin (IVIG), survival of ABO-incompatible organs is comparable to those of ABO matched organs.

The ASFA gives a category II recommendation for TPE in ABO Incompatible Heart (< 40 months of age) and Kidney, and a Category III recommendation for ABO Incompatible Liver (liver perioperative).[1] The goal is to decrease the IgG and IgM titers to ≤ 8 in liver and < 4 in kidney and heart transplantations.[66–68] For liver transplants, antibody titer of < 8 should be aimed for 2 weeks post-transplant. For kidney transplants, the goal should be antibody titer is < 8 during the 1st week and < 16 during the 2nd week.[69,70] The recommended TPE replacement fluid is either albumin or plasma. For liver transplantation, plasma should be considered if there is significant coagulopathy.

Neurological Disorders

The ASFA gives strong recommendations (categories I and II's) for TPE in critically ill patients with a variety of primary neurological disorders.[1] The proposed mechanism of these disorders seems to stem from molecules (i.e. auto-antibodies) that have developed in the patient's plasma that cause injuries to the central and/or peripheral nervous systems. These patients often present with focal neurologic deficits and may progress to generalized devastating neurologic injuries. For example, these patients may present with gross or fine motor weakness progressing to paralysis, hyporeflexia progressing to areflexia, paresthesia, pain, cranial nerve deficit, seizures, strokes, autonomic dysfunction, and neuropsychiatric symptoms. TPE is often utilized by the clinicians when a short trial of steroids, cytotoxic agents and/or IVIG has been unsuccessful in halting the progression of signs and symptoms.[71–75]

The ASFA gives a category I recommendation for TPE in Acute Inflammatory Demyelinating Polyneuropathy (Guillain-Barre Syndrome), Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections and Sydenham's Chorea (PANDAS), Multiple Sclerosis, and Myasthenia Gravis. The ASFA gives a category II recommendation for TPE in Acute Disseminated Encephalomyelitis, Neuromyelitis Optica, Chronic Focal Encephalitis (Rasmussen's Encephalitis), and Lambert-Eaton Myasthenic syndrome.[1]

TPE is thought to remove auto-antibodies to various components of the neurologic system:

- myelin in Guillain-Barre, CIDP, Multiple Sclerosis, and Acute Disseminated Encephalomyelitis;
- neurons in the basal ganglia in PANDAS;
- acetylcholine receptor on the post-synaptic surface of the motor end plate in Myasthenia Gravis;
- aquaporin-4, a water channel on astrocyte foot process at the blood brain barrier in Neuromyelitis Optica;
- glutamate receptor GluR3 in Rasmussen's Encephalitis;
- voltage gated calcium channel of the pre-synaptic neuron in Lambert-Eaton Myasthenic syndrome.[71,74,76,77]

Because the underlying problem is the presence of pathologic auto-antibodies and not the deficiency of plasma molecules, the recommended TPE replacement fluid is albumin.

Renal

Rapidly Progressive Glomerulonephritis (RPGN)

RPGN encompasses three distinct histopathologic processes of glomerular crescent formation in at least 50% of glomeruli seen in renal biopsies. Clinically, these patients might present with a rapid course of renal failure. Therapy involves a combination of steroids and anti-cytotoxic agents. TPE is considered when these patients present critically ill and in particular, with pulmonary hemorrhage. The recommendation for TPE is also dependent on the histopathologic process.

Type I RPGN: Anti-Glomerular Basement Membrane Disease (Goodpasture's Syndrome)

Histopathology of this entity reveals linear deposits of IgG to the non-collagenous domain (NC1) of the alpha-3 chain of collagen type IV in the glomerular basement membrane. The ASFA gives a category I recommendation for TPE in Anti-Glomerular Basement Membrane disease with diffuse alveolar hemorrhage and/or with dialysis independence.[1] The ASFA does not recommend (category IV) TPE for this entity with dialysis dependence and without diffuse alveolar hemorrhage.[1] Case series have shown that TPE in those with creatinine < 6.6 mg/dL had recovery of kidney function, whereas those with creatinine > 6.6 mg/dL did not. The recommended TPE replacement fluid is albumin, but if pulmonary hemorrhage is present, then plasma is recommended. [78–81]

Type II RPGN: Immune Complex Rapidly Progressive Glomerulonephritis

Histopathology of this entity reveals granular deposits of immune complexes from a wide range of causes including post-streptococcal glomerulonephritis, membranoproliferative glomerulonephritis, lupus nephritis, IgA nephropathy, and Henoch-Schonlein purpura.[82,83] The ASFA gives a category III recommendation for TPE in Immune Complex RPGN.[1] The recommended TPE replacement fluid is albumin.

Type III RPGN: Anti-Neutrophil Cytoplasmic Anti-bodies (ANCA) – Associated RPGN (Wegener's Granulomatosis)

Histopathology of this entity reveals minimal immune deposits in the glomerulus. However, the serum contains the distinctive biomarker ANCA. The ASFA gives a category I recommendation for TPE in ANCA-associated RPGN with diffuse alveolar hemorrhage and/or with dialysis dependence, and a category III for those with dialysis independence.[1] The recommended TPE replacement fluid is albumin but, if pulmonary hemorrhage is present, then plasma is recommended.[84–87]

Other Conditions

Hemophagocytic Lymphohistiocytosis: Pathologic Hyperactive Inflammation

Secondary Hemophagocytic Lymphohistiocytosis (HLH) has been increasingly diagnosed in the intensive care unit. HLH is a syndrome of pathologic hyperactive inflammation due to unchecked immune activation. [88] Primary HLH is associated with genetic mutations such as those in the perforin gene. Perforin is normally secreted from cytotoxic T-lymphocytes and natural killer cells into the membrane of target cells and acts to trigger cell death. HLH occurs when lymphocyte-mediated cytotoxicity is impaired and apoptosis is unable to be triggered. This leads to abnormal T-cell activation and pathologic inflammatory cytokine production. Clinically these patients progress to multiple organ failure with the following clinical criteria: 1) fever; 2) splenomegaly; 3) cytopenia; 4) hypertriglyceridemia; 5)

hemophagocytosis in bone marrow, spleen, lymph nodes, or liver; 6) low or absent NK-Cell activity; 7) Ferritin > 500 ng/mL, and 8) elevated serum CD 25 (alpha-chain of soluble IL-2 receptor).[88,89] The primary treatment for familial/primary HLH is a course of immunosuppression and bone marrow transplantation. Secondary HLH is an acquired form of pathologic hyperactive inflammation due to a trigger. Epstein Barr Virus is the most commonly recognized infection associated with secondary HLH. For other associated viral, bacterial and fungal infections, the line between secondary HLH versus sepsis-induced multiple organ failure due to other mechanisms, such as immune paralysis with unresolved infection and thrombotic microangiopathy, is blurred.[90] Much research is still needed to define the best strategy to balance the immune modulation. Too much immune suppression in an immune paralyzed patient with unresolved infection could be detrimental. Inadequate immune suppression in an uncontrolled pathologic hyperactive inflammation (i.e. secondary HLH) could also be detrimental.

TPE has been reported in many small case series to be beneficial in calming the cytokine storm and to provide hematologic support in patients with primary and secondary HLH.[91–99] A recent small study found significant improved survival in patients with secondary HLH who received plasma exchange, steroids, and IVIG (n = 17) versus those who received plasma exchange, steroids, and/or cyclosporine, and/or etoposide (n = 6).[100] Currently, the ASFA has not commented on the use of TPE in HLH. Further research is warranted for this difficult therapeutic strategy.

Conclusions

TPE is a modern approach to the ancient therapy of bloodletting. Recently, the American Society for Apheresis, using an evidence-based approach, published a comprehensive apheresis guideline to aid physicians caring for critically ill patients who depend on plasmapheresis as a therapeutic strategy. We are indebted to them for their hard work. It seems that TPE as a therapy has seen an increase in usage, particularly by those who take care of critically ill patients. Using an evidence-based approach is the best way to standardize care and also to provide a platform for innovation to move the field forward.

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