

Acute Dialysis Quality Initiative

3rd International Consensus Conference

Workgroup 2

Plasma Therapies in Thrombotic Syndromes

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Introduction

Plasma therapies are currently applied in a variety of ways and for a variety of indications. There are a limited number controlled studies and general consensus as to how these therapies should be applied or to whom has not previously been assessed.

What are plasma therapies and how are thrombotic syndromes defined?

Plasma therapies, a group of interventions that either add and/or remove plasma components in patients (e.g. plasma infusion, plasma exchange by centrifugation or filtration, adsorptive columns), have been applied to many disease states in the intensive care units worldwide. Thrombotic syndromes are the most common indications for the application of plasma therapies; however, there are only a handful of controlled studies and a diverse number of protocols. We define thrombotic syndromes as consumptive or non-consumptive coagulopathic states leading to multiple organ dysfunction syndrome (MODS). Many investigators have chosen the following criteria listed in Table 1 as **consumptive coagulopathy** or **non-consumptive coagulopathy** (1-2). Thrombotic syndrome is primary if the etiology is unknown as in Thrombotic Thrombocytopenic Purpura (TTP), and secondary if it is associated with an underlying disease process (e.g. sepsis, Hemolytic Uremic Syndrome [HUS], TTP/HUS, cancer, transplantations, immunologic disorders, pregnancy, drug exposure, pancreatitis, etc.).

Consensus Statement: Consensus criteria consumptive and non-consumptive coagulopathy are provided in table 1.

Is there biological plausibility for the use of plasma therapies to reverse coagulopathy?

Thrombotic Thrombocytopenic Purpura (TTP) is a non-consumptive thrombotic syndrome that is heralded by new onset thrombocytopenia leading to multiple organ failure and death if left untreated. The underlying defect is the deficiency of ADAMTS13 (e.g. von Willebrand factor cleaving protease), and the presence of the thrombogenic ultra-large von Willebrand factors (vWf) in the plasma (3-4). There has been a large randomized controlled trial (RCT) showing that plasma exchange significantly increased survival in TTP patients compared to plasma infusion alone (5). Plasma exchange is postulated to remove the ultra-large vWf multimer, with size up to 12 million Daltons, and the ADAMTS13 inhibitors, while replenishing the deficient ADAMTS13 (4,6-8) (Table 2). Although the cause of TTP is idiopathic, nonconsumptive and consumptive coagulopathies can also be triggered by systemic endotheliopathy caused by infection, toxins or drug exposure, and cancer which activate coagulation, complement, and inflammatory mediator cascades. In consumptive thrombotic syndromes such as DIC (disseminated intravascular coagulation), procoagulants such as tissue factor, and anti-fibrinolytic factors such as plasminogen activator inhibitor type 1 are released and activated leading to a prothrombotic/antifibrinolytic state. Anti-coagulants such as protein C and antithrombin III are consumed leading to thrombosis with further consumption of coagulation factors including factor VII causing subsequent microvascular thrombosis and a bleeding diathesis. Plasma therapies have been reported to remove, and replenish these factors to the homeostatic milieu (6, 9-12, 34-35) reversing DIC and its coagulopathy (Table 2).

Consensus Statement: there is biological rationale for plasma therapies to reverse the coagulopathy in non-consumptive and consumptive thrombotic syndromes. This rationale has been strengthened by advances in the understanding of the molecular mechanisms involved in some of the diseases that result in thrombosis (e.g. TTP) while others (e.g. sepsis) remain poorly understood.

How do the different types of plasma therapies compare?

There is a variety of methods to alter plasma components of patients. Plasmapheresis, separating plasma components from whole blood, can be accomplished by two distinct techniques. Plasmapheresis by centrifugation technique has the advantage of removing all sizes of plasma components (13-14). This process is commonly used by the blood bank. With plasmafiltration, the size of the molecules removed is dependent on the filter used (15). This technique is used by nephrologists and intensivists by applying a filter to the continuous veno-venous circuit. Replacing the removed plasma with a particular type of fluids and/or blood products alters the plasma components differently. Fresh frozen plasma (FFP), liquid-stored plasma, cryosupernatant, 5% albumin, crystalloids, or the mixtures of these products has widely different plasma components (16). Adsorptive columns or sorbent-based hemoperfusion also has been used to remove toxins in patients with sepsis (17-19) Blood products and/or crystalloid infusions alone only add or dilute plasma components.

The pros and cons of different plasmapheresis techniques have been vigorously debated. Plasmafiltration, compared to centrifugation, has been reported to activate platelet and complement cascade (13, 20). The filter in plasmafiltration may not be able to remove the ultra large vWF multimers with sizes up to 12,000kD. There have been positive randomized controlled trials using plasma exchange by centrifugation method for thrombotic syndromes (5) and sepsis (21). Currently, there is no reported positive randomized controlled trial using plasmafiltration in thrombotic syndromes and/or sepsis (15).

Consensus Statement: There is currently no evidence or consensus of opinion as to which form of plasma therapy should be used to treat thrombotic syndromes. Studies comparing various forms of therapy are urgently needed. Patients with thrombotic syndromes (primary or secondary) have a high risk of mortality. Plasma exchange by centrifugation is the current recommendation for primary thrombotic syndrome (Grade C), and could be beneficial in secondary thrombotic syndromes (Grade E).

Is there consensus on the use of plasma therapies for thrombotic syndromes and/or sepsis?

Because of the diverse biological effects dependant on the types of plasma therapies used, each type must be evaluated accordingly. Currently, there are only a few randomized controlled trials, but many case series reporting the effect of plasma therapies in thrombotic syndromes and/or sepsis. In a large randomized controlled trial comparing plasma exchange (centrifugation technique) versus plasma infusion alone for the treatment of TTP, Rock et al. reported improved survival in patients receiving plasma exchange (78% vs. 50% for no crossover, and 71% for crossover; $p = 0.002$). The patients in the plasma-exchange group received an average of 15.8 treatments (range, 3-36) over two or three 9-day cycles. The volume exchanged was 1.5 times the predicted volume for the first 3 days followed by 1.0 times the predicted volume daily (5). Since this study, plasma exchange has been the standard therapy for patients diagnosed with TTP. In a large prospective randomized controlled trial of 106 patients, Busund et al reported plasma exchange (centrifugation technique) improved survival in patients with severe sepsis and septic shock. The mortality rate was 33.3% in the plasma exchange group and 53.8% in the control group (21). In a smaller multicenter prospective RCT of 30 patients, Reeves et al. reported plasma exchange (plasmafiltration technique) did not improve survival in septic patients, but there was a trend toward fewer organ failures. These patients received plasma exchange of five times the predicted plasma volume over 34 hours (15). In a large retrospective case series, Stegmayr et al. reported that plasma exchange (centrifugation technique) improved survival in patients with progressive DIC and multiple organ failure. Seventy-six consecutive patients received plasma exchange with a resultant survival rate of 82%, whereas the previously observed survival rates in this patient population were <20%. Median number of plasma exchanges was 2 (range 1-14), and of organ dysfunction was 5 (range 1-6) (14).

Consensus Statement: Plasma therapies, in particular plasma exchange, appear to be safe in patients with primary or secondary thrombotic syndrome and sepsis. Plasma exchange by centrifugation is indicated for

primary thrombotic syndrome (Grade A recommendation based on Level I evidence), sepsis (Grade C, based on a single Level II and several weaker studies), and secondary thrombotic syndrome (Grade D based on Level IV and V evidence). Available evidence is limited with respect to plasma exchange by filtration.

What is the current practice with plasma therapies in thrombotic syndromes?

Patients with thrombotic syndromes are at high risk for mortality if the coagulopathy is not being addressed. Currently, there are only a few randomized controlled trials (mentioned above) and many case series reporting the use of plasma therapies for a variety of disease state. There are many studies evaluating the use of plasma exchange in primary thrombotic syndrome TTP (5, 22-23). There are many more studies appraising plasma exchange in secondary thrombotic syndromes such as: hemolytic uremic syndrome (HUS) (24); TTP/HUS syndrome (25-26); thrombocytopenia associated multiple organ failure (14, 27); sepsis (9-10, 13, 21); status-post bone marrow transplantation (23, 25); status-post solid organ transplantation (25); HELLP Syndrome (Hemolytic Anemia, Elevated Liver Enzymes, Thrombocytopenia associated with pregnancy) (23, 28); neoplasm (23, 29); immunologic Disorders (23, 30); drug exposure (31-32); and pancreatitis (33).

For secondary thrombotic syndrome, no consensus has been formed on the patient selection, methods of plasma therapies, and biologic plausibility of the therapy. However, there has been an increased interest and application of the plasma therapies in thrombotic syndrome and sepsis worldwide.

The following recommendations are made (Grade E) on a variety of factors that should be standardized in future studies of plasma therapies, especially for use in sepsis and MODS: i. optimal ICU care; ii. aggressive search and eradication of septic focus; iii. adequate antimicrobial agents, iv. ultrafiltration for fluid overload unresponsive to diuretics, and especially for pediatrics, consideration of extracorporeal membrane oxygenation (ECMO) for refractory shock despite adequate resuscitation. In addition, adjunctive therapies such as corticosteroids, activated protein C, protein C concentrates, and antithrombin III should be standardized across treatment arms. Close monitoring of treatment efficacy includes monitoring of coagulation, inflammation and organ failure markers. Cessation of plasma therapies should be considered with reversal of coagulopathy and resolution of organ dysfunction. Risks of the procedure include complications of placing a large bore central line, using systemic or local anticoagulants, risks associated with blood product administration and of potentially removing beneficial molecules from the plasma.

Consensus Statement: The application of plasma therapies is highly variable across centers. Currently, both centrifugation and filtration are used depending on local practice patterns. There appears to be wide consensus for the use of plasma therapies for primary thrombotic syndrome (TTP) and some secondary syndromes (e.g. HUS) while other indications including sepsis remain controversial.

Who should be considered for plasma therapies, when and for how long?

For primary thrombotic syndrome (TTP), plasma exchange is recommended as soon as the diagnosis of TTP is suspected – new onset thrombocytopenia, hemolytic anemia, central nervous system, and/or renal involvements, +/- schistocytes, fever, elevated LDH, low ADAMTS13 activity, elevated vWf antigen, and +/- ultra large vWf (Grade A).

For secondary thrombotic syndrome, plasma therapies have been used for patients with coagulopathy and progressive multiple organ failure. The use for these indications is based on limited evidence. Criteria for initiation of plasma therapies have included the following: thrombotic syndromes with coagulopathy, and 2 or more failing organs; disseminated intravascular coagulation (DIC); or TTP/HUS. Plasma therapies should be initiated within 30 hours and preferable within 6 hours (Grade E). However, with certain diseases such as meningococemia and super antigen mediated infection, it is advisable to start urgently after reversal of shock (Grade D). Available evidence suggests that between 2 to 28 days of therapy will be required (Grade D).

Consensus Statement: For primary thrombotic syndrome, there is consensus that therapy should begin immediately after the diagnosis is established. For secondary syndromes, there is no consensus on patient selection or timing.

What physiological, biochemical, and clinical end points should be used for future studies involving plasma therapies?

Possible physiologic and biochemical end points for plasma therapies are: improved organ function and coagulation. Possible clinical end points for plasma therapies are: reduced numbers of organ dysfunction; 28-day survival; survival to hospital discharge; ventilator-free day; duration of ICU stay; duration of hospital stay; and/or adverse events.

In the RCT by Rock et al, primary thrombotic syndrome was reversed with the evidence of rise in platelet count and no further neurologic deterioration after a 9-day cycle with plasma exchange (5). Busund et al showed in their RCT that APACHE III score decreased significantly from day 1 to day 2 with plasma exchange (21). Reeves et al. reported in their RCT that there was trend toward fewer organs failing with plasmfiltration (15). Case series had reported that coagulation factors, fibrinogen, plasminogen-activator-inhibitor type-1, endotoxin, inflammatory mediators normalized after plasma exchange (6, 9, 11-12, 34-35).

Consensus Statement: There are sufficient preliminary data to recommend performance of definitive randomized controlled trials to investigate the role of plasma exchange in secondary thrombotic syndromes. Secondary clinical research goals include evaluation of the role of plasmfiltration compared to centrifugation, as well as the role of various replacement fluids compared to fresh frozen plasma.

Table 1. Criteria for consumptive and non-consumptive coagulopathy

Consumptive Coagulopathy	Non-consumptive Coagulopathy
New onset thrombocytopenia (platelet count < 100K or decreased daily by 40K in the presence of MODS with a megakaryocytes response)	New onset thrombocytopenia (platelet count < 100K or decreased daily by 40K in the presence of MODS with a megakaryocytes response)
APTT > 1.5 normal value	Increased LDH
Antithrobin III < 80%	+/- Hemolytic anemia
Increased fibrinogen degradation products	+/- Increased fibrinogen degradation products
Decreased fibrinogen level	Normal to high fibrinogen level
Increased von Willebrand factor antigen	Increased von Willebrand factor antigen
	+/- Schistocytes

Table 2. Primary and secondary thrombotic syndromes after plasma exchange by centrifugation

	Primary Thrombotic Syndrome	Secondary Thrombotic Syndrome
ADAMTS13 activity	Replenished	Replenished
Inhibitors to ADAMTS 13	Removed	Removed
vWF Antigen	Removed	Removed
Ultra Large vWf	Removed	Removed
Plasminogen Activator Inhibitor type-1	Removed	Removed
Coagulation Factors	Normal	Replenished
ATIII/Protein C	Unknown	Replenished
Tissue Factor	Unknown	Removed

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