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Therapeutic Plasma Exchange as a Strategy to Reverse Multiple Organ Dysfunction Syndrome in Patients Receiving Extracorporeal Life Support

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Therapeutic plasma exchange (TPE) as a strategy to reverse multiple organ dysfunction syndrome (MODS) in severe sepsis has been gaining interest for the past decade. In an abstract earlier this year at the 43rd Critical Care Annual Congress, Ruth and colleagues reported the use of extracorporeal therapies in pediatric severe sepsis by using the Pediatric Health Information System (PHIS) database of 561,947 critically ill children from 37 hospitals during 2004–2012 (1). 39,372 patients met criteria for severe sepsis. These investigators found that TPE was used in 4.2% pediatric severe sepsis patients with a mortality of 20.9%. Other extracorporeal therapies such as continuous renal replacement therapy (CRRT) and extracorporeal life support (ECLS) were used in 5.3% and 4.2% in the same patient population with mortalities of 45% and 49.5% respectively. Recently Dr. Fink wrote an informative review highlighting numerous failed phase II and III randomized controlled trials during the past three decades of **specific** mono-pharmacological adjuvant or 'silver bullet' agents for sepsis (2). This experience has likely contributed to the rise of interest in the use of **non-specific therapies** for sepsis such as TPE. Based on the existing evidenced based literature on the use for TPE for severe sepsis induced MODS, the American Society for Apheresis gives the following category III recommendation, which is that "Optimum role of apheresis therapy is not established' and 'Decision making should be individualized" (3). In a recent meta-analysis of randomized trials of blood purification for

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sepsis, Zhou and colleagues reported that blood purification for sepsis decreased mortality compared to no blood purification (35.7% vs 50.1%; risk ratio, 0.69 [95% CI, 0.56–0.84]; p<0.001; 16 trials, n = 827) (4). They found that blood purification using hemoperfusion (risk ratio, 0.63 [95% CI, 0.50–0.80]; p<0.001; 10 trials, n = 557) or TPE (risk ratio, 0.63 [95% CI, 0.42–0.96]; p<0.03; 2 trials, n = 128) was associated with a decrease in mortality. In adults with severe sepsis, two of three randomized studies have reported that TPE had a significant beneficial treatment effect. Busund and colleagues reported that TPE significantly decreased the 28-day mortality (5). Darmon and colleagues reported that TPE significantly decreased hospital mortality and reversed MODS (6). Reeves and colleagues reported that there was a trend toward reversing MODS (7) but not improvement in survival.

In pediatrics, there are ‘three proof of concept’ published studies reporting the beneficial treatment effect of TPE in inflammation phenotype specific sepsis-induced MODS. We previously reported a small study of pediatric patients with the thrombocytopenia-associated multiple organ failure (TAMOF) phenotype who had low ADAMTS-13 (a.k.a. von Willebrand factor(VWF)-cleaving protease) activities and elevated VWF activities(8). We demonstrated on autopsies that these TAMOF patients died with disseminated VWF-rich microvascular thromboses, which was the proposed mechanism of MODS in this phenotype. Using TPE as it is used to treat thrombotic thrombocytopenic purpura (3), we demonstrated that TPE replenishes ADAMTS-13, removes pathologic ultra-large VWF multimers, and reverses organ dysfunction in sepsis-induced TAMOF patients. Sevketoglu and colleagues recently reported from the Turkish TAMOF Network that TPE was associated with improved survival in pediatric TAMOF (9). Demirkol and colleagues reported from the Turkish Secondary Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)Critical Care Study Group that TPE along with IVIG and methylprednisone improved survival in HLH/MAS associated with TAMOF (10). In support of this observation, we found that 50% of HLH patients at Texas Children’s Hospital had clinical TAMOF with autopsy evidence of disseminated microvascular thromboses (11). Because TPE removes other soluble plasma molecules and replenishes the septic plasma milieu with normal fresh frozen plasma, others have hypothesized that TPE would have effects in other pathophysiologic processes of sepsis-induced MODS.

In this issue of Pediatric Critical Care Medicine Journal, Kawai and colleagues reports their institutional experience of using TPE as strategy to reverse MODS in pediatric patients requiring ECLS for refractory septic shock (12). This study is significant for several reasons. First, it provides information on the technical aspect of combining two different extracorporeal therapies together into an existing circuit such as TPE and CRRT onto an existing ECLS circuit. Second, it reports a very high survival rate of 71.4% for sepsis-induced MODS patients receiving TPE with ECLS, whereas the PHIS database reports a survival rate of 50.5% for ECLS with severe sepsis and the ELSO registry 50% for severe sepsis. Third, it reports a decrease in Organ Failure Index and Vasoactive-Inotropic Score after 2–6 treatments with TPE. This reduction in severe sepsis-induced MODS could be related in part to reversal of TAMOF as described above, or to other ECLS specific mechanisms such as removal of free plasma hemoglobin caused by circuit induced hemolysis. Free hemoglobin is associated with mortality and MODS in ECLS (13). Despite this encouraging report, the use of TPE on or off ECLS is not without challenges. Use of

citrated blood products in TPE chelates calcium and can lead to hypotenson, therefore careful attention to hypocalcemia and appropriate calcium replacement therapy is required. This need for calcium replacement increases with younger age because bone mass relative to body size is decreased reducing the ability of the patient to maintain and mobilize calcium stores. Loss of catecholamines and sedatives from the blood compartment also occurs and leads to the need for replacement of both during the procedure. There are also risks specific to patients on ECLS. Plasma exchange will normalize INR and remove heparin therefore careful monitoring of anticoagulation as well as treatment with anticoagulants is needed during the procedure.

In summary there is accumulating and encouraging evidence of better outcomes being associated with blood purification for sepsis-induced MODS. However, there are still very limited data on blood purification for the very critically patients requiring ECLS for refractory shock. Current available blood purification meta-analysis data suggest that the hemoperfusion and TPE techniques are the first choice to study and use for severe sepsis. There are still limited data for clinicians to make a decision on important details including: type of replacement fluids such as albumin versus FFP; duration of TPE; and time to initiation of TPE. There are sufficient preliminary data to support design of randomized controlled trials to evaluate the role of TPE in sepsis-induced MODS. It would be prudent to stratify randomization in those who are and are not receiving ECLS at the time of enrollment.

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