Updates in atypical hemolytic syndrome

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Purpose of review
This review aims to summarize how scientific advances in complement biology have not only improved the diagnosis and management of aHUS but also continue to offer insights into the pathophysiology of complement-mediated disease that may be leveraged for future therapeutic developments.

Recent findings
Updated information on the clinical and epidemiological features, pathophysiology, diagnosis, management, and potential for future therapeutic advancements in the treatment of aHUS are reviewed.

Summary
aHUS is a rare but potentially life-threatening disease that requires prompt diagnosis and treatment as well as long-term management via a multidisciplinary team providing coordination of primary and specialty care as well as outreach and education for children and families affected by this life-long disease.

Keywords
atypical hemolytic uremic syndrome, complement dysregulation, complement inhibitors, complement therapeutics, plasmapheresis

INTRODUCTION

Hemolytic uremic syndrome (HUS) encompasses distinct forms of thrombotic microangiopathy (TMA) characterized by a triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Although the classification of HUS has been debated since its first description in 1955 [1], its diverse etiologies share the common pathophysiology of endothelial injury from platelet aggregation, thrombocytopenia via platelet consumption, and anemia from the mechanical destruction of red blood cells. In a recent initiative, etiology-based classifications have been recommended to prioritize the clinical relevance underlying disease mechanisms in directing therapeutic decisions [2▪]. Although infection-associated HUS (i.e. due to Shiga toxin-producing *Escherichia coli*, *Streptococcus pneumoniae,* and viruses such as influenza A, HIV, etc.) has been historically distinguished from all other etiologies as 'atypical HUS' (aHUS), further specification of primary aHUS typically includes conditions with abnormalities in the complement pathway as well as *DGKE*-HUS, *WT1*-HUS, and metabolism-associated HUS (i.e. cobalamin C deficiency) vs. secondary aHUS including a broad list of associated conditions including transplant-associated, drug-induced, and pregnancy-induced HUS, as well as malignant hypertension, systemic lupus erythematosus, malignancy, and antiphospholipid antibody syndrome, as detailed in other excellent reviews [3▪▪,4,5]. Here, we specifically focus on how advances in complement biology have impacted 'primary aHUS' or 'aHUS due to a defect in the complement pathway' to improve the diagnostic and management challenges in patients with this rare but life-threatening disease.

EPIDEMIOLOGY

aHUS is an exceptionally rare disease with an estimated incidence of 0.25–2 cases per 1 000 000 in North America [6]. Although aHUS can manifest at any age, it is more commonly seen in children than adults, representing about 10–20% of all HUS cases [7].

ALTERNATE COMPLEMENT PATHWAY AND REGULATION

aHUS results from uninhibited activation of the alternative pathway of the complement system,

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KEY POINTS

- aHUS is a rare, life-threatening disease involving dysregulation of alternative complement pathway that often presents diagnostic challenges.
- Hemolytic uremic syndrome (HUS) is a triad of nonimmune hemolytic anemia, thrombocytopenia, and acute kidney injury with additional laboratory findings, including low haptoglobin, increased lactate dehydrogenase, and the presence of schistocytes on peripheral blood smear.
- If aHUS is suspected, early initiation of complement inhibitor therapy is recommended if available, and in its absence, plasmapheresis should be commenced.

which can occur secondary to gain-of-function variants in activating genes or loss-of-function mutations in regulatory proteins. Given that the alternative pathway is constitutively active at low levels, it must be tightly regulated to prevent damage to host cells from excess activation and yet contribute to the immune response via activation in response to pathogens. Figure 1 depicts the activation and regulation of the alternative pathways, with aHUS resulting from the dysregulation of this signaling cascade.

CLINICAL PRESENTATION

Presentation of aHUS is typically sudden, marked by the triad of hemolytic anemia, thrombocytopenia, and kidney dysfunction [10] often triggered by an infection, including diarrheal illnesses either as a trigger or part of the prodrome in up to 50% of patients with aHUS [11], making the initial diagnosis challenging to differentiate from Shiga-toxin-mediated HUS. Insidious presentations have been less commonly reported, with fluctuating anemia, thrombocytopenia, varying proteinuria with preserved renal function, generalized symptoms of poor weight gain, poor appetite, and fatigue. Although renal microvasculature is the primary site of microangiopathy, extra-renal involvement (Table 1) ranges from 20 to 50% of aHUS patients [12,13], with central nervous system involvement being the most common with a reported incidence of 8–48% [12]. Although cardiovascular [13,14] and pulmonary manifestations [15,16] can either occur as direct and/or secondary complications (i.e. due to fluid overload as well as multiorgan dysfunction), additional complications such as ocular involvement [17,18], skin [12], and muscle [19] involvement have been reported.

GENETICS OF ATYPICAL HEMOLYTIC UREMIC SYNDROME

Genetic mutations in the alternate pathway complement proteins are identified in approximately 60% of children with aHUS and, as described above, occur as gain-of-function variants in activating genes (i.e. *CFB* and *C3*) or loss-of-function mutations in regulatory proteins (i.e. *CFH*, *CFI*, *MCP,* and *THBD*). Table 2 provides an overview of various complement protein mutations, including their associated disease frequency, risk of progression to end-stage kidney disease (ESKD), likelihood of post-transplant recurrence, and the functional roles of the complement proteins involved.

ANTICOMPLEMENT FACTOR ANTIBODIES

As further studies have examined the role of autoantibodies in complement-mediated diseases, many well characterized autoantibodies have shown a pathogenic role and diagnostic value in their detection; however, in other cases, the relevance of the autoantibodies has remained somewhat unclear [27]. Toward the former point, coexisting genetic variants in patients with antifactor H (FH)-associated aHUS have been shown to have significant diagnostic and management implications [28]. Although prior cohort studies have reported FH autoantibodies (FHAA) in 5–25% of aHUS cases, the global aHUS registry suggested higher rates of detection at 45% [29]. Approximately 90% of patients with FHAA have been shown to carry a genetic polymorphism, given the known association between FHAA positivity and factor H genes, *CFHR1* and *CFHR3*, though it is well documented that not all patients with FHAA have an identifiable genetic polymorphism [30]. Although other autoantibodies have been less frequently reported [31,32], their pathogenic role is less established, and the clinical relevance of these findings remains to be determined.

DIAGNOSTIC EVALUATION

Identifying aHUS at its initial presentation is a diagnosis of exclusion and, therefore, a stepwise approach is recommended. Given that approximately 10% of HUS cases in children are due to aHUS, the initial general evaluation of a patient who presents with the clinical triad of HUS would include: infectious work-up (i.e. stool culture, stool PCR, detection for Influenza, bacterial culture for *S. pneumoniae*, etc.), plasma ADAMTS13 activity and/or ADAMTS13 antibodies, and evaluation for cobalamin C deficiency (i.e. plasma homocysteine and

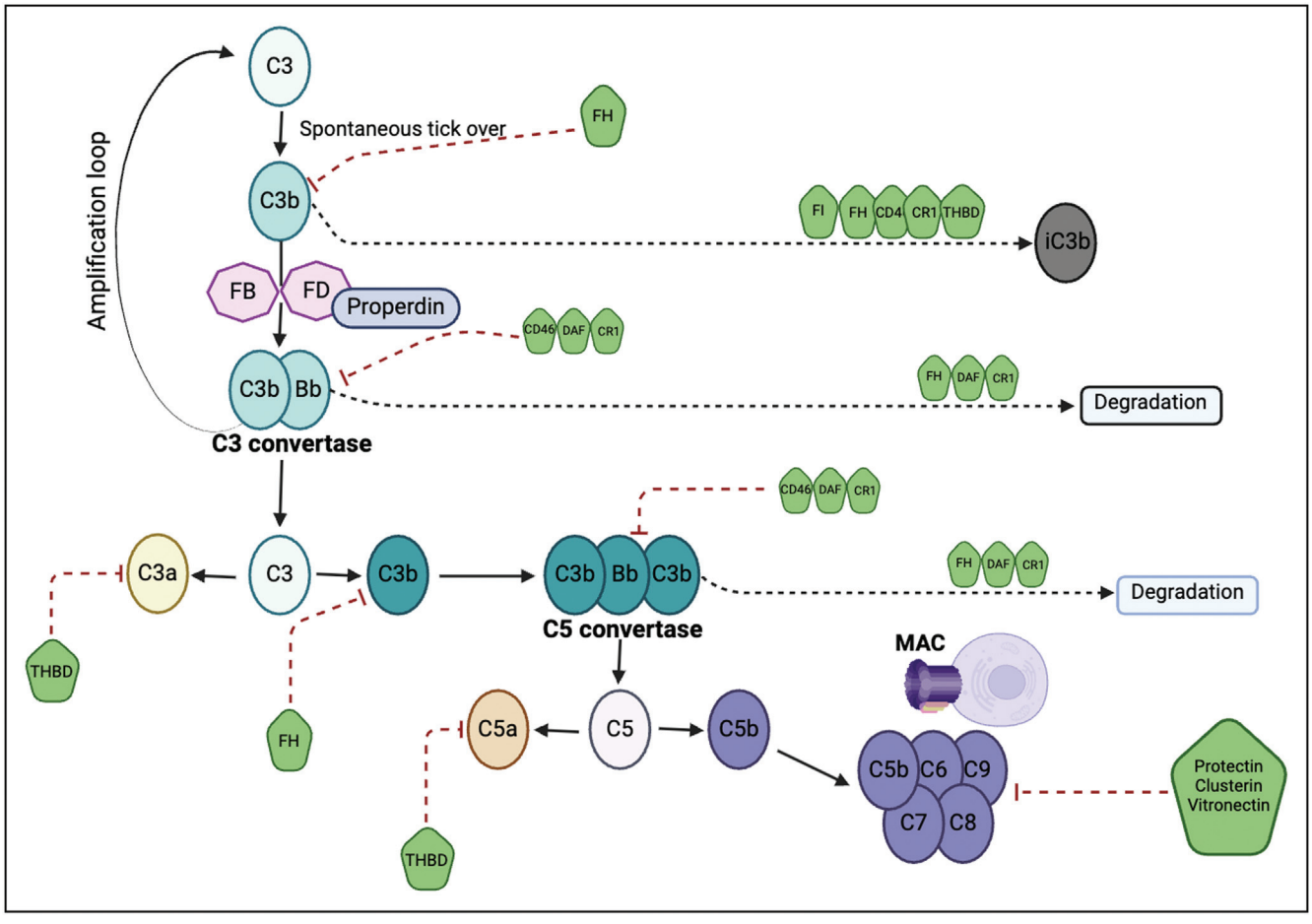

FIGURE 1. Alternate complement pathway regulation. Spontaneous, continuous low-level hydrolysis of C3 into C3a and C3b (or 'tick-over') in the circulation is amplified by bacterial and/or viral proteins. C3b fragments and complement factor B (CFB) form C3 convertase (C3bBb). C5 convertase (C3bBbC3b) is formed with further activation of complement. C5 convertase cleaves C5 and generates C5b, which forms the membrane attack complex (C5b-9) after binding with C6, C7, C8, and C9 and inserts pore-like structures into the cell membrane resulting in cell lysis. Complement activation on the cell surface of the host cell is prevented by complement regulatory proteins complement factor H (CFH), complement factor I (CFI), and membrane cofactor protein (MCP) [8,9]. CFH competes with CFB for binding with C3b, displaces Bb, and hastens the decay of C3 and C5 convertases. MCP, C3b receptor (CR1), and decay-accelerating factor (DAF) are inhibitors of C3 and C5 convertases. CFH, MCP, and CR1 also act as cofactors for CFI in the cleavage of C3b to inactive C3b (iC3b). Thrombomodulin (THBD) is an anticoagulant and is a cofactor activation of protein C and plays an important role in the regulation of complement activation.

methylmalonic acid levels). Although no specific single test can confirm the diagnosis of aHUS at presentation if the initial testing as outlined above is negative and secondary causes of HUS (i.e. systemic lupus erythematosus, antiphospholipid syndrome, malignancy, drugs, transplant, etc.) are ruled out, then aHUS and noncomplement-mediated HUS (i.e., *DGKE* and *WT1* mediated HUS) remain high on the differential. Additional testing includes a complement functional panel (i.e. C3, C4, CFH, CFI, factor B, C5a, C5b-9, and anti-CFH antibody levels); however, it is important to note that normal C3, CFH, and CFI levels do not exclude aHUS. Conversely, high C5a and C5b-9 levels lack specificity as they can be elevated in Shiga toxin-induced HUS [33]. Simultaneously, genetic testing should also be considered. With multiple genetic panels currently available, the clinician should ensure that the panel includes *CFH*, *CFI*, *MCP*, *C3*, *CFB*, *THBD*, *DGKE*, *MMACHC*, and *MTR* genes and multiplex ligation-dependent probe amplification (MLPA) for the detection of CFH region deletion/duplication, as well as *WT1*, with whole-exome sequencing considered in children who are resistant to complement inhibitor therapy or if known genes were omitted from the initial genetic panel [3▪▪,5].

Table 1. Clinical manifestations of atypical hemolytic uremic syndrome

Renal manifestations
Acute kidney injury (AKI)
Urinalysis abnormalities (i.e. hematuria, proteinuria)
Electrolyte abnormalities (i.e. hyperkalemia, hyponatremia, metabolic acidosis, etc.)
Hypertension
Fluid overload
Central nervous system
Symptoms of altered mental status (i.e. irritability, altered consciousness, encephalopathy, coma) and/or headaches
Abnormal exam findings: nystagmus and/or focal neurological deficits
Abnormal MRI findings (i.e. white matter changes in the brain stem, basal ganglia, posterior cortex, and thalami)
Gastrointestinal symptoms
Symptoms of abdominal pain, nausea/vomiting, and anorexia
Pancreatitis and/or pancreatic necrosis
Transaminitis, hepatitis, and cholelithiasis
Ischemic colitis and intestinal perforation
Protein losing enteropathy
Cardiovascular complications
Cardiac dysfunction, including dilated and hypertrophic cardiomyopathy, myocardial infarction and sudden cardiac death
Left ventricular hypertrophy
Tachycardia
Large vessel steno-occlusive disease
Intra-cardiac thrombus
Pulmonary complications
Pulmonary hemorrhage
Pulmonary embolism
Pulmonary hypertension
Secondary pulmonary complications due to fluid overload, pulmonary edema, and/or cardiac dysfunction
Ocular involvement
Symptoms of pain, blurred vision, and/or decreased visual acuity
Rarely intraretinal/choroidal hemorrhage, retinal ischemia, central retinal vein occlusion, and optic disc edema
Other rarely reported complications
Skin manifestations, including gangrene
Muscle involvement and/or rhabdomyolysis

MANAGEMENT OF ATYPICAL HEMOLYTIC UREMIC SYNDROME

Treatment of children with aHUS involves a combination of complement-targeted therapy and supportive care, including optimal and timely management of acute complications, such as fluid overload, hypertension, electrolyte abnormalities, uremia, anemia, and thrombocytopenia. Platelet transfusions are generally avoided, except in the setting of active or increased risk of bleeding (i.e. at the time of a surgical procedure). Additionally, the monitoring and management of extrarenal complications are crucial components of care.

Eculizumab is a humanized monoclonal IgG C5 antibody that binds and blocks C5 cleavage and the production of membrane attack complex (MAC, C5b-9) [34]. A 2016 international consensus approach [5] recommended eculizumab as first-line therapy in aHUS initiated within 24–48 h of clinical diagnosis while waiting for confirmatory tests. Clinical trials have demonstrated both short-term and long-term efficacy in the treatment of aHUS in children and adults with weight-based eculizumab dosing regimen administered every 2 weeks during the maintenance phase [35–38]. However, many clinicians have adapted this eculizumab dosing schedule based on desired eculizumab trough level of 50–100 μg/ml and complement functional test demonstrating complement blockade instead of fixed weight-based dosing regimen given several reports supporting the need for personalized eculizumab dosing [39,40].

Ravulizumab is also a humanized anti-C5 monoclonal antibody but with extended half-life and has demonstrated efficacy in pediatric studies with administration intervals of 4–8 weeks [41]. However, eculizumab remains the preferred treatment in the acute setting of aHUS, with consideration to transition to ravulizumab once the patient stabilizes given the limited data for individualized ravulizumab dosing compared with the studies reported for eculizumab. Importantly, poor response to eculizumab (and presumably ravulizumab) has been described in patients with missense mutations in C5 primarily noted in Japanese, Korean, Finnish, and African ethnicities [42].

Blockade of the terminal complement pathway is associated with life-threatening infection risk with encapsulated organisms, specifically *Neisseria meningitidis*. Patients should initiate meningococcal vaccination (MenACWY and Men B) and antibiotic prophylaxis prior to receiving eculizumab. Booster doses of meningococcal vaccination need to be given every 2–5 years. Although antibiotic prophylaxis is mandatory for the first 2 weeks after starting eculizumab, many clinicians opt to continue prophylaxis for the duration of eculizumab treatment. While the duration of eculizumab in aHUS and peritransplant management is an active area of study, its discontinuation vs. use is generally individualized based on 'risk of aHUS recurrence' as shown in

Table 2. Overview of mutations in complement proteins in aHUS

Gene mutation	Mutation frequency	C3 levels	Risk of ESKD after initial presentation or at 1 year	Posttransplant recurrence	Mechanisms and/or protein function
Inactivating mutation of *CFH*	20–30%	Low in ~70%	31–58%	80–90%	Cofactor for CFI in inactivating C3b, inhibits C3 convertase synthesis and hastens its degradation, and competes for CFB binding to C3b
Inactivating mutation of *CFI*	5–10%	Low in ~60%	17–60%[a]	70–80%	CFI inactivates C3b
Inactivating mutation of *MCP*	10–15%	Normal	6–63%[b]	15–20%	Cofactor for CFI in inactivating C3b
Inactivating mutation of *THBD*	3–5%	unknown	15–25%	Unknown	Facilitates degradation of C3b by factor I and inactivation of C3a and C5a
Gain of function mutation of C3	5–10%	Low in ~70%	11–63%	40–50%	Cleavage of C3 releases C3a and C3b fragments. Important component of C3 and C5 convertase
Gain of function mutation of CFB	1–4%	Low in ~100%	33%	100%	Binds to C3 and forms C3 convertase
Homozygous deletion in *CFHR1–3* gene	5–50%[c]	Low in ~60%	10–37%	High, if antibody titer is high	Predisposition to FHAA, which interfere with the FH binding to the alternative pathway C3 convertase

CFB, complement factor B; CFH, complement factor H; CFI, complement factor I; ESKD, end-stage kidney disease; FHAA, factor H autoantibody; MCP, membrane cofactor protein; THBD, thrombomodulin.
[a]Approximately 30% of patients with CFI mutations have heterozygous mutations in other aHUS-susceptible complement genes.
[b]Children have a lower risk of ESKD compared with adults [3▪▪,5,20–26].
[c]Based on a recent study reporting higher rates of FHAA and genetic polymorphisms [29].

Table 3 and summarized in the supplemental figures of a recent review [3▪▪].

Plasma therapy (plasma exchange or plasma infusions) is no longer first-line therapy, except where eculizumab is not available or in patients with FHAA, as there remain outstanding questions regarding the management of these specific patients. Although plasma exchange has been associated with a more rapid hematological remission compared to patients treated via eculizumab in patients with FHAA, with a recent approach to these options as well as the indications for additional immunosuppressive therapy proposed are detailed in a recent review [43▪].

Table 3. Risk of recurrence postkidney transplant

High risk
Recurrence in prior allograft
Pathogenic mutation in *CFH, C3, factor B*, and multiple variants
High titers of anti-CFH antibody
Moderate risk
Isolated CFI mutation
Negative genetic screen for complement genes
Complement gene mutation of unknown significance
Low titer of FHAA at the time of transplant
Low risk
Isolated *MCP* and *DGKE* mutation
Undetectable titer of anti-CFH antibody at the time of transplant
WT1 mutation

CFH, complement factor H; CFI, complement factor I; FHAA, factor H autoantibody; MCP, membrane cofactor protein.

Dual kidney–liver transplantation is a viable option for patients with ESKD who do not respond adequately to complement inhibitor therapy. In contrast, kidney transplantation alone carries a risk of aHUS recurrence, with risk stratification detailed in Table 3.

Additionally, crovalimab, a long-acting C5 inhibitor that binds to a different epitope than eculizumab and prevents the formation of MAC, is actively being studied in children with aHUS (NCT04958265). Currently, clinical trials are underway in patients with aHUS with newer complement inhibitors including: factor B inhibitor (iptacopan, NCT05935215), inhibitor of mannan-binding lectin-associated serine protease-2 (narsoplimab, NCT03205995), factor D and C3 inhibitors, and synthetic fusion protein (MFHR1) [3▪▪,44,45]. These emerging therapeutic agents hold promise for patients with aHUS.

CONCLUSION

Advances in identifying mutations and polymorphisms in the genes that alone or in combination may lead to aHUS, along with improved biomarkers to interrogate dysregulation of the complement system, have already improved the management and outcomes for patients with aHUS. However, a significant portion of patients still do not have an underlying driver detected for their disease and the clinical relevance of such findings in the general population is still being understood. Thus, current and future work directed at understanding complement biology, developing new diagnostic tools, and advancing drug discovery offer the potential to fill the current gaps in the diagnosis and management of patients with aHUS. Nevertheless, the importance of a multidisciplinary approach in the specialty and primary care cannot be overlooked in the complex delivery of care for aHUS patients and families to optimize outcomes [46▪].

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Conflicts of interest

There are no conflicts of interest.

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