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THROMBOTIC THROMBOCYTOPENIC PURPURA/ HEMOLYTIC UREMIC SYNDROME (TTP/HUS)

Joseph E. Kiss, MD, Medical Director, Hemapheresis and Blood Services, Institute for Transfusion Medicine
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The last ten years have witnessed extraordinary progress in understanding the pathophysiology of thrombotic thrombocytopenic purpura (TTP) and the related disorder, hemolytic uremic syndrome (HUS). These disorders are characterized by the presence of thrombocytopenia in association with microangiopathic hemolytic anemia, both resulting from microvascular platelet thrombi. Small vessel occlusion in various organs, notably the brain and kidney, is responsible for the clinical manifestations which include fluctuating neurologic abnormalities and a variable degree of renal insufficiency. On clinical grounds, cases with more of a neurologic presentation have been termed TTP, while those with more pronounced renal involvement often are referred to as HUS. However, clinical overlap is common and some authors use the combined term "TTP/HUS."[1]

TTP/HUS may occur on an idiopathic basis or in association with pregnancy (a recent publication addresses the risk for recurrence of TTP/HUS during a subsequent pregnancy[2]), autoimmune conditions, infections, malignancy, stem-cell transplantation, and exposure to certain medications (see Table I). The mainstay of therapy, plasma exchange, has reduced mortality in idiopathic TTP from more than 90% to less than 20%.

PATHOPHYSIOLOGY. Under physiologic conditions vWF (von Willebrand Factor) is released from endothelial cells as circulating ultra-large molecular weight multimers (ULvWF; M.W. approximately 1 to 1.5 x 10^6 daltons) and is rapidly cleaved by a plasma metalloprotease that regulates the multimeric composition of vWF (ADAMTS-13 – a disintegrin and metalloprotease with thrombospondin type I motifs) into smaller molecular weight multimers. The presence of ULvWF, found in many patients with TTP/HUS, has been attributed to a deficiency of ADAMTS-13.[3] Endothelial injury and apoptosis play a critical role in perpetuating the disorder. The higher molecular weight forms of vWF have greater adhesive properties, and hence, a greater propensity to promote platelet-platelet and platelet-subendothelial interactions. The pathological hallmark consists of microvascular occlusion of terminal arteries and capillaries. The lesions contain platelets and vWF; small amounts of fibrin may be present when the kidney is predominantly involved, as in HUS. This is in contrast to disseminated intravascular coagulation (DIC), where fibrin deposition predominates.

Mutations in the ADAMTS-13 gene have been found to cause familial (chronic/relapsing) TTP. Interestingly, only homozygotes with a total absence of protease appear to be affected. Although most patients present during childhood, some do not develop the clinical syndrome of TTP until later. In the more common idiopathic TTP, deficiency of ADAMTS-13 has been associated with IgG inhibitors in 44 to 83% of the cases.[4,5] Recent studies have reported that severe deficiency of ADAMTS-13 (<5%) is specifically associated with idiopathic TTP.[4,5,6] Clinical differences have also been reported, including faster response to plasma exchange, lower mortality, and higher relapse rates in idiopathic TTP compared with secondary cases (see Table I). Patients with idiopathic TTP and moderate deficiency (between 5 and 50% of normal) also appear to respond to plasma exchange.[6] At this time, TTP/HUS remains a clinical diagnosis: the use of ADAMTS-13 measurements in making the clinical decision to initiate plasma exchange in a patient with presumed TTP/HUS is considered investigational.

SUMMARY

- **TTP/HUS is a life-threatening disorder that represents both a diagnostic and management challenge.**
- **Rapid institution of plasma exchange has resulted in dramatic improvement in prognosis.**
- **Considering the mortality rate of nearly 20%, much work remains to be done to translate advances in our understanding of pathophysiology into clinical practice.**
- **Improvements in medical management using pharmacological agents that shorten the duration of treatment would be welcome.**
- **The advent of recombinant or plasma-derived ADAMTS13 for infusion could substantially change the outlook for this disorder.**

CLINICAL MANIFESTATIONS. The classic "pentad" findings, consisting of thrombocytopenia, microangiopathic hemolytic anemia, fever, neurologic changes, and renal dysfunction, are seen in only a minority of patients. A high clinical index of suspicion is appropriate because delays in recognition may adversely affect outcomes. Acceptable criteria for a provisional diagnosis include thrombocytopenia and microangiopathic hemolytic anemia in the absence of an alternative cause. Microangiopathic hemolysis is suggested by the presence of fragmented RBCs (schistocytes) on the blood smear. Neurological symptoms include episodes of focal weakness, visual disturbances, reduced mentation/decreased consciousness, headache, seizure, and coma. Platelet transfusions may worsen the condition and are contraindicated unless serious bleeding occurs. Abdominal pain resulting from intestinal and/or pancreatic ischemia may also occur along with nausea, vomiting, and ileus. Even in cases without severe azotemia, renal

involvement may be evident, including proteinuria and hematuria. Epidemic HUS in patients with acute renal failure may be associated with bloody diarrhea caused by enterotoxigenic *E. coli* or *shigella* species.

TABLE I. Classification of Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS): A syndrome with diverse clinical presentations

PRIMARY (Idiopathic)
- Acute
- Chronic relapsing (familial)

SECONDARY
- Autoimmune diseases, vasculitis
- Drug-induced
- Ticlopidine, clopidogrel, cyclosporine, tacrolimus, quinine, cancer chemoRx[1]
- Cancer-associated
- Transplant-related: allogeneic stem cell transplantation
- Pregnancy/post-partum
- Infection
- Toxin-associated (E. coli 0157:H7, Shigella strains)
- HIV
- Post-operative *Mitomycin, cis-platinum, gemcitabine, pentostatin, others*

MANAGEMENT. The only randomized controlled clinical trial in TTP/HUS was conducted by the Canadian Apheresis Study Group. The study compared plasma infusion (15 ml/kg) with plasma exchange (1.5 plasma volume/day x 3 days, followed by 1 plasma volume per day) and demonstrated a survival advantage in the plasma exchange arm (78% *vs.* 63%).[7] Based in part on the results of this study, plasma exchange has become the standard of care for the management of TTP/HUS. In addition to replacing missing ADAMTS-13, plasma exchange delivers a higher plasma dose and removes antibodies to ADAMTS-13, which have been associated with idiopathic TTP. Although plasma exchange is considered a safe procedure, it should be remembered that serious complications may occur. Recent data from the University of Oklahoma report a major complication rate of 28% on a per-patient basis, primarily catheter related, including 3 deaths over 6 years.[8]

Plasma infusion (15-30 ml/kg) may be given when plasma exchange is not immediately available. The treatment approach includes a 1 to 1.5 plasma volume exchange using fresh frozen plasma (FFP) daily until clinical symptoms resolve and the platelet count reaches a normal level (>150,000/ul). LDH level should also be followed closely since it reflects tissue ischemia. However, due to its non-specificity, near normal levels may be an acceptable endpoint. The overall published relapse rate is between 30-40%. A retrospective study conducted by the US TTP Apheresis Study Group found no statistical difference in the rate of relapse when comparing taper to no-taper apheresis schedules.[9]

Cryosupernatant (AHF, cryoprecipitate removed) may be used as alternative replacement solution for plasma exchange. This product has the theoretical advantage of containing reduced levels of vWF. Although small and uncontrolled case series suggest a benefit, a recent small randomized clinical trial found no difference in outcome compared to FFP.[10] However, cryosupernatant contains adequate levels of ADAMTS-13 and is commonly used in place of FFP in refractory cases. If the switch is made, periodic assessment of fibrinogen levels should be performed.

Adjuvant pharmacological therapy of TTP/HUS falls into two groups: 1) antiplatelet agents and 2) immunosuppressive medications.[11] Antiplatelet agents have not proved to be particularly beneficial in the treatment of TTP and may increase the risk of hemorrhage, particularly with severe thrombocytopenia. Both ticlopidine and clopidogrel have been associated with induction of autoantibodies to ADAMTS-13, resulting in drug-induced TTP and should not be used as therapy. Convincing data for an autoimmune basis to idiopathic TTP has renewed interest in the use of immunosuppressives. The role of glucocorticoids remains unclear with comparable mortality rates reported in the literature. If not used initially, they are frequently added later if response to plasma exchange is delayed. Vincristine may be useful as a second line therapy in refractory cases. In one retrospective case series, 7 of 8 patients responded to vincristine 1.4 mg/m^2 IV on day 1 followed by 1 mg on days 4 and 7 (6 responded after the first week of therapy and 1 after the second week).[12] Another immunosuppressive approach involves the anti-CD20 monoclonal antibody, retuximab. Reports of using the drug at conventional doses of 375 mg/ m^2 on a weekly basis for between 4 to 8 weeks have shown responses in 7 of 8 treated patients.[13] The time until remission averaged 2 to 5 weeks. Splenectomy has also proven successful in preventing relapses, reducing the attack rate from 2.3 +/- 2 events per year to 0.1 +/- .1 events per year. [14]

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TMU Editor: Donald L. Kelley, MD, MBA: dkelley@itxm.org
For questions regarding this TMU, please contact Joseph E. Kiss, MD at: (412) 209-7326.
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