

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Recent Advances in the Management of Atypical Hemolytic Uremic Syndrome



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H&O What is atypical hemolytic uremic syndrome (aHUS)?

SC In patients with atypical hemolytic uremic syndrome (aHUS), mutations of proteins that regulate complement activation (factor H, membrane cofactor protein [MCP], factor I) or gain of function mutations of complement factors (factor B, C3) can lead to pathologic complement activation and widespread end organ injury. Patients with thrombotic microangiopathies, and especially aHUS patients, can present with renal issues, including renal failure. aHUS was previously thought to be more common in children than adults, but it is now recognized to occur in all age groups. It is a rare disorder, affecting approximately 2–4 patients per million.

H&O How does aHUS differ from hemolytic uremic syndrome and thrombotic thrombocytopenic purpura?

SC Patients with aHUS may present with a higher platelet count and more pronounced renal issues than patients with thrombotic thrombocytopenic purpura (TTP). The ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) can be used to help distinguish TTP from aHUS. Patients with aHUS will typically have measurable ADAMTS13 activity (>10%), while patients with acquired TTP will commonly have severely deficient ADAMTS13 activity (<10%) and evidence of an antibody inhibitor of ADAMTS13.

aHUS and typical HUS can be challenging to differentiate (Table 1). HUS is a thrombotic micro-

Table 1. Similarities and Differences Between Atypical and Typical Hemolytic Uremic Syndrome

	aHUS	HUS
Caused by a bacteria or virus	No	Yes
Severe initial symptoms	No	Yes
Accompanied by severe diarrhea	No	Yes
Dialysis often needed	Yes	Yes
Blood pressure dysregulation	Yes	Yes
Common temporary kidney failure	Yes	Yes
Common permanent kidney failure	Yes	No
Disease often recurs	Yes	No
Complications persist throughout life	Yes	No
May be caused by a genetic problem	Yes	No

HUS=hemolytic uremic syndrome.

Adapted from the Foundation for Children with Atypical HUS. What is aHUS? <http://atypicalhus.ning.com/page/what-is-ahus>. Accessed July 24, 2012.

angiopathy that is typically associated with a bloody diarrheal prodrome. HUS is caused by infection with a Shiga toxin–producing bacteria, commonly *Escherichia coli*. HUS is typically a disorder of young children. In patients with HUS, the hemorrhagic diarrheal illness typically precedes the development of the thrombotic microangiopathy by 5–10 days, whereas patients with aHUS can also present with diarrhea and other gastrointestinal symptoms, but simultaneously with the thrombotic microangiopathy.

H&O What are the triggering events of aHUS?

SC As in TTP, aHUS episodes have been reported to be triggered by infections. aHUS episodes can be triggered by any clinical event that can increase complement activity, including infections and surgery. In addition, acute episodes can occur during pregnancy and the postpartum period.

H&O What was the traditional approach to management of aHUS?

SC Previously, it was less important to distinguish aHUS from TTP because the initial treatment for both was the same, plasma exchange therapy. However, only a minority of aHUS patients, approximately 20–30%, respond to plasma-based therapy, with the majority having poor long-term outcomes. Within a year of diagnosis, half of aHUS patients were either dead or had end-stage renal disease requiring hemodialysis. This outcome appears to be changing in recent years with the development of eculizumab (Soliris, Alexion Pharmaceuticals, Inc), an antibody inhibitor of terminal complement activity.

H&O How is eculizumab being used in the management of aHUS?

SC Eculizumab was approved by the US Food and Drug Administration (FDA) for the treatment of aHUS in September 2011. (Eculizumab had already been approved for the treatment of paroxysmal nocturnal hemoglobinuria in March 2007.) FDA approval was based on results from 2 studies: C08-002A/B (Open Label Controlled Trial of Eculizumab in Adolescent Patients With Plasma Therapy-Resistant aHUS) and C08-003A/B (Open Label Controlled Trial of Eculizumab in Adolescent Patients With Plasma Therapy-Sensitive aHUS). The data from these studies have not yet been published, but were reported in abstract form at the 2011 European Hematology Association Congress. The 002 study included patients who were refractory to plasma-based therapy and not responding to plasma exchange or infusion. In the 003 study, all patients were receiving and responding to plasma-based therapy, but clinicians were trying to transition them off of plasma therapy due to concerns about potential complications. In both studies, the response was remarkable, particularly in terms of renal disease. In the 002 study, of the 5 patients who were dialysis-dependent, 4 were able to discontinue dialysis. Improvement in renal function was more pronounced in patients who were refractory to plasma-based therapies. However, even patients who

had some response to plasma-based therapies showed further improvement in kidney function during treatment with eculizumab. Another endpoint of the studies was hematologic improvement and normalization, which was seen in nearly all patients. Hematologic improvement and normalization can be considered a surrogate for suppression of the thrombotic microangiopathy. The outcomes of these studies match our clinical experience with eculizumab in the treatment of patients with aHUS at the Wexner Medical Center at the Ohio State University.

H&O Do you anticipate changes in the management of aHUS?

SC I expect a paradigm shift in how patients with aHUS are treated. There is no question that treatment with eculizumab is superior to plasma exchange therapy for aHUS. Our biggest challenge presently lies in being able to accurately differentiate aHUS from TTP. It is not possible to differentiate aHUS from TTP based on clinical symptoms alone. Although patients with aHUS will more likely have measurable ADAMTS13 protease activity (>10%), this testing is not readily available to clinicians at the time of the patient's initial presentation. Even when aHUS is suspected, patients should still receive plasma exchange therapy to avoid potentially withholding this therapy in a patient with acquired TTP. The diagnosis of aHUS should be considered in a patient with a thrombotic microangiopathy, measurable (>10%) ADAMTS13 protease activity, and a suboptimal response to plasma exchange therapy over the first 4–5 days in terms of the hematologic parameters and renal function. Genetic studies to evaluate a patient for mutations of complement proteins may help confirm the diagnosis, but they are not available to clinicians in real time to help with the initial identification of aHUS, which remains a clinical diagnosis.

H&O Are there any other areas of research in aHUS?

SC The remarkable clinical outcomes with eculizumab therapy have certainly raised questions regarding the length of treatment, and more specifically, whether therapy can ever be stopped in a patient with a clinical diagnosis of aHUS. Another important area of study involves the development of better clinical assays to differentiate aHUS patients from other thrombotic microangiopathies, including acquired TTP. Improving our ability to differentiate aHUS from other thrombotic microangiopathies will allow those patients who are most likely to benefit from therapy with eculizumab

to receive therapy as soon as possible, and to prevent potential complications from prolonged courses of plasma exchange therapy.

Suggested Readings

Cataland SR, Yang S, Wu HM. The use of ADAMTS13 activity, platelet count, and serum creatinine to differentiate acquired thrombotic thrombocytopenic purpura from other thrombotic microangiopathies. *Br J Haematol*. 2012;157:501-503.

ClinicalTrials.gov. Open label controlled trial of eculizumab in adolescent patients with plasma therapy-resistant aHUS. <http://clinicaltrials.gov/ct2/show/NCT00844844>. Identifier: NCT00844844.

ClinicalTrials.gov. Open label controlled trial of eculizumab in adolescent patients with plasma therapy-sensitive aHUS. <http://clinicaltrials.gov/ct2/show/NCT00844428?term=eculizumab+ahus&rank=3>. Identifier: NCT00844428.

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Loirat C, Muus P, Legendre C, Douglas K, Hourmant M, Delmas Y, et al. A phase II study of eculizumab in patients with atypical hemolytic uremic syndrome receiving chronic plasma exchange/infusion. Poster presented at the 16th Congress of European Hematology Association (EHA); June 9-12, 2011; London, UK. Abstract 0979.

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