**Brief Overview of Atypical Hemolytic Uremic Syndrome**

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Atypical hemolytic-uremic syndrome (aHUS) is a systemic disease that primarily affects the kidneys. The rare condition is associated with genetic mutations or polymorphisms that result in chronic, uncontrolled activation of the alternative complement pathway.1 The dysregulated alternative complement pathway activation causes blood clot (thrombi) formation in the glomerular capillaries (groups of small blood vessels of the kidneys) and thickening of the glomerular capillary walls. Other possible changes include fibrinoid necrosis of the vessels that supply blood to the kidneys (afferent arterioles), mucoid intimal hyperplasia accompanied by narrowing of the vessel lumen, and fibrin deposits in the glomeruli and vessel walls.1Hemolytic anemia and thrombocytopenia are typical with aHUS.

The prevalence of aHUS is approximately 2 in 1 million, and it accounts for an estimated 10% of HUS diagnoses.2 Although many gene abnormalities have been implicated in the pathogenesis of aHUS, 40% of patients have no known mutation.3 The most prevalent mutation is CFH, which is identified in 25% to 30% of cases.1,4 Other more common mutations are CFI, MCP, andC3. Only 20% of mutations appear to be inherited; the rest are acquired. Patients may have more than 1 mutation.

Environmental triggers also appear to play a role in aHUS, as individuals who have a mutation at birth often do not develop symptoms until adulthood.1,3Onset of aHUS in middle-age is common. Respiratory and gastrointestinal infections, certain medications, chronic diseases, cancer, pregnancy, or other conditions are believed to provoke unregulated, continual activation of the complement system in 50% of genetically susceptible individuals.5

Prognosis for patients with aHUS is poor. Patients whose aHUS is not diagnosed and treated within the first year of onset have a high risk of morbidity and mortality.1 One-half of patients with aHUS ultimately develop end-stage renal disease, which occurs in approximately 65% of adults and 36% to 48% of children within 3 to 5 years after diagnosis.1 Prognosis appears to correlate with the genetic subtype of disease: Patients with anMCP mutation have the best outcomes, and patients with a CFH, CFI, or C3mutation have poorer outcomes.4

Between 10% and 20% of patients have extra-renal manifestations.1 In these patients aHUS may affect the cardiovascular, gastrointestinal, or central nervous system. The most frequent extra-renal complications are neurologic, with studies suggesting that 16% of patients have neurologic involvement. Delayed treatment has been implicated in neurologic manifestations.6

aHUS, which is a type of major thrombotic microangiopathy (TMA), can be difficult to distinguish from other TMAs such as thrombotic thrombocytopenic purpura (TTP) and typical HUS due to the Shiga-like toxins produced byEscherichia coli.7 Because these conditions are treated differently, conducting the appropriate tests is essential. Microbiological analysis can be used to rule out Shiga-associated HUS, and testing for thrombospondin type 1 motif, member 13 (ADAMTS13) activity can distinguish between TTP and aHUS. If ADAMTS13 activity is greater than 10%, aHUS is the probable diagnosis.6,7

Patients were typically started on plasma exchange as soon as possible after diagnosis, which was continued until hemolysis was controlled.1Outcomes with plasmapheresis in aHUS have been mixed, with some patients developing rare but serious complications.8 In 2011, the US Food and Drug Administration (FDA) approved eculizumab (Soliris) for children and adults with aHUS.

Eculizumab is a recombinant humanized monoclonal antibody that inhibits complement component 5 expression.2 Eculizumab is effective at improving thrombotic microangiopathy and reversing renal damage in patients with and without complement mutations. Data suggests that eculizumab may be more effective than plasma exchange at preserving kidney function, although no head-to-head study has been conducted.1 Some patients treated with eculizumab have developed meningococcal infections, and the drug must be administered under a Risk Evaluation and Mitigation Strategy.9

Kidney transplant may be another option for patients with aHUS. However, outcomes after transplant are typically poor. Within the first year post transplant, 70% of patients develop graft failure, generally due to aHUS recurrence.1 Some evidence suggests that eculizumab may be an effective prophylactic treatment in patients who have undergone a kidney transplant, and studies are ongoing in this setting.1,6

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