Plasma exchange in thrombotic microangiopathies (TMAs) other than thrombotic thrombocytopenic purpura (TTP)

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Thrombotic microangiopathies (TMAs) are a diverse group of disorders that are characterized by common clinical and laboratory features. The most commonly thought-of TMA is thrombotic thrombocytopenic purpura (TTP). Because of the marked improvement in patient mortality associated with the use of therapeutic plasma exchange (TPE) in TTP, this therapy has been applied to all of the TMAs. The issue, however, is that the pathophysiology varies and in many instances may represent a disorder of the endothelium and not the blood; in some cases, the pathophysiology is unknown. The use of TPE is further obscured by a lack of strong supporting literature on its use, with most consisting of case series and case reports; controlled or randomized controlled trials are lacking. Evidence supporting the use of TPE in the treatment of TMAs (other than TTP and TMA–complement mediated) is lacking, and therefore its role is uncertain. With the greater availability of genetic testing for mutations involving complement regulatory genes and complement pathway components, there seems to be a percentage of TMA cases, other than TMA–complement mediated, in which complement pathway mutations are involved in some patients. The ability of TPE to remove abnormal complement pathway components and replace them with normal components may support its use in some patients with TMAs other than TTP and TMA–complement mediated.

Learning Objectives

- List the characteristics of thrombotic microangiopathies (TMAs) and those disorders considered to be TMAs
- Describe the pathophysiology of common TMAs
- Describe the role of therapeutic plasma exchange in the treatment of these TMAs

Introduction

Thrombotic microangiopathies (TMAs) are a diverse group of disorders that share common clinical and laboratory features (Table 1).[1] These features are a result of microvasculature thrombosis or occlusion that, depending on the disorder, may be due to acquired or inherited abnormalities of the plasma or endothelium. Historically, TMAs have been arbitrarily divided into thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), with the former further subdivided into "idiopathic" and "secondary" TTP and the latter as "typical" and "atypical" HUS. This terminology, however, fails to recognize the true complexities of the TMAs and does not distinguish between the different pathologic mechanisms. As a result, the terminology proposed by George and Nester[1] and applied in the American Society for Apheresis (ASFA) guidelines[2] and in other publications discussing these entities[3,4] is used in the present article.

The most frequently thought of TMA is TTP. TTP is characterized by the features listed in Table 1, as are all the TMAs, and results from either an inherited or acquired deficiency of ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type I motif, member 13). Initially, this disorder was almost universally fatal until the use of exchange transfusions and plasma infusions resulted in improved survival. A subsequent randomized controlled trial by Rock et al[5] of the Canadian Apheresis Study Group showed the superiority of therapeutic plasma exchange (TPE) in the treatment of patients with TTP compared with plasma infusion. As a result, this treatment has become the standard of care for TTP. Because this treatment was developed before understanding the pathologic mechanism of TTP, or any of the TMAs, TPE was subsequently applied to all TMAs based on the improved patient survival in TTP. The TPE parameters commonly used in TTP,[2] as described in Table 2, are routinely used in the treatment of the other TMAs and are discussed in the context of each.

Given the diverse pathophysiology of the various TMAs, the use of TPE in many of these disorders may not correct the underlying pathologic abnormality. In fact, a study by Li et al[6] examining the use of TPE in TMAs, in which severe ADAMTS13 deficiency (activity $<10\%$) was lacking, found no benefit when treated patients were compared with matched untreated patients. For the remainder of the present article, the role of TPE in the treatment of those TMAs described in Table 3 will be discussed; TTP will not be discussed further. The entities listed in Table 3 were selected for discussion based on their inclusion in the ASFA guidelines as well as the author's experience in supervising a busy therapeutic apheresis unit at an academic medical center performing >1000 TPEs each year.

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Table 1. Laboratory and clinical features of TMA

Laboratory features	Microangiopathic hemolytic anemia
	Anemia
	Fragmented red blood cells (schistocytes)
	Decreased haptoglobin
	Thrombocytopenia
	Evidence of end-organ damage/ischemia
	Elevated lactate dehydrogenase levels
Clinical features	Evidence of end-organ damage/ischemia
	Brain, neurologic dysfunction
	Kidneys, elevated creatinine/renal failure
	Fever

Before discussing the individual disorders summarized in Table 3, it is necessary to mention two important factors. First, there are numerous "mimics" of TMA, such as malignant hypertension, disseminated intravascular coagulation, and preeclampsia, for which TPE would not be indicated. A discussion of the diagnosis is beyond the scope of this article, and the interested reviewer is referred to the article by Go et al.[3] Second, it is necessary to briefly describe TPE and the potential mechanisms of action of TPE. TPE is defined by ASFA as "a therapeutic procedure in which blood of the patient is passed through a medical device which separates plasma from other components of blood. The plasma is removed and replaced with a replacement solution such as colloid solution (eg, albumin and/or plasma) or a combination of crystalloid/colloid solution."[2] It is important to note that this procedure is different from plasmapheresis, in which the volume of plasma removed does not require replacement. These terms are frequently used interchangeably, although this usage is incorrect. In TPE, there is the bulk removal and replacement of plasma, resulting in the nonselective removal of everything present in the plasma. This action is accomplished by using 1 of 2 separation techniques, either separating the components of the blood based on their density (utilizing centrifugation) or separating the components according to their size (utilizing filtration).[7]

Regardless of the separation technique used, numerous possible mechanisms of action of TPE have been described depending on the disease being treated. These mechanisms are not mutually exclusive, and all may be present in a given disease. The mechanisms include the removal of pathologic antibodies and substances, sensitization of antibody-producing cells to immunosuppressants and chemotherapeutic agents, removal of immune complexes with improvement in monocyte/macrophage function, removal of circulating cytokines and adhesion molecules, replacement of missing plasma components, and alterations in immune system function (including alterations in T- and B-cell function).[8] In the context of the TMAs, it is believed that the primary mechanisms of action of TPE are the removal of pathologic antibodies and other abnormal plasma components, with the replacement of missing or abnormal proteins by "normal" proteins present within the donor plasma most commonly used as the primary replacement fluid. The other possible mechanisms of action could also play a role in the efficacy of TPE in TMAs.

A shortcoming of the apheresis literature is its lack of appropriately powered, randomized controlled trials to allow for clear evidence-based guidance on the use of any apheresis procedure in the treatment of disease.[9] To address this situation, ASFA publishes guidelines, based on a comprehensive review of the published medical literature, every 3 years.[2] A component of these guidelines is the assignment of an ASFA category to each of the evaluated diseases/disorders. The ASFA categories guide clinicians in the appropriate role for apheresis therapies, including TPE, in the treatment of disorders. The ASFA categories, which are provided for each of the disorders subsequently discussed, are defined in Table 4. It is important to note that randomized controlled trials for all of the disorders discussed are lacking; the majority of the available literature consists of case series, case reports, and the occasional historic controlled or cohort controlled trial.

TMA–Shiga toxin mediated (typical hemolytic uremic syndrome, diarrhea-associated hemolytic uremic syndrome)

TMA–Shiga toxin mediated has an incidence of 0.5 to 2 per 100 000 of the population and represents the most common TMA. Although TMA–Shiga toxin mediated is seen in adults, it is a disorder predominantly of younger children (most commonly those aged <5 years).[10] The disorder typically presents with bloody diarrhea and abdominal pain without fever. These findings are followed 2 to 10 days later by the onset of TMA with renal failure, requiring dialysis in one-third of cases. Neurologic impairment may also develop, with death occurring in 1% to 5% of cases and complications of end-stage renal disease, hypertension, and neurologic symptoms in 30% of cases.

The disorder is due to direct endothelial injury caused by Shiga toxin through prothrombotic effects and stimulation of endothelial cell release of ultra-large von Willebrand multimers. This action, in turn, activates platelets, leading to aggregation and occlusion of the microvasculature.[10] In the United States, the most common causative organism is *Escherichia coli* O157:H7, whereas in developing countries, *Shigella dysenteriae* type 1 predominates. In 2011, an outbreak due to *E coli* O105:H4 occurred in Europe.[11] The source of exposure to these organisms varies depending on the organism but is a result of fecal contamination (either from humans or livestock) of food and water. The classic source for *E coli* O157:H7 is undercooked ground beef.

Given that TMA resulting from Shiga toxin is due to direct endothelial cell injury and not a result of circulating antibodies or abnormal plasma proteins, it is difficult to hypothesize how TPE would be effective in this disorder. It is possible that the removal of Shiga toxin, cytokines, and ultra-large von Willebrand multimers could reduce endothelial damage, although evidence supporting this theory is lacking.[2] The ASFA guidelines state that "there is no compelling evidence from the available literature that TPE benefits patients." Data from the 2011 European *E coli* O105:H4 outbreak revealed mixed findings. A small observational study of 5 patients found early improvement with TPE.[12] In addition, a retrospective analysis of a large database examining those treated with supportive care, TPE, or TPE and eculizumab,[13] and a case-controlled study from the same outbreak examining the efficacy of steroids, TPE, and eculizumab,[14] reported no benefit of these treatments. Despite the lack of supporting

Table 2. Characteristics of TPE procedures in TMA

Frequency: Daily
Duration: Until resolution of neurologic symptoms, lactate dehydrogenase levels approaching normal, and platelet count ≥150 000/μL for 2 consecutive days. This may be followed by discontinuing therapy or weaning. See Discussion.
Volume exchanged: 1 to 1.5 plasma volumes. See Discussion.
Replacement fluid: Plasma (eg, fresh frozen plasma, thawed, plasma, frozen plasma 24 hours) with the potential exception of TMA–*S pneumonia* associated, in which albumin is recommended by some authors. See Discussion.

Table 3. TMAs other than TTP

Disorder	Pathophysiology	ASFA category for the role of TPE (see Table 4)
TMA–Shiga toxin mediated	Direct endothelial damage with apoptosis due to effects of Shiga toxin	Presence of severe neurologic symptoms, III Absence of severe neurologic symptoms, IV
TMA–complement mediated	Endothelial damage from unregulated complement activation resulting from the development of anti–factor H autoantibodies or mutations leading to abnormal complement regulatory proteins or abnormal complement factors	Complement factor gene mutations, III Factor H autoantibodies, I MCP mutations, III
TMA–hematopoietic stem cell transplantation associated	Endothelial damage due to infection, chemotherapy, radiation therapy, or graft-versus-host disease due to transplant. Of note, a significant percentage of affected individuals may have complement regulatory pathway mutations	III
TMA–drug associated	Mechanism varies depending on drug and includes direct endothelial damage as well as the development of ADAMTS13 autoantibodies	Depending on drug, I, III, or IV
TMA–malignancy associated	Activation of coagulation by tumor tissue factor expression. Possible complement regulatory pathway mutations	NC
TMA–*Streptococcus pneumonia* associated	Exposure of normally hidden endothelial antigens by bacterial neuramidase resulting in complement mediated endothelial damage	III
TMA–coagulation mediated	Mutations in DGKE, plasminogen, and thrombomodulin resulting in thrombosis and complement activation	III
HELLP syndrome	Mutations in alternate complement pathway regulatory elements	Postpartum, III Antepartum, IV

DGKE, diacylglycerol kinase-ε; HELLP, hemolysis, elevated liver enzyme levels, low platelet counts; NC, not categorized.

evidence for the use of TPE, some have suggested that TPE should be initiated in patients with severe neurologic symptoms because of the risk of death.[15]

When TPE is used to treat TMA–Shiga toxin mediated, the treatment course is that used for the treatment of TTP, as outlined in Table 2. Again, this approach simply represents the application of the "usual" course of TPE used in TTP to other TMAs.[2]

ASFA assigns the use of TPE for the treatment of TMA–Shiga toxin mediated in the absence of severe neurologic symptoms as a category IV indication; that is, TPE is ineffective or harmful. Due to the difficulties in performing apheresis procedures in children, such as obtaining vascular access and complications of the anticoagulant used and present in the plasma replacement fluid, the use of TPE in pediatric patients has been found to represent a harmful intervention and not merely an ineffective one. In adults, these issues are still present but are not as significant; the lack of documented benefit in the face of potential complications, however, speaks against utilization of this treatment. In the presence of severe neurologic symptoms, ASFA categorizes the use of TPE as a category III indication; that is, the role of TPE is uncertain, and decision-making should be individualized.[2] Here, the severity of symptoms may warrant the risks of the procedures, although once again, obvious evidence regarding the benefit of TPE is lacking.

TMA–complement mediated (atypical hemolytic uremic syndrome)

TMA–complement mediated has an incidence of 3.3 per 1 000 000 in those aged >18 years and 7 per 1 000 000 in children.[16] It may present as a catastrophic TMA with renal injury or as chronic, progressive renal disease with crises, including acute kidney injury, stroke, retinal vein thrombosis, liver and pancreas injury, peripheral thrombosis, pulmonary hemorrhage, and bloody diarrhea. Minimal to no hematologic findings can be seen in 20% of cases, especially those in young adults. Historically, 73% of patients have developed end-stage renal failure within 5 years of diagnosis, and depending on the underlying causative mutation (see later discussion of pathophysiology), disease recurrence occurs in up to 100% of transplanted kidneys.[17]

The disorder is again characterized by endothelial damage; in this case, however, the damage is due to complement activation and vascular surface deposition resulting from dysregulation of the alternate complement pathway.[17,18] Dysregulation results from loss of function mutations in complement regulatory proteins such as factor H, membrane cofactor protein (MCP) (CD46), and factor I (60%); gain in function mutations in complement activators such as factor B and C3; or the development of autoantibodies to factor H (6%-10%). Factor H mutations are the most commonly identified (20%-30%) regulatory protein abnormality. Irrespective of the underlying cause, the results are the same: the development of TMA.

Table 4. ASFA categories

ASFA category	Definition
I	Primary treatment, either stand-alone or in conjunction with other therapies
II	Secondary treatment, either stand-alone or in conjunction with other therapies
III	Role of apheresis is uncertain, and decision-making should be individualized
IV	Evidence demonstrates apheresis to be ineffective or harmful

Testing for abnormalities in the complement pathway consists of either a serologic evaluation or molecular evaluation for mutations in the pathway. Serologic evaluation usually consists of screening for activity of the classical and alternate pathways via the CH50 and AH50 assays, respectively.[3] Patients with TMA will usually have low AH50 activity. This finding can then be followed by an assessment of individual components and the presence of split products indicating activation. A variety of patterns have been described, and the reader is referred to the review by Go et al for a discussion of these patterns. The important thing to note about the serologic analysis is that although it may be readily available, it is neither specific nor sensitive; it can be influenced by the presence of infection and other disease processes, and it may be affected by preanalytical factors because it is essential to stop complement activation in the samples by freezing them to −70°C or less within 30 minutes of collection.

Molecular testing for the presence of mutations is not affected by those factors that influence serologic assays, but they have their own shortcomings.[3] Both false-positive and false-negative results can be seen, and the presence of >400 mutations may make interpretation of test results difficult. In addition, testing is complex, requiring specialized laboratories to perform, and may have turn-around times that make such testing of limited use in determining when to initiate TPE.

With TMA–complement mediated, TPE results in the removal of aberrant complement regulatory proteins, abnormally activated complement cascade components, and autoantibodies toward factor H. It does not, however, address the underlying genetic abnormality, and patients may not respond. It has therefore been recommended that TPE be used as an initial treatment until the presence of mutations are confirmed, excluding other causes of TMA, and to control the crisis at presentation; subsequent therapy should consist of eculizumab to block the terminal component of the complement cascade.[2,18]

Response to TPE varies depending on the mutation. Better responses occur among those with factor H, C3, and factor H autoantibodies (55%-80%) compared with those with factor I mutations (25%).[19] The presence of combined mutations does not result in a worse outcome with TPE compared with single gene mutations.[20]

TPE does not correct the underlying abnormalities in MCP (CD46) mutations because this regulatory protein is located on the cell surface and is therefore not affected by TPE.[2] In the presence of MCP mutations, however, TMA resolves in 90% of patients with or without TPE.[21] In addition, renal transplantation can be successful with MCP mutations due to the cell membrane location of the regulatory protein.

When TPE is used to treat TMA–complement mediated, the treatment course is that used for the treatment of TTP (Table 2).[2] There is no "usual" course of TPE for these disorders, with therapy determined by patient response. It has been suggested that TPE be continued if there is ongoing organ response and discontinued, with initiation of eculizumab therapy, if patients are refractory to or dependent on TPE.[3] Definitions of TPE refractoriness and dependence are lacking, but it has been proposed that failure to respond to TPE within 3 to 5 days be considered refractoriness.[18]

ASFA assigns the use of TPE for the treatment of TMA–complement mediated as a category III indication; that is, the role of TPE is uncertain, and decision-making should be individualized for complement factor gene mutations and MCP mutations.[2] For the presence of autoantibodies to factor H, ASFA assigns TPE a category I indication; that is, as first-line therapy, either stand-alone or in conjunction with other therapies.

TMA–hematopoietic stem cell transplantation associated

The incidence of TMA–hematopoietic stem cell transplantation associated is unclear due predominantly to a historic lack of uniform diagnostic criteria, with competing criteria from the International Working Group[22] and the Blood and Marrow Transplant Clinical Trials Network Toxicity Committee.[23] The criteria differ with regard to the definition of significant schistocytosis and the inclusion of unexplained renal and neurologic dysfunction. An additional criticism of both criteria has been a lack of exclusion of disseminated intravascular coagulation, a common finding in this patient population. Consensus criteria have been proposed,[24] with reported incidences of TMA–hematopoietic stem cell transplantation associated in 12.7% of adult allogeneic transplants and 39% of pediatric allogeneic transplants.[25] TMA–hematopoietic stem cell transplantation associated presents with thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, and neurologic symptoms, usually within the first 6 months after allogeneic transplant.[22] Hypertension and proteinuria may occur before evidence of thrombocytopenia and microangiopathic hemolytic anemia. A mortality rate of 75% within 3 months of diagnosis of TMA–hematopoietic stem cell transplantation associated has been reported.[26]

The pathophysiology of this TMA is again endothelial damage, with potential causes including infection, chemotherapy, radiation therapy, and graft-versus-host disease.[27] A small study of 6 pediatric patients identified the presence of genetic variations in the alternate complement pathway as a risk factor for the development of TMA–hematopoietic stem cell transplantation associated, linking this form of TMA to TMA–complement mediated.[25] In this study, a high prevalence of factor H gene deletions was seen in affected recipients (83%) compared with the general population and donors (33%). Three patients also exhibited antibodies to factor H.

In TMA–hematopoietic stem cell transplantation associated, as with the previously described TMA, TPE was applied based on the former positive experience with TTP. Given the pathophysiology of endothelial damage due to a myriad of nonplasma-based causes, the therapeutic effect of TPE is questionable, although the identification of alternate complement pathway mutations in some patients suggests a possible therapeutic mechanism. Response rates to TPE have varied significantly in the medical literature. An average response rate of 36.5% (range, 0%-80%) was shown in reports from 1991 to 2003[23] and response rates of 27% to 80% in reports from 2003 to 2011.[27] The response rate in the only controlled trial, which also included discontinuation of cyclosporine, was 64%.

When TPE is used, the treatment course described in Table 2 is followed. The difficulty with monitoring response to therapy, however, is that the platelet count and lactate dehydrogenase levels may be affected by engraftment and transplant complications. Patients may therefore never achieve all of the usual criteria for discontinuation of TPE.[2]

In 2005, the Blood and Marrow Transplant Clinical Trials Network Toxicity Committee consensus statement recommended that TPE not be considered standard of care.[23] Because some patients will respond

Table 5. ASFA categories for the use of TPE to treat TMA–drug associated

Drug	Pathophysiology	Reported response to TPE	ASFA category
Ticlopidine	ADAMTS13 autoantibodies	87%	I
Clopidogrel	Endothelial damage	50%	III
Calcineurin inhibitors (cyclosporine, tacrolimus, and sirolimus)	Endothelial damage	NA	III
Gemcitabine	Endothelial damage	18%	IV
Mitomycin C	Endothelial damage	30%	NC
Quinine	Drug-dependent antibodies	NA	IV
VEGF inhibitors (bevacizumab, sunitinib, and VEGF Trap)	Renal podocyte injury	NA	NC

NA, not available; VEGF, vascular endothelial growth factor. Other abbreviation is explained in Table 3.

and because of the recent identification of mutations in the alternate complement pathway in some patients, an empiric trial of TPE may be warrented.[2] For this reason, ASFA assigns the use of TPE for the treatment of TMA–hematopoietic stem cell transplantation associated as a category III indication; that is, the role of TPE is uncertain, and decision-making should be individualized.

TMA–drug associated

Numerous medications have been implicated in the development of TMA. In the 2015 systemic review by Al-Nouri et al,[28] 78 different medications were reportedly associated with TMA. Of these, however, only 22 had definitive evidence supporting a causal association, and 9 accounted for the majority (76%) of reports. The presentation of TMA–drug associated is the same as that seen with other TMAs: microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. The time from initial drug exposure until onset of TMA varies according to the drug involved. For example, the onset of symptoms with ticlopidine-associated TMA occurs in <2 weeks from start of the medication, whereas onset with mitomycin C can be delayed as long as 4 months after initial exposure.[29]

The pathophysiology of TMAs seen with different medications varies according to the implicated drug and includes direct endothelial injury, development of antibodies directed toward ADAMTS13, and drug-dependent antibodies.[29] The reported pathophysiology for a number of associated drugs is provided in Table 5.

As with the previously described TMAs, TPE has been applied to TMA–drug associated based on the former positive experience with TTP. Also, as with previous TMAs, the therapeutic mechanism of TPE in this setting is unclear. In those rare drugs (eg, ticlopidine) in which autoantibodies to ADAMTS13 develop, TPE would be expected to be effective, whereas it would not be with those medications in which direct endothelium injury occurs. For example, with ticlopidine, the use of TPE has been associated with survival of 87% when treated with TPE compared with survival of 50% when TPE is used to treat TMA associated with clopidogrel in which direct endothelial injury is responsible for the development of TMA.[29]

When TPE is used, the treatment course described in Table 2 is followed. In addition, discontinuation of the implicated medication is a critical component of therapy.[29] ASFA categories for the use of TPE in the treatment of TMA–drug associated are given in Table 5.

TMA–malignancy associated

The development of TMA in patients with underlying malignancies has been widely described.[30,31] This form may represent TMA due to drugs used to treat the underlying malignancy, such as gemcitabine or mitomycin C (as described earlier), or may be a direct consequence of the malignancy. Criteria for the diagnosis of TMA–malignancy associated include the following: cancer diagnosis, direct antiglobulin test result negative for microangiopathic hemolytic anemia, thrombocytopenia, decreased serum haptoglobin level, and indirect hyperbilirubinemia. In a study by Elliot et al,[30] TMA–malignancy associated patients exhibited, in addition to the laboratory parameters provided earlier, elevations in D-dimers in the absence of other markers of disseminated intravascular coagulation, a median serum creatinine level of 1.2 mg/dL, and ADAMTS13 >10%. Patients also exhibited bone pain, respiratory symptoms, anorexia, and weight loss, symptoms not see in TTP or other TMAs. Patients were also older and had a longer history of symptoms than patients with either TTP or other forms of TMA.[32] The most commonly associated malignancies include those of the stomach, breast, prostate, and lung.

The pathophysiology of TMA–malignancy associated is unclear. As mentioned, it may represent TMA–drug associated or may also be due to expression of tissue factor in widespread tumor.[33] Of note, mutations in factor H have also been identified, similar to the findings in TMA–hematopoietic stem cell transplantation associated and TMA–complement associated; these findings indicate that underlying abnormalities in the regulation of the alternate complement pathway may be involved.[34]

The usual course of therapy again matches that for TTP as described in Table 2. Evidence supporting efficacy of TPE in this setting is lacking, and the use of TPE may result in a delay in treating the underlying malignancy.[30] ASFA has not categorized the use of TPE in the treatment of this form of TMA.[2]

TMA–*S pneumoniae* associated

TMA–*Streptococcus pneumoniae* associated is a disorder of children, predominantly those aged <2 years who are experiencing either *S pneumoniae* pneumonia or meningitis; the majority of cases result from pneumonia. This TMA complicates 0.4% to 0.6% of invasive *S pneumoniae* infections.[2,35] As with other TMAs, it is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal injury.[35]

The TMA results from direct injury of the endothelium, red blood cell lysis, and platelet destruction through complement activation. In significant, life-threatening *S pneumoniae* infections, the burden of the bacteria is such that neuraminidase produced by the bacteria can cleave sialic acid residues from the surface of red blood cells, platelets, and endothelium, resulting in the exposure of a cryptic antigen, the Thomsen-Friedenreich (TF) antigen. Naturally occurring anti-TF immunoglobulin M is present in almost all individuals and

results in red blood cell agglutination and complement-mediated endothelial injury.[35] In addition, the neuraminidase may remove sialic acid residues from factor H–binding sites such that it can no longer interact with C3 convertase, resulting in dysregulation of the alternate complement cascade. Just as in other TMAs, there have been reports of the presence of mutations in the complement pathway or complement regulatory genes in a subset of patients, leading to activation and complement consumption.[36] The mortality rate in this TMA is as high as 50%.[35]

The rationale for the use of TPE is to remove both the neuraminidase and the naturally occurring anti-TF immunoglobulin M antibodies. However, usual therapy is supportive care, not TPE, with avoidance of plasma and washing of cellular blood products due to the ubiquitous presence of anti-TF in most individuals.[35,37] The need for the use of washed products and the avoidance of plasma, although commonly mentioned, may not be necessary. Series have not reported worsening of patients' hemolysis or clinical condition when plasma or unwashed cells were transfused,[37] and an experimental study by Crookston et al[38] reported red blood cell removal in the absence of anti-TF. TPE has been used in the setting of severe sepsis with multiorgan failure.[37] Because of the presence of anti-TF in most human sera, albumin (and not plasma) is used as the replacement fluid for this disorder, unlike all of the other TMAs described in the present article. Of note, there are reports of the use of "low titer anti-TF plasma" as the replacement fluid in this disorder to provide coagulation factor replacement in these critically ill patients.[39] The author has received this request on a number of occasions; unfortunately, however, the reports describing this blood product fail to define "low titer anti-TF" as well as describe the methods used to determine the anti-TF titer, thus making the provision of this blood product impossible.[37]

ASFA defines plasma exchange as a category III indication; that is, the optimum role is uncertain for TMA–S pneumonia associated.[2] The usual course of therapy, except the use of albumin as the replacement fluid, is outlined in Table 2.

TMA–coagulation mediated

TMA–coagulation mediated is a rare form of TMA resulting from mutations in diacylglycerol kinase-ε (DGKE), plasminogen, or thrombomodulin (THBD). With DGKE mutations, there is promotion of thrombosis through protein kinase C. DGKE mutations have been implicated in 27% of cases of TMA occurring during the first year of life.[3] Plasminogen mutations produce decreased fibrin degradation, resulting in thrombosis. Finally, THBD enhances the anticoagulation effects of thrombin and assists factor H in inactivating C3b, regulating the complement cascade. Mutations in THBD impair these functions. Plasminogen and THBD mutations are seen in 5% of inherited TMAs.

The usual treatment of these disorders is plasma infusion therapy.[2,3] Data are limited on the role of TPE, with a single case series of 6 patients showing no benefit of TPE compared with plasma infusion.[2] ASFA categorizes the role of TPE in the treatment of these disorders as category III; that is, the optimum role for apheresis is uncertain.

HELLP syndrome

HELLP syndrome is an obstetric disorder characterized by hemolysis, elevated liver enzyme levels, and low platelet counts; it is considered a severe form of preeclampsia. The diagnosis is made after 20 weeks' gestation according to the presence of the previously described findings along with elevated blood pressure. Additional presenting signs and symptoms include proteinuria, abdominal pain, headache, and visual changes. HELLP syndrome can be life-threatening due to hepatic rupture, disseminated intravascular coagulation, and multiorgan failure.

The pathogenesis of HELLP syndrome has not been clarified, but new evidence suggests that as in many of the TMAs discussed in this article, mutations leading to dysregulation of the alternate complement pathway play a role.[40,41] Immediate delivery of the child is the definitive management of HELLP syndrome; however, delivery can be delayed by 24 to 48 hours to allow administration of steroids to enhance fetal lung maturity. HELLP syndrome can persist after delivery, and it is in this context in which TPE is used. If improvement does not occur within 72 hours after delivery, TPE can be initiated. There is no role for antepartum TPE because delaying delivery is associated with maternal and fetal loss.[2]

As outlined in Table 2, the usual course of TPE as used in TTP is also used in HELLP syndrome.[2] ASFA categorizes the use of TPE in postpartum HELLP syndrome as category III; that is, the optimum role of TPE is uncertain. The use of TPE antepartum has been categorized as a category IV indication due to the increased risk of death associated with delaying delivery.[2]

Conclusions

Limited published information exists for the use of TPE in the treatment of TMAs due to a variety of causes. In many instances, the proposed pathologic mechanism behind these disorders would not seem to be amenable to TPE, with a lack of pathologic substances within the plasma. This theory is borne out by a study failing to identify benefit in patients with TMA lacking severe ADAMTS13 deficiency. However, in a number of disorders, including TMA–complement associated, TMA–hematopoietic stem cell transplantation associated, TMA–malignancy associated, TMA–*S pneumoniae* associated, and HELLP syndrome, mutations within the alternate complement pathway and its regulatory proteins may be present in a significant portion of patients. These patients could therefore derive benefit from TPE, utilizing plasma as the replacement fluid. The course of therapy used when TPE is initiated imitates that used for TTP. This approach is not due to any evidence supporting such a method but rather simply the application of an effective treatment of TTP to other similar disorders. In closing, further investigation is needed, preferably in the form of randomized controlled trials, into the role of TPE in these disorders.

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