Atypical HUS Facts: 2025 SEPT 2026

• *Atypical Hemolytic Uremic Syndrome* •

Understanding aHUS

Atypical Hemolytic Uremic Syndrome (aHUS) is a rare disease which causes decline in kidney function & can damage other major organs. It's among a larger group of thrombotic microangiopathy (TMA) conditions, affecting blood flow and blood cells. Atypical HUS is characterized by clotting in small blood vessels, destruction of red blood cells (hemolysis), and reduced platelet counts (thrombocytopenia), and which progresses to acute kidney injury.

Most people with aHUS develop the condition because the complement system, part of the body's immune defenses, doesn't 'turn off' as it should and this uncontrolled activity causes damage. Less commonly, aHUS may occur for reasons other than complement dysfunction. Atypical HUS can occur at any age and can be caused by a combination of environmental factors (like infections, pregnancy, or certain medications) and genetics (with mutations in the CFH gene most common, in about 30% of aHUS cases).

Occurring in only 2–9 people per million, the rarity and variability of aHUS activity makes diagnosis and treatment challenging. Symptoms often mimic more common diseases, leading to misdiagnosis and delayed care. Since timely intervention improves outcomes, closing knowledge gaps and raising awareness are essential so patients receive accurate, rapid diagnosis and appropriate treatment. (Woodward et al. aHUS Alliance Global Action)

Symptoms Onset symptoms may be vague or mistaken for other conditions. Common ones include: fatigue, bruising or pale skin, nausea/vomiting, abdominal pain, shortness of breath, or discolored/reduced urine. (Licht et al, 2015)

Diagnosis Diagnosis is difficult, with no universal criteria (Fakhouri F, 2023). Atypical HUS is usually a 'diagnosis of exclusion', after conditions with similar clinical presentations are ruled out. Tests that may support diagnosis include bloodwork, ADAMTS13 levels, kidney function rates, genetic testing, biomarker studies, and complement analysis.

Genetic Factors Genetic predisposition can run in families through complement-regulatory gene mutations such as CFH, MCP, or CFI (Noris, M and Goodship, THJ et al, 2009). Around 10-25% of aHUS cases may be linked to inherited genetic mutations, but the majority of aHUS cases occur sporadically: randomly or infrequently, without a clear pattern of inheritance or environmental cause (Kavanagh D et al, 2013). Dysregulation of the alternative complement pathway is identified in 40–60% of patients (Spasiano, 2023).

Triggers Atypical HUS activity is often triggered by factors that abnormally activate the complement system (Brocklebank et al, 2023). These include infections, pregnancy (Meena, 2025), vaccines, or drugs like immunosuppressants or chemotherapy (Yerigeri, 2023). Autoimmune diseases and cancers may also trigger activity by producing substances that activate complement.

Treatment effective for the 40–60% of patients with complement-mediated TMA (genetic abnormalities or complement-related autoantibodies: Bogdan et al. 2025). Treatment guidelines have evolved from plasma therapy (infusion or pheresis) to therapeutic drugs, namely complement inhibitors or their biosimilars. Patients with mutations in coagulation genes such as DGKE (Westra et al 2016), or those with autoimmune or secondary forms, may need different approaches.

Research now suggests that lifelong medication may not always be required for every aHUS patient. (Studies: SETS aHUS, Bryant et al. 2024 and CUREiHUS,Bouwmeester et al. 2023), However, discontinuation of them requires a personalized assessment to include both clinical profile and genetics, with individualized close and ongoing monitoring supported by access to rapid retreatment if relapse occurs. New drugs are being developed to address diverse aHUS/TMA needs and to provide lower-cost options so more nations can ensure access to appropriate therapy.

TREATMENT UPDATES

New Global Document (aHUS & other): Vivarelli M et al. *The role of Complement in Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference*. doi: 10.1016/j.kint.2024.05.015.

Drug Discontinuation, 10 yr Study: *Bryant et al. Eculizumab Withdrawal and Monitoring in atypical haemolytic uraemic syndrome (SETS aHUS)*. doi.org/10.1016/j.lanepe.2025.101392

FDA Approvals, Biosimilar Drugs (reference drug, eculizumab): Bkemv® from Amgen, also Epysqli® from Samsung Bioepis & Teva. (Others currently under study)

aHUS Drug Candidates in Clinical Trial (as of Sept 2025, NCTs on ClinicalTrials.gov): *Crovalimab* from Hoffmann-La Roche, NCT04958265 and NCT04861259; *Iptacopan* from Novartis, NCT05935215, NCT05795140, and NCT04889430; *Narsoplimab OMS721* from *Omeros*, NCT03205995, NCT02355782 and NCT02222545; *Ruxoprubart* NM8074 from NovelMed, NCT05684159. See these & others at https://bit.ly/aHUSclinicalTrialsSept2025

Targeted Treatment, Goals *(diverse aHUS patient subtypes):* More precise naming (nomenclature) to classify conditions by causes (etiology) and genetic or clinical differences - and shifting away from the catch-all term 'atypical HUS' - will advance disease management and accelerate the development of effective, personalized treatments.

— continued on page 2

Multi-Organ Involvement

Kidneys: All aHUS patients experience kidney damage, ranging from functional injury to renal failure. aHUS activity can affect multiple organs simultaneously. (Raina et al, 2019)

Central Nervous System (CNS)/ Brain: Occurring in 20–40% of cases, symptoms may include seizures, confusion, stroke, or other impairments. Effects range from mild to serious, often causing memory or cognitive difficulties..

Cardiovascular System: Blood vessel linings are damaged during aHUS activity. Along with kidney decline, this commonly results in hypertension. In 10–20% of cases, serious complications occur, including myocardial infarction, ischemia, or heart failure.

Gastrointestinal Tract: GI issues affect about 20–25% of cases and may include abdominal pain, nausea, vomiting, diarrhea, or rare severe problems such as pancreatitis. (Yerigeri, 2023)

Pulmonary Involvement / Lungs: Found in about 5–10% of cases, respiratory issues may involve pulmonary hypertension, distress, or hemorrhage.

Liver, Eyes, Skin: Less often affected, but possible issues include liver involvement (measured by ALT/AST), visual disturbances or loss, and skin problems such as lesions, jaundice, or petechiae.

Impact at

Home - Work - School

- aHUS may be chronic or episodic, varying in severity, duration, and organs affected. Because people with aHUS show few visible symptoms, patients and their caregivers often deal with a lack of understanding about its life-threatening and unpredictable nature.
- Patients face rapid, unpredictable health changes, often with few warning signs. Adjustments may be needed for sudden medical care, memory issues, slower task completion, or difficulty focusing due to anemia or kidney dysfunction.
- Social impact and economic burden affect patients, families, and caregivers, including mental health, daily routines, relationships, and lifestyle changes. (Bouwmeester, 2024)

aHUS Affects More than a Patient's Physical Health

A Study with Long-Term follow up of aHUS Patient Reported Outcomes (PROs) concluded: "...patients with aHUS report chronically impaired global health status with reduced physical and cognitive function, and higher levels of fatigue, anxiety, depression, and sleep disturbances compared with the general population." (Hubben A et al, 2024. doi:10.1182/blood-2024-200224)

Impact on Quality of Life & Mental Health for aHUS Families: "Kidney diseases involving complement overactivation can profoundly affect patients and caregivers, limiting participation in important activities." and "For young patients, lack of natural history data creates uncertainty about disease course and impact, influencing career and family planning." (Vivarelli et al, 2024. doi:10.1016/j.kint.2024.05.015)

aHUS Activity can affect Health for not only Pregnant Mothers, but also their developing Baby: Maternal health problems included preeclampsia (36%) and HELLP syndrome (30%), with 5% mortality. Fetal complications included stillbirth, growth restriction, low birth weight, and prematurity. (Meena P et al, 2025. doi: 10.1097/MD.0000000000041403)

Taming aHUS: Complement & Thrombotic Microangiopathy

Medical advances now frame atypical HUS as a spectrum of related conditions, complicating rapid diagnosis and treatment. That concept is behind research designed to close more of the knowledge gaps in complement-related conditions and thrombotic microangiopathies, to create a shift in understanding that supports improved diagnosis, monitoring, and targeted interventions.

The *complement* system is a protein cascade that fights disease, reduces inflammation, and aids healing. Atypical HUS is one type of *thrombotic microangiopathy* (TMA), marked by red blood cell and platelet destruction as microclots form in small vessels. Overactive complement can drive inflammation and tissue damage. Conversely, complement deficiencies or missing components reduce the body's ability to clear pathogens. Although abnormal complement activity explains the majority of aHUS cases, involvement of the coagulation pathway or metabolic defects would render complement blockade therapeutics ineffective and require a different approach to treatment.

Treatment, therapeutic drugs, management, and relapse risk vary by complement involvement and genetics. Clearer identification of aHUS subtypes and causes (etiology) is vital to improving patient outcomes.

Nester C et al. *An Expert Discussion on aHUS Nomenclature: Identifying a road map to Precision* (NKF) doi: 10.1016/j.kint.2024.05.021

Vivarelli M et al. *The role of complement in kidney disease:* (KDIGO) Controversies Conference. 2024 Sep doi: 10.1016/j.kint.2024.05.015

A Global Rare Disease Network to

aHUS Alliance

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www.aHUSallianceAction.org

24 September aHUS Awareness Day SEPT 24

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