Atypical HUS Facts: 2026 SEPT 2027

• 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. (Vivarelli et al, KDIGO 2024)

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. (Ardissino et al, 2026). 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). (Noris et al, 2021)

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 and Nester et al, 2024).

Diagnosis Diagnosis is difficult, with no universal criteria (Fakhouri et al 2023 and Cole et al 2025). 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. (Simmons 2026 and 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 et al, 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 et al, 2025), vaccines, or drugs like immunosuppressants or chemotherapy (Yerigeri et al, 2023). Autoimmune diseases and cancers may also trigger activity by producing substances that activate complement.

Treatment Complement inhibitors are effective for the 40–60% of patients with complement-mediated TMA (genetic abnormalities or complement-related autoantibodies (Java et al 2024 and Alyamany, 2026). 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 (Lemaire et al 2013, 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.

aHUS: Moving Forward

Research and clinical findings continue with developments to close knowledge gaps across many areas of aHUS. The topic most far-reaching is the classification and renaming of this rare disease (see reverse).

Discontinuation of Complement Inhibitors Stopping treatment risks relapse, but long-term outcomes depend heavily on a patient's genetic profile. Close, case-by-case monitoring is essential to protect kidney function. (Hockman et al, 2025; Vujović et al, 2025)

Biomarkers Biomarkers evaluate disease activity, organ damage, and treatment response. Elevated C5b-9 may signal an aHUS relapse, making monitoring of kidney function, hemolysis markers, and complement activity essential for those discontinuing treatment. Some research markers like plasma C5b-9, C5a, and Ba reflect complement activation and may detect low level disease activity. (Tohidi et al, 2026)

Infection Risk Factors The complement system provides immune defense, but excessive activation drives injury to blood vessels and organs. Complement inhibitors weaken immune defenses, significantly raising the risk of life-threatening infections from encapsulated bacteria and Neisseria species, such as sepsis and meningitis. (Bettoni et al, 2026) Patients on these drugs must stay current with meningococcal vaccination and seek prompt evaluation for any illness.

Drug Candidates The toolkit of anticomplement drugs relevant to aHUS has expanded, though most remain in trials for—or approved for—other complement diseases (e.g., PNH or C3G) rather than aHUS itself. Complement inhibitors work well for most aHUS patients, but the small percentage whose aHUS stems from mutations in other body systems (such as blood-clotting or cell-structure genes, e.g. DGKE) will need different treatment.

Since drug mechanisms carry over across diseases, therapeutics developed for other conditions may still be relevant to aHUS. Joining the approved C5 inhibitors already in use (eculizumab, ravulizumab) are drugs targeting C5 (crovalimab, C5+ nomacopan), C3 (pegcetacoplan), factor B (iptacopan), factor D (danicopan, vemircopan), C5aR1 (avacopan), and MASP-2 (narsoplimab). This field moves fast, so watch for updates on studies like APPELHUS (iptacopan: NCT04889430, completed Aug 2026) and COMMUTE-a & -p (crovalimab: both Phase III), and track trial and approval progress via ClinicalTrials.gov, the FDA (US), and the EMA (EU).

—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 et al, 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 All Areas of Life

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 et al, 2024)

Impact on 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 KDIGO:2024)

Pregnancy: aHUS can affect maternal health but may impact the developing complications for the fetus or premature birth (Meena et al, 2025).

Living with atypical HUS imposes substantial economic burdens on patients and families, from treatment-related costs to lost income when caregivers must alter work schedules around infusions and hospitalizations. The disease's unpredictable, relapsing course can force families to sacrifice career, educational, and personal opportunities in favor of constant vigilance (Mauch et al, 2023 and Hubben et al, 2025).

Re-Naming aHUS?

Patients deserve a diagnosis that reflects what is happening inside their bodies—not merely what their disease is not. The term atypical HUS emerged when understanding of complement, genetics, and TMA was far less developed. Today, research increasingly has revealed a spectrum of conditions with related but distinct characteristics.

Atypical HUS has remained a catch-all label for patients with different genetic drivers, triggers, disease courses, and treatment responses. (Nester al, NFK working group 2024) Most aHUS cases are caused by complement dysregulation, but up to 30% may involve non-complement mutations (e.g. DGKE, PLG) or considered ideopathic (of unknown cause). (Bognan et al, 2025) Complement inhibition will be ineffective for those subsets of aHUS patients because it does not address their underlying disease mechanism, so alternate treatment options must be explored.

More precise terminology has evolved and been adopted for other conditions, resulting in 'Precision Medicine' approaches that deliver individualized disease management tailored to improve patient outcomes. Establishing revised, consensus-driven aHUS terminology would allow multidisciplinary care teams to better share clinical insights and coordinate complex care.

Updating the naming system (nomenclature) does not mean abandoning patients, established treatments, or pharmaceutical investment. It means listening to all groups to ensure that regulatory systems, reimbursement policies, and clinical decisions reflect an elevated standard of the modernized landscape now revealed.