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Evaluation of Serum Factor H and Anti-Factor H Antibodies in Childhood Hemolytic Uremic Syndrome: A Comprehensive Review

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ABSTRACT

***Background*:** Hemolytic uremic syndrome (HUS) is a leading cause of acute kidney injury (AKI) in children, characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment. While typical HUS is often linked to Shiga toxin–producing *Escherichia coli* (STEC), atypical HUS (aHUS) results from dysregulation of the alternative complement pathway. Complement factor H (CFH), a regulatory glycoprotein that inhibits uncontrolled complement activation, plays a critical role in maintaining endothelial integrity. Deficiency or functional impairment of CFH—whether due to genetic mutations or acquired autoantibodies—has been implicated in the pathogenesis of aHUS. Anti-factor H antibodies, predominantly targeting the C-terminal domains of CFH, have emerged as an important cause of complement-mediated thrombotic microangiopathy in children, particularly in certain geographic and ethnic populations.

Aim: This review aims to comprehensively evaluate current evidence on serum factor H levels and anti-factor H antibodies in pediatric HUS, emphasizing their diagnostic, prognostic, and therapeutic implications. Specific objectives include (1) describing the role of CFH in complement regulation; (2) outlining the prevalence and pathogenic mechanisms of anti-CFH antibodies in children with HUS; (3) summarizing available laboratory methods for CFH and antibody measurement; (4) correlating CFH-related biomarkers with disease severity, renal outcomes, and relapse risk; and (5) discussing therapeutic strategies targeting complement dysregulation, including plasma therapy, immunosuppression, and complement inhibitors such as eculizumab.

Conclusion: Current literature highlights the critical role of CFH and anti-CFH antibodies in the pathogenesis and clinical course of pediatric HUS, particularly aHUS. Detection of low CFH levels or the presence of anti-CFH antibodies not only aids in accurate diagnosis but also informs treatment choices, such as early initiation of plasma exchange or complement blockade, and guides long-term follow-up to prevent relapses and chronic kidney disease. Despite advances in laboratory diagnostics and targeted therapies, challenges remain in the standardization of assays, determination of pathogenic antibody titers, and prediction of long-term outcomes. Future research should focus on integrating CFH and anti-CFH antibody profiling into personalized management algorithms, exploring novel biomarkers, and evaluating cost-effective screening strategies in high-risk pediatric populations. This will enhance early recognition, optimize treatment, and ultimately improve renal survival in affected children.

Keywords: Factor H, Childhood, Hemolytic Uremic Syndrome

INTRODUCTION

Hemolytic uremic syndrome (HUS) remains one of the most important causes of acute kidney injury in children, contributing significantly to morbidity and long-term renal complications. It is classically defined by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal impairment, resulting from endothelial injury and thrombotic microangiopathy in the renal microvasculature [1]. The syndrome is broadly categorized into typical HUS, usually triggered by *Escherichia coli* O157:H7 or other Shiga toxin–producing strains, and atypical HUS (aHUS), which is non–Shiga toxin-mediated and often linked to dysregulation of the complement alternative pathway [2]. While typical HUS accounts for the majority of cases in developed countries, aHUS is less common but associated with a worse prognosis and higher recurrence rates [3].

Complement factor H (CFH), a soluble plasma glycoprotein, plays a central role in regulating the alternative complement pathway by accelerating the decay of C3 convertase and acting as a cofactor for factor I–mediated cleavage of C3b [4]. Mutations in the CFH gene or the development of autoantibodies against CFH can lead to excessive complement activation on endothelial surfaces, culminating in microvascular injury and thrombus formation [5]. Anti-factor H antibodies (anti-CFH Abs) are increasingly recognized as a major acquired cause of aHUS, particularly in children and adolescents, and may account for up to 10–25% of pediatric aHUS cases in certain populations [6].

Early and accurate evaluation of CFH levels and anti-CFH antibodies is essential for diagnosis, prognosis, and therapeutic decision-making in pediatric HUS. The detection of low CFH levels may suggest genetic deficiency, while high-titer anti-CFH antibodies indicate an autoimmune etiology, often associated with CFHR1 and CFHR3 gene deletions [7]. Importantly, these biomarkers not only inform etiology but also influence treatment selection—children with anti-CFH antibodies often respond to plasma exchange combined with immunosuppressive therapy, while complement inhibitors like eculizumab are highly effective in refractory or severe cases [8].

Despite substantial progress in understanding the immunopathology of anti-CFH antibody–mediated aHUS, several research gaps remain. These include the lack of standardized laboratory assays for antibody quantification, limited data on optimal monitoring intervals, and uncertainty regarding the long-term outcomes of treated patients. Moreover, the interplay between genetic predisposition and environmental triggers in the development of anti-CFH antibody–associated HUS is not fully elucidated [9]. This review aims to synthesize current knowledge on serum factor H and anti-factor H antibodies in childhood HUS, highlight diagnostic and prognostic implications, and explore emerging therapeutic strategies to improve renal survival and quality of life in affected children.

Overview of Hemolytic Uremic Syndrome

HUS is a thrombotic microangiopathy (TMA) that predominantly affects the renal microvasculature but may also involve other organs, particularly the central nervous system, heart, and gastrointestinal tract [10]. It is histologically characterized by endothelial swelling, fibrin deposition, and microthrombi in arterioles and capillaries, leading to ischemic injury. Clinically, HUS manifests with pallor due to anemia, petechiae from thrombocytopenia, and signs of acute kidney injury such as oliguria, edema, and hypertension [11]. In children, HUS represents one of the most common causes of AKI after dehydration and glomerulonephritis, with an incidence of 2–3 per 100,000 annually in Europe and North America [12].

The classical, or typical, form of HUS is usually precipitated by gastrointestinal infection with Shiga toxin–producing *Escherichia coli* (STEC), particularly serotype O157:H7. The Shiga toxin binds to globotriaosylceramide (Gb3) receptors on endothelial cells, triggering cell injury, platelet activation, and microvascular thrombosis [13]. In contrast, atypical HUS (aHUS) is not associated with Shiga toxin but results from uncontrolled activation of the alternative complement pathway due to genetic mutations or acquired autoantibodies against complement regulatory proteins [14]. While typical HUS often resolves with supportive care, aHUS tends to recur and is associated with worse long-term renal outcomes [15].

The age distribution of HUS varies between subtypes. Typical HUS commonly affects children under 5 years of age, often following outbreaks of diarrheal illness, while aHUS may present at any age from infancy to adolescence [16]. Seasonal variation is also noted, with STEC-HUS peaking during summer months, whereas aHUS shows no consistent seasonal pattern [17]. Although STEC-HUS remains more prevalent globally, the recognition of aHUS has increased due to advances in complement diagnostics and genetic testing [18].

From a pathophysiological standpoint, both typical and atypical HUS share common final pathways involving endothelial injury,

complement activation, and platelet aggregation, but differ in their initiating triggers. In aHUS, mutations in genes encoding CFH, membrane cofactor protein (MCP/CD46), factor I, or complement factor B, as well as deletions in CFHR1/CFHR3, have been implicated [19]. The autoimmune form of aHUS is strongly associated with high-titer anti-CFH antibodies, which inhibit CFH function and promote unrestrained complement activation on cell surfaces [20].

Long-term prognosis in HUS depends on the underlying etiology, severity at presentation, and timeliness of treatment. Typical HUS often has a favorable prognosis if managed promptly, though up to 30% may develop chronic kidney disease (CKD) or hypertension [21]. In contrast, aHUS is associated with a higher risk of end-stage kidney disease (ESKD), with up to 60% of untreated patients progressing to ESKD or death within the first year [22]. Early recognition of complement-mediated disease and targeted therapy with agents such as eculizumab have significantly improved renal survival, underscoring the need for early diagnostic biomarkers such as CFH and anti-CFH antibodies [23].

Complement System and Factor H

The complement system is a critical component of innate immunity, comprising more than 30 plasma and membrane-bound proteins that collectively function to identify and eliminate pathogens, clear immune complexes, and modulate inflammation [24]. It operates through three activation pathways—classical, lectin, and alternative—that converge on the cleavage of complement component C3 into C3a and C3b. The alternative pathway is unique in that it is continuously active at a low level ("tick-over" activation), providing a rapid response to pathogens but also posing a risk of damaging host cells if unregulated [25]. Therefore, the system depends on a group of soluble and membrane-bound regulators to maintain homeostasis and prevent autologous injury [26].

Complement factor H (CFH) is the most important soluble regulator of the alternative pathway. It is a 155-kDa plasma glycoprotein synthesized mainly by the liver and circulating at a concentration of approximately 200–500 μg/mL [27]. Structurally, CFH consists of 20 short consensus repeats (SCRs), with its N-terminal domains responsible for complement regulation in the fluid phase, and its C-terminal domains mediating recognition of host surfaces through interactions with glycosaminoglycans and sialic acid [28]. CFH exerts its regulatory effects by accelerating the decay of the C3 convertase (C3bBb) and serving as a cofactor for factor I–mediated proteolytic inactivation of C3b [29]. This dual role is crucial in protecting endothelial cells from complement-mediated injury.

Genetic abnormalities involving CFH are a well-established cause of atypical hemolytic uremic syndrome. Mutations often occur in the C-terminal domains (SCR19–20), impairing the protein's ability to recognize and protect host cell surfaces despite retaining fluid-phase regulation [30]. These mutations predispose to unrestrained complement activation on endothelial cells, leading to microangiopathy and the clinical phenotype of aHUS. Studies have shown that CFH mutations account for approximately 20–30% of all pediatric aHUS cases, and these patients often have a poor prognosis with a high risk of recurrence after kidney transplantation [31].

Acquired CFH dysfunction can also occur in the absence of genetic mutations, most notably through the development of anti-CFH autoantibodies. These antibodies predominantly target the C-terminal SCR20 region, mimicking the functional effects of certain genetic mutations by inhibiting CFH's ability to bind to endothelial surfaces and extracellular matrix components [32]. The presence of anti-CFH antibodies is particularly frequent in certain geographic regions, such as the Indian subcontinent, and is often associated with homozygous deletion of CFHR1 and CFHR3 genes [33]. These findings highlight the critical role of CFH in maintaining endothelial integrity and underscore the pathogenic potential of both inherited and acquired disruptions in its function.

Anti-Factor H Antibodies

Anti-factor H antibodies (anti-CFH Abs) are pathogenic autoantibodies that interfere with the regulatory function of CFH in the alternative complement pathway. They primarily target epitopes in the C-terminal short consensus repeat 20 (SCR20) region of CFH, which is crucial for binding to host cell surfaces [34]. By blocking this interaction, anti-CFH Abs prevent CFH from protecting endothelial cells from complement-mediated injury, thereby promoting uncontrolled C3 activation, deposition of C3b, and formation of the membrane attack complex (MAC) [35]. Unlike neutralizing antibodies against other complement proteins, anti-CFH Abs do not usually cause a quantitative deficiency of CFH but instead lead to a functional defect, which can be equally detrimental [36].

The epidemiology of anti-CFH Ab–associated aHUS shows marked geographic variation. These antibodies are particularly prevalent in pediatric populations from North Africa, India, and the Middle East, where they may account for up to 50% of aHUS cases [37]. In contrast, their prevalence is lower in European and North American cohorts, where genetic causes predominate [38]. The median age of onset for anti-CFH Ab–associated aHUS is around 8 years, which is older than the age of presentation for many genetic forms of aHUS [39]. This form is strongly associated with a homozygous deletion of complement factor H–related proteins 1 and 3 (CFHR1/CFHR3), suggesting a loss of immune tolerance to CFH as a possible pathogenic mechanism [40].

The clinical presentation of anti-CFH Ab–mediated aHUS is often indistinguishable from other forms of aHUS, with patients developing acute microangiopathic hemolytic anemia, thrombocytopenia, and renal failure [41]. However, several features have been noted more frequently in this subset, including preceding febrile illness, upper respiratory tract infections, and relapsing disease course [42]. High antibody titers at presentation have been correlated with increased disease severity, poorer initial renal function, and greater likelihood of relapse [43]. Furthermore, persistence of high titers despite treatment is associated with chronic kidney disease progression, highlighting the importance of regular monitoring [44].

From an immunological perspective, anti-CFH Abs are predominantly of the IgG subclass, with IgG1 and IgG3 being the most common [45]. They are thought to arise through a break in peripheral tolerance, potentially triggered by molecular mimicry following infection. The absence of CFHR1 and CFHR3 proteins may facilitate autoreactivity by altering the processing or presentation of CFH-derived peptides to the immune system [46]. Understanding these mechanisms is critical not only for refining diagnostic approaches but also for developing targeted immunotherapies aimed at preventing relapses and preserving renal function in affected children [47].

Laboratory Evaluation of Factor H and Anti-Factor H Antibodies

The assessment of serum CFH levels and anti-CFH antibodies is central to diagnosing and subclassifying atypical hemolytic uremic syndrome. Quantification of CFH concentration is typically performed using enzyme-linked immunosorbent assay (ELISA) or nephelometry, with normal plasma concentrations ranging from approximately 200 to 500 μg/mL in healthy individuals [48]. Reduced levels may indicate genetic deficiencies, consumptive loss during acute complement activation, or rare acquired conditions unrelated to aHUS. Interpretation must therefore be contextualized with the clinical picture, other complement parameters (such as C3 and C4), and genetic testing [49]. Importantly, CFH measurement should be performed prior to the initiation of plasma therapy to avoid confounding results due to exogenous CFH replacement [50].

Detection of anti-CFH antibodies relies on ELISA-based immunoassays, which use purified CFH as the target antigen. These assays measure antibody titers and can distinguish between different immunoglobulin subclasses, most commonly IgG1 and IgG3 in aHUS [51]. A positive test is generally defined by titers exceeding the 95th percentile of healthy control values, although cut-off thresholds vary between laboratories [52]. Because antibody titers may fluctuate over the course of the disease and during treatment, serial measurements are recommended for prognostic purposes and to guide immunosuppressive therapy [53]. High titers at presentation have been correlated with greater disease severity and higher relapse risk, whereas declining titers typically accompany clinical remission [54].

Despite their diagnostic value, both CFH and anti-CFH Ab assays have limitations. Lack of assay standardization between laboratories can lead to variability in results, complicating interpretation and cross-study comparisons [55]. Additionally, functional assays—such as hemolytic assays using sheep erythrocytes or assays measuring C3 convertase decay acceleration—can provide complementary information about CFH activity, particularly in cases where concentration is normal but function is impaired [56]. Incorporating a panel of complement tests, including C3, C4, factor B, soluble membrane attack complex (sMAC), and genetic screening for CFH and CFHR gene variants, provides the most comprehensive evaluation [57]. In resource-limited settings, logistical challenges in performing specialized assays highlight the need for accessible and validated point-of-care diagnostic tools for timely identification of complement-mediated HUS [58].

Clinical Correlations

The measurement of serum CFH and anti-CFH antibodies in pediatric HUS has direct implications for understanding disease severity at presentation. Several studies have demonstrated that children with markedly reduced CFH levels or high-titer anti-CFH antibodies tend to present with more severe renal impairment, higher serum creatinine, and more profound thrombocytopenia compared to those without complement abnormalities [59]. In anti-CFH antibody–associated HUS, the degree

of antibody elevation correlates with the intensity of complement activation, reflected by low C3 levels, elevated soluble membrane attack complex (sMAC), and extensive microvascular injury on renal biopsy [60]. These laboratory findings align with clinical observations of rapid disease progression and greater need for dialysis during the acute phase [61].

Relapse risk is another important clinical correlation. Children with persistent high anti-CFH antibody titers are significantly more likely to experience recurrent episodes of thrombotic microangiopathy, often triggered by infections or vaccinations [62]. Relapses can occur weeks to years after the initial episode and may contribute cumulatively to chronic kidney damage [63]. Early identification of patients at high relapse risk allows for timely initiation or continuation of immunosuppressive therapy to maintain remission [64]. Serial monitoring of antibody titers, in conjunction with complement activity assays, provides valuable prognostic information and can guide tapering of treatment to minimize relapse while reducing long-term immunosuppression exposure [65].

Long-term renal outcomes are closely linked to CFH status. Pediatric patients with pathogenic CFH mutations typically have a poor prognosis, with over 50% progressing to end-stage kidney disease (ESKD) within 3–5 years in the absence of targeted therapy [66]. Anti-CFH antibody–mediated aHUS has a somewhat better prognosis if diagnosed early and treated aggressively, but up to one-third of affected children still develop chronic kidney disease or hypertension [67]. Eculizumab therapy has been shown to improve renal survival in both genetic and autoimmune CFH-associated HUS, though the duration of treatment remains a matter of clinical judgment and ongoing research [68].

Beyond renal outcomes, systemic complications are also more frequent in children with severe CFH dysfunction. Neurological manifestations such as seizures, stroke, and encephalopathy occur in up to 20% of aHUS cases and are often associated with high antibody titers or severe complement dysregulation [69]. Cardiac involvement, including myocarditis and arrhythmias, though less common, has been reported and underscores the systemic nature of complement-mediated endothelial injury [70]. Recognizing these extracranial and extra-renal complications is crucial for holistic patient management and reinforces the importance of comprehensive evaluation in all children diagnosed with HUS [71].

Therapeutic Implications

Management of complement-mediated HUS, particularly cases associated with CFH abnormalities or anti-CFH antibodies, has evolved considerably over the past two decades. Plasma exchange (PEX) was historically the cornerstone of therapy, aiming to replace deficient or dysfunctional CFH with normal plasma and remove circulating anti-CFH antibodies [72]. In pediatric patients with anti-CFH Ab–associated aHUS, intensive daily PEX during the acute phase has been associated with rapid hematologic recovery and improved renal function [73]. PEX is often combined with high-dose corticosteroids to suppress antibody production, and in some cases, additional immunosuppressants such as cyclophosphamide or rituximab are introduced to achieve sustained remission [74].

Immunosuppressive therapy plays a critical role in reducing relapse risk in anti-CFH Ab–positive patients. Steroid tapering is typically followed by maintenance with mycophenolate mofetil (MMF) or azathioprine, particularly in children with persistently elevated antibody titers [75]. Rituximab, a monoclonal anti-CD20 antibody, has shown efficacy in refractory cases by depleting B cells and reducing antibody production, often leading to prolonged remission [76]. Long-term maintenance therapy is generally individualized based on relapse history, antibody kinetics, and treatment tolerance, with close monitoring to balance relapse prevention against risks of immunosuppression [77].

The introduction of eculizumab, a humanized monoclonal antibody targeting complement protein C5, has revolutionized the treatment of aHUS, including CFH mutation– and anti-CFH Ab–associated forms. By blocking the terminal complement cascade, eculizumab prevents formation of the membrane attack complex and halts ongoing endothelial injury [78]. In pediatric trials and observational studies, eculizumab has led to rapid normalization of hematologic parameters, recovery of renal function, and prevention of relapses, even in cases resistant to PEX [79]. However, discontinuation of eculizumab remains controversial, as relapse risk after withdrawal is not fully predictable; some centers adopt lifelong therapy for high-risk patients [80].

In resource-limited settings, access to eculizumab may be restricted by high cost and limited availability, making plasma-based therapy and immunosuppression the mainstay of management [81]. In such contexts, early identification of anti-CFH Ab–positive patients allows prioritization of PEX initiation and targeted immunosuppressive strategies to maximize renal survival. Future therapeutic approaches may involve novel complement inhibitors with longer half-lives, oral formulations, or dual-pathway blockade, potentially reducing treatment burden and improving access globally [82]. Ultimately, integrating CFH and

anti-CFH antibody profiling into individualized management algorithms can help optimize therapy, minimize relapses, and improve long-term outcomes in children with HUS [83].

Challenges and Controversies

One of the most persistent challenges in the evaluation of CFH and anti-CFH antibodies is the lack of assay standardization across laboratories. ELISA protocols for anti-CFH antibody detection vary in antigen source, coating concentrations, blocking reagents, and cut-off thresholds, leading to inconsistencies in reported prevalence and titer interpretation [84]. Similarly, CFH concentration measurement by nephelometry or ELISA is influenced by sample handling, acute phase status, and concurrent plasma therapy [85]. Without harmonized methodologies, comparing results between studies or establishing universally accepted diagnostic thresholds remains problematic, ultimately affecting clinical decision-making [86].

Treatment-related controversies also remain unresolved, particularly regarding the optimal duration of eculizumab therapy in CFH- and anti-CFH Ab–associated HUS. While some patients maintain long-term remission after withdrawal, others relapse rapidly, sometimes with irreversible renal damage [87]. Biomarkers capable of reliably predicting relapse risk—such as residual complement activity, antibody persistence, or genetic risk scores—are still under investigation [88]. The decision to discontinue therapy is often individualized, balancing the risks of relapse against the cost, treatment burden, and infection risks associated with prolonged complement blockade, especially meningococcal disease [89]. This uncertainty underscores the need for prospective multicenter trials to define evidence-based treatment cessation criteria.

A further source of debate lies in the stark disparity in diagnostic and therapeutic access between high-income and low-resource settings. In many parts of Africa, Asia, and Latin America, specialized complement testing and eculizumab are either unavailable or prohibitively expensive [90]. As a result, plasma exchange combined with immunosuppression remains the mainstay of treatment, despite being less effective for some patients and associated with greater procedural risks [91]. The development of affordable point-of-care complement assays, biosimilar complement inhibitors, and simplified treatment algorithms could help narrow this global gap in care [92]. Addressing these inequities is critical to ensuring that advances in understanding CFH biology and antibody-mediated disease translate into improved outcomes for all affected children, regardless of geography or healthcare resources.

Conclusion

Complement factor H and anti-factor H antibodies occupy a central role in the pathogenesis, diagnosis, and management of atypical hemolytic uremic syndrome in children. Their evaluation provides critical insight into disease mechanism, identifies patients at high risk for severe or relapsing disease, and guides targeted therapy, including plasma exchange, immunosuppressive strategies, and complement inhibition. Early recognition and prompt biomarker testing can markedly improve renal outcomes, reduce the risk of end-stage kidney disease, and prevent long-term complications.

Despite significant advances in understanding the molecular and immunologic underpinnings of CFH-related disease, important gaps remain. Standardized assays, validated prognostic markers, and cost-effective diagnostic approaches are urgently needed, particularly in resource-limited settings. Emerging therapeutics—such as next-generation complement inhibitors—offer promise for safer, more accessible, and potentially curative treatment. Moving forward, integrating CFH and anti-CFH antibody profiling into personalized care pathways will be key to optimizing outcomes, minimizing relapses, and improving the quality of life for children affected by this rare but devastating condition.

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