CHAPTER 160

The Role of Plasmapheresis in Critical Illness

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OBJECTIVES

This chapter will:
1. Review the techniques of plasmapheresis.
2. Review the indications and evidence for plasmapheresis and therapeutic plasma exchange in critical illness.

Extracorporeal blood purification by plasmapheresis has been more streamlined and gained more interest by intensivists during the past decade. A useful document is the regularly updated "Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach" published by the American Society for Apheresis in 2007.[1]

Plasmapheresis is a method that separates and removes the plasma component from the blood of a patient. Blood has four major components: red blood cells, white blood cells, platelets, and plasma. When the soluble plasma molecules are thought to cause harm to a patient, clinicians can employ plasmapheresis to remove the harmful substances from the patient's plasma.

TECHNIQUES OF PLASMAPHERESIS

Currently, clinicians can use two main techniques to perform plasmapheresis: centrifugation and filtration. With centrifugation technique, whole blood is spun such that the four blood components of red blood cells, white blood cells, platelets, and plasma are separated into layers according to their different densities. The plasma layer then is withdrawn and discarded. With filtration technique,

whole blood passes through a filter to separate the plasma component from the larger cellular component of red and white blood cells and platelets.

Plasmapheresis by centrifugation is performed commonly by blood bankers. The advantage of using centrifugation is that there is no limit on the size of the molecules being removed. The disadvantage is that this requires an extra resource with consultation to the blood bank service. Plasmapheresis by filtration is performed commonly by nephrologists and intensivists. The advantage of using this technique is that a large filter can be added easily onto an existing continuous venovenous renal replacement therapy circuit. The disadvantage of using filtration is that there is a limit on the size of the molecules being removed, which is dependent on the pore size of the filter. The efficiency of removing plasma molecules with a standard 1 to 1.5 plasma volume exchange ranges from 63% to 83%.[2] For example, if a patient has 100 harmful molecules in the plasma, after a standard 1 to 1.5 volume exchange, there will be from 37 to 17 harmful molecules left in the plasma.

Replacement Fluid

Currently, there is no consensus on which type of replacement fluid to use during plasmapheresis. The more common options are albumin and fresh frozen plasma. The goals of the replacement fluid are to (1) prevent hypovolemia, (2) maintain appropriate plasma oncotic pressure, (3) maintain appropriate levels of coagulation factors, and (4) replenish depleted beneficial plasma substances. For example, if the pathophysiologic processes can be narrowed down to the presence of a few substances such as autoantibodies to the peripheral nerve myelin in Guillain-Barré syndrome, then the replacement fluid can be albumin. However, if the intensity and frequency of plasmapheresis is high, then after a couple of plasmapheresis sessions with albumin, fresh frozen plasma should be used as a replacement fluid to prevent significant dilutional coagulopathy. However, more often, because the pathophysiologic processes of critical illness involve multiple complex and interrelated pathways, there is an accumulation and deficiency of harmful and beneficial substances respectively in the patient's plasma. Sepsis-induced multiple organ failure is an example of such a complex pathology. In these cases, a strategy of removing harmful substances and replacing beneficial substances often is recommended. Therapeutic plasma exchange (TPE) is the commonly used term to indicate plasmapheresis followed by replacement with fresh frozen plasma infusion.

Indications and Evidence of Plasmapheresis and Therapeutic Plasma Exchange in Critical Illness

In the latest version of the "Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach" published by the American Society for Apheresis (ASFA), the recommendations are divided into four categories:

- Category I: Disorders for which apheresis is accepted as first-line therapy, either as a primary stand-alone treatment or in conjunction with other modes of treatment
- Category II: Disorders for which apheresis is accepted as second-line therapy, either as a stand-alone 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. Institutional Review Board (IRB) approval is desirable if apheresis treatment is undertaken in these circumstances.

The ASFA document gives an extensive review of the literature on the rationale for plasmapheresis in 72 diseases, including technical recommendations such as duration and types of replacement fluid. In this chapter, we briefly review diseases in critically ill patients for whom plasmapheresis/TPE is recommended as first-line therapy by the ASFA. We can group these recommendations into thrombotic microangiopathies, acute liver failure, neurologic disorders, renal disorders, and ABO-incompatible solid organ transplantation. We also discuss the current evidence and research for TPE in sepsis-induced multiple organ failure, because this still has a high mortality rate without specific therapeutic strategy other than support care.

THROMBOTIC MICROANGIOPATHIES

Thrombotic microangiopathies (TMA) are a family syndrome associated with disseminated microvascular thromboses. The clinical features include microangiopathic hemolytic anemia, thrombocytopenia, and if untreated, MOF.[3] The ASFA gives a category I recommendation to use TPE for thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) resulting from factor H autoantibodies, and ticlopidine-mediated TMA.

Thrombotic Thrombocytopenic Purpura

The clinical pentad of TTP includes thrombocytopenia, hemolytic anemia, fever, and neurologic and renal abnormalities. Common laboratory findings of lactate dehydrogenase elevation and the presence of schistocytes support the evidence for a thrombotic microangiopathic process. However, the specific ADAMTS-13 activity and von Willebrand factor (VWF) assays are required to confirm the diagnosis of TTP. The underlying pathology is the deficiency of ADAMTS-13 (also known as VWF-cleaving protease) resulting in uncleaved thrombogenic ultra-large and large VWF multimers in the plasma. These ultra-large VWF multimers can aggregate platelets spontaneously. Autopsies of patients who died with TTP reveal disseminated VWF- and platelet-rich microthrombi.

There are two forms of TTP: inherited and acquired. In both forms, the ADAMTS-13 activity level is less than 10%. There have been more than 80 mutations of the *ADAMTS13* gene identified causing TTP.[4] Inhibitory autoantibody immunoglobulin G (IgG) has been reported to cause acquired TTP.[5,6]

TPE has been shown in a large randomized controlled trial to significantly improve survival in TTP compared with plasma infusion alone.[7] TPE is considered a standard therapy for TTP. TPE is thought to remove ADAMTS-13 inhibitors such as autoantibodies IgG and ultra-large VWF and replenish ADAMTS-13.

Complement-Mediated Thrombotic Microangiopathies and Atypical Hemolytic Uremic Syndrome

Atypical HUS is considered a problem of uncontrolled activation of the alternative complement pathway. Similar to TTP, the clinical signs and symptoms include thrombocytopenia, microangiopathic hemolytic anemia, and renal and neurologic abnormalities. The dysregulation of

the alternative complement pathway can be caused by a genetic mutation or acquired inhibitory autoantibodies. More than 120 complement genetic mutations have been linked to atypical HUS.[8] Inhibitory autoantibodies IgG for factor H have been described in up to 10% of patients with atypical HUS.[9] Factor H regulates and inhibits the alternative complement pathway. These complement regulatory factors are expressed and bound to the endothelium. They protect the endothelium from complement-induced damage. Overall mortality is approximately 25% for all complement-mediated TMA.[9]

The ASFA gives a category I recommendation to use TPE in factor H autoantibodies mediated TMA. TPE is thought to remove factor H autoantibodies and replace the deficient complement regulators. Confirming the diagnosis of complement-mediated TMA is difficult because it depends on specialized assays, including Shiga toxin PCR, ADAMTS-13, factor H IgG, and genetic testing. It still is considered the standard of care to initiate TPE before TTP is ruled out.

Drug-Associated Thrombotic Microangiopathies

Ticlopidine, an antiplatelet drug that inhibits adenosine diphosphate receptor, has been shown to inhibit ADAMTS-13 activity levels to less than 10%. The clinical signs and symptoms are similar to that of TTP. The pathogenesis for drug-associated TMA is thought to be multifactorial, including endotheliopathy, drug-dependent antibodies, and autoimmunity. The ASFA gives a category I recommendation to use TPE in ticlopidine-associated TMA.[1]

LIVER FAILURE

Acute Liver Failure

Acute liver failure can occur from a previously healthy liver or from chronic liver failure. The liver has four major functions, including protein synthesis, toxin clearance, gluconeogenesis/glycolysis, and biliary clearance. The liver synthesizes most of the coagulation factors such that when this function is compromised, the patient can develop significant coagulopathy that can lead to spontaneous intracranial hemorrhages. The liver clears toxins such as ammonia, endogenous benzodiazepines, and aromatic amino acids. When these toxins accumulate during liver failure, these patients can develop severe cerebral edema and herniation. The mortality rate for acute liver failure from a previously normal liver is 50% to 90%.

The rationale for TPE in acute liver failure is to remove toxins and support coagulation without fluid overloading while waiting for the liver to recover or bridging to liver transplantation. Larsen et al. reported in a recent randomized controlled trial that high-volume TPE, defined as 15% of ideal body weight with fresh frozen plasma, for 3 consecutive days was associated with a significant improvement in liver transplant-free survival.[10] This has led to an ASFA category I recommendation to use TPE-high volume in acute liver failure from a previously healthy liver. The ASFA still gives a category III recommendation to use TPE (not high volume) in acute liver failure.[1]

Fulminant Wilson Disease With Acute Liver Failure

Wilson disease is an autosomal-recessive genetic disorder that results in excessive accumulation of copper in the liver, brain, cornea, kidney, and heart. The pathogenesis is the impaired biliary copper excretion and linkage of copper to ceruloplasmin, a copper-carrying protein. As copper continues to accumulate in the liver, the liver progresses from hepatitis to fulminant liver failure. Plasma-free copper also causes rapid destruction of red blood cells, leading to elevation of plasma-free hemoglobin. Plasma-free hemoglobin can cause oxidative stress, nitric oxide depletion, endotheliopathy, microvascular thrombosis, and MOF. The only definitive therapy is liver transplantation. The ASFA gives a category I recommendation to use TPE in fulminant Wilson disease with acute liver failure. TPE is thought to (1) remove copper, plasma-free hemoglobin, and toxins accumulated from acute liver failure and (2) support coagulation.[1]

NEUROLOGIC DISORDERS

Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), myasthenia gravis, and N-methyl D-aspartate receptor (NMDAR) antibody encephalitis have a category I recommendation from the ASFA to use plasmapheresis/TPE. These patients often have focal neurologic deficits that can progress to generalized devastating injuries. For example, the patients can have distal muscle weakness or psychiatric manifestations and progress to paralysis, respiratory failure, seizures, autonomic dysfunction, and strokes. The pathogenesis is thought to be caused by developing autoantibodies to various components of the neurologic systems, such as autoantibodies to (1) myelin in Guillain-Barré and its chronic form CIDP, (2) acetylcholine receptor on the postsynaptic surface of the motor end plate in myasthenia gravis, and (3) NMDAR in NMDAR-encephalitis. TPE often is used after a short trial of steroids, cytotoxic agents, and/or intravenous immunoglobulin have been unsuccessful in halting the disease progression. TPE is thought to remove the autoantibodies that are causing the destruction.[1]

RENAL DISORDERS

Rapidly progressive glomerulonephritis (RPGN) is classified into three types based on histopathologic findings. Patients with RPGN often have a rapid course of acute kidney injury/failure, and some may present with diffuse alveolar pulmonary hemorrhage. Plasmapheresis/TPE is recommended for types I and III RPGN when these patients are critically ill, in particular, with severe active kidney injury and/or pulmonary hemorrhage.

Type I RPGN (antiglomerular basement membrane disease) is characterized by the deposition of autoantibodies IgG against the noncollagenous domain of the alpha3 chain of collagen type IV in the glomerular basement membrane. In some cases, these autoantibodies also attack the basement membrane of the lung alveoli, leading to Goodpasture syndrome. The ASFA gives a category I recommendation to use plasmapheresis/TPE in antiglomerular basement membrane disease with diffuse alveolar hemorrhages and/or dialysis independence with Cr more than 6 mg/dL at presentation.[1]

Type III RPGN (antineutrophil cytoplasmic antibodies [ANCA]) has minimal immune deposits in the glomerulus. However, the serum contains the distinctive biomarker ANCA. Similar to the recommendation to type I RPGN, the ASFA gives a category I recommendation to use

plasmapheresis/TPE for ANCA-associated RPGN with diffuse alveolar hemorrhages and/or dialysis-dependence with Cr more than 6 mg/dL at presentation.[1]

Focal segmental glomerulosclerosis (FSGS) has a distinct histologic finding of focal areas of sclerosis of some glomeruli adjacent to other intact glomeruli. Patients with FSGS have nephrotic syndrome and progress to end-stage renal disease within 3 to 7 years. The pathogenesis is unclear but is thought to result from harmful substances in the plasma. Recurrent focal segmental glomerulosclerosis in a transplanted kidney often responds to a combination of TPE, steroids, immunosuppression, and/or angiotensin-converting enzyme inhibitors. TPE is thought to remove these unidentified harmful substances and to prevent premature allograft loss. The ASFA gives a category I recommendation to use plasmapheresis/TPE in recurrent FSGS in a transplanted kidney.[1]

ABO-Incompatible Renal Transplantation

Because of the shortage of compatible organs for renal transplantation, ABO-incompatible living donors are used frequently. During and after an ABO-incompatible kidney transplantation, the recipient's natural antibodies to the A and/or B antigen on the donated organ start to cause destruction of the newly grafted organ. This can occur as a hyperacute or acute humoral rejection. The goal of TPE is to reduce the antibody titer to a less than critical threshold before transplant. This threshold titer is determined by each transplant program. The number of TPE sessions required depends on the baseline IgG titer and on the rate of antibody rebound. With the adjunct of TPE during the pre- and posttransplant periods, along with immunosuppressive treatment, survival of ABO-incompatible kidney transplants is comparable to those with ABO-matched kidneys. The ASFA gives a category I recommendation to use plasmapheresis/TPE in ABO-incompatible kidney transplantation.[1]

SEPSIS WITH MULTI-ORGAN FAILURE

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[11] Even with the best effort in septic shock resuscitation and early infection source control, a subset of septic patients still progress to significant tissues injuries and MOF. How each host responds so differently from each other to septic shock resuscitation depends on the time to source control and to the genetic makeup and environment factors of the host and pathogen. Organ failure has a cumulative effect on sepsis mortality such that mortality rates in septic adults increase from 15% without organ failure to 70% with three or more failing organs.[12] Over the past three decades, more than 60 failed phase II and III randomized controlled trials of specific monopharmacologic adjuvant for sepsis have been conducted. Many of these failed trials aimed to modulate the inflammation, coagulation, and fibrinolysis pathways.[13] As a result of these failed trials, there is a rise in interest of nonspecific therapies for sepsis-induced MOF such as TPE. In a recent meta-analysis of randomized trials of blood purification for sepsis, Zhou et al. reported that TPE was associated with a decrease in mortality (risk ratio, 0.63 [95% CI, 0.42–0.96]; $p < .03$; two trials, n = 128).[14]

Investigators are proposing that there are certain types of MOF pathobiologic phenotypes that can benefit from TPE. For example, thrombocytopenia-associated MOF (TAMOF) is a clinical syndrome characterized by new-onset thrombocytopenia in a setting of evolving MOF.[15] TAMOF represents a spectrum of mixed thrombotic microangiopathies and coagulopathies including TTP, HUS, and disseminated intravascular coagulation (DIC). The drop in platelet count in this syndrome suggests the pathologic involvement of platelets as they form disseminated microvascular thromboses in the vascular bed of tissues, which leads to ischemia and injury resulting in the observed MOF. Nguyen et al. reported that pediatric patients with new-onset thrombocytopenia with platelet counts less than 100,000/mm^3 and at least three failing organs had a pathophysiologic process similar to that of TTP, such as low ADAMTS-13 activities (<57%), the presence of ultra-large VWF, and high VWF activities.[16] A subset of these TAMOF patients also had prolonged prothrombin time and increased plasminogen activator inhibitor type-1 activities, suggesting fibrin pathway activation and impaired fibrinolysis as in DIC. On autopsies, pediatric TAMOF have disseminated VWF- and platelet-rich microthrombi similar to patients with TTP, and fibrin-rich microthrombi similar to patients with DIC. These investigators reported in a small randomized controlled trial that TPE restored ADAMTS-13 activities, reduced organ dysfunction, and improved survival in pediatric TAMOF.[16] Since then others have reported in larger cohorts of pediatric TAMOF that TPE was associated with improved survival compared with standard therapy.[17–19]

The rationale to use TPE is that the pathophysiologic processes in sepsis-induced MOF involve many interrelated and dysregulated pathways, including inflammation, coagulation, and fibrinolysis, resulting in numerous circulating molecules that are either pathologically elevated or depleted. Therefore inhibiting or replenishing one molecule is probably inadequate. Because TPE by centrifugation removes all soluble plasma molecules and replenishes septic plasma milieu with normal fresh frozen plasma, investigators have hypothesized that TPE can have effects other than previously mentioned in the mechanisms of sepsis-induced MOF. Based on the current evidence, the ASFA gives a category III recommendation for the use of TPE in sepsis with multi-organ failure.[1]

CONCLUSION

Plasmapheresis/TPE is considered standard therapy in a number of critical illnesses. The evidence-based guidelines from various societies have helped to educate and streamline the use of this invasive and resource-demanding procedure by critical care physicians. Encouraging reports on the use of TPE from small cohorts of patients for numerous other conditions in critically ill patients have garnered appreciable interest from critical care physicians worldwide. Large multicenter randomized controlled trials are needed to move the field forward to standardize the use of plasmapheresis/TPE in these critical illnesses.

Key Points

1. Plasmapheresis separates and removes the plasma component from blood.
2. Plasmapheresis can be accomplished by two major techniques: centrifugation or filtration.

3. Therapeutic plasma exchange (TPE) is a commonly used term to indicate plasmapheresis followed by replacement with fresh frozen plasma infusion.
4. Plasmapheresis/TPE is accepted as first-line therapy, either as a primary stand-alone treatment or in conjunction with other modes of treatment in

a. Thrombotic thrombocytopenic purpura
b. Complement factor H inhibitory autoantibodies mediated thrombotic microangiopathy
c. Ticlopidine-mediated thrombotic microangiopathy
d. Acute liver failure (using high-volume TPE)
e. Fulminant Wilson disease with acute liver failure
f. Guillain–Barré syndrome
g. Chronic inflammatory demyelinating polyradiculoneuropathy
h. Myasthenia gravis
i. N-methyl D-aspartate receptor antibody encephalitis
j. Antiglomerular basement membrane disease with diffuse alveolar hemorrhages and/or severe active kidney injury with dialysis-independence
k. Anti-neutrophil cytoplasmic antibodies (ANCA)–associated rapidly progressive glomerulonephritis with diffuse alveolar hemorrhages and/or severe active kidney injury with dialysis-dependence
l. Recurrent focal segmental glomerulosclerosis in transplanted kidney
m. Desensitization during perioperative ABO incompatible kidney transplantation

5. New indications such as sepsis with multi-organ failure warrant investigation with large randomized controlled trials.

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A complete reference list can be found online at ExpertConsult.com.

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