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EDITORIAL COMMENTARY

# Managing anti-factor H antibody-associated hemolytic uremic syndrome: time for consensus

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Atypical hemolytic uremic syndrome (aHUS) is an ultra-rare disease affecting approximately 2 cases per 100,000 per year, of which children comprise 0.26–0.75 cases per 100,000 [1]. It is a rapidly progressive illness, frequently causing severe acute kidney injury requiring dialytic support and multisystem complications [2]. Dysregulation of the alternative complement pathway is key to its pathogenesis, either due to inherited genetic defects in ~ 20–40% of patients or acquired autoantibodies to factor H (anti-FH), the chief regulatory protein of the alternative pathway [3].

Anti-FH antibody-associated aHUS is a distinct disease affecting 6–45% of children with aHUS, chiefly between the ages of 5 and 15 years [4–7]. A higher prevalence is reported in recent cohorts of Czech (62%), Chinese (65%), and Egyptian (43%) children, compared to previous reports [8–10]. Figure 1 shows the pooled prevalence of anti-FH-associated aHUS in 2856 adults and children, with a particularly high prevalence in children at 27% (95% CI 16–40). Given that a standard assay for determining anti-FH antibody titers is not widely available, the data suggests under-recognition of this disorder. We emphasize the need for testing for anti-FH antibodies in all children with aHUS irrespective of ethnicity or geographical location.

Early diagnosis and treatment are crucial. The strategy of rapid depletion of anti-FH antibody titers with plasma exchanges (PEX), along with immunosuppression, is recommended as a primary therapeutic intervention by experts [11, 12]. Since 2009, the availability of eculizumab has dramatically altered the management of aHUS and significantly improved patient outcomes, especially in patients with inherited defects in complement regulation [11, 13]. Centers in the developed countries therefore initiate empiric therapy with eculizumab in all patients with aHUS, including those with anti-FH antibodies. Subsequent therapy may either be continued eculizumab (with or without immunosuppression) or switch to PEX and immunosuppression [13, 14]. Therefore, we read with interest an article by Ferri et al., published in this edition of *Pediatric Nephrology* that describes the long-term outcome following the administration of eculizumab and immunosuppression in patients with anti-FH-associated aHUS [15].

## Results of the study by Ferri et al. [15]

This multicenter study provides information on clinical features, therapy, and outcome of 12 children with mild to moderate anti-FH associated aHUS, with 16% requiring transient dialytic therapy, and 8–25% with extrarenal manifestations at the onset of illness. Anti-FH titers at onset differed by ~ 25-fold between centers, reflecting the challenges of standardizing the assay across laboratories, which limits the comparability of antibody titers measured against specific standards. Ten patients received eculizumab induction therapy (three of whom also received PEX), followed by maintenance immunosuppression (chiefly mycophenolate mofetil, MMF). The most important finding of the study is that eculizumab was safe and effective in inducing remission, and anti-FH titers declined by ~ 50% and ~ 70% by 3- and 12 months, respectively, regardless of the type of immunosuppression. Most patients could be weaned off eculizumab and MMF at a median of 11 and 36 months, respectively. The authors concluded that long-term treatment with eculizumab and MMF was satisfactory for therapy of mild anti-FH aHUS, and could perhaps replace PEX altogether. While the strength of the conclusions is limited by the sample size and retrospective design, the study highlights the promising role of C5 inhibitors and the interest in utilizing them as the primary management of

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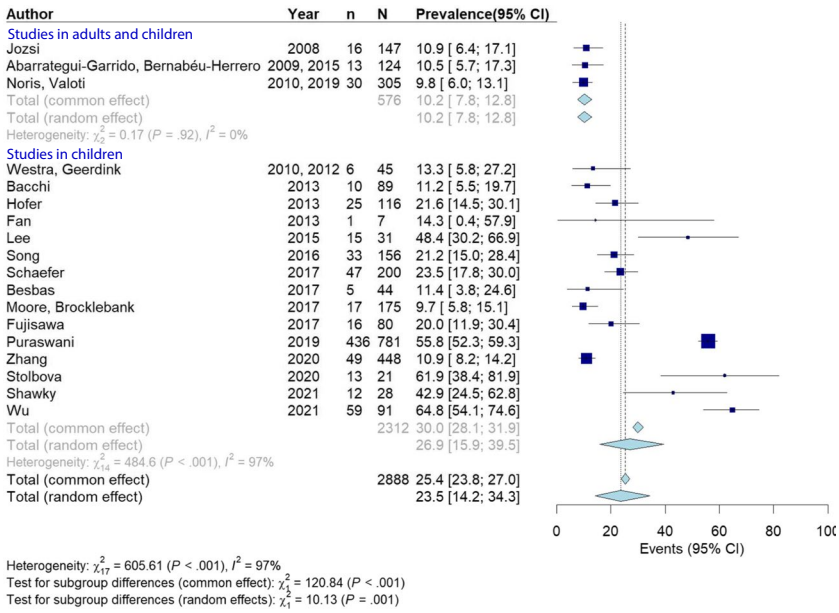


**Fig.1** Forest plot showing pooled prevalence (95% confidence interval) of patients with anti-factor H associated atypical hemolytic uremic syndrome

anti-FH-associated aHUS, especially in regions where the medication is available.

## Limited experience with eculizumab in anti-FH associated aHUS

Prospective studies on eculizumab therapy for anti-FH-associated HUS are limited. Few retrospective studies and anecdotal reports describe therapy with eculizumab (with or without PEX or immunosuppression) for anti-FH-associated aHUS [16]. Brocklebank et al. described a series of 17 patients with anti-FH-associated aHUS from the Newcastle cohort, with titers ranging from 227 to 4000 AU/ml. Four patients were managed with eculizumab without immunosuppression; two had a concomitant rare complement genetic *CFI* variant [13]. All patients treated with eculizumab achieved sustained remission. Another recent report from France describes two children with mild disease but with high anti-FH antibody titers at onset (18,520–40,500 UA/ml). Brief therapy with eculizumab (9–18 months) and MMF led to sustained remission [17]. Series from Japan and the Czech Republic report 8 and 6 patients treated with a combination of eculizumab (with or without PEX) and immunosuppression, respectively. Remission was achieved in 14 patients, while one patient developed kidney failure [10, 18]. Notably, all these reports included patients with relatively mild disease, with dialytic support required in 17–50% of patients [10, 13, 18]. Eculizumab discontinuation has also been reported from a prospective multicenter open-label study that included four patients with anti-FH-associated aHUS. Eculizumab was discontinued when antibody titer decreased to 473–1500 AU/ml, compared to 9000–60,000 AU/ml during active disease, following which none experienced relapse within the next 2 years [19]. A recent review recommends treatment discontinuation once the anti-FH titers are below 1000 AU/ml [20].

## Generalizability of findings with cohorts managed with PEX

We have shown satisfactory long-term outcomes with a combination of PEX and immunosuppressive therapy in a nationwide database of 436 patients with anti-FH-associated HUS [21]. Other colleagues have reported smaller case series from Europe, Egypt, and China managed with a similar approach [6, 8, 9, 14, 22]. Patients in these series had severe disease with the majority having oligoanuria and needing dialysis in 68–83% of cases [6, 8, 9, 14, 22]. Severe hypertension with neurological manifestations [21], cardiac and gastrointestinal complications, and nephrotic range proteinuria were present in a significant proportion of patients [14, 23]. Given the marked differences in severity of presentation between the cohorts managed with PEX, and patients treated with eculizumab in the series reported by Ferri et al. and others, there is limited data on withholding PEX in children who are severely ill and/or require dialytic support at onset.

## Importance of prompt remission

A delay in achieving hematological remission results in patients remaining at risk of persistent microvascular thrombi and organ damage during the acute phase of aHUS

and adversely impacts medium-term outcomes [21]. PEX is associated with a rapid fall in anti-FH titers with hematological remission in 96% of patients within a week of starting PEX [24]. In contrast, in the article by Ferri et al., while eculizumab was initiated rather promptly, the mean time to hematological remission was late (~40 days after therapy), and the decline in levels of anti-FH was lower compared to the data using PEX. However, kidney function recovered promptly, given the milder presentation.

The fall in anti-FH titers might not be relevant in patients administered eculizumab due to the blockade of C5a and C5b9, preventing thrombotic microangiopathy. An intriguing theoretical possibility in patients receiving eculizumab with high circulating levels of anti-FH antibodies is the occurrence of C3-mediated extravascular hemolysis due to red cell opsonization by excess C3b. This phenomenon has been observed in patients with paroxysmal nocturnal hemoglobinuria treated with eculizumab [25]. Careful evaluation of patients with high titers of anti-FH antibodies is therefore required when administered agents that selectively block the terminal complement pathway, especially in those with delayed hematological remission, as reported by Ferri et al. [15].

## Evolution of anti-FH antibody titers and long-term outcomes

The limited number of patients managed with eculizumab precludes statistical analyses of the association of anti-FH levels at onset and adverse outcomes. In contrast, we have consistently shown an independent association of high antibody titers at onset (> 8000 AU/ml; normal threshold 150 AU/ml) with acute mortality and the long-term risk of advanced kidney disease [21]. Since prevention of endothelial damage by eculizumab is expected to induce disease remission, Ferri et al. conclude that eculizumab use renders the reduction of anti-FH titers less urgent. However, we are

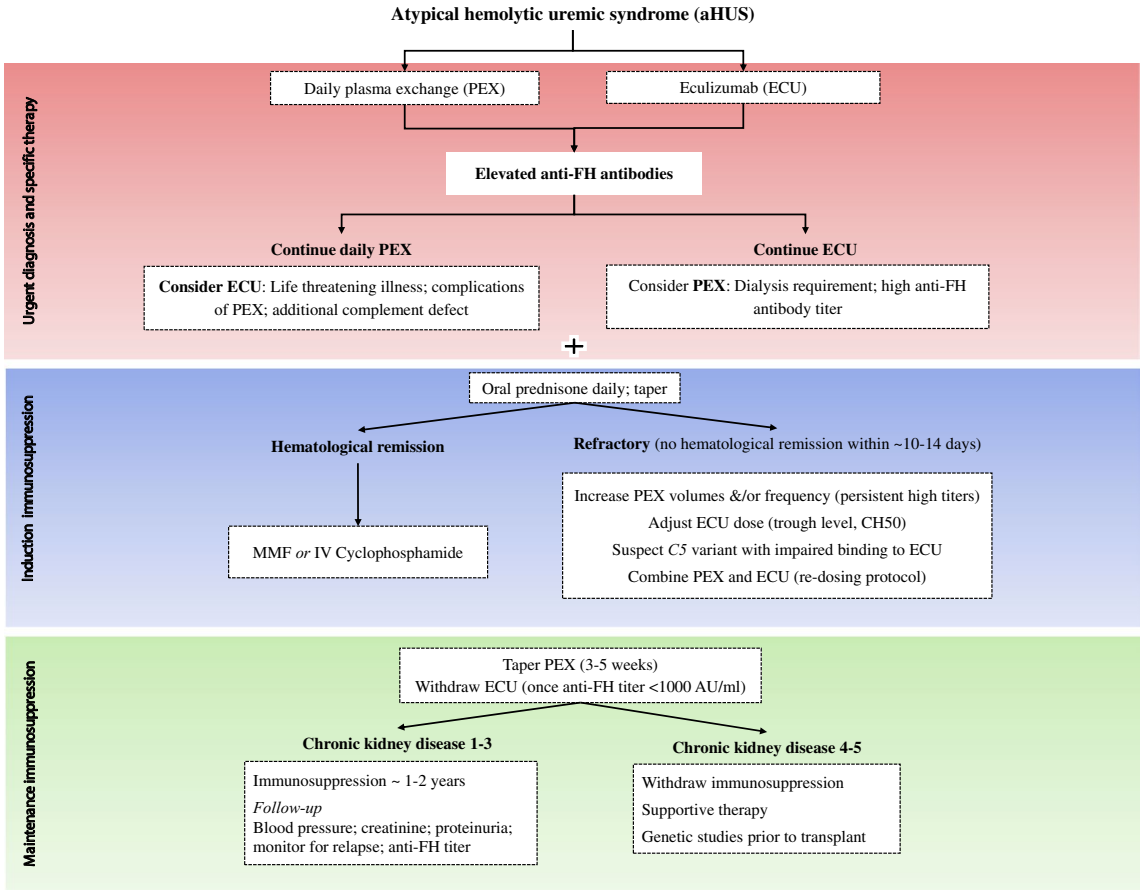


**Fig. 2** Management of anti-factor H (FH) antibody-associated aHUS. It is important to test for anti-FH antibodies in all suspected cases of aHUS and begin therapy with plasma exchanges (PEX) or eculizumab. Either PEX or eculizumab-based treatment options are reasonable, with additional immunosuppression. If the therapy is not effective within 7–10 days, early decisions are necessary, which may include optimizing doses/frequency, switching between PEX/eculizumab, or their combination. Therapy with eculizumab may be discontinued if anti-FH antibodies are below 1000 AU/ml. The duration of maintenance immunosuppression varies between 1 and 2 years and is individualized according to anti-FH antibody titers

not inclined to agree with this conclusion, given the delay in hematological remission in patients managed with eculizumab compared to experience with PEX. We advocate early aggressive management aiming for a hematological and renal remission within at least a fortnight of initiation of therapy. On the other hand, there is a need to prospectively study the efficacy of eculizumab in patients with anti-FH HUS who do not respond satisfactorily to PEX. Since eculizumab does not impact the generation of antibodies, additional immunosuppression might still be required. Due to the susceptibility to life-threatening invasive meningococcal infections in patients with eculizumab, the safety of combined therapy with MMF also needs to be evaluated.

About 11–75% of patients with anti-FH associated HUS managed with PEX and immunosuppressive therapy relapse, usually within the first 12–24 months' follow-up [21–23]. This is in contrast with remarkably absent rates of relapses in patients treated with eculizumab. High anti-FH antibody titers (> 1300 AU/ml) and low free FH < 400 ng/ml predispose to risk of relapse [21]. Therefore, anti-FH titers should be carefully monitored, especially in the first year of illness, especially when eculizumab or immunosuppression is planned to be withdrawn.

## Coexisting variants in complement regulatory genes in anti-FH aHUS

Homozygous polymorphism involving deletion of *CFHR1/3* is present in almost 85% of patients with anti-FH autoantibodies [3]. Apart from this polymorphism, a very small proportion of patients with anti-FH antibodies show significant variants in complement regulatory genes. A meta-analysis of 19 studies (384 patients) showed that the pooled prevalence of pathogenic or likely pathogenic variants was 3% in anti-FH-associated HUS [26]. We believe that there is a limited role for genetic testing for significant complement variants in patients with anti-FH-associated aHUS. Complement blockade with eculizumab should be considered in rare patients with anti-FH antibodies and a significant variant in complement regulatory genes.

## Conclusions

There are multiple unmet needs in the management of anti-FH-associated aHUS. These include early recognition, standardization of anti-FH assays across laboratories, wider availability of facilities for testing, and data on real-world experience of therapies. The potential benefits of the use of eculizumab must be balanced against concerns regarding its efficacy in acutely sick patients, safety when combined with immunosuppression, and unresolved issues about the duration of therapy and its cost. Moreover, the limited availability of eculizumab would definitely hinder the widespread adoption of a PEX-free approach. A recommended strategy for the management of anti-FH antibody-associated aHUS is shown in Fig. 2. We believe that in order to establish a treatment algorithm, the optimal combination, intensity, and duration of therapies need to be studied in multicenter cohorts.

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