Thrombotic microangiopathy is a group of disorders that is characterized by thrombocytopenia and microangiopathic hemolytic anemia (intravascular hemolysis and presence of peripheral blood schistocytes), neurological symptoms, fever, and renal dysfunction. Ischemic organ injury can occur to the brain, kidneys, heart, pancreas, liver, and lungs.

**MANAGEMENT OF TMA PATIENTS**

Because of the variety of TMA disorders and different treatment options for each, prompt and accurate diagnosis can significantly impact a patient’s outcome. The various disorders include congenital and idiopathic thrombotic thrombocytopenic purpura (TTP), secondary TTP including TMAs in patients with metastatic cancer, HELLP - a syndrome characterized by hemolysis, elevated liver enzyme levels, and a low platelet count that may rarely occur in pregnancy, Shiga toxin-producing E. coli hemolytic uremic syndrome (STEC-HUS), disseminated intravascular coagulation (DIC), and atypical hemolytic uremic syndrome (aHUS).

- The large majority of congenital and idiopathic TTP patients initially present with thrombocytopenia and peripheral blood evidence of microangiopathy, and in the absence of any other potential explanation for such findings, satisfy criteria for early initiation of plasma exchange, which is critical for patient survival. Plasma exchange is the treatment of choice for TTP and should be initiated even if there is some uncertainty about the diagnosis because it has been shown to reduce the TTP-associated mortality from around 90% to less than 20%. The diagnosis of TTP may be confirmed with ADAMTS13 activity and inhibition studies. If an alternative condition is diagnosed, the role of plasma exchange can be re-evaluated depending on the underlying cause of the microangiopathy.

- Patients who are diagnosed with STEC-HUS should be treated with intravenous volume expansion early in the infection to potentially decrease renal damage. In addition, antibiotics should be avoided because they could cause the release of toxins.

- If congenital TTP, idiopathic TTP, and STEC-HUS are ruled out, based on other clinical indications, management for DIC or secondary TTP (usually the patient has >10% ADAMTS13 activity) would include finding and treating the underlying cause while managing the coagulopathy. Alternatively, aHUS management may include eculizumab, while therapy directed toward cancer would be appropriate for metastatic cancer patients.

- aHUS is caused by dysregulation of the complement alternative pathway. Patients with aHUS will benefit from complement testing. A classic pattern seen in aHUS patients is a low functional activity of the alternative pathway of the complement system (AH50), decreased Factor H or Factor B, with elevation of the activation products sC5b-9 and Bb. At the same time, classical pathway markers such as complement component 4 (C4) should be within reference intervals.
TEST OFFERINGS

- **ADAMTS13 Activity and Inhibitor Profile (Mayo ID: ADM13)**
  
  ADAMTS13 testing is useful for assisting with the diagnosis of congenital or acquired thrombotic thrombocytopenic purpura. Testing begins with ADAMTS13 activity assay to evaluate the percent activity. If the activity is decreased, an inhibitor screen will be performed to look for specific ADAMTS13 inhibition. If specific inhibition is apparent, the titer of the inhibitor will be determined.
  
  **Analytic Time:** 1 day  
  **Days Performed:** Monday–Sunday

- **Shiga Toxin, Molecular Detection, PCR, Feces (Mayo ID: STFRP)**
  
  If a patient presents with diarrhea, consider ordering Shiga toxin testing at the same time as the ADAMTS13 profile. Shiga toxin PCR is a sensitive, specific, and rapid test for the detection of the presence of Shiga toxin-producing organisms such as *Escherichia coli* O157:H7 and *Shigella dysenteriae* type 1 in stool. Unlike enzyme immunoassays and many other PCR assays targeting Shiga toxin, the real-time PCR assay done at Mayo Clinic can be performed directly on stool, without an enrichment step. This means that the results of testing are available the same day the specimen arrives into the laboratory—a significant benefit in turnaround time.
  
  **Analytic Time:** 1 day  
  **Days Performed:** Monday–Sunday

- **Eculizumab Monitoring Panel, Serum (Mayo ID: ECUMP)**
  
  Eculizumab (Soliris, Alexion Pharmaceuticals) is a humanized hybrid monoclonal antibody (IgG2/IgG4) that is FDA-approved for treatment of atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH) and neuromyelitis optica. Therapy efficacy may be monitored by measuring the extent of the complement system blockage. Blockade by eculizumab prevents the carboxypeptidases cleavage of C5 and subsequent generation of C5a, and C5b, thereby preventing the assembly of the membrane attack complex (MAC) formed by C5b, C6, C7, C8 and C9. When eculizumab is blocking all the C5 in circulation, the formation of the sC5b-9 should be minimal.
  
  **Analytic Time:** 2 days  
  **Days Performed:** Monday–Friday

- **Atypical Hemolytic Uremic Syndrome (aHUS) Complement Panel, Serum and Plasma (Mayo ID: AHUSD)**
  
  The dysregulation of the alternative pathway of complement plays a role in the pathogenesis of atypical hemolytic syndrome (aHUS), a thrombotic microangiopathy (TMA) characterized by normal ADAMTS13 activity - a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 which cleaves von Willebrand factor, more severe renal failure compared to thrombotic thrombocytopenic purpura (TTP) and variable treatment response to plasma exchange. Similar to TTP, without early recognition and treatment, aHUS causes significant morbidity and mortality. The pathophysiologic mechanism involves increased continuous spontaneous hydrolysis of complement component C3 to C3b, leading to tissue deposition of C3b, membrane attack complex (MAC) formation, and subsequent tissue injury. The underlying susceptibility factors include germline mutations in complement proteins or their regulators or acquired autoantibodies that result in a failure to protect the glomerular endothelium from complement activation, resulting in TMA and renal failure. Over 100 mutations in complement pathway proteins have been described. The suggested approach is to rule-out other causes of TMAs first, since aHUS is one of the rarer causes of TMAs. The use of quantitative serologic complement assays can be used in conjunction with complement genetic testing; however genetic testing may not be available in a timely manner thereby postponing time to a final diagnosis and initiation of treatment.
  
  Because complement activation is also involved in several other medical conditions (e.g. sepsis, trauma, autoimmune diseases, severe infections), and given the labile nature of complement proteins, it is important that a global survey of the complement system be performed. This allows providers to differentiate an acute phase reaction from the classical pathway from consumption caused by in vitro complement activation. Our panel is comprised of 9 analytes from the classical, alternative and terminal pathways. Complement function is assessed, as well as complement component concentrations and activation products, providing a thorough study of the complement system and a brief interpretation of findings provided by the section consultant. A result suggestive of aHUS includes abnormalities in markers of the alternative pathway: decreased AH50, decreased Factor B and/or Factor H, and elevated activation products sC5b-9 and/or Bb.
  
  **Analytic Time:** 2 days  
  **Day Performed:** Tuesday