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Review article

Recurrent complement-mediated *Hemolytic uremic syndrome* after kidney transplantation

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ABSTRACT

Hereditary forms of *hemolytic uremic syndrome* (HUS), formerly known as atypical HUS, typically involve mutations in genes encoding for components of the alternative pathway of complement, therefore they are often referred to as complement-mediated HUS (cHUS). This condition has a high risk of recurrence in the transplanted kidney, leading to accelerated graft loss. The availability of anti-complement component C5 antibody eculizumab has enabled successful transplantation with a notably reduced recurrence rate and improved prognosis. Open questions are related to the potential for complement inhibitor discontinuation, ideal timing of treatment withdrawal, and patient selection based on genetic abnormalities. Our review delves into the pathophysiology, classification, genetic predispositions, and management strategies for cHUS in the native and transplant kidneys.

1. Introduction

Complement-mediated *hemolytic uremic syndrome* (cHUS) is a rare form of thrombotic microangiopathy (TMA), predominantly affecting the kidney. Formerly known as atypical HUS (aHUS), this genetic condition typically involves mutations in genes encoding for components of the alternative pathway of complement. Until recently, approximately 50% of patients with cHUS progressed to kidney failure [1]. Advancements in understanding the role of complement gene variants, combined with the introduction of anti-complement C5 therapy with eculizumab, have transformed the prognosis of cHUS. Before the advent of eculizumab, transplantation was deemed inadvisable due to the alarmingly high recurrence rates associated with cHUS. Presently, the prophylactic use of eculizumab has rendered kidney transplantation a viable option. Nevertheless, as most data have been derived from retrospective cohort studies, the optimal treatment strategy for cHUS patients on the kidney transplant waitlist is unclear and numerous questions are still open, including the feasibility of its discontinuation, the ideal timing for cessation, and the criteria for patient selection based on complement genetics.

2. Methods

We scanned the relevant literature through PubMed. The search utilized the following keywords: “Complement-mediated thrombotic microangiopathy”, “Atypical hemolytic uremic syndrome,” “thrombotic microangiopathy”, and “kidney transplant”. The literature review spanned from January 1, 2023, to December 31, 2023.

2.1. Histology and classification

TMA is a pathological feature of vascular damage caused by various etiologies. Endothelial damage mainly occurs in the kidney, accompanied by fibrin and platelet thrombi in capillaries, endothelial swelling, and corrugation of glomerular basement membrane (GBM). Chronic changes may be associated with duplication of GBM, showing a membranoproliferative pattern of injury or focal segmental glomerulosclerosis and global glomerulosclerosis [2].

Hemolytic uremic syndrome (HUS) is a type of TMA classically characterized by a triad of hemolytic anemia, thrombocytopenia, and acute kidney injury. HUS occurs through several mechanisms (Fig. 1). The Shiga-like toxin-producing *Escherichia coli* infection, the most common type of HUS (STEC-HUS), impairs cell protein synthesis and leads to apoptosis, vascular injury and TMA [3]. aHUS, distinguished

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from STEC-HUS, is subclassified into aHUS without coexisting disease (or primary aHUS) and aHUS with coexisting disease (or secondary HUS). Primary aHUS includes cHUS and rare genetic forms like *DGKE* and *WT1* mutation-associated HUS or cobalamin-deficiency HUS [4,5]. cHUS is a condition in which genetic mutations or acquired abnormalities in the complement system lead to uncontrolled complement activation, resulting in vascular endothelial damage [6,7]. In contrast, secondary HUS is linked to various underlying conditions such as malignant hypertension, malignancy, infections, pregnancy, stem cell and solid organ transplantation, drugs, and autoimmune diseases, which lead to endothelial damage and TMA [8].

2.2. Diagnosis

Diagnosing cHUS is challenging as only 10% of patients present with the typical triad of TMA symptoms [9], making it difficult to suspect TMA initially. In addition, cHUS is diagnosed by excluding other causes of TMA. Once TMA is suspected, initial measures should aim to exclude thrombotic thrombocytopenic purpura (TTP), a deadly condition responsive to timely plasma exchange [10]. TTP differs from HUS in its reduced activity of ADAMTS 13 (a disintegrin-like metalloprotease with thrombospondin type 1 motif, member 13) due to autoantibodies or genetic mutation, leading to excessive von Willebrand factor multimers and widespread thrombosis [1–3,11]. ADAMTS13 activity of <10% confirms TTP; however, treatment with plasma therapy often begins before these results are available. Predictive scores like the PLASMIC and French scores help clinicians decide on empirical plasma therapy for TTP [12–14].

The next step is to rule out STEC-HUS and secondary HUS. STEC-HUS, prevalent in children, presents with diarrhea and TMA, diagnosed through stool cultures and Shiga toxin tests. Secondary HUS is caused by malignant hypertension, malignancy, infections, pregnancy, stem cell and solid organ transplantation, drugs, and autoimmune diseases. There are two difficult situations to distinguish between cHUS and secondary HUS: malignant hypertension and pregnancy. 53–55% of cHUS patients present with severe hypertension (>200/120 mmHg) [15,16], and 5–15% of patients with malignant hypertension are complicated by TMA [15,17]. Several clinical features might provide clues to differentiate the two conditions. Compared to aHUS, HTN-induced TMA typically occurs in older individuals, shows rapid improvement with blood pressure control, requires dialysis less frequently, and is associated with long-term HTN or left ventricular hypertrophy [6]. HTN-induced TMA can respond well to blood pressure control whereas early administration of eculizumab is crucial for cHUS. TMA in pregnant patients is another complex scenario, with conditions like eclampsia, preeclampsia, and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome being more common than pregnancy-associated aHUS (p-aHUS) [18]. An international working group recently summarized how to differentiate and approach p-aHUS [18]. Once cHUS is left among differential diagnosis of TMA, Kidney Disease Improving Global Outcomes (KDIGO) recommends complement tests, including C3, C4, Complement Factor H (CFH), Complement Factor I (CFI), MCP (Membrane Cofactor Protein), CH50 (Total complement activity 50), anti-CFH antibodies, and genetic tests, including *CFH, CFI, C3, MCP, THBD, DGKE* and *CFB* besides genomic rearrangements across the *CFH-CFHR* locus [7,46]. While low C3 and high C4 levels imply activation of the alternative pathway, 46% to 53% of patients have normal systemic complement profiles regardless of disease phase [19], making it inconclusive for diagnosis. Additionally, the absence of genetic abnormalities does not exclude the diagnosis of cHUS, as around 60% of cHUS patients have rare variants in specific genes [1].

In post-transplant TMA, in addition to the differential etiologies listed above, other causes of TMA are important, including drugs such as calcineurin inhibitor (CNI) or mammalian target of rapamycin (mTOR) inhibitors, antibody-related rejection, and opportunistic infections such as cytomegalovirus and BK virus under the influence of immunosuppressive drugs [20]. Additionally, post-transplant cHUS often lacks clinical symptoms such as microangiopathic hemolytic anemia or thrombocytopenia, which necessitates renal biopsy for diagnosis [21]. Not all patients need to be screened for complement abnormalities. Nevertheless, it is warranted to evaluate complement dysregulation in

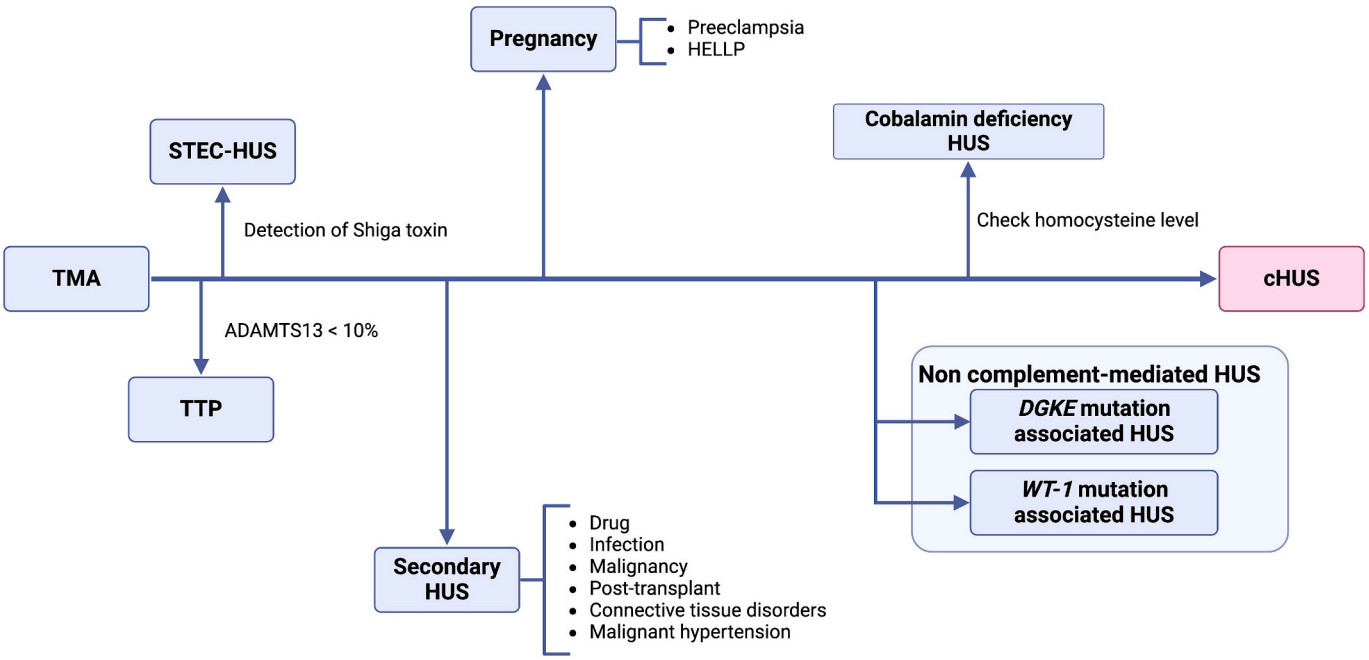

Fig. 1. Classification of thrombotic microangiopathy.
TMA: Thrombotic microangiopathy; TTP: Thrombotic thrombocytopenic purpura; STEC-HUS: Shiga-like toxin producing *Escherichia coli* hemolytic uremic syndrome; HUS: hemolytic uremic syndrome; DGKE: diacylglycerol kinase epsilon; WT-1: Wilms' tumor-1; cHUS: complement-mediated hemolytic uremic syndrome; Created with BioRender.com

relatively young patients with unknown underlying renal disease, recurrent cHUS, or patients who develop cHUS after a second transplantation [20].

2.3. Complement cascade and regulation

2.3.1. The complement cascade

The complement system comprises over 50 proteins or activation fragments and activates *via* three pathways: classical, lectin, and alternative. The classical pathway is triggered primarily by C1q binding to an antigen-linked antibody. This activates C1r and C1s, which then split C4 and C2. The resulting split products, C4b and C2a, respectively, assemble to form the C3 convertase (C4b2a) [22,23]. The lectin pathway resembles the classical pathway but functions without immunoglobulins. When mannose-binding lectin (MBL) or ficolins detect pathogen-associated molecular patterns, they stimulate MBL-associated serine proteases (MASPs), also leading to the formation of C3 convertase (C4b2a) [24,25]. Finally, the alternative pathway stands out as it is constantly active at a low level [26]. The core molecule, C3, undergoes spontaneous hydrolysis in the plasma to become C3(H2O), known as "tick-over" effect. It can bind to Complement Factor B (CFB). When bound, Complement Factor D (CFD) splits CFB into Ba and Bb. The resulting C3(H2O)Bb complex acts like a C3 convertase [27]. The C3 (H2O)Bb complex can split C3 into C3a and C3b. C3a works as an anaphylatoxin, triggering smooth muscle cell contraction and leukocyte recruitment and increasing the permeability of blood capillaries [28]. C3b can bind to the membrane surface of host cells or pathogens. Then, CFB binds to C3b, allowing its cleavage by CFD to form C3bBb, the main alternative pathway C3 convertase. This convertase further cleaves C3 into C3a and C3b, amplifying the generation of more C3 convertase molecules [29]. This complex is stabilized by properdin, which enhances its cleaving activity [30]. Nearby C3b molecules can form a larger C3bBbC3b complex, acting as C5 convertase. This cleaves C5 into C5a and C5b. C5a is also an anaphylatoxin. C5b, along with C6, C7, C8, and multiple C9 molecules, assembles the membrane attack complex (MAC) on the cell membrane, lysing non-eukaryotic cells [31].

2.3.2. Complement regulators

The alternative pathway constantly operates at a low level in the bloodstream to respond to pathogens, but it is kept under control by regulators of complement activation (RCAs) to prevent damage to healthy tissues [32]. CFH, consisting of 20 short consensus repeats (SCR) domains, plays a crucial role in this regulation. An SCR consists of 56–70 amino acids featuring four cysteines and a tryptophan, allowing for diverse binding capabilities [33]. The C-terminal (SCR 19 and 20) has a surface-binding activity, while the N-terminal portion binds to C3b, preventing the formation of C3 convertase. CFH also aids CFI in deactivating C3b into iC3b. Similarly, MCP assists in the CFI-mediated cleavage of C3b on cellular surfaces [34]. The decay-accelerating factor (DAF, CD55) accelerates the decay of the C3 and C5 convertase in the host cell [35]. Lastly, CD59 is a glycosylphosphatidylinositol-anchored glycoprotein that prevents the final assembly of MAC by binding C8 [36].

Within the glomeruli, endothelial cells possess membrane-bound RCAs; however, these are absent in the gaps between the glomerular endothelial cells. Therefore, CFH emerges as a key complement activation regulator in the glomerulus [22].

Complement Factor H-related proteins (CFHRs) also play roles in modulating the alternative pathway. Five types of CFHRs exist: type 1 CFHRs (CFHR1, CFHR2, and CFHR5), which can either homodimerize or heterodimerize, and type 2 CFHRs (CFHR3, CFHR4A, and CFHR4B) present as serum monomers. While they lack regulatory domains, CFHRs have SCR 19 and 20, akin to CFH. Due to these shared features, CFH and CFHRs might functionally overlap, though the specific roles of each CFHR are yet to be fully understood [37,38].

2.3.3. Pathophysiology of cHUS

The driving force of cHUS is complement dysregulation in the alternative pathway. Three underlying mechanisms have been identified. First, inactivating mutations in RCAs such as *CFH*, *CFI*, and *MCP* impair the breakdown of C3 convertase, leading to dysregulation in the alternative pathway [39–41]. Secondly, gain-of-function mutations in *C3* and *CFB* are also associated with cHUS [42,43]. For instance, mutated C3 does not properly interact with MCP, which acts as a cofactor to degrade C3b and C4b on the cell surface, resulting in the unregulated production of C3 convertase. C3 convertase or C3bBb formed by mutated CFB is more resistant to degradation by RCAs, increasing the activity of the alternative pathway. Finally, the formation of CFH-neutralizing autoantibodies prevents CFH from working both as a decay-accelerating factor and a cofactor for CFI, resulting in unregulated C3 convertase production [44]. Uncontrolled amplification of the alternative pathway *via* these pathways leads to the accumulation of MAC, resulting in endovascular damage.

2.3.4. Genetic abnormalities

CFH, *CFI*, *CFB*, *C3*, and *MCP* are known to be involved in the pathogenesis of cHUS, as well as hybrid genes generated by non-homologous recombinant rearrangement between *CFH* and *CFHR1*. These five gene abnormalities account for 61% of cHUS cases [6].

Mutations in *THBD* gene, encoding for thrombomodulin - an endothelial protein that modulates coagulation cascade and complement regulation - are also implicated in the pathogenesis of cHUS [6,45]. However, the importance of *THBD* mutations is currently under reevaluation due to several factors: the initially reported mutation occurs in about 5% of healthy individuals in other ethnic groups [5]; a French aHUS registry reported no isolated *THBD* mutations [6]; and another study has indicated that patients with isolated *THBD* variants presented a clinical course similar to secondary HUS, where those had causes associated with secondary HUS, and none of them experienced recurrent disease [5].

The penetrance of cHUS is notably low and known to be influenced by the presence of risk alleles such as *CFH-H3* and *MCPggaac* [1,47,48]. One study looking at the familial risk of cHUS, showed that the penetrance of relatives with known pathogenic variants was only 6.8% by age 35 and 9.6% by age 48, whereas none of the non-carrier relatives developed cHUS. Of note, the co-presence of both *CFH-H3* and *MCPggaac* can increase penetrance two to threefold among carriers [47]. These findings support that genetic mutations predispose to cHUS development, rather cause the disease [49].

2.4. Post-transplant cHUS recurrence

cHUS is characterized by a high post-transplant recurrence rate and poor prognosis, with the frequency of recurrence closely associated with underlying genetic abnormalities [50]. *CFH* mutations are the most frequent genetic abnormalities, accounting for 15% to 30% of cases [1,51]. The recurrence rate after transplantation is high, up to 85% [52,53]. Pathogenic variants in *C3* and *CFI* are 5% to 10%, respectively, with a high recurrent rate of 40% to 80% [54]. Isolated *MCP* mutation is the second most frequent genetic abnormality in cHUS, ranging from 10% to 15% [4]. cHUS associated with *MCP* mutation is considered at low risk of recurrence after transplantation since MCP is expressed in the cell membranes of the kidney, and the donor kidney should express normal MCP. Nevertheless, post-transplant cHUS occurred in 7.6% of patients with isolated *MCP* mutation [48]. *CFB* mutations are rare, ranging from 1% to 4% of frequency. The recurrence rate is reportedly high, up to 100% [55].

Given the very high recurrent rate of cHUS, transplantation was considered a contraindication except for patients with isolated *MCP* mutation. With the advent of C5 inhibitor eculizumab, transplantation can now be performed, even for patients with a high risk for recurrence. The KDIGO guidelines divide the risk of post-transplantation cHUS

recurrence into three groups according to family history, pathogenetic genes, and CFH autoantibody [7]. High-risk patients are those who relapsed in a previous allograft or carried a pathogenic variant of *CFH*, *C3*, *CFB*. Patients with negative complement screening results, pathogenic variants in *CFI*, or detectable circulating anti-CFH antibodies are considered at moderate risk. Lastly, low risk for recurrence is characterized by isolated mutations in *MCP*, *DGKE*, or the absence of detectable anti-CFH antibodies at the time of transplantation. For patients with high risk, prophylactic administration of eculizumab is recommended at the time of transplantation [7].

2.5. Clinical presentation of cHUS recurrence

Following transplantation, recurrent cHUS can present with microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure [56]. However, recurrent cHUS does not always display the laboratory hallmarks of HUS, such as hemolytic anemia and thrombocytopenia. Instead, it may present with an isolated elevation in serum creatinine with mild reduction in hemoglobin and platelets, and some schistocytes on peripheral blood smear. Only renal graft biopsy allows us to suspect recurrent cHUS.

Duineveld et al. reported the clinical course of cHUS recurrence after transplantation in 15 adults [57]. Seven patients had early recurrence of cHUS symptoms post-transplant (median three months). Eight relapsed late (median 46 months), three showed clinical cHUS, and five displayed declining estimated glomerular filtration rate (eGFR) without laboratory TMA signs (schistocytes, elevated lactate dehydrogenase, low hemoglobin, and thrombocytopenia). Of these five, three had acute TMA on biopsy, and two showed chronic TMA and antibody-mediated rejection. Recurrent cHUS often occurs early after transplantation [58] and is thought to be triggered by endothelial cell damage, leading to complement activation and recurrence of cHUS. Endothelial cell damage can be induced by reperfusion injury, immunosuppressants such as CNI and mechanistic target of mTOR inhibitors, infection, or rejection [52]. Specifically, given the high risk of rejection in the early post-transplantation, high doses of immunosuppressants are required, increasing the risk of infection. Nevertheless, recurrence in late post-transplant is not rare, as shown in the above case series. Clinicians must be vigilant, as a modest reduction in eGFR could herald recurrent disease.

2.6. Management of cHUS in native kidneys

2.6.1. Eculizumab

Eculizumab has emerged as a cornerstone in managing cHUS, owing to its efficacy demonstrated in case reports and single-arm prospective studies [59–61]. Before the introduction of eculizumab, kidney failure was observed in 29% to 56% of patients within the first year post-diagnosis [1]. This rate has substantially decreased in the eculizumab era, ranging between 6% to 16% [62].

However, a new challenge arised concerning the optimal duration of eculizumab therapy. While its therapeutic benefits are undeniable, long-term use presents both economic burden and potential risks, including specific infections. To address these concerns, several studies have been undertaken to discern the right time and criteria for discontinuation. Table 1 summarizes the recurrence rate after eculizumab discontinuation and differences in genetic variants from several observational retrospective and prospective studies [63–67]. A meta-analysis showed a relapse rate of 29.6% (83 out of 280 patients) [68]. The relapse rate was higher among patients with identified genetic variants compared to those without identified variants (42.3% *vs.* 10.7%, respectively). The authors recommend long-term or life-long eculizumab therapy for patients with pathogenic or likely pathogenic variants in *CFH*, *MCP*, *C3*, *CFI*, and *CFB*. Conversely, stopping eculizumab therapy might be considered for patients with certain genetic abnormalities, specific anti-CFH antibody levels, or those without a variant of uncertain significance in *CFH*, *C3*, and splice region variants in *MCP* [68].

When eculizumab is discontinued, it is crucial to ensure meticulous monitoring and prompt treatment in case of relapse. The prospective study CUREiHUS assessed the outcome of early eculizumab withdrawal in patients with cHUS in native kidneys. Recurrent cHUS occurred in 22% of cases after discontinuation. Despite the small sample size, kidney function over the long term appeared unaffected by these relapses [65], in line with most previous retrospective studies [64,65,69–73].

In summary, risk stratification is essential for better predicting recurrence. Furthermore, the management of recurrence disease is critical for preserving renal function, necessitating rigorous monitoring in patients undergoing eculizumab cessation.

2.6.2. Ravulizumab

Ravulizumab, engineered from eculizumab, is a long-acting C5 inhibitor allowing eight-week dosing intervals. Phase III trial evaluated the safety and efficacy in cHUS patients naive to complement blockade [74,75]. The primary endpoint was complete TMA remission at 26 weeks, considering both hematologic and renal improvement. Results paralleled the eculizumab study by Fakhouri et al., with 56.1% of adults and 77.8% of children showing a complete TMA remission [59]. Direct comparisons between the two antibodies are challenging due to differing treatment timings, plasma therapy utilization, and baseline pathogenic variants. While short-acting agents are suitable for uncertain diagnoses, transitioning to long-acting inhibitors is financially and practically advantageous for prolonged therapy.

2.6.3. Plasma therapy

In the pre-eculizumab era, plasma therapy, plasma infusion or exchange, was the first-line treatment for cHUS, but up to 46% of patients

Table 1
Recurrence risk after eculizumab discontinuation in patients with complement-mediated hemolytic uremic syndrome based on genetic abnormalities.

Author and year	Fakhouri et al. 2017 [63]	Wijnsma et al. 2018 [59]	Fakhouri et al. 2021 [65]	Ariceta et al. 2021 [66]	Bouwmeester et al. 2022 [67]
Total % (n)	31.6% (12/38)	20% (5/20)	23% (13/55)	21.9% (33/151)	22.2% (4/18)
Genetic abnormalities					
CFH % (n)	72.8% (8/11)	50% (4/8)	50% (3/6)	33.3% (4/12)	16.7% (1/6)
MCP % (n)	50% (4/8)	N/A	50% (6/12)	30% (3/10)	0% (0/3)
C3% (n)	0% (0/1)	25% (1/4)	25% (1/4)	33.3% (1/3)	50% (3/6)
CFI % (n)	0% (0/1)	0% (0/1)	33.3% (2/6)	50% (1/2)	50% (1/2)
CFB % (n)	N/A	0% (0/1)	N/A	33/3% (1/3)	N.A
Anti-CFH antibodies % (n)	0% (0/1)	0% (0/1)	0% (0/4)	4.29% (2/19)	0% (0/2)
Others % (n)	N/A	0% (0/3)	N/A	N/A	25% (1/4)
No pathogenic variants % (n)	0% (0/16)	0% (0/2)	4.3% (1/23)	17.7% (11/62)	0% (0/2)
Medial follow-up after eculizumab withdrawal (year)	1.83	2.28	1.65	N/A	1.98
Patients	Adults and children	Adults and children	Adults and children	Adults and children	Adults and children

CFH: Complement Factor H; MCP: Membrane Cofactor Protein; CFI: Complement Factor I; CFB: Complement Factor B.

with cHUS experienced kidney failure or death despite this treatment [1,48,76]. In contrast, the combination of plasma therapy and immunosuppressive medications has excellent efficacy in controlling cHUS with anti-CFH antibody [77]. Consensus guideline suggest that plasma exchange should be initiated daily for five days, five times a week for two weeks, followed by three times a week for two weeks, but plasma therapy dosage, frequency, and duration are only based on expert opinions or case series [78].

2.7. Management of recurrent cHUS after kidney transplantation

2.7.1. Eculizumab prophylaxis vs. rescue therapy

The post-transplant recurrence rate of cHUS varies from approximately 20% to 90% depending on gene mutations [55,58], with up to 93% of graft loss rate in recurrent patients in the pre-eculizumab era [53]. In the pre-eculizumab era, given the high risk of recurrent disease, kidney transplantation for cHUS patients was contraindicated except for patients with isolated *MCP* mutations [79]. Two case reports of cHUS successfully treated with eculizumab opened the possibility of kidney transplantation for these patients [80,81]. In 2012, following these and several similar case reports [82–84], Zuber et al. proposed a protocol of eculizumab prophylaxis for transplantation in patients at moderate to high risk for recurrent cHUS [52]. Five years later, a conference report from KDIGO recommended prophylactic eculizumab therapy on the day of transplantation in patients at high risk for recurrent cHUS, such as those with a history of previous recurrent disease, known pathogenic mutations, or gain-of-function mutations [7]. This strategy is well supported by the retrospective study from the national registry in France, in which eculizumab significantly reduced the risk of cHUS recurrence and improved graft survival in the high-risk group [85]. Reports from other countries echoed these results (Table 2) [85–89].

Nonetheless, there are concerns about the cost of eculizumab and the risk of infection with the long-term use. Duineveld et al. reported a case series of 17 living-donor kidney transplantat recipients without eculizumab prophylaxis. Sixteen of the 17 patients were considered high risk per KDIGO guidelines, and one was at moderate risk for recurrence. The transplant protocol was geared to protect endothelial injury using relatively low-dose CNI, statins, renin-angiotensin-aldosterone system inhibitors, and strict blood pressure control protocol. The results showed recurrence in only 1 of 17 patients [90]. The favorable result was attributed to the protocol to mitigate ischemia-reperfusion injury and endothelial damage, which can trigger cHUS relapse.

The same group tested eculizumab rescue therapy in 15 patients with recurrent cHUS post-kidney transplantation without eculizumab prophylaxis. Eculizumab rescue therapy proved successful in 14 patients, evidenced by TMA remission and eGFR stabilization or improvement. However, 3 patients developed kidney failure and 3 experienced declined kidney function of eGFR <30 mL/min per 1.73 m^2 by the study's end (medial follow-up of 29 months). Due to the limited number of comparisons, the findings are not conclusive, but it was observed that patients with late recurrence of cHUS, those who did not present clear laboratory signs of TMA, and those whose treatment initiation was delayed, often experienced accelerated graft function loss [57].

Another cohort from the global cHUS registry showed differences in outcomes between patients on eculizumab prophylaxis and those on rescue therapy post-transplant. Only 3% of those pre-treated with eculizumab faced graft loss, *versus* 13% of the post-transplant rescue group and 35% of newly diagnosed cHUS treated with rescue therapy [91]. A meta-analysis by Suarez et al. further supported these findings, revealing a graft loss rate due to cHUS of 5.5% in prophylaxis cases, contrasting with 22.5% in the rescue group [92].

In summary, transplantation without eculizumab prophylaxis is unsafe in patients at a high risk of recurrence. Further development of recurrence risk assessment is pivotal to determine candidates who can be safely transplanted without eculizumab.

2.7.2. When to discontinue eculizumab prophylaxis in a kidney transplant patient

Eculizumab can be safely discontinued in native kidneys, especially in patients without genetic mutations [65]. However, cHUS is at higher risk of recurrence in transplant patients than in native cases. Endothelial cell damage caused by CNI is a trigger for cHUS recurrence. In addition, immunosuppressive drugs increase susceptibility to infection, which is also a trigger. Combined data from cohort studies and case series showed that 1 out of 10 (10%) patients without a known variant relapsed after prophylaxis withdrawal, whereas 3 out of 14 (21%) with moderate to high risk for recurrence experienced cHUS after discontinuation of eculizumab prophylaxis [65,71,88,93–96]. Additionally, it is important to consider risk alleles such as *CFH-H3* or *MCPggaac* before eculizumab discontinuation, although the impact of these alleles on recurrence after transplantation is not fully clear yet. Most studies have short follow-up periods, and more data are needed on the long-term recurrence rate and graft survival. Even so, discontinuation of eculizumab may be feasible, especially in patients without a pathogenic mutation. Recurrence can occur at any point in the late transplantation, and delayed treatment of recurrence can lead to worsening renal function and graft loss. Therefore, careful monitoring is critical.

3. Conclusion

Management of native and recurrent forms of cHUS has evolved significantly with the advent of complement inhibitors like eculizumab and ravulizumab. While these medications have shown promise in reducing the recurrence of cHUS post-transplantation, determining the optimal timing for their discontinuation remains challenging. The role of genetic testing is paramount in assessing the risk of recurrence, yet it does not eliminate the disease's unpredictability. Moreover, while eculizumab prophylaxis has proven effective in many cases, the associated

Table 2
Outcomes of prophylactic eculizumab in transplant patients *vs.* non-prophylactic eculizumab.

Author and year	Zuber et al. (2019) [85]		Nga et al. (2021) [87]			Portoles et al. (2020) [88]		Glover et al. (2023) [89]		Kant et al. (2020) [86]	
Location	French		Brazil			Spain		United Kingdom		Johns Hopkins	
Research	RC		RC			RC		RC		RC	
Treatment group	ECU Ppx	No-Ppx	ECU Ppx	Non-Ppx	Tx	ECU Ppx	Non-Ppx	ECU Ppx	Non-Ppx	ECU Ppx	Non-Ppx
Patients (N)	52	74	10	11	17	9	5	38	32	10	9
High risk of recurrence	39 (75%)	35 (47%)	N/A	N/A	N/A	5 (56%)	3 (60%)	26 (68%)	19 (58%)	N/A	N/A
Moderate risk of recurrence	13 (25%)	30 (40%)	N/A	N/A	N/A	4 (44%)	2 (40%)	12 (31%)	14 (42%)	N/A	N/A
Low risk of recurrence	0 (0%)	5 (6.7%)	N/A	N/A	N/A	0	0	0	0	N/A	N/A
cHUS recurrence	1 (1.9%)*	30 (40%)	N/A	N/A	N/A	0	3 (60%)	1 (2.6%)	14 (42%)	0	2 (22%)
Graft loss	2 (3.8%)	28 (38%)	1 (10%)	1 (5.9%)	10 (91%)	0	1 (20%)	7 (18%)	22 (67%)	1 (10%)	4 (44%)
Medial follow-up (Months)	56.6	70.1	N/A	N/A	N/A	69.6		13.2	94.8	41.8	45.6

RC: retrospective cohort; cHUS: complement-mediated hemolytic uremic syndrome; ECU Ppx: eculizumab was used as prophylaxis; No-Ppx: No eculizumab use as prophylaxis; Tx: Eculizumab was used after the diagnosis of thrombotic microangiopathy; N/A: Not available; Data are presented as n (%) otherwise indicated. *Recurrence occurred after eculizumab was discontinued.

costs and potential for infection raise concerns and highlight the need for personalized treatment strategies. The delicate balance between preventing cHUS recurrence and mitigating treatment-associated risks underscores the need for ongoing research.

It is exciting to see many new complement inhibitors being studied in clinical trials (NCT04889430, NCT04958265) [97,98], which may help reducing costs and may potentially provide more treatments options for cHUS. Future studies should focus on refining risk assessment tools, exploring alternative treatment options, and establishing protocols for monitoring patients post-transplant to optimize both the safety and efficacy of cHUS management in transplant recipients.

Declaration of competing interest

None.

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