The Physician’s Guide to
Atypical Hemolytic Uremic Syndrome (aHUS)

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Introduction

Welcome to the NORD Physician Guide to Atypical Hemolytic Uremic Syndrome (aHUS). The NORD Online Physician Guides are written for physicians by physicians with expertise on specific rare disorders. This guide was reviewed by Larry Greenbaum, MD, PhD, Division Director of Pediatric Nephrology, Marcus Professor of Pediatrics, Emory University School of Medicine and Children’s Healthcare of Atlanta (see acknowledgements for additional information).

NORD is a nonprofit organization representing all patients and families affected by rare diseases. The information NORD provides to medical professionals is intended to facilitate timely diagnosis and treatment for patients.

aHUS, a form of thrombotic microangiopathy associated with excess activation or dysregulation of the alternate pathway of complement, is a life-threatening disorder that can lead to ischemic injury and damage to any organ.

What Is aHUS?

Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening disorder characterized by hemolytic anemia, thrombocytopenia, and acute kidney injury, which results from the formation of microthrombi in the small blood vessels serving the kidneys and other organs. Potentially, ischemic injury can result in damage to any organ. Onset is frequently in childhood, but the first episode may occur from infancy to well into adulthood. aHUS may be genetic or acquired. The majority of cases involve genetic mutations that impair regulation of the alternative pathway of complement. Multiple genes have been linked to the disorder. Less often, the disorder results
from autoantibodies directed against complement proteins. aHUS is usually chronic, with patients experiencing repeated episodes even after recovering from the initial episode. Episodes are often triggered by a specific event, such as an infection or pregnancy. Approximately 60% of cases of genetic aHUS progress to end stage renal failure. The new agent, eculizumab, dramatically improves the outcomes of these patients.

One study estimated the incidence in the United States as 2 per million people, but the exact incidence is unknown. In Europe, one multicenter study estimated the incidence at .11 cases per every million individuals between the ages of 0 and 18 years. aHUS accounts for approximately 5%-10% of all cases of HUS. In childhood, males and females are affected in equal numbers. There are more female cases in adulthood, most likely due to pregnancy being a common triggering event.

**Classification And Nomenclature**

aHUS is categorized as a form of thrombotic microangiopathy (TMA), which is broadly broken down into two main subgroups – thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS). HUS is further broken down into two main subtypes – aHUS and Shiga toxin-producing *Escherichia Coli* hemolytic uremic syndrome (STEC-HUS). More than 90% of cases of HUS are STEC-HUS, which occurs most commonly in childhood. aHUS is a much rarer disorder.

For years, aHUS was used to denote any form of HUS not due to STEC. In recent years, many researchers have noted that the term aHUS is best reserved for cases of TMA associated with excess activation or dysregulation of the alternate pathway of complement. This would exclude so-called “secondary HUS”, which can occur in the setting of malignancy, HIV infection, solid organ transplants, hematopoietic stem cell transplants, or various drugs including quinine, calcineurin inhibitors, antiplatelet agents, and certain chemotherapy drugs. HUS can also occur concurrently with autoimmune or rheumatologic disorders.

Most cases of aHUS are associated with mutations in proteins involved in the alternative pathway of complement. Mutations in the gene for factor H, a protein that regulates the alternative pathway of complement, is the most common etiology of aHUS. In addition, some patients have DEAP-HUS (Deficiency of CFHR (complement factor H-related) plasma proteins and
Autoantibody Positive form of Hemolytic Uremic Syndrome]. These patients have autoantibodies to factor H, usually in the setting of an absence of specific complement factor H-related proteins.

Historically, the term aHUS included TMA secondary to infection with *Streptococcus pneumonia* or due to cobalamin C deficiency, an inborn error of metabolism. These disorders are now considered separate causes of HUS different from aHUS.

aHUS was once also known as diarrhea-negative HUS as a way to distinguish it from STEC-HUS, which is almost always associated with a diarrheal illness. However, a diarrheal illness can trigger an episode of aHUS and thus this term is inaccurate and many physicians have recommended that it no longer be used.

Idiopathic aHUS refers to cases in which the underlying etiology is unknown. Most likely, many of these patients have unidentified mutations in the complement systems. As more genetic loci are discovered, the number of patients classified as having idiopathic aHUS will decrease.

**Clinical Manifestations**

Onset in young children is often sudden and usually follows an infection, particularly an upper respiratory infection or gastroenteritis. Most triggering infections are mild. In some cases, onset is insidious. A variety of nonspecific symptoms including poor feeding, vomiting, fatigue, edema, and lethargy may be seen. In adults, fatigue and general malaise are the most common complaints. More severe findings, as described below, may prompt urgent evaluation. Signs and symptoms generally lead to basic laboratory testing, and marked abnormalities generally result in hospitalization.

The three major laboratory findings are a microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Most patients present with all three findings, but this is not universal.

The microangiopathic hemolytic anemia is due to mechanical red cell destruction during passage through the damaged blood vessels. Accompanying findings include schistocytes on the peripheral smear, an elevated lactate dehydrogenase (LDH) and low haptoglobin. Hemolytic anemia can cause pallor, fatigue, systolic murmur, and tachycardia.
Although frequent, thrombocytopenia is not always present. Spontaneous bleeding and petechiae are uncommon.

Acute kidney injury may be mild or severe. The extent of permanent kidney injury tends to worsen with each episode. Hematuria and proteinuria are common, especially during acute episodes, but proteinuria may become chronic. Some patients may develop nephrotic syndrome, which is especially frequent in patients with DGKE mutations. Approximately 30%-40% of patients develop end stage renal disease or die during the first clinical manifestation of the disorder. Within one year of diagnosis, up to 65% of patients treated with plasma therapy develop permanent renal damage and progress toward renal failure, or die. These statistics reflect aHUS patients before the development of eculizumab as a therapy.

Hypertension, often severe, is common and may result from either kidney damage or from ischemia due to TMA. Hypertension can cause headaches and seizures and can contribute to encephalopathy or cardiac dysfunction.

Any organ system can be affected by aHUS due to microthrombi formation in the small vasculature. Findings in aHUS are especially common in the cardiovascular, gastrointestinal and central nervous systems. Cardiovascular manifestations can include cardiomyopathy and myocardial infarction. Gastrointestinal bleeding and ischemic injury may occur. Pancreatitis may be symptomatic or only be noted because of elevations in amylase and lipase. Neurologic findings include drowsiness, irritability, diplopia, cerebral edema, seizures, headache, facial paralysis, transient ischemic attacks, stroke, and coma.

Pulmonary involvement may include pulmonary edema or hemorrhage. Elevated liver enzymes are quite common, but clinically significant liver involvement is unusual. Cutaneous manifestations may be mild, with patches of skin rash that may be painful. In contrast, gangrene of digits may lead to permanent loss of fingers and toes. Retinal disease may also occur. In less than 5% of cases, multiorgan failure due to diffuse TMA has been reported.

Prompt diagnosis during the initial stage is critically important because aHUS is chronic and relapsing, and organ damage is progressive. The earlier treatment is initiated, the greater the chance that serious complications can be avoided or that kidney function can be salvaged. Most patients
experience multiple episodes. An acute episode is not always preceded by a triggering event.

**Genotype-Phenotype Correlation**

The clinical features of aHUS, including response to treatment, correlate with the specific underlying etiology.\(^1,3\)

Patients with *MCP* mutations have a lower risk of permanent kidney failure and a low risk of disease recurrence following a kidney transplant. These patients rarely develop extrarenal involvement, although they relapse more frequently than those patients with other mutations. Patients with *CFH* and *THBD* mutations usually present during childhood. *DGKE* mutations are associated with disease development during the first year of life, with relapsing episodes of TMA during childhood. These patients often have nephrotic range proteinuria, even between episodes.

Establishing true genotype-phenotype correlations is difficult because of the presence of genetic modifiers, the possibility of mutations in more than one complement gene, and the presence and impact of various environmental triggers. Research is ongoing to better understand the complex genetic and environmental interactions involved in aHUS.

**Causes**

aHUS is associated with mutations in multiple genes involved in the alternate pathway of complement. Most mutations are heterozygous and thus inheritance is usually autosomal dominant. A mutation in one of these genes is usually not sufficient to cause the disorder and most likely conveys a predisposition to developing aHUS. Thus, only approximately 50% of individuals who carry a genetic mutation in a complement gene develop aHUS. In approximately 30%-50% of cases, no genetic mutation can be identified.

One or two additional factors may be required for development of aHUS – an environmental trigger and a second genetic abnormality. In most patients, there is a triggering event such as an acute infection. Pregnancy is a common trigger in women. A genetic modifier could be a mutation in a second complement gene or the presence of a polymorphism that increases the risk of uncontrolled activation of the complement system.\(^8,9\)
Most of the genes associated with aHUS encode proteins active in the alternate pathway of complement. Complement is a key component of the body’s innate system that provides a defense against bacterial infection. While complement deposition and activation on bacteria is beneficial, complement activation on host cells is potentially deleterious. Hence, the body has an elaborate network of proteins that down-regulate the complement system on host cells. There are approximately 30 different proteins in the complement system, most of which are synthesized in the liver. In aHUS, gene mutations or autoantibodies cause a defect in complement regulation, and this leads to an overactive alternative pathway of complement.

Endothelial cells, since they are in direct contact with the blood, are especially vulnerable to an overactive alternative pathway of complement with inadequate down-regulation. Endothelial injury from the complement system causes cell injury and a hypercoagulable state. Hence, microthrombi may form on the surface of small blood vessels, leading to tissue ischemia. The small blood vessels of the kidneys are particularly susceptible to this process, which accounts for the high rate of acute kidney injury in aHUS patients. Moreover, these microthrombi contain platelets and platelet consumption causes thrombocytopenia. The microthrombi also create jagged surfaces within the blood vessels, which cause red blood cells to be damaged and eventually lyse as they travel through the vessels.

### Table – Gene Mutations that Cause aHUS

<table>
<thead>
<tr>
<th>Gene Mutations that Cause aHUS</th>
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<tr>
<td><strong>CFH</strong> – accounting for approximately 30% of cases.</td>
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<tr>
<td><strong>CD46</strong>, also known as MCP – accounting for approximately 12% of cases.</td>
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<tr>
<td><strong>CFI</strong> – accounting for approximately 5%-10% of cases.</td>
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<tr>
<td><strong>C3</strong> – accounting for approximately 5% of cases.</td>
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<tr>
<td><strong>CFB</strong> – extremely rare, &lt;2% of cases.</td>
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<tr>
<td><strong>THBD</strong> – accounting for approximately 3% of cases.</td>
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<tr>
<td><strong>DGKE</strong> – accounting for approximately 27% of cases with onset before age of 1 year. It is considered a distinct disorder by some researchers because this gene does not encode for a complement protein or complement regulatory protein.</td>
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Most of the genes associated with aHUS encode proteins active in the alternate pathway of complement. Complement is a key component of the body’s innate system that provides a defense against bacterial infection. While complement deposition and activation on bacteria is beneficial, complement activation on host cells is potentially deleterious. Hence, the body has an elaborate network of proteins that down-regulate the complement system on host cells. There are approximately 30 different proteins in the complement system, most of which are synthesized in the liver. In aHUS, gene mutations or autoantibodies cause a defect in complement regulation, and this leads to an overactive alternative pathway of complement.

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**DGKE-HUS**

DGKE-associated aHUS is caused by recessive mutations of the *DGKE* gene. The protein product of the *DGKE* gene is not associated with the complement system and appears to be involved in the coagulation process. Deficiency of the DGKE protein product may cause a prothrombotic state that results in TMA.

**Other Genes**

Because many patients do not have an identifiable genetic mutation related to aHUS, physicians have theorized that comprehensive screening of genes in the complement and coagulation pathways will reveal additional genes that contribute to the development of the disorder. A recent study implicated several new genes, in particular the *PLG* gene. This gene is involved in coagulation and encodes plasminogen. Patients with *PLG* gene mutations who have aHUS often have mutations of gene(s) in the alternative pathway of complement.

**DEAP-HUS**

In rare instances, sporadic cases of aHUS result from autoantibodies to the protein products of genes of the complement system, most commonly to complement factor H. The reason for the formation of these autoantibodies is unknown, but in approximately 90% of cases there are deletions of the *CFHR1* and *CFHR3* genes, which are adjacent to the *CFH* gene that encodes for complement factor H.

**Diagnosis**

A diagnosis of aHUS is often suspected in individuals with the classic triad of hemolytic anemia, thrombocytopenia, and acute kidney injury. The first step in making a diagnosis is by establishing the presence of TMA.

Laboratory findings that support a diagnosis of TMA include:

- Reduced hemoglobin levels, i.e. less than 10 g/dL.
- Elevated levels of lactate dehydrogenase (LDH) levels, which is released when red blood cells breakdown.
- Reduced or undetectable haptoglobin levels. Haptoglobin binds to released hemoglobin and is cleared from the body.
- Decreased platelet counts, i.e. less than 150,000/mm³.
- The presence of fragmented red blood cells (schistocytosis).
An elevated creatinine concentration indicates decreased kidney function.

A negative Coombs test is helpful in ruling out other causes of hemolytic anemia.

**Differentiating TMAs**

After a diagnosis of TMA is made, further testing is necessary to determine the underlying etiology. Because these disorders share similar clinical presentations, establishing the diagnosis can be difficult. Screening for STEC is accomplished by testing for Shiga-toxin in the stool. A blood test is performed to determine the activity levels of ADAMTS13, an enzyme important in blood clotting. Severe ADAMTS13 deficiency, defined as <5-10%, is indicative of congenital or acquired TTP. Additional testing (e.g., HIV, cobalamin C, pneumococcal infection or SLE) is important to rule other causes of TMA, but is typically tailored to the clinical situation.

Serum levels of complement or complement regulatory proteins are decreased in some patients with aHUS (C3, C4, factor H, and factor I)\(^5\)\(^,\)\(^{14}\). However, in many patients these levels are within the normal range, and thus this testing is not very sensitive, especially since protein levels may be normal even in the presence of a disease causing mutation that affects function, but not protein expression. Similarly, MCP expression by flow cytometry on peripheral leukocytes is low in a subset of patients with MCP gene mutations \(^{14}\). Screening patients for autoantibodies to factor H is critically important since it provides a specific diagnosis of a form of aHUS with a specific treatment.

Genetic testing can support a diagnosis of aHUS, but is not required for a diagnosis. In approximately 30%-50% of cases no genetic mutation can be identified. In addition to confirming a diagnosis, molecular genetic testing can also provide prognostic information and help to guide treatment \(^1\). Patients should be screened for all known mutations because they may have mutations in multiple genes. Molecular genetic testing is only available as a diagnostic service at specialized laboratories and the results often taken weeks to months. Consequently, initial therapy should not be delayed while awaiting the results of genetic testing \(^{12}\).
Treatment

Treatment by a medical team familiar with the unique challenges of aHUS is warranted. Genetic counseling is of benefit for certain families, but can be difficult because penetrance is only 50%.

Supportive Therapy

Initially, patients require supportive care. Blood transfusions are frequently necessary due to hemolysis causing severe anemia. Hemolysis may be ongoing, potentially necessitating multiple transfusions. Blood transfusions are reserved for patients who experience severe symptoms or in whom hemoglobin is below 6-7 g/dL. A higher cutoff may be used if hemolysis is brisk or a procedure is planned. Platelet transfusions can worsen TMA and are usually contraindicated, except in cases where significant bleeding is a concern or in advance of an invasive procedure with a risk of major blood loss.

Many patients already have acute kidney injury when first diagnosed with aHUS and may require supportive measures such as hemodialysis or peritoneal dialysis. The acute kidney injury requires judicious management of fluid balance and electrolyte disorders. Hypertension is more common than in other patients with acute kidney injury, with management necessitating correcting volume overload and appropriate use of antihypertensive medications.

Initial Therapeutic Options

Clinical studies have consistently demonstrated that prompt recognition and treatment is critically important. Early initiation of eculizumab is associated with increased recovery of renal function. In the past, patients were initially treated with plasma therapy, but many physicians now advocate beginning with eculizumab due to its greater efficacy in preventing and treating episodes of aHUS.

Recommended first-line uses of eculizumab:

- In children with a probable first episode of aHUS and no evidence of STEC-HUS or a secondary cause.
- In adults with TMA and no evidence of STEC-HUS, TTP or a secondary cause.
- Patients with TMA and a family history of aHUS.
• Patients with a diagnosis of aHUS and TMA, either before or after transplantation.

Eculizumab

Eculizumab (Soliris®) is widely considered the first-line therapy for most patients with a confirmed diagnosis of aHUS \cite{1,9,12} and is becoming the standard of care for this disorder \cite{12}. In 2011, both the U.S. Food and Drug Administration (FDA) and the European Medications Agency (EMA) approved eculizumab for the treatment of aHUS. The drug is a humanized monoclonal antibody that binds to terminal complement component C5. Eculizumab is a complement inhibitor and blocks the uncontrolled activity of the complement system, thereby preventing the endothelial injury seen in aHUS. Eculizumab has stabilized hematological abnormalities (i.e. reduced acute hemolysis and normalized platelet counts) and stabilized renal disease and can reverse acute kidney injury. Some patients on dialysis became dialysis-independent following eculizumab therapy \cite{7}.

Many physicians strongly encourage the use of eculizumab once a diagnosis of aHUS is confirmed or strongly suspected. Clinical trial results suggest that the chance of recovering renal function is greatly enhanced by the prompt initiation therapy. The response is often rapid, occurring in days to weeks. Unfortunately, eculizumab is not available in all countries \cite{12}.

Side Effects

The major adverse event associated with eculizumab therapy is an increased susceptibility to developing meningococcal disease \cite{12}. Meningococcal infections can become serious or life-threatening if not recognized and treated promptly. Patients require vaccination prior to initiating eculizumab therapy and periodically afterward. Prophylactic treatment with antibiotics such as amoxicillin may be necessary until vaccination is effective, usually 2 weeks after the initial vaccine dose. Recommendation for vaccinations and ongoing prophylactic antibiotics vary in different countries.

Plasma Therapy

For many years, the mainstay of treating aHUS was plasma therapy, either infusions of fresh frozen plasma (plasma infusion) or plasma exchange (plasmapheresis). Plasma infusion is believed to work on the principle of delivering sufficient levels of complement proteins or complement regulatory proteins. Plasma exchange has the added benefit of removing
mutant factors and autoantibodies. The success rate of plasma therapy is controversial. Although the mortality rate dropped after the introduction of plasma therapy, no controlled studies have been conducted on patients with aHUS.

Although a subset of patients with aHUS achieves remission with plasma therapy, they often require long-term maintenance therapy to remain in remission (plasma dependence). Many of these patients have been moved to therapy with eculizumab. Other patients, despite hematological improvement, continue to experience progressive renal disease and ultimately end stage renal disease. As many as 50% of patients undergoing plasma therapy may develop end stage renal failure within one year of diagnosis. Plasma therapy is still used if eculizumab is unavailable.

**Kidney Transplant**

Patients who develop end stage renal disease require a kidney transplant. Because a kidney transplant does not treat the underlying problem, the procedure is controversial as a therapy for aHUS. Kidney transplantation has been associated with a high risk of aHUS recurrence in the allograft. The risk varies depending upon the specific genetic mutation present. In patients with a CFH or CFI mutation the risk may be as high as 80%. A MCP mutation is the only mutation not associated with a high risk of recurrence, unless a patient has a mutation in a second complement gene, which greatly increases the risk. Living donor kidneys should only be used from donors who are not genetically related to the recipient because of the concern for the transplant procedure triggering aHUS in the donor since the donor may have a genetic predisposition of aHUS.

Eculizumab has been used to treat disease recurrence following a kidney transplant or to prevent recurrence by giving it to patients before and after the transplantation procedure.

**Liver Or Combined Kidney/Liver Transplant**

A liver transplant has also been used to treat some patients because CFH and other complement proteins are synthesized in the liver. Initially, liver transplants proved ineffective due to high mortality from perioperative TMA. More recent attempts were undertaken with perioperative conditioning protocols involving eculizumab or plasma therapy and were effective. A combined kidney/liver transplant has also been successful.
Liver transplant recipients with aHUS should receive a preparative regimen of eculizumab or plasma therapy \textsuperscript{9,12}. Despite some favorable outcomes, the risk of liver transplant is significant. Liver transplantation is much less common since the availability of eculizumab.

**Immunosuppressive Therapy**

Immunosuppressive therapy combined with plasmapheresis effectively treats most patients who have autoantibodies to CFH (DEAP-HUS). Plasmapheresis reduces antibody titers, but antibody titers often increase when plasmapheresis is stopped without the addition of immunosuppressive therapy \textsuperscript{1,3}. Medications that have been used include corticosteroids, azathioprine, mycophenolate mofetil, cyclophosphamide, and rituximab \textsuperscript{3}. Eculizumab is effective in treating these patients when they do not respond well to plasmapheresis. There is no consensus regarding the optimal treatment of DEAP-HUS \textsuperscript{9}.

**DGKE Mutations**

The appropriate therapeutic approach to patients with aHUS due to \textit{DGKE} mutations remains uncertain. There is evidence arguing against a response to eculizumab, although definitive evidence is lacking \textsuperscript{1}. Plasma therapy has not been effective in most cases, although there is one report of benefit \textsuperscript{16}. At least six children with mutations in the \textit{DGKE} gene received kidney transplants without recurrence of HUS \textsuperscript{9}. 
References


Resources

American Kidney Fund
11921 Rockville Pike
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www.atypicalhus.net

National Kidney Foundation (NKF)
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Clinical Centers And Medical Experts

View the Foundation for Children with Atypical HUS Medical Advisory Panel here: http://atypicalhus.ning.com/page/medical-advisory-board
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NORD helps patients and families affected by rare disorders by providing:

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- Publications for physicians and other medical professionals

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