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Overview of Thrombotic Microangiopathy Including COVID-19

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Thrombotic microangiopathy (TMA) is the pathological process that is the final common pathway of many disease processes as "the final events". Clinically features for TMA include microangiopathic hemolytic anemia (MAHA, sheer stress from vessel lumen occlusion produces fragmented red cells), thrombocytopenia (platelets are consumed by local thrombosis), and organ ischemia (renal failure or neurological symptoms). Pathological features for TMA include increased vessel wall thickness, swelling and/or detachment of endothelial cells, platelet aggregation/thrombosis, accumulation of debris/material in subendothelial space, and partial or complete vessel occlusion. The initial step in the diagnostic pathway is to recognize TMA, defined by the presence of thrombocytopenia and MAHA. MAHA is diagnosed when there is evidence of anemia and hemolysis, including schistocytes in the blood smear, increased LDH, free hemoglobin in serum, and reticulocytosis. Decreased haptoglobin is a sensitive, but nonspecific feature. Not all of these items are needed simultaneously to confirm the presence of MAHA. Thrombotic thrombocytopenic purpura (TTP), Shiga toxin-associated hemolytic uremic syndrome (STEC-HUS), and atypical HUS (aHUS) are the major important causes of TMA in clinical practice. Since the etiology of each is different, it is necessary to properly diagnose and treat the disease based on an understanding of the disease.

Thrombotic thrombocytopenic purpura (TTP) results from excessive platelet aggregation in multiple organs with, consequently, a dramatical increase in shear stress caused by the accumulation of unfolded high-molecular-weight von Willebrand factor multimers in plasma. Failure to process these multimers into smaller, less adhesive forms is related to a dysfunction in a disintegrin and metalloproteinase with thrombospondin type 1 motif-13 (ADAMTS-13). ADAMTS-13 deficiency may result from mutations of the encoding gene or from autoantibodies in the acquired form. If ADAMTS-13 activity is less than 10%, the clinical suspicion of TTP is confirmed. Detection of anti-ADAMTS-13 IgG is the second-rank assay, whereas ADAMTS-13 gene sequencing for evaluation of inherited TTP is a third-rank assay limited to selected indications. Therapeutic plasma exchange (usually 1.5× plasma volume exchange for the first procedures, followed by 1.0× patient plasma volume thereafter) should be started as soon as the diagnosis of TTP is established or even suspected.

Shiga toxin-associated hemolytic uremic syndrome (STEC-HUS) is a systemic disease process characterized by microvascular endothelial damage that occurs mainly in the gastrointestinal tract and in the kidneys, and sometimes also in the brain and the liver. It typically occurs in children younger than 5 years of age, but may also occur in adults, and among the elderly. Shiga-toxin producing serotype 0157:H7 is the most frequent causing strain. Polymerase chain reaction testing of patient stools for enterohemorrhagic Escherichia coli is required for the diagnosis of STEC-HUS. Treatment of STEC-HUS is primarily supportive care consisting of volume expansion, antihypertensive therapy, and renal replacement therapy.

In aHUS, inherited genetic abnormalities cause chronic dysregulation of the complement alternative pathway and complement activation ultimately results in TMA, including acute kidney injury. 65% of all patients die, require dialysis, or have permanent renal damage within 1 year after diagnosis despite plasma exchange or plasma infusion. The initial diagnosis of aHUS (or 'complement-mediated TMA') is currently based on the exclusion of STEC-HUS and TTP, hence requiring confirmation of ADAMTS-13 activity ≥10% and STEC negative. Exclusion of STEC-HUS and TTP may in fact be sufficient for a diagnosis of aHUS, although it has been argued that either of aHUS or secondary TMA remains possible.

Eculizumab, a terminal complement C5 inhibitor, can control the activation of the complement pathway. Eculizumab therapy results in rapid and significant improvement in hematologic parameters including platelet count and results in significant and continued reversal of renal damage. Earlier intervention with eculizumab in patients with aHUS is critical to maximizing clinical benefit.

Secondary TMA signifies a TMA occurring in the context of another disease process, such as infection, malignant hypertension, autoimmune disease, malignancy, transplantation, pregnancy, or drugs. The clinical and laboratory features of COVID-19-associated coagulopathy (CAC) partially overlap with sepsis-induced coagulopathy (SIC)/disseminated intravascular coagulation (DIC), hemophagocytic syndrome (HPS)/ hemophagocytic lymphohistiocytosis (HLH), antiphospholipid syndrome (APS), and thrombotic microangiopathy (TMA). Thrombosis is more common than bleeding in CAC, which is explained by thrombo-inflammation. Transfusion support is more focused on patients with bleeding or needing invasive procedures. VTE prophylaxis post-discharge is a feasible option for high-risk patients.