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Complement C5-inhibiting therapy for the thrombotic microangiopathies: accumulating evidence, but not a panacea

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Abstract

Thrombotic microangiopathy (TMA), characterized by organ injury occurring consequent to severe endothelial damage, can manifest in a diverse range of diseases. In complement-mediated atypical haemolytic uraemic syndrome (aHUS) a primary defect in complement, such as a mutation or autoantibody leading to over activation of the alternative pathway, predisposes to the development of disease, usually following exposure to an environmental trigger. The elucidation of the pathogenesis of aHUS resulted in the successful introduction of the complement inhibitor eculizumab into clinical practice. In other TMAs, although complement activation may be seen, its role in the pathogenesis remains to be confirmed by an interventional trial. Although many case reports in TMAs other than complement-mediated aHUS hint at efficacy, publication bias, concurrent therapies and in some cases the self-limiting nature of disease make broader interpretation difficult. In this article, we will review the evidence for the role of complement inhibition in complement-mediated aHUS and other TMAs.

Key words: atypical haemolytic uraemic syndrome, complement, eculizumab, thrombotic microangiopathy

Introduction

Thrombotic microangiopathy (TMA) is characterized by thrombocytopenia, microangiopathic haemolytic anaemia and organ injury [1], and can manifest in a diverse range of diseases. There is overlap in the pathogenic mechanisms involved in the different TMAs, and as a consequence classification is challenging. The introduction into clinical practice of complement-inhibiting therapy has stimulated particular interest into the role that complement plays. The prognosis of individuals with complement-mediated atypical haemolytic uraemic syndrome (aHUS), a term that we apply here specifically to individuals with TMA caused by a primary defect in the complement system that results in dysregulation, has been transformed by the terminal complement inhibitor eculizumab. This paradigm shift has understandably led to the question: who else with a TMA might benefit from this treatment? In this review, we will consider the contribution of complement dysregulation (resulting from a primary defect) and complement activation (as a secondary effect) to the pathogenesis of the different TMAs, and evaluate the strength of the evidence supporting clinical benefit of complement-inhibiting therapy. There has never been a randomized controlled trial (RCT) that demonstrates efficacy of complement-inhibiting therapy in any TMA. Complement has important physiological roles, for example in the immune

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defence against encapsulated organisms, so complement inhibition does not come without potential for significant harm; appropriate selection of individuals who are likely to benefit from therapy is therefore paramount.

Complement

The complement system comprises >30 plasma and cell surface-bound proteins that operate in a regulated network of signalling and amplification [2]. It functions to protect the host against infection, by stimulating the inflammatory response and opsonizing and lysing pathogens as a fundamental component of the innate immune system, as well as modulating the adaptive immune system; it also facilitates the disposal of damaged host cells and potentially injurious immune complexes [3]. Complement can be initiated by three pathways (Figure 1): in the classical pathway, pattern recognition molecules such as immunoglobulins are recognized by C1q, and in the lectin pathway mannose-binding lectin (MBL) recognizes pathogen-associated carbohydrates; these pathways generate the C3 convertase C4b2b. The alternative pathway can be initiated by pattern recognition molecules, but in addition is constitutively active, with spontaneous hydrolysis (tickover) of C3 leading to it interacting with factor B (FB) to generate the C3 convertase $C3_{H2O}Bb$, and the pathways converge in the amplification loop, in which C3 is cleaved and activated by C3bBb. This leads to C5 cleavage, and results in the production of anaphylatoxins and activation of the terminal pathway, which initiates the assembly of the cell-lysing membrane attack complex (MAC). The amplification loop allows for rapid response to pathogens, but leaves the host vulnerable to bystander damage if the tick over component is unchecked. The system is therefore tightly regulated by plasma and cell surface proteins; for the alternative pathway the most important are factor H (FH), factor I (FI) and membrane cofactor protein (MCP, CD46). Rarely, complement dysregulation due to a defect in a component or regulator can directly cause disease, and commonly, in many diseases, tissue damage activates complement, which intensifies the inflammation [4]. Consequently, there has been much interest and investment in developing complement-targeted therapy [5].

Complement-inhibiting therapy

The complexity of the complement system means that there are multiple potential therapeutic targets: drugs that target the activation pathways, the anaphylatoxins, the amplification loop and the terminal pathway have been developed and have entered preclinical and clinical trials [5]. Alexion Pharmaceuticals developed in the 1990s a recombinant humanized monoclonal antibody that functionally blocked C5 [6], and this agent, named eculizumab (Soliris), entered early clinical trials for a range of inflammatory conditions [5, 7]. Trials of eculizumab in patients with paroxysmal nocturnal haemoglobinuria (PNH), a disease characterized by complement-mediated intravascular haemolysis and caused by a somatic mutation that results in disruption of erythrocyte complement regulation, yielded the most impressive efficacy [8, 9] and eculizumab was approved for use in PNH in 2007 by the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) [10]. Because genetic and functional analysis had also identified aHUS as a disease caused by complement dysregulation, the PNH breakthrough encouraged the use of eculizumab in patients with complement-mediated aHUS; promising case reports [11, 12] were followed by successful clinical trials [13] and it was approved by the FDA and EMA for use in complement-mediated aHUS in 2011 [10].

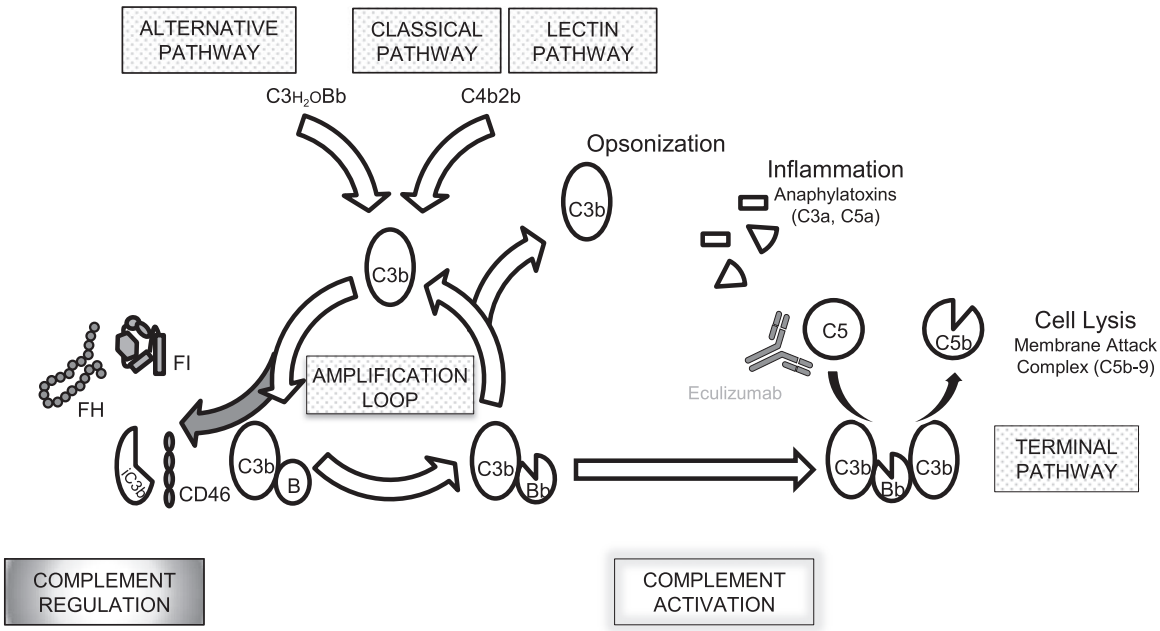

Fig. 1. Complement activation, regulation and therapeutic intervention. The alternative pathway of complement is a positive amplification loop. C3b interacts with factor B, which is then cleaved by factor D to form the C3 convertase C3bBb. Unchecked, this leads to activation of the terminal complement pathway with generation of the effector molecules, the anaphylatoxin C5a and the MAC (C5b-9). To protect host cells from bystander damage the alternative pathway is down-regulated by complement regulators including FH, FI and CD46. In complement-mediated aHUS, activating mutations in *C3* and *CFB* and loss-of-function mutations in *CFH, CFI* and *CD46*, in addition to autoantibodies to FH and FI, result in over-activation of the alternative pathway with resultant endothelial damage and thrombus formation. Eculizumab is a humanized monoclonal antibody that binds to C5 and prevents activation of the terminal pathway, thereby preventing the generation of the effector molecules that cause TMA.

Potential complications of complement-inhibiting drugs

The terminal complement pathway is fundamental to the immune response against encapsulated organisms, so the major concern with terminal complement inhibition is infection, and individuals deficient in terminal complement components are particularly susceptible to *Neisseria* infections [10, 14]. Disseminated gonococcal infection has been reported in patients treated with eculizumab, and the risk of meningococcal infection is increased by up to 10 000 times by treatment with eculizumab [14]. For this reason meningococcal vaccination and antibiotic prophylaxis is recommended in patients receiving eculizumab [15], though meningococcal infection can still occur despite these measures [16, 17].

There may be other infectious associations: respiratory tract infections are reported to be more common in patients on eculizumab compared with placebo [14], and a case of progressive multifocal leucoencephalopathy, an opportunistic infection of the CNS caused by reactivation of the polyomavirus JC, was recently reported in a patient treated with eculizumab, though they had also received multiple immunosuppressants [18].

In addition to infection complications, other concerns may emerge as use of complement-inhibiting therapy in clinical practice increases. Eculizumab-associated hepatotoxicity has been reported in children [19], and glomerular deposition of eculizumab in individuals with C3 glomerulopathy (C3G) [20], though not complement-mediated aHUS [21], has been reported although the long-term clinical consequences are as yet unclear.

TMAs

TMAs are the consequences of severe endothelial injury with pathological features representing the tissue response to injury [15]. TMAs are characterized by thrombocytopenia (due to aggregation and consumption of platelets), microangiopathic haemolytic anaemia (haemolysis consequent to mechanical injury to erythrocytes in partially occluded vessels) and organ injury (ischaemia) [1]. They can manifest in a diverse range of diseases and result in a range of clinical presentations, though they commonly comprise acute kidney injury (AKI) due to the apparent propensity of the glomerular circulation to endothelial damage and occlusion.

The classification and nomenclature of the TMAs can be challenging. Thrombotic thrombocytopenic purpura (TTP) refers to individuals with ADAMTS13 activity <5%, and Shiga toxin-producing *Escherichia coli*-associated HUS is defined as STEC-HUS. The term atypical haemolytic uraemic syndrome (aHUS) has broadly been used to describe any TMA that was not TTP or STEC-HUS, thus describing a heterogeneous mixture of conditions. There is a move towards using the term 'complement-mediated aHUS' to define those individuals with a complement abnormality as the primary underlying pathology, to distinguish them from individuals with TMA consequent to an underlying disorder; this is important because it may help guide therapeutic strategies [22, 23]. However, this distinction is not unequivocal: it is well recognized that complement gene mutations exhibit variable penetrance, and individuals with a genetic predisposition usually require an environmental trigger for TMA to manifest [3]. Conversely, in cases of TMA where no genetic or acquired complement abnormality is found, complement can be seen to be activated and may play a role in pathogenesis (Figure 2). TMA diagnosis, classification and treatment decisions are difficult; there may be no definitive diagnostic test, and no refined methods of monitoring disease activity or therapeutic response beyond crude tests of haemolysis parameters and organ recovery [24].

Evidence for the role of complement in the TMAs

Complement-mediated aHUS

The pathogenesis of complement-mediated aHUS is archetypal for diseases occurring due to over activation of the complement system. Ever since 1998, when genetic studies first produced molecular evidence that *CFH* mutations are associated with complement-mediated aHUS [25], there have been major advances in the understanding of the pathogenesis. Genetic studies and functional analysis in individuals, families and large cohorts [26, 27] have identified pathogenic activating mutations in the genes encoding the alternative pathway components *C3* and *CFB*, and loss of function mutations in the genes encoding the alternative pathway regulators *CFH*, *CFI* and *CD46* [3, 28–30]. A mutation is identified in ∼60% of individuals [23]. Autoantibodies that bind to FH [31, 32] and FI [33] resulting in complement dysregulation [34] have also been identified in 5–56% of individuals with complement-mediated aHUS [35]. Even in those individuals with a complement mutation or autoantibody a trigger, for example infection or pregnancy, is frequently required for disease to manifest [3].

The evidence that this disease is mediated by a primary complement defect is strong, so there is mechanistic rationale for complement-inhibiting therapy, though there has never been an RCT. The landmark trials of eculizumab for complement-mediated aHUS published in 2013 [13] were single-arm studies; however, given the high morbidity and mortality in individuals with complement abnormalities [3- to 5-year survival without established renal failure (ERF) of 52–64% in children and 33–36% in adults, even with plasma exchange (PEX) [26, 27]], it is accepted that comparison with historical controls is justified. The positive results (Table 1) paved the way for the first-line use of eculizumab in clinical practice, and its efficacy has been validated in subsequent prospective studies [37–39] and cohort analysis [42]. The prognosis of complement-mediated aHUS has been transformed: full recovery of renal function is now expected, other than in those who present late in the course of disease. Kidney Disease: Improving Global Outcomes (KDIGO) recommends that all patients with a clinical diagnosis of complement-mediated aHUS are eligible for treatment with a complement inhibitor [15]. International consensus recommendations are that in children with a clinical diagnosis of complement-mediated aHUS, eculizumab (or PEX if eculizumab is not available) should be started within 24–48 h (results of complement genetic tests are not required for this decision) [290].

More recently, with increased use in clinical practice, it has become clear that not all patients respond to eculizumab [94, 263]; in a non-randomized, uncontrolled trial of eculizumab in children, improvement in renal function was seen in all patients with a complement mutation or autoantibody, but not in 27% of those without an identified complement abnormality [39, 291]. The initial trials in adults included a higher proportion of patients with mutations than is seen in clinical practice. Further research is therefore required to inform a stratified approach to treatment [292] and it may be that the most clinically relevant classification would differentiate eculizumab responsive and eculizumab-resistant aHUS.

Prophylaxis and recurrence of complement-mediated aHUS after kidney transplantation

The outcomes of kidney transplantation in patients with complement-mediated aHUS were historically very poor: a retrospective

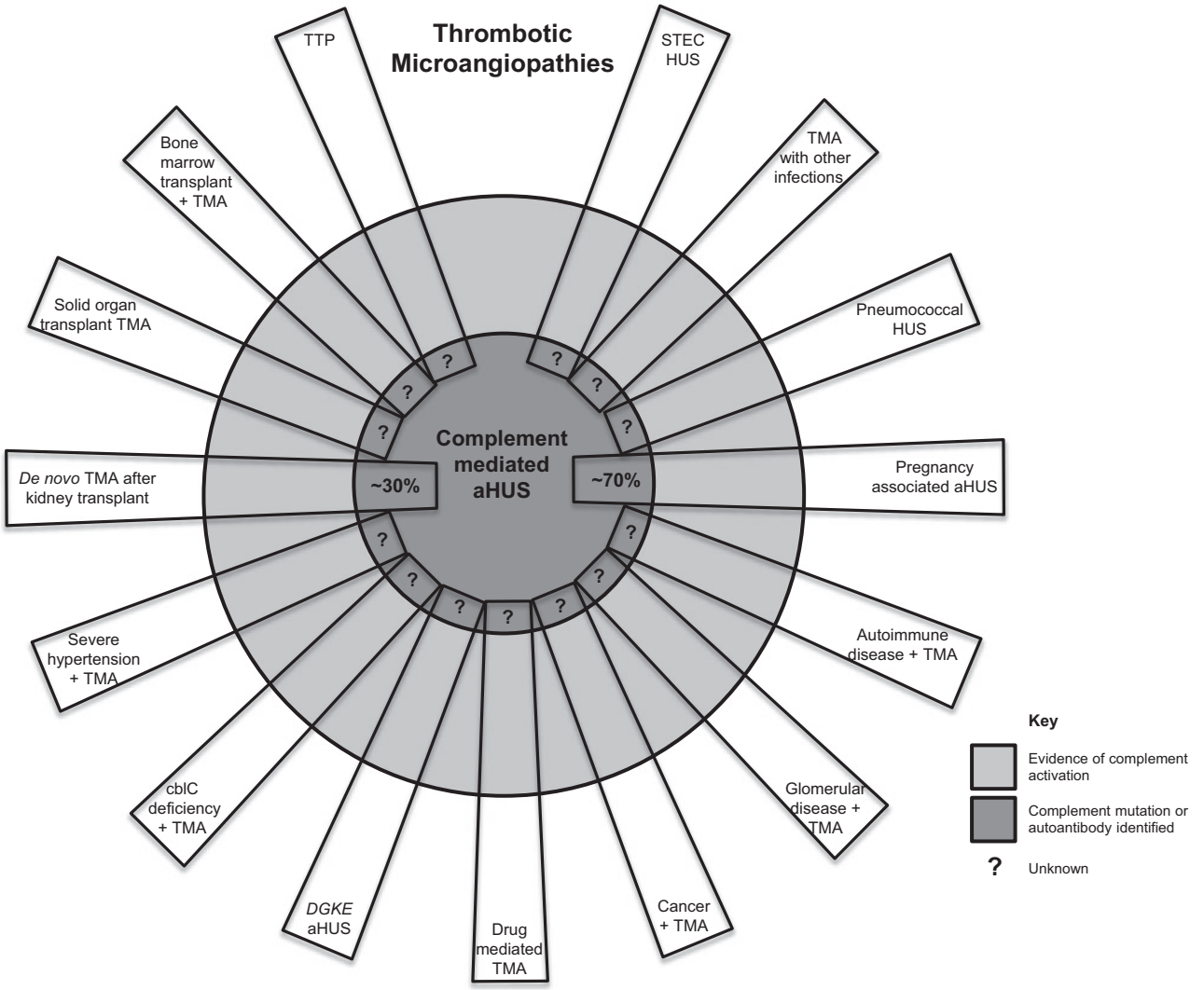

Fig. 2. The role of complement in TMAs: causative, modifier or bystander? In complement-mediated aHUS, a mutation or autoantibody resulting in complement dysregulation predisposes to disease. However, often disease only manifests upon exposure to an environmental trigger, which can include other causes of TMA. In some TMAs, a high proportion of individuals carry a mutation (e.g. pregnancy-associated aHUS, ~70%, and *de novo* post-transplant TMA, ~30%) but in others the incidence of mutations is unknown or low (e.g. STEC-HUS). In other TMAs, complement activation may be seen *in vivo* but whether it plays a role as a disease modifier or is simply a bystander is yet to be clarified.

analysis reported recurrence of 68%, and 5-year death-censored graft survival of 51% [63]; even if patients with recurrence were treated with PEX, 59% of grafts failed [65]. The genetic background predicts the risk of recurrence and graft failure: rates of >70% have been reported in individuals with *CFH* mutations, but the risk is very low if the mutation is in *CD46* [64, 293]. Some patients were therefore considered 'untransplantable'. One option was combined liver and kidney transplantation, but experience is very limited internationally and short-term risk is significant: for 20 published cases, the success rate was 80% but the mortality rate was 15% [55]. There are no trials that specifically examine the use of eculizumab for prophylaxis or for treatment of recurrence in kidney transplantation, although the single-arm eculizumab trials included small numbers of adults [13, 37, 38] and children [39] with prior kidney transplant, and reported efficacy. Retrospective cohort analyses have reported successful use of eculizumab to facilitate transplantation [42–44] and to treat recurrence [43], and there are multiple case reports (Table 1). Again, despite the lack of RCT evidence, the favourable results with eculizumab compared with historical outcomes are felt to justify that prophylactic eculizumab is now the gold standard approach to kidney transplantation in those with a high-risk genetic background.

De novo TMA after transplantation

In kidney transplant recipients, the incidence of *de novo* TMA has been reported as 0.8% in the United States Renal Data System (USRDS) [294], but single-centre studies report incidences of up to 14% [295]. Multiple associations and risk factors have been observed, including viral infections such as cytomegalovirus (CMV), immunosuppressant drugs such as calcineurin inhibitors (CNIs) and sirolimus [295], and antibody-mediated rejection (AMR) [72]. These factors, together with ischaemia-reperfusion injury, create an 'endothelial damaging milieu' that transplant recipients are exposed to [296], and it is not clear to what extent complement is involved. Underlying complement mutations may play a role especially where the initial cause of end-stage renal failure was unclear. In one cohort analysis, mutations were identified in 29% of patients with *de novo* TMA [66]. Evidence regarding management is also limited; good

Table 1. Evidence for the role of complement in the TMAs

TMA	Evidence for complement involvement in pathogenesis	Evidence for complement-targeted therapy	Evidence for other management
Complement-mediated aHUS	• 2 large aHUS cohorts (>200 patients): complement gene mutation identified in 48–60% [26, 27]; functional significance of mutations in *CFH, CFI, CD46, C3, CFB* demonstrated [3]. • Anti-FH Ab identified in 5–25% of aHUS cohort in Europe, 56% in India [35]; functional analyses demonstrate pathogenicity of anti-FH Ab [36].	• No RCTs. • 3 prospective, single-arm, phase 2 trials of eculizumab in adults: 88% TMA event-free status and 76% >25% improvement in sCr at 2 years in 17 patients with progressive TMA and renal impairment; complement mutation/anti-FH Ab in 76% [13, 37]. • 95% TMA event-free status and 55% >25% improvement in sCr at 2 years in 20 patients with stable TMA and renal impairment; complement mutation/anti-FH Ab in 70% [13, 37]. • Complete TMA response at 26 weeks in 73% in 41 patients. 2 cases of meningococcal infection. Complement mutation/anti-FH Ab in 49% [38]. • 1 prospective, single-arm, phase 2 trial of eculizumab in 22 children: complete TMA response in 64% at 26 weeks; ≥25% improvement in sCr in 73%; complement mutation/anti-FH Ab in 50%. No deaths/meningococcal infection [39].	High morbidity and mortality prior to eculizumab availability, best available treatment was PEX: • Retrospective analysis of 2 large cohorts: 5-year survival without ERF 64% in children and 36% in adults (214 patients); worst prognosis with *CFH* mutations: 50% ERF at first episode despite high intensity PEX [26]. 3-year survival without ERF 52% in children and 33% in adults (273 patients); 23% if *CFH* mutation, 6% if *CD46* mutation. Complete remission with PEX in 5% with *CFH* mutation [27]. • Review of all published case series of patients (278 patients) with anti-FH Ab: ERF in 27–63% [40]. • 2 case reports of isolated liver transplant in patients with *CFH* mutation: 1 successful, 1 fatal [41].
Kidney transplant Complement-mediated aHUS prophylaxis	As above.	• Successful use of eculizumab to facilitate transplantation without recurrence reported in retrospective cohort analyses [42–44]. • Case reports of successful use of eculizumab with [45, 46] and without [47–54] PEX.	• Combined liver kidney transplantation: 20 published cases reviewed; success rate 80%, mortality 15% [55]. • 7 patients with ERF secondary to HUS (no genetic analysis or aetiology details reported) transplanted with pre-emptive CNI-free immunosuppression regimen, with no TMA recurrence [56].
Complement-mediated aHUS recurrence	As above.	• No RCTs or trials specific to transplant recurrence. • The prospective, single-arm, phase 2 trials of eculizumab included some patients with prior kidney transplant (total 24 adults [13, 37, 38] and 2 children [39]) and reported efficacy. • Retrospective cohort analysis included 13 patients treated with eculizumab for recurrence: all responded. The delay of eculizumab initiation after TMA onset inversely correlated with the degree of renal function improvement [43].	High rates of recurrence and graft loss prior to eculizumab availability: • Retrospective review of 57 patients (71 transplants); 68% had a complement mutation. 68% aHUS recurrence. 7% mortality. 1- and 5-year post-transplantation death-censored graft survival were 76% and 51%. Pre-emptive PEX reduced graft loss but disease-driven PEX did not [63]. • Review of 100 kidney transplants: *CFH* mutation 73.7% recurrence, 77.8% graft failure; *CFI* mutation: 100% recurrence, 100%

(continued)

Table 1. (continued)

TMA	Evidence for complement involvement in pathogenesis	Evidence for complement-targeted therapy	Evidence for other management
		• Case reports of successful use of eculizumab [57–62].	graft failure; *CD46* mutation: no recurrence/graft failure [64]. • 27 published cases of PEX for aHUS recurrence: only 41% of grafts survived [65].
De novo TMA	• Genetic analysis in 24 patients with *de novo* TMA after transplantation identified *CFH* or *CFI* mutation in 29% [66].	• 3 case reports of successful use of eculizumab for TMA following kidney transplantation [67, 68] and SPK transplantation [69–71], though in all cases eculizumab was used concurrently with other treatment (such as immunosuppression switch, PEX).	• Case series: 29 patients with *de novo* TMA treated with discontinuation of CNI and PEX: graft salvage rate was 80% [72]. • Case reports of TMA resolution following immunosuppression switch, CNI to belatacept [73] or everolimus [74]. • 2 cases of TMA following PAK transplant successfully treated with PEX and immunosuppression switch [75].
AMR-associated TMA	• No evidence specific to AMR with TMA. • C4d deposition in peritubular capillaries suggests classical complement pathway activation [76].	Case reports of eculizumab for AMR with TMA: • TMA resolved, but graft failed of BKV nephropathy [77]. • TMA resolved but ongoing AMR [78]. • Successful use (concurrent with other treatment) [79, 80]. Trials of eculizumab for treatment of AMR (not specific to TMA related): • Efficacy and safety of eculizumab for treatment of AMR following renal transplantation. Eculizumab versus PEX + IVIG. Terminated due to lack of efficacy. ClinicalTrials.gov Identifier NCT01895127 (unpublished). • Eculizumab to prevent AMR in patients with a positive cross match against their live donor: 26 patients compared with historical cohort of 51 patients; single-centre, open label. ClinicalTrials.gov Identifier: NCT006707 Eculizumab reduced acute AMR episodes but did not prevent chronic AMR [81, 82]. • Pilot RCT of eculizumab for chronic AMR: no significant difference, but underpowered [83]. • Case reports/series of successful [84–87], unsuccessful [88] and mixed success [89–91] in use of eculizumab for AMR (no TMA), concurrent with other treatment in most cases.	• Therapeutic strategies for AMR (not specific to AMR with TMA) include PEX, IVIG and rituximab, but there is insufficient evidence to determine optimal treatment [92].

(continued)

Table 1. (continued)

TMA	Evidence for complement involvement in pathogenesis	Evidence for complement-targeted therapy	Evidence for other management
DGKE-associated aHUS	• No evidence for complement involvement in pathogenesis. • *DGKE* silencing in endothelial cells does not induce complement deposition *in vitro* [93].	Only a small number of cases have been published: • Cohort of 13: 1/7 treated with eculizumab relapsed while on treatment. All developed progressive CKD/ERF [94]. • 4 cases; 1 treated with eculizumab and responded—but had concomitant C3 mutation [95].	• 5 patients; multiple relapses, treated supportively or with PI/PEX. Normal renal function in all at last follow-up [96]. • 2 cases, responded to PI [97].
TTP	• Mouse model: C3 deposition in kidneys [98]. • *In vitro*: TTP serum caused C3 and MAC deposition on HMEC-1; cytotoxic effect was abolished by complement inhibition [99]. Observational clinical data: • Elevated Bb [100], C3a and C5b-9 [101], C3a and C5a (compared with remission) [102]; C3 and C5b-9 deposition in 2 kidney biopsies [98]. • Significantly higher levels of Bb, C3a, C5a and C5b-9 in individuals who died vs survivors [103]. Genetics: • 32 patients with TTP, 13 of whom had severe renal impairment: no complement gene mutations [104]. • Case report: 2 sisters with congenital TTP: 1 developed ERF and had concomitant *CFH* variant (likely non-pathogenic) [105].	• Case report of efficacy of eculizumab in TTP case refractory to PEX, corticosteroids, rituximab, NAC and vincristine. However, a later update reported positive Anti-FH Ab, and ADAMTS13 not sufficiently low [106, 107]. • Case report, efficacy of eculizumab in a child with congenital TTP (*ADAMTS13* mutation) and no complement gene abnormality/anti-FH Ab [108].	• American society of apheresis guidelines: grade IA evidence for PEX as first-line treatment: PEX decreased mortality from universally fatal to < 10%. 7 RCTs (301 patients) [109]. • Phase 2 studies demonstrate efficacy of rituximab in preventing relapse in acquired TTP [110–112]: 10% relapse compared with 57% in historical controls [110]. • Phase 2 study of caplacizumab (monoclonal antibody against vWF) versus placebo in addition to PEX + immunosuppression in acquired TTP more rapid resolution of TMA [113].
Pregnancy associated			
Complement-mediated aHUS	Genetics: cohort of 21 females with pregnancy-associated aHUS (P-aHUS): 86% had a complement gene mutation [114].	2 case reports of successful use of eculizumab in P-aHUS in context of mutations in *CFH* [115] and *CFI* [116].	In the cohort of 21 with P-aHUS, 83% were treated with PEX (none received eculizumab): 76% developed ERF [114].
TTP	No evidence.	No published reports.	UK cohort of pregnancy-associated TTP. Congenital TTP: fetal survival 58% for index presentation, and 100% if actively managed. Acquired TTP: fetal survival 58% [117].
HELLP	*In vitro*: eculizumab plus HELLP serum resulted in less cell killing [118]. Observational clinical data: • Reports of elevated C3a in HELLP [119]; elevated C3a and C5b-9 in pre-eclampsia [120]; elevated C3a, C5a, Bb and C5b-9 in pre-eclampsia [121]. • But also report of no difference in C3 and FH levels in healthy pregnant women versus pre-eclampsia with and without HELLP [122]. Genetics: • 4/11 consecutive women with HELLP and renal impairment had a complement gene mutation [123]. • 2/33 women with HELLP had a complement gene mutation (only 30% had renal impairment) [124]. • 7/40 women with SLE and/or APS, and pre-eclampsia, had a complement gene variant [125].	• 75 pregnancies in 61 women on eculizumab for PNH: 8% developed pre-eclampsia [126]. • 5 pregnancies in 3 women with complement-mediated aHUS on eculizumab: 2 women experienced pre-eclampsia and 1 HELLP despite complement inhibition [127]. • Case report of eculizumab use in addition to expectant management for HELLP at 26 weeks gestation: delivery delayed until 29 weeks [128].	Clinical studies have reported complete biochemical resolution rates of 29–43% with expectant management of severe pre-eclampsia/HELLP, but fetal/neonatal mortality of 14–20% [128].

(continued)

Table 1. (continued)

TMA	Evidence for complement involvement in pathogenesis	Evidence for complement-targeted therapy	Evidence for other management
Metabolic (cobalamin C deficiency)	Genetics: • Concomitant anti-FH Ab (patient died) and *CFH* mutation (patient responded to PEX) in one cohort with established cb1C defect [129]. • Child with aHUS attributed to *CD46* mutation; died after renal transplantation from pulmonary veno-occlusive disease; subsequently found to have *MMACHC* mutation [130]. • Case report: 2 sisters with cbC1 deficiency; 1 also had *CFH* mutation, and had more severe disease, though both responded to metabolic therapy [131].	• Case series of 36 patients: 2 received eculizumab and did not respond [129]. • Case report: adult presenting with TMA, dialysis dependent. No response to eculizumab. Subsequently found to have *MMACHC* mutation. Metabolic therapy resulted in resolution of TMA and renal recovery [132].	Case series of 36 patients: 54% had clinical recovery with metabolic therapy. Mortality 100% in untreated group, 44% overall, 79% in group with cardiopulmonary involvement [129].
Infection associated STEC	Mouse models: • *In vitro* and *in vivo* experiments demonstrated Stx-induced complement activation and C3a-dependent microvascular thrombosis (via P-selectin) [133]. • MBL2 inhibition protected against complement activation and renal injury induced by Stx-2 [134]. • Stx-induced activation of the alternative complement pathway results in podocyte injury [135]. *In vitro:* • Stx2 binds to FH and delays cofactor activity [136]. • Stx2 binds to CFHR1 and competes with FH for Stx2 binding, with resultant reduction in FH cofactor activity [137]. • Stx and O157LPS induced the release of microparticles with surface-bound C3 and C9 [138]. • Stx2-induced complement-mediated haemolysis [139]. • Observational clinical data: elevated C5b-9 levels [140–142]. Genetics • Case reports of complement gene mutations in STEC HUS [140, 143–145]. • Complement gene variant in 7/25 STEC HUS cases [146].	Ongoing RCT: eculizumab in Shiga toxin-related HUS pediatric patients. ClinicalTrials.gov Identifier: NCT02205541 Retrospective analysis of the 2011 O104:H4 outbreak: • 491 registry patients. Compared best supportive care (57 patients, 12%), PEX (241 patients, 49%) and PEX + eculizumab (193 patients, 39%). Direct comparison not possible because patients who received eculizumab had more severe illness. Mortality was 10.5% for best supportive care, 3.7% for PEX and 2.6% for PEX + eculizumab—no statistical significance between PEX and PEX + eculizumab. Median creatinine at the time of discharge was lowest in best supportive care group. Concluded that the data did not support a beneficial role of eculizumab [147]. • 298 adults. No clear benefit of PEX (251 patients, 84%) or eculizumab (67 patients, 22%). Possible benefit of antibiotics [148]. • Case series: full neurological and renal recovery in 3 children with STEC-HUS treated with eculizumab [149].	• Natural history is of good prognosis. Long-term outcome data: 70% fully recover, 3% develop ERF, 9–18% develop CKD [150]. • American Society of Apheresis guidelines: PEX in STEC-HUS is grade 2C category III (and grade 1C category IV if absence of severe neurological symptoms) [109]. • Prospective non-controlled trial: 12 patients in 2011 O104:H4 outbreak treated with IgG immunoadsorption and IgG replacement. 8 patients also received eculizumab. No deaths. Complete renal and neurological recovery in 10/12 [151]. • 2009 systematic review: 7 RCTs in 476 children (no distinction between STEC-HUS and aHUS; >70%, were diarrhoea-associated cases). No advantage over supportive care was identified for FFP, anticoagulation, steroids and Shiga toxin-binding agent [152]. • Retrospective analysis of 90 children with STEC-HUS in the 2011 O104:H4 outbreak. 74% received supportive care only. 10 received PEX, 6 eculizumab and 7 received both. 71% required dialysis. Mortality was 1%. At 4 months follow-up 94% had normal renal function, 1% remained on dialysis and 3% had CKD3/4 [153].
Pneumococcal	• Mouse model: suggests that the interaction between pneumococcal surface protein C (PspC) and FH contributes to pneumococcal virulence [154]. • Hypothesis: that the cleavage of sialic acid residues by pneumococcal produced neuraminidase results in disruption of the binding of FH/C3b, and therefore a function FH deficit at the cell surface [155].	Case report: child with pneumococcal HUS treated with eculizumab due to lack of response to supportive care: recovered renal function (dialysis for 30 days) [156].	• Role of PEX controversial; theoretical risk of worsening the TMA with donor plasma because it may contain anti-T IgM [158]. • American Society of Apheresis guidelines: PEX in pneumococcal HUS: grade 2C, category III recommendation [109].

(continued)

Table 1. (continued)

TMA	Evidence for complement involvement in pathogenesis	Evidence for complement-targeted therapy	Evidence for other management
	• Observational clinical data: case reports/series have reported transient low C3 and complement gene mutations [156, 157].		• Death usually results from the complications of pneumococcal infection [155].
HIV	No evidence.	Case report: TMA in a patient non-compliant with HAART: treated with PEX and eculizumab and recovered (HAART also presumably restarted) [159].	Observational data suggest incidence of TMA in patients with HIV historically was 7% [160] and 35% if AKI [161], but has markedly reduced in HAART era to 0.3% [162].
CMV	No evidence.	Case report of *de novo* TMA after kidney transplant in the context of CMV infection, and recurrence of TMA with recurrence of CMV viraemia in the absence of CNI; successfully treated with valganciclovir and eculizumab [163].	No evidence.
BMT	Mouse models: evidence that conditioning for BMT with radiation activates complement [164, 165] and treatment with a C5aR inhibitor reduced GvHD morbidity [165]. Observational clinical data: • Kidney C4d deposition in TMA in context of GvHD [166, 167]. • Proteinuria (>30 mg/dL) and elevated sC5b-9 associated with poor survival [168]. • Normal C3 and C4 levels [169]. Genetics: • Heterozygous *CFHR1/3* and *CFHR1/4* deletion and detectable Anti-FH Ab [170]. • Genetic analysis of 34 patients with TMA after BMT: multiple complement gene variants of uncertain significance reported [171].	Use of eculizumab: • No trials. • Retrospective analysis: 30 patients: 1 year survival 62% compared with 9% in 11 historical controls [172]. 12 patients: 50% haematological response, 33% mortality [173]. 6 children: 4 fully recovered, 2 died; therapeutic drug levels not achieved in the 2 who died [174]. • Case reports/series: Good outcome [175–178]. Response but died [179]; 4/5 responded, 2/5 died [180].	• Review of 5423 published cases: response to PEX reported in 0–80%, but mortality in those treated with PEX was 44–100% [181]. • American Society for Apheresis guidelines: >300 reported patients (no trials): grade 2C, category III recommendation for PEX [109]. • Mortality 50–60% despite treatment, with death due to complications of renal failure or GvHD, or infection [182]. • 20% response rate to PEX [173]. • Response rate to PEX 55%, but mortality 80% [175]. • Retrospective analysis of 11 cases: treatment was with CNI withdrawal and PEX: 64% responded, but mortality 38% (versus 13% without TMA) [183]. • Case reports of some response to rituximab, but mortality still high [184, 185].
Severe hypertension	• Mouse model of angiotensin II-induced hypertension: C5aR knock-out mice exhibited reduced cardiac remodelling and inflammation [186] and a C5aR antagonist reduced cardiomyocyte hypertrophy, cardiac inflammation and perivascular fibrosis [187]. • Observational clinical data: longitudinal cohort study (2178 males): higher plasma C3 levels associated with development of hypertension [188]. • Genetics: population-based cohort study (3210 individuals): *CFHR3/1* deletion and an AMD related *CFH* SNP were significantly associated with hypertension risk [189].	No evidence.	• Case series of 7 patients with severe hypertension and TMA treated with anti-hypertensive medication: TMA resolved in all [190]. • Literature review: 19 cases with severe hypertension and TMA; all were treated with anti-hypertensive medication and 1/3 also had PEX: symptomatic improvement 100%, thrombocytopenia improvement in 84%, but significant sCr improvement in only 58% [191]. • Case report: complete recovery of TMA and PRES with anti-hypertensive medication [192].

(continued)

Table 1. (continued)

TMA	Evidence for complement involvement in pathogenesis	Evidence for complement-targeted therapy	Evidence for other management
Drug mediated	• Genetics: *CFH* variants in 4 patients with ticlodipine-associated TMA (all had ADAMTS13 <5%) [193]. • Case report: low C3 in a patient with clopidogrel-associated TMA (no genetic analysis) [194].	Case reports/series of eculizumab: • Successful use reported in TMA associated with mitomicin C [195], gemcitabine [196–198], though given concurrently with other treatment (such as drug withdrawal, PEX); despite TMA response prognosis still poor due to malignancy [198]. • 1 patient with proteasome inhibitor associated TMA had persistent TMA after eculizumab and died [199].	• American Society for Apheresis guidelines: based on available evidence (no trials, only case series and reports) PEX recommended for ticlodipine-associated TMA (which should be considered TTP due to ADAMTS13 deficiency) but for all other drug-associated TMAs the role of PEX has not been established and may be harmful [109]. • 7 patients with TMA associated with ticlodipine and ADAMTS13 deficiency: all recovered with PEX and drug discontinuation [200]. • Review of 44 patients with gemcitabine-associated TMA: worse outcome with PEX than drug withdrawal alone [201]. • 2 cases of TMA associated with carfilzomib did not respond to PEX, but recovered with supportive care and drug discontinuation [202].
Malignancy associated	No evidence.	Case reports of eculizumab use are all in the context of chemotherapy—see above.	• Case series of 10 patients thought to have TTP and so treated with PEX but subsequently found to have disseminated malignancy (only 1 received chemotherapy). Only 1 had a response to PEX, and all died soon after TMA diagnosis [203]. • Registry report: 85 cases with malignancy-associated HUS. 99% received mitomycin C, 80% received 5-FU. 30% said to respond to PEX [204]. • Registry report: 20 cases with malignancy-associated HUS. 50% 30-day mortality; chemotherapy associated with better outcome than PEX/PI [205].
Autoimmune condition/glomerulopathy associated SLE	• Mouse model of SLE (not with TMA): C5 inhibition increased survival (80% versus <5% at 40 weeks) [206]. • Observational clinical data: correlation of hypocomplementaemia, secondary to complement activation and consumption, with disease activity [207]. • Genetics: GWAS study identified association between *CFHR3/1* deletion and susceptibility to SLE [208].	• Phase 1 trial: single dose of eculizumab in patients with SLE: pharmacokinetic and pharmacodynamics analysis [207]. • Case reports of successful use of eculizumab in SLE with TMA (but no APS) [209–213].	• No specific evidence outwith the context of APS. • Historical outcomes: in a review of 56 published cases of SLE with 'TTP' (prior to ADAMTS13 availability) mortality was 34%: 32% in PEX group versus 44% without PEX [214].
APS	Mouse models:	• No RCTs. • A prospective, single-arm, phase 2 trial is ongoing: eculizumab to enable renal	• CAPS registry: 522 episodes. Most frequent treatment was AC + GC (19%) or AC + GC + PEX ± IVIG (18%); only 0.2% received

(continued)

Table 1. (continued)

TMA	Evidence for complement involvement in pathogenesis	Evidence for complement-targeted therapy	Evidence for other management
	• Complement-dependent and complement-independent pathways in a mouse model of TMA induced by aPL Ab [215]. • Passive transfer of human aPL Ab: complement activation plays a role in fetal loss and tissue injury [216]. • Factor B inhibitor prevented aPL Ab-induced pregnancy loss [217]. • C5 inhibitor rEV576 inhibits *in vivo* effects of aPL Ab [218]. Observational clinical data in APS: • C5b-9 and C4d deposition in kidney allografts with TMA due to APS recurrence [219]. • (Not specific to APS with TMA): low C3 and C4, high C3a [220] and low C3 and C4 more frequent if renal involvement [221]. anti-FH Ab in patients with APS, and association with VTE recurrence [222].	transplantation in patients with history of catastrophic antiphospholipid antibody syndrome. ClinicalTrials.gov Identifier: NCT01029587. • Case reports/series of successful use of eculizumab: CAPS [223–228]. CAPS recurrence in renal transplant [229, 230]. Prophylactic anticoagulation and eculizumab to enable renal transplantation in 3 patients [231]. 3 cases with recurrence after kidney transplant: TMA resolved with eculizumab but chronic APS nephropathy not prevented [219].	eculizumab. Overall mortality 37% (no subgroup analysis according to treatment modality) [232]. • In kidney transplant recipients with APS: 7/10 treated with sirolimus had a functioning graft 144 months after transplantation versus 3/27 untreated patients [233].
IgA nephropathy	Observational clinical data: • Mesangial C3 deposition in ∼90% of patients [234]. • Glomerular deposition of MBL [235–237] observed, and associated with more severe renal disease [238]. • Normal FH levels and no mutations in *CFH* exons 18–23 in 46 patients [234]. • Low FH levels associated with IgA nephropathy in 2 families [239]. Genetics: • GWAS identified association between *CFHR3/1* deletion (protective) and IgA nephropathy [240]. • Rare variants in *CFHR5* may contribute to genetic susceptibility to IgA nephropathy [241].	• Trial ongoing (not in patients with TMA): open-label phase 2 study to evaluate the safety and efficacy of CCX168 in subjects with IgA nephropathy on stable RAAS blockade. ClinicalTrials.gov Identifier: NCT02384317. • 2 case reports of use of eculizumab for crescentic IgA nephropathy with TMA: transient response, but did not prevent progression to ERF [242, 243].	No evidence specific to IgA nephropathy with TMA.
ANCA-associated vasculitis	• Mouse models suggest complement important in pathogenesis of AAV [244, 245] and C5aR blockade protects against AAV [246]. Observational clinical data: • Hypocomplementaemia in AAV associated with concurrent TMA and higher mortality [247] and poor renal prognosis [248]. • Majority of AAV renal biopsies are negative for immune complexes but are positive for C3d, C4d and C5b-9 staining [249].	RCT of CCX168 (C5aR inhibitor) plus standard of care in AAV: results awaited. ClinicalTrials.gov Identifier: NCT02222155 (not specific to cases with TMA).	• No trials specific to AAV with TMA. • In AAV RCTs have demonstrated efficacy of cyclophosphamide and rituximab [250, 251].

(continued)

Table 1. (continued)

TMA	Evidence for complement involvement in pathogenesis	Evidence for complement-targeted therapy	Evidence for other management
Membranous	• Rat model of MN: C3 and C5b-9 co-localize with immune deposits, and urinary podocytes are coated in C5b-9 [252]. • *In vitro*: anti-PLA2R IgG4 autoantibodies from MN patients can bind to C4 via MBL [252]. Observational clinical data: • glomerular deposition of FH and C3b [253], MBL and C5b-9 [254], and urinary C5b-9 excretion predicts poor prognosis [255].	• No evidence specific to MN with TMA. • RCT of eculizumab in MN: 200 patients. Never published (abstract only). Negative results but inadequate dosing and short (16 weeks) follow-up [252].	• No trials specific to MN with TMA. • RCT in MN demonstrated efficacy of cyclophosphamide and corticosteroids versus supportive treatment [256]. • Case reports/series of MN with TMA describe some response to FFP [257]; rituximab [258], together with corticosteroids [259] and PEX [260].
FSGS	Observational clinical data: • Raised plasma and urine Ba, C4a, sC5b-9 levels [261]. • Combined IgM and C3 glomerular deposition was an independent risk factor for inferior treatment responses and worse renal outcomes [262].	Case report: no response to eculizumab in a patient with TMA and *INF2* mutation [263].	No evidence specific to FSGS with TMA, and very limited trial evidence for FSGS.
SRC	• Peritubular capillary C4d score associated with non-recovery of renal function [264]. • C5b-9 deposition detected in skin biopsies of SSc patients but not in healthy subjects [265].	Case reports of eculizumab use: • SRC with TMA in pregnancy; low C3 and C4, high C5b-9; no complement mutations. Management was Caesarean and ACE inhibitor and eculizumab: haematological response but no renal recovery; died of heart failure [266]. • PM-Scl overlap syndrome: prompt resolution of MAHA and AKI with eculizumab, having not responded to enalapril, aliskiren, PEX, glucocorticoids [267].	• Observational data: the use of ACE inhibitors has reduced mortality from ∼85% at 6 months to 25–35% [268]. • Case series of 7 patients with SRC and TMA treated with PEX in addition to ACE inhibitors: 1 died, 1 ERF at 1 year [269].
MPGN/C3G with TMA	• Mouse model of MPGN: lower creatinine and reduced mortality in $C5^{-/-}$ mice [270]. • *In vitro:* functional studies of anti-FH Ab; different binding epitopes compared with aHUS [34]. • Genetics: complement gene mutations in 17–20% [271, 272]. • C3NeF in 78–86% with DDD [271, 272].	• Trial: open-label, non-blinded, proof of concept efficacy and safety study of eculizumab in C3G. 6 adults (3 C3GN, 3 DDD): Renal function improved in 2, was stable in 2, and deteriorated in 2 (no TMA) [273]. • Review of 16 published cases with MPGN and TMA. 2 had anti-FH Ab, 6 had complement gene mutations. ERF/death in 9/16 [258]. 2 received eculizumab—TMA resolved in 1 [274], no long-term follow-up data [275]. • Case reports/series (not specific to cases with TMA) have reported partial [276, 277] and good response to eculizumab in native kidneys [278–286] and in transplant recurrence [287, 288].	3 cases of MPGN/C3GN with TMA: 2 (with MPGN I) received PEX + corticosteroids + cyclophosphamide and developed ERF, 1 (with C3GN) received corticosteroids + cyclophosphamide and developed CKD [258].
DIC	No evidence.	Speculation about use of eculizumab [289].	

anti-FH Ab, anti-factor H autoantibody; sCr, serum creatinine; PI, plasma infusion; HMEC, human microvascular endothelial cells; NAC, *N*-acetylcysteine; Stx, Shiga toxin; LPS, lipopolysaccharide; FFP, fresh frozen plasma; AMD, age-related macular degeneration; SNP, single nucleotide polymorphism; PRES, posterior reversible encephalopathy syndrome; GWAS, genome-wide association study; AC, anticoagulation; GC, glucocorticoids; AAV, ANCA-associated vasculitis; MN, membranous nephropathy; anti-PLA2R, anti-phospholipase A2 receptor; SSc, systemic sclerosis; SRC, scleroderma renal crisis; PM-Scl, polymyositis-scleroderma; MPGN, mesangioproliferative glomerulonephritis; C3G, C3 glomerulopathy; C3Nef, C3 nephritic factor; DDD, dense deposit disease; C3GN, C3 glomerulonephritis; DIC, disseminated intravascular coagulation; 5-FU, fluorouracil; APS, anti-phospholipid syndrome; PAK, pancreas after kidney transplant.

outcomes with CNI withdrawal, with and without PEX, have been described in case reports and series [72, 74, 75]. A small number of case reports describe good outcomes with eculizumab for *de novo* TMA after kidney [67, 68] and simultaneous pancreas and kidney (SPK) [69–71] transplantation, but in all cases this was in combination with other strategies such as immunosuppression alteration and PEX. *De novo* TMA has also been reported to occur in 4% of liver transplant recipients and 2.3% of lung transplant recipients; the cause again is likely to be multifactorial [297].

For those carrying a complement mutation where the initial diagnosis may not have been made there is a clear rationale for eculizumab. In those without underlying complement abnormalities, the role of eculizumab is less clear and in many cases removal of CNIs or treatment of viral infections is sufficient to stop the TMA. Despite this, evidence of complement activation can be seen in these scenarios and it is unclear whether eculizumab would have an additional benefit to removal of the offending stimuli.

Antibody mediated rejection

TMA can manifest in the context of AMR; it was observed in 13.6% of C4d-positive biopsies in one large retrospective study [298]. There is no evidence for the role of complement in AMR triggering a TMA. The deposition of C4d in peritubular capillaries suggests classical complement pathway activation [76], though this feature is not requisite for the diagnosis of AMR according to the 2013 Banff criteria [299]. Therapeutic strategies for AMR (not specific to AMR with TMA) include PEX, intravenous immunoglobulin (IVIG) and rituximab, but there is insufficient evidence to determine the optimal treatment [92]. A trial of eculizumab for treatment of AMR was negative (unpublished; NCT01895127) and a non-randomized trial of eculizumab in sensitized recipients found that acute episodes were reduced but not chronic AMR [81]. Case reports of eculizumab for AMR with [77, 79, 80, 278] and without [84–91] TMA describe both good and poor outcomes. In summary, further research is required to define the role of eculizumab in TMA associated with AMR.

DGKE-mediated renal disease

Recessive mutations in the *DGKE* gene causing TMA were first reported in 2013 [94]. Genetic pleiotropism is also seen in *DGKE*-mediated renal disease with a separate report describing a membranoproliferative glomerulonephritis-like disease [300]. *In vitro* experiments suggest that the development of TMA due to loss of DGKε expression or activity is independent of complement activation [93]. Data regarding outcomes and treatment response are limited. Good outcomes have been reported with supportive treatment and PEX or plasma infusion [96, 97], but in the largest published cohort all patients developed progressive chronic kidney disease (CKD) or ERF regardless of treatment, and the single patient who received eculizumab relapsed on treatment [94]. One child with a *DGKE* mutation in the paediatric eculizumab trial did respond [39, 291] although given the relapsing/remitting nature of *DGKE*-mediated disease, attributing efficacy is difficult. In a separate case report of eculizumab response, the patient had a concomitant *C3* mutation [95]. More data are required before the role of complement in the pathogenesis of *DGKE*-mediated aHUS and thus eculizumab treatment can be defined.

Methylmalonic aciduria and homocystinuria, cobalamin C (cblC) type

Homozygous or compound heterozygous mutations in the *MMACHC* gene result in a disorder of cobalamin (cbl; vitamin B12) metabolism. The severity of phenotype may vary but includes developmental, ophthalmological, neurological, cardiac and renal manifestations. TMA is associated with *MMACHC* mutations although the pathophysiological mechanisms that result in endothelial damage are unclear [129]. It can present in childhood or adulthood, and prognosis is very poor if untreated or if there is cardiopulmonary involvement; however, metabolic therapy with hydroxycobalamin is very effective [129]. The role of complement is not clear; there are isolated reports of concomitant complement gene mutations and polymorphisms that may modify the disease [129–131], but the small number of published reports of eculizumab use describe non-response [129, 132]. As such, treatment with metabolic therapy remains the gold standard.

Thrombotic thrombocytopenic purpura

TTP is a TMA mediated by deficiency of ADAMTS13, a von-Willebrand factor (VWF)-cleaving protease, which can be hereditary (*ADAMTS13* mutations) or acquired (anti-ADAMTS13 autoantibody), and is characterized by unusually large VWF multimers and consequent occlusive microvascular platelet aggregation [22]. There is some evidence of complement involvement in a mouse model [98] and *in vitro* [99], and observational clinical data suggesting that the alternative complement pathway is activated [98, 100–103] (Table 1). One study analysed the complement genetics in patients with TTP and found no mutations [104]. The advent of PEX in the treatment of TTP decreased mortality to <10% from essentially universal fatality and numerous RCTs demonstrate its efficacy [109], and rituximab rituximab reduces the relapse rate in acquired TTP [110–112]. PEX is unquestionably the first-line treatment in TTP and should be instituted urgently once the diagnosis is suspected. There is speculation about an adjuvant role for complement inhibiting therapy in severe TTP [301], but there is only a single case report that describes a response to eculizumab in a patient with TTP and no complement mutation or FH autoantibody [108], so currently there is no evidence to support this.

Pregnancy-associated TMAs

Pregnancy-associated complement-mediated aHUS

Pregnancy appears to be the trigger for complement-mediated aHUS to manifest in ∼20% of women, and this usually presents in the post-partum period [302]. In a pregnancy-associated aHUS cohort, complement mutations were identified in 86%, and though a high proportion were treated with PEX, 76% developed ERF [303]. Pregnancy-associated complement-mediated aHUS was not included in the initial trial of eculizumab, although good outcomes have been published in case reports [116, 117]. Given that pregnancy-associated aHUS appears to have a high incidence of complement mutations there is a good rationale for complement inhibition and, based on this, the authors' opinion is that pregnancy-associated complement-mediated aHUS should be treated with eculizumab.

Pregnancy-associated TTP

It has been reported that 10–36% of women with TTP present during pregnancy [304], particularly during the second or third trimesters [303]; in normal pregnancy, there is increased release

of VWF, which consumes ADAMTS13, therefore its activity falls, and in women with a genetic predisposition it can fall low enough for TTP to manifest [303]. There is no evidence regarding complement and complement therapeutics in pregnancy-associated TTP.

Syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP)

The HELLP syndrome is a TMA-like syndrome that occurs in 0.5–0.9% of all pregnancies, and complicates 5–10% of cases of severe pre-eclampsia [124]. The pathogenesis is poorly understood, though there is some evidence suggesting an association with increased circulating levels of the syncytiotrophoblast-derived antiangiogenic factors soluble endoglin and the soluble form of the vascular endothelial growth factor (VEGF) receptor (sFlt-1) [305, 306]. Unlike pregnancy-associated complement-mediated aHUS only a minority (8–10%) of patients with pre-eclampsia and HELLP syndrome harbour complement genes variants, mostly of unknown significance or non-pathogenic [125]. There is some observational data that suggests the alternative complement pathway is activated in HELLP [119] and pre-eclampsia [120, 121], and *in vitro*, eculizumab added to HELLP serum resulted in reduced cell killing [118]. Complete biochemical resolution has been observed with expectant management, which includes bed rest, sodium-restricted diet, antihypertensive treatment, anticonvulsant treatment and non-invasive monitoring, but fetal mortality is high [128]. The use of eculizumab (in addition to expectant management) to delay delivery in a patient with HELLP has been reported [128]. However, it is notable that in a cohort of women with PNH taking eculizumab, 8% still developed pre-eclampsia [126], and in a small case series of women with complement-mediated aHUS, both pre-eclampsia and HELLP occurred despite ongoing eculizumab treatment during pregnancy [127]. Although it is possible that complement does play a role in HELLP pathogenesis, the current available evidence does not support the use of complement-inhibiting therapy.

Infection associated

STEC-HUS

In STEC-HUS endothelial damage occurs following ribosomal inactivation, and inhibition of protein synthesis by Shiga toxin, which enters the cells after binding to the Gb3 receptor [22, 307]. In addition, Shiga toxin can activate signalling pathways inducing an inflammatory response in affected cells [308]. The prognosis is good compared with that of most other TMAs; long-term outcome data suggest that 70% fully recover, 3% develop ERF and 9–18% develop CKD [150], and it is considered to be a self-limiting condition.

There is evidence suggesting that the lectin [134] and alternative [133, 135, 138, 139] complement pathways are activated or dysregulated [137] in *in vitro* and animal models of STEC-HUS [309]. In patients with STEC-HUS, increased levels of C5b-9 have been observed, suggesting that the terminal pathway is activated [140–142]. However, mutations in complement genes are only rarely detected in these patients, and in these cases the clinical picture is unusually severe [21, 140, 143–146].

A small case series published in 2011 first reported full renal and neurological recovery in three children with severe disease who were treated with eculizumab [149]. Subsequently, in the 2011 O104:H4 outbreak in Europe, which was characterized by severe disease in adults as well as children, a significant proportion were treated with eculizumab. The retrospective analyses did not demonstrate a beneficial role of eculizumab or PEX over supportive care [147, 148, 153], though direct comparison is difficult because the patients who were treated with eculizumab had more severe disease. A further case series of eculizumab use in STEC-HUS with neurological involvement has been published [310], and many unanswered questions remain regarding any potential role [311]. An RCT of eculizumab for STEC-HUS in children is ongoing (NCT02205541) and in such a self-limiting illness only this will define the role of complement inhibition.

Pneumococcal HUS

TMA is reported in association with *Streptococcus pneumoniae* infection; a hypothesized mechanism is that neuraminidase produced by pneumococci cleaves sialic acid residues from glycoproteins on erythrocyte, platelet and endothelial cell membranes, exposing the cryptic Thomsen-Friedenreich antigen (T-antigen) to which IgM in the plasma can then bind, resulting in cell damage and TMA [158]. Pneumoccocal HUS is therefore Coombs test positive. The natural history is of poor prognosis, with high morbidity and mortality [312–315], usually reflecting the severity of the infection [155]. The role of complement is unclear although transient low serum C3 levels [156, 157] and rare complement gene mutations [129] have been reported. There is also speculation that neuraminidase may induce a functional FH deficit [155, 316]. A single case report describes a good outcome in a child treated with eculizumab after poor response to supportive care [156]. Currently, there is insufficient evidence to recommend eculizumab treatment in a situation where there is active infection.

HIV

Prior to the advent of highly active anti-retroviral therapy (HAART), TMA was not uncommon in people with HIV infection [317]: incidences of 7% [160], and 35% in those with AKI [161], have been reported. The pathogenic mechanisms remain undefined, despite investigation in Macaque models of HIV-associated TMA [318]. With the introduction of HAART the incidence has fallen to 0.3% [162]. There is a single case report describing good outcome with eculizumab in an individual who had been non-compliant with HAART, presumably concurrently with the reintroduction of anti-retrovirals [159]. Again, treatment of the underlying infection should remain the mainstay of treatment.

Bone marrow transplant-associated TMA

A multisystem TMA complicates 10–20% of allogenic bone marrow transplants (BMTs) [175] although individual centres have reported an incidence as high as ~40% [171]. There are multiple risk factors, including CNIs, graft versus host disease (GvHD), HLA mismatch, chemotherapy, radiation therapy and infections [319]. In common with solid organ transplantation, it is likely that these factors contribute to an endothelial-damaging milieu. Prognosis is very poor, with mortality rates variously reported at 21–75% [168, 169, 181, 183]. There has been much interest in the possible role of complement. Mouse models suggest that complement is activated during radiation conditioning [164, 165] and observational data in humans suggest that complement may be activated [166–168]. Rare functionally significant variants in known aHUS-associated complement genetic risk factors [171] and factor H autoantibodies [170] have been reported rarely. There is no evidence that PEX results in reduced mortality [175, 181, 183] and its role has not been established [109]. There are no prospective trials of complement inhibiting therapy. In the largest retrospective analysis, 1-year survival (62%) was favourable in those treated with

eculizumab compared with historical controls [172]. In some case series and reports, mortality has been high despite a haematological response [179, 180], though in others the outcome was good [175–178]. Trial evidence will likely be required before a consensus on the role of complement-inhibiting therapy can be achieved.

Severe hypertension

Case series of patients with severe hypertension have identified TMA in 27–44% [190, 320–322]. The pathophysiology of severe hypertension is complex and not completely understood, and the role of complement has not been fully defined [323, 324]. Conversely, any patient with a TMA may have severe hypertension, and distinguishing between severe hypertension-associated TMA and complement-mediated aHUS at the time of the acute presentation to guide appropriate management strategy is a major challenge. In a retrospective case series, genetic analysis identified rare variants in complement genes in patients in whom TMA was initially attributed to severe hypertension; eight of nine patients progressed to ERF despite management of hypertension [324]. However, in the majority of patients with TMA associated with severe hypertension, renal function and microangiopathic haemolytic anaemia (MAHA) usually recover with the management of blood pressure [323, 325] and therefore in practice the failure of the TMA to respond to blood pressure control often informs the diagnosis and future investigation and management.

Drug-mediated TMA

There are many published reports that describe drug-mediated TMA, either by acute, immune-mediated reactions [326] or by dose-dependent toxicity [327–329]. A systematic review in 2015 found evidence of a definite association in only 28% of the 78 drugs reported, the most common of which included quinine (immune mechanism) and ciclosporin, tacrolimus, sirolimus and interferon, and chemotherapy agents such as gemcitabine and mitomycin (toxic mechanism) [326]. There is no strong evidence for the role of complement, and recovery has been reported following drug withdrawal [201, 202]. The only recognized role for PEX is in ticlodipine-associated TMA, which is associated with severe ADAMTS13 deficiency [109].

Malignancy-associated TMA

TMA can manifest in malignancy, though it can be challenging to differentiate between chemotherapy-induced TMA and malignancy-induced TMA [330]. One proposed mechanism for TMA is erythrocyte shearing following direct contact with microvascular embolic tumour cells [203, 331, 332], and when TMA is associated with disseminated malignancy the prognosis is predictably very poor regardless of treatment strategy [203–205].

Complement factor H autoantibodies have also been associated with malignancy, although not in the setting of TMA [333]. Case reports of eculizumab use in patients with cancer and treated with chemotherapy agents have suggested a TMA response [195–198], though in most cases the eculizumab was concurrent with drug withdrawal or PEX.

TMAs associated with glomerular diseases

Focal segmental glomerulosclerosis (FSGS) and INF2-mediated renal disease

TMA has been reported in patients with primary FSGS [258, 334–336], and FSGS is a frequent pathological sequelae of STEC-HUS [337]. There is some observational data suggesting that complement is activated in FSGS [261] and may be associated with worse outcomes [262]. Mutations in *INF2* are the most common cause of familial autosomal dominant nephrotic syndrome; however, more recently it has also been associated with TMA [263]. In this report, all individuals with *INF2* mutations presenting with a TMA also had complement-mediated aHUS risk haplotypes, potentially accounting for the genetic pleiotropy. Despite this eculizumab was ineffective in controlling the TMA, suggesting that the mechanism is not dependent on the terminal pathway of complement.

IgA nephropathy

Histopathological evidence of TMA has been reported in 2.3–53% [338, 339] of IgA nephropathy biopsies although few also had laboratory evidence of MAHA. In those with TMA a very high proportion had uncontrolled hypertension, so it is difficult to distinguish between TMA associated with severe hypertension and TMA associated with IgA nephropathy. There is some evidence that complement genetics are associated with IgA nephropathy: *CFHR3/1* deletion may be protective [240, 340] and *CFHR5* rare variants may contribute to genetic susceptibility [241]. Mesangial C3 deposition is seen in ∼90% of patients [234], and deposition of MBL suggests the lectin pathway may be activated [235–237] and associated with more severe disease [238]. Two case reports describe the use of eculizumab for crescentic IgA nephropathy with TMA: there was a transient response, but it did not prevent progression to ERF [242, 243]. A single-arm trial of the C5a inhibitor CCX168 in IgA nephropathy (not restricted to cases with a TMA) is ongoing, but there is currently not strong evidence for complement-inhibiting therapy in cases with a TMA.

ANCA-associated vasculitis

Histopathological evidence of TMA has also been reported to occur in 14% of ANCA-associated vasculitis (AAV) biopsies [341], again without laboratory evidence of MAHA. Prognosis among those with concomitant TMA is poor: death or ERF occurs in up to 60% [258]. Mouse models suggest that complement is important in pathogenesis [244, 245] and C5aR blockade is protective [246]. In humans, the majority of AAV biopsies show deposition of C3d, C4d and C5b-9 [249], and hypocomplementaemia is associated with higher mortality [247] and worse renal prognosis [248]. There are no published reports of complement-inhibiting therapy in patients with AAV and TMA. An RCT of the C5aR inhibitor CCX168 in AAV (not restricted to cases with TMA) is ongoing.

Membranous nephropathy

There are case reports of TMA occurring with membranous nephropathy [257–260, 342, 343]. There is strong evidence that complement is activated in membranous nephropathy: in rat models [252], *in vitro* (lectin pathway) [252] and in observational clinical studies [253–255]. There is no evidence regarding management specific to membranous nephropathy with TMA, but an early trial of eculizumab in membranous nephropathy (presented in abstract form but never published) [252] was negative, though dosing was inadequate and follow-up was short.

C3G/mesangioproliferative glomerulonephritis with TMA

Both C3G and mesangioproliferative glomerulonephritis (MPGN) are complement-mediated diseases with autoimmune (C3 nephritic factor, factor H autoantibodies) and inherited (*CFH*, *C3*, *CFHRs* mutations) complement abnormalities [344–348] underlying many cases. Despite the role of complement in C3G, in a small

single-arm trial of eculizumab in C3G not all patients responded [273], potentially suggesting a role of complement downstream of C5. Concurrent [258, 275, 349, 350] and sequential [351] manifestation of C3G and TMA has been reported. There is one case report of MPGN with TMA describing TMA resolution with eculizumab [274]. Despite the lack of efficacy of eculizumab in C3G where the presentation is nephrotic syndrome, given that C3G and complement-mediated aHUS share many of the same complement autoimmune and genetic predispositions it seems likely that eculizumab would have a role where a TMA supervenes, though definitive evidence is not available.

TMAs associated with autoimmune conditions

Systemic lupus erythematosus

Concurrent TMA has been observed in 8–15% of systemic lupus erythematosus (SLE) biopsies and was reported to have no influence on outcome [352, 353] in some cohorts, but was associated with worse renal outcome in another [354]. In a mouse model of SLE, C5 inhibition increased survival [206]; in humans hypocomplementaemia correlates with disease activity [207], and *CFHR3/1* deletion is associated with susceptibility to SLE [208]. Successful use of eculizumab for SLE with TMA has been published in case reports [209–213], but the only trial of eculizumab in SLE to date is a phase 1 study [207].

Antiphospholipid syndrome

The catastrophic antiphospholipid syndrome (CAPS) international registry reports the incidence of TMA to be 14% [232]. In a mouse model of antiphospholipid antibody (aPL Ab)-mediated TMA both complement-dependent and complement-independent pathways were described [215] and C5 blockade inhibited *in vivo* effects of aPL Ab [218]. There is observational data in humans suggesting that complement is activated [219–221]. Case reports and series describe the successful use of eculizumab for CAPS in native kidneys [223–228] and transplant kidneys [229–231]. There are no RCTs of complement-inhibiting therapy but the evidence supports the rationale, and a prospective, single-arm trial of eculizumab to enable renal transplantation in CAPS is ongoing (NCT01029587).

Scleroderma renal crisis

Scleroderma renal crisis (SRC) occurs in ~10% of people with systemic sclerosis, and TMA manifests in 45–50% [355]. The use of angiotensin-converting enyzme (ACE) inhibitors has transformed prognosis: from ~85% mortality at 6 months to 25–35% [268]. There is no strong evidence that complement is involved in the TMA. In two case reports eculizumab was used in addition to ACE inhibitors: there was haematological response in both, though one died [266, 267].

Summary

Ensuring that complement inhibitory therapy is used appropriately is critically important, principally to avoid exposing patients unnecessarily to the risks of terminal complement inhibition, but the financial implications to health services (eculizumab costs £327 600 per person per year in the UK [356]) also need to be considered.

In addition to its central role in the pathogenesis of complement-mediated aHUS, complement activation is seen in many other forms of TMA. Despite this, it is unclear if this is the primary event, a modifying event or has no contribution to the TMA whatsoever.

Although the seminal trial of eculizumab did not use a control arm to demonstrate efficacy, the high historical morbidity and mortality of aHUS in individuals with complement abnormalities suggested effectiveness. For other cases of TMA, the evidence for utility of eculizumab comes mainly from case reports with the inherent publication bias. Additionally, interpretation of available data in other TMAs is difficult because: some disorders are self-limiting (e.g. STEC-HUS); some have a clear precipitant that can be treated/removed (e.g. severe hypertension and drug-mediated TMA); some are complex and multifactorial (e.g. TMAs occurring after bone marrow or solid organ transplantation); and in some the prognosis of the underlying disorder may be very poor (e.g. TMA associated with disseminated malignancy).

For those individuals with an established complement-mediated aHUS (mutation or autoantibody), treatment is not informed by RCTs, and while the current recommendation is for lifelong treatment with eculizumab there is no evidence that this is necessary. Research is needed to determine who can stop it and when, as well the appropriate monitoring strategy. A number of cases of eculizumab withdrawal have been published [23], and Alexion Pharmaceuticals are collecting data on individuals in whom eculizumab is stopped ('EVIDENCE' observational study), a trial is being conducted in France (NCT02574403) and a prospective trial of eculizumab withdrawal in complement-mediated aHUS is under way in the UK.

In summary, further research is needed to define the role of complement in the spectrum of TMAs, and complement C5-inhibiting therapy should not be considered a panacea.

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Conflict of interest statement

D.K. has received honoraria for consultancy work from Alexion Pharmaceuticals, and is a director of and scientific advisor to Gyroscope Therapeutics.

References

1. Moake JL. Thrombotic microangiopathies. *N Engl J Med* 2002; 347: 589–600
2. Ricklin D *et al*. Complement: a key system for immune surveillance and homeostasis. *Nat Immunol* 2010; 11: 785–797
3. Kavanagh D, Goodship TH, Richards A. Atypical hemolytic uremic syndrome. *Semin Nephrol* 2013; 33: 508–530
4. Thurman JM, Nester CM. All things complement. *Clin J Am Soc Nephrol* 2016
5. Morgan BP, Harris CL. Complement, a target for therapy in inflammatory and degenerative diseases. *Nat Rev Drug Discov* 2015; 14: 857–877
6. Thomas TC *et al*. Inhibition of complement activity by humanized anti-C5 antibody and single-chain Fv. *Mol Immunol* 1996; 33: 1389–1401

7. Kaplan M. Eculizumab (Alexion). *Curr Opin Invest Drugs* 2002; 3: 1017–1023
8. Hillmen P *et al*. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. *N Engl J Med* 2004; 350: 552–559
9. Risitano AM, Marotta S. Therapeutic complement inhibition in complement-mediated hemolytic anemias: Past, present and future. *Semin Immunol* 2016; 28: 223–240
10. Wong EK, Kavanagh D. Anticomplement C5 therapy with eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. *Transl Res* 2015; 165: 306–320
11. Gruppo RA, Rother RP. Eculizumab for congenital atypical hemolytic-uremic syndrome. *N Engl J Med* 2009; 360: 544–546
12. Nurnberger J *et al*. Eculizumab for atypical hemolytic-uremic syndrome. *N Engl J Med* 2009; 360: 542–544
13. Legendre CM *et al*. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med* 2013; 368: 2169–2181
14. Benamu E, Montoya JG. Infections associated with the use of eculizumab: recommendations for prevention and prophylaxis. *Curr Opin Infect Dis* 2016; 29: 319–329
15. Goodship TH *et al*. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney Int* 2016
16. Cullinan N *et al*. Case report: benefits and challenges of long-term eculizumab in atypical hemolytic uremic syndrome. *Pediatrics* 2015; 135: e1506–e1509
17. Struijk GH *et al*. Meningococcal sepsis complicating eculizumab treatment despite prior vaccination. *Am J Transplant* 2013; 13: 819–820
18. Gomez-Cibeira E *et al*. Eculizumab-related progressive multifocal leukoencephalopathy. *Neurology* 2016; 86: 399–400
19. Hayes W *et al*. Eculizumab hepatotoxicity in pediatric aHUS. *Pediatr Nephrol* 2015; 30: 775–781
20. Herlitz LC *et al*. Pathology after eculizumab in dense deposit disease and C3 GN. *J Am Soc Nephrol* 2012; 23: 1229–1237
21. Dowen F, Wood K, Brown AL *et al*. Rare genetic variants in Shiga toxin–associated haemolytic uraemic syndrome: genetic analysis prior to transplantation is essential. *Clin Kidney J* 2017
22. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med* 2014; 371: 654–666
23. Nester CM *et al*. Atypical aHUS: State of the art. *Mol Immunol* 2015; 67: 31–42
24. Teoh CW, Riedl M, Licht C. The alternative pathway of complement and the thrombotic microangiopathies. *Transfus Apher Sci* 2016; 54: 220–231
25. Warwicker P *et al*. Genetic studies into inherited and sporadic hemolytic uremic syndrome. *Kidney Int* 1998; 53: 836–844
26. Fremeaux-Bacchi V *et al*. Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. *Clin J Am Soc Nephrol* 2013; 8: 554–562
27. Noris M *et al*. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. *Clin J Am Soc Nephrol* 2010; 5: 1844–1859
28. Kavanagh D *et al*. Characterization of mutations in complement factor I (CFI) associated with hemolytic uremic syndrome. *Mol Immunol* 2008; 45: 95–105
29. Ferreira VP *et al*. The binding of factor H to a complex of physiological polyanions and C3b on cells is impaired in atypical hemolytic uremic syndrome. *J Immunol* 2009; 182: 7009–7018
30. Caprioli J *et al*. Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. *Blood* 2006; 108: 1267–1279
31. Dragon-Durey MA *et al*. Anti-Factor H autoantibodies associated with atypical hemolytic uremic syndrome. *J Am Soc Nephrol* 2005; 16: 555–563
32. Moore I *et al*. Association of factor H autoantibodies with deletions of CFHR1, CFHR3, CFHR4, and with mutations in CFH, CFI, CD46, and C3 in patients with atypical hemolytic uremic syndrome. *Blood* 2010; 115: 379–387
33. Kavanagh D *et al*. Factor I autoantibodies in patients with atypical hemolytic uremic syndrome: disease-associated or an epiphenomenon? *Clin J Am Soc Nephrol* 2012; 7: 417–426
34. Blanc C *et al*. Anti-factor H autoantibodies in C3 glomerulopathies and in atypical hemolytic uremic syndrome: one target, two diseases. *J Immunol* 2015; 194: 5129–5138
35. Sinha A *et al*. Prompt plasma exchanges and immunosuppressive treatment improves the outcomes of anti-factor H autoantibody-associated hemolytic uremic syndrome in children. *Kidney Int* 2014; 85: 1151–1160
36. Blanc C *et al*. Overall neutralization of complement factor H by autoantibodies in the acute phase of the autoimmune form of atypical hemolytic uremic syndrome. *J Immunol* 2012; 189: 3528–3537
37. Licht C *et al*. Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. *Kidney Int* 2015; 87: 1061–1073
38. Fakhouri F *et al*. Terminal complement inhibitor eculizumab in adult patients with atypical hemolytic uremic syndrome: a single-arm, open-label trial. *Am J Kidney Dis* 2016; 68: 84–93
39. Greenbaum LA *et al*. Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome. *Kidney Int* 2016; 89: 701–711
40. Brocklebank V, Johnson S, Sheerin TP *et al*. Factor H autoantibody associated atypical haemolytic uraemic syndrome in children in the United Kingdom and Ireland (2000–2015). *Kidney Int* 2017
41. Forbes TA *et al*. Changing strategies for organ transplantation in atypical haemolytic uraemic syndrome: a tertiary case series. *Pediatr Transplant* 2013; 17: E93–E99
42. Sheerin NS *et al*. A national specialized service in England for atypical haemolytic uraemic syndrome-the first year's experience. *QJM* 2016; 109: 27–33
43. Zuber J *et al*. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation. *Am J Transplant* 2012; 12: 3337–3354
44. Matar D *et al*. Atypical hemolytic uremic syndrome recurrence after kidney transplantation. *Transplantation* 2014; 98: 1205–1212
45. Nester C *et al*. Pre-emptive eculizumab and plasmapheresis for renal transplant in atypical hemolytic uremic syndrome. *Clin J Am Soc Nephrol* 2011; 6: 1488–1494
46. Zimmerhackl LB *et al*. Prophylactic eculizumab after renal transplantation in atypical hemolytic-uremic syndrome. *N Engl J Med* 2010; 362: 1746–1748
47. Krid S *et al*. Renal transplantation under prophylactic eculizumab in atypical hemolytic uremic syndrome with CFH/CFHR1 hybrid protein. *Am J Transplant* 2012; 12: 1938–1944
48. Weitz M *et al*. Prophylactic eculizumab prior to kidney transplantation for atypical hemolytic uremic syndrome. *Pediatr Nephrol* 2011; 26: 1325–1329

49. Roman-Ortiz E *et al*. Eculizumab long-term therapy for pediatric renal transplant in aHUS with CFH/CFHR1 hybrid gene. *Pediatr Nephrol* 2014; 29: 149–153
50. Pelicano MB *et al*. Anti-C5 as prophylactic therapy in atypical hemolytic uremic syndrome in living-related kidney transplantation. *Transplantation* 2013; 96: e26–e29
51. Ranch D *et al*. Prophylactic eculizumab for kidney transplantation in a child with atypical hemolytic uremic syndrome due to complement factor H mutation. *Pediatr Transplant* 2014; 18: E185–E189
52. Xie L *et al*. Tailored eculizumab therapy in the management of complement factor H-mediated atypical hemolytic uremic syndrome in an adult kidney transplant recipient: a case report. *Transplant Proc* 2012; 44: 3037–3040
53. Mallett A *et al*. Atypical haemolytic uraemic syndrome treated with the complement inhibitor eculizumab: the experience of the Australian compassionate access cohort. *Intern Med J* 2015; 45: 1054–1065
54. Riddell A, Goodship T, Bingham C. Prevention of recurrence of atypical hemolytic uremic syndrome post renal transplant with the use of higher-dose eculizumab. *Clin Nephrol* 2016; 86: 200–202
55. Saland J. Liver-kidney transplantation to cure atypical HUS: still an option post-eculizumab? *Pediatr Nephrol* 2014; 29: 329–332
56. Oyen O *et al*. Calcineurin inhibitor-free immunosuppression in renal allograft recipients with thrombotic microangiopathy/hemolytic uremic syndrome. *Am J Transplant* 2006; 6: 412–418
57. Chatelet V *et al*. Safety and long-term efficacy of eculizumab in a renal transplant patient with recurrent atypical hemolytic-uremic syndrome. *Am J Transplant* 2009; 9: 2644–2645
58. Alachkar N, Bagnasco SM, Montgomery RA. Eculizumab for the treatment of two recurrences of atypical hemolytic uremic syndrome in a kidney allograft. *Transpl Int* 2012; 25: e93–e95
59. Duran CE *et al*. Rescue therapy with eculizumab in a transplant recipient with atypical haemolytic-uraemic syndrome. *Clin Kidney J* 2012; 5: 28–30
60. Iqbal Z *et al*. Thrombotic microangiopathy as a cause of chronic kidney transplant dysfunction: case report demonstrating successful treatment with eculizumab. *Transplant Proc* 2015; 47: 2258–2261
61. Larrea CF *et al*. Efficacy of eculizumab in the treatment of recurrent atypical hemolytic-uremic syndrome after renal transplantation. *Transplantation* 2010; 89: 903–904
62. Davin JC *et al*. Maintenance of kidney function following treatment with eculizumab and discontinuation of plasma exchange after a third kidney transplant for atypical hemolytic uremic syndrome associated with a CFH mutation. *Am J Kidney Dis* 2010; 55: 708–711
63. Le Quintrec M *et al*. Complement genes strongly predict recurrence and graft outcome in adult renal transplant recipients with atypical hemolytic and uremic syndrome. *Am J Transplant* 2013; 13: 663–675
64. Bresin E *et al*. Outcome of renal transplantation in patients with non-Shiga toxin-associated hemolytic uremic syndrome: prognostic significance of genetic background. *Clin J Am Soc Nephrol* 2006; 1: 88–99
65. Noris M, Remuzzi G. Managing and preventing atypical hemolytic uremic syndrome recurrence after kidney transplantation. *Curr Opin Nephrol Hypertens* 2013; 22: 704–712
66. Le Quintrec M *et al*. Complement mutation-associated de novo thrombotic microangiopathy following kidney transplantation. *Am J Transplant* 2008; 8: 1694–1701
67. Safa K *et al*. Eculizumab for drug-induced de novo post-transplantation thrombotic microangiopathy: A case report. *Clin Nephrol* 2015; 83: 125–129
68. Ikeda T *et al*. Two cases of kidney transplantation-associated thrombotic microangiopathy successfully treated with eculizumab. *Nephrology (Carlton)* 2016; 21: 35–40
69. Juega-Marino FJ *et al*. Late onset of de novo atypical hemolytic-uremic syndrome presented on a simultaneous pancreas and kidney transplant recipient successfully treated with eculizumab. *Nefrologia* 2016; 36: 328–329
70. Wilson CH *et al*. Successful treatment of de novo posttransplant thrombotic microangiopathy with eculizumab. *Transplantation* 2011; 92: e42–e43
71. Chandran S *et al*. Eculizumab for the treatment of de novo thrombotic microangiopathy post simultaneous pancreas-kidney transplantation–a case report. *Transplant Proc* 2011; 43: 2097–2101
72. Karthikeyan V *et al*. Outcome of plasma exchange therapy in thrombotic microangiopathy after renal transplantation. *Am J Transplant* 2003; 3: 1289–1294
73. Cicora F *et al*. Use of belatacept as alternative immunosuppression in three renal transplant patients with de novo drug-induced thrombotic microangiopathy. *Case Rep Med* 2013; 2013: 260254
74. Cortina G *et al*. De novo tacrolimus-induced thrombotic microangiopathy in the early stage after renal transplantation successfully treated with conversion to everolimus. *Pediatr Nephrol* 2015; 30: 693–697
75. Lipshutz GS *et al*. Thrombotic microangiopathy following pancreas after kidney transplants. *Clin Transplant* 2008; 22: 236–241
76. Stegall MD, Chedid MF, Cornell LD. The role of complement in antibody-mediated rejection in kidney transplantation. *Nat Rev Nephrol* 2012; 8: 670–678
77. Noone D *et al*. Antibody mediated rejection associated with complement factor h-related protein 3/1 deficiency successfully treated with eculizumab. *Am J Transplant* 2012; 12: 2546–2553
78. Tran D *et al*. Eculizumab for the treatment of severe antibody-mediated rejection: a case report and review of the literature. *Case Rep Transplant* 2016; 2016: 9874261
79. Gonzalez-Roncero F *et al*. Eculizumab treatment of acute antibody-mediated rejection in renal transplantation: case reports. *Transplant Proc* 2012; 44: 2690–2694
80. Stewart ZA *et al*. Case report: eculizumab rescue of severe accelerated antibody-mediated rejection after ABO-incompatible kidney transplant. *Transplant Proc* 2012; 44: 3033–3036
81. Stegall MD *et al*. Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. *Am J Transplant* 2011; 11: 2405–2413
82. Cornell LD *et al*. Positive crossmatch kidney transplant recipients treated with eculizumab: outcomes beyond 1 year. *Am J Transplant* 2015; 15: 1293–1302
83. Kulkarni S *et al*. Eculizumab therapy for chronic antibody-mediated injury in kidney transplant recipients: a pilot randomized controlled trial. *Am J Transplant* 2016
84. Ghirardo G *et al*. Plasmapheresis-resistant acute humoral rejection successfully treated with anti-C5 antibody. *Pediatr Transplant* 2014; 18: E1–E5
85. Locke JE *et al*. The use of antibody to complement protein C5 for salvage treatment of severe antibody-mediated rejection. *Am J Transplant* 2009; 9: 231–235

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86. Chehade H *et al*. Eculizumab to treat antibody-mediated rejection in a 7-year-old kidney transplant recipient. *Pediatrics* 2015; 135: e551–e555
87. Biglarnia AR *et al*. Prompt reversal of a severe complement activation by eculizumab in a patient undergoing intentional ABO-incompatible pancreas and kidney transplantation. *Transpl Int* 2011; 24: e61–e66
88. Burbach M *et al*. Report of the inefficacy of eculizumab in two cases of severe antibody-mediated rejection of renal grafts. *Transplantation* 2014; 98: 1056–1059
89. Orandi BJ *et al*. Eculizumab and splenectomy as salvage therapy for severe antibody-mediated rejection after HLA-incompatible kidney transplantation. *Transplantation* 2014; 98: 857–863
90. Bentall A *et al*. Antibody-mediated rejection despite inhibition of terminal complement. *Transpl Int* 2014; 27: 1235–1243
91. Yelken B *et al*. Eculizumab for treatment of refractory antibody-mediated rejection in kidney transplant patients: a single-center experience. *Transplant Proc* 2015; 47: 1754–1759
92. Kidney Disease: Improving Global Outcomes Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; 9: S1–S155
93. Bruneau S *et al*. Loss of DGKepsilon induces endothelial cell activation and death independently of complement activation. *Blood* 2015; 125: 1038–1046
94. Lemaire M *et al*. Recessive mutations in DGKE cause atypical hemolytic-uremic syndrome. *Nat Genet* 2013; 45: 531–536
95. Sanchez Chinchilla D *et al*. Complement mutations in diacylglycerol kinase-epsilon-associated atypical hemolytic uremic syndrome. *Clin J Am Soc Nephrol* 2014; 9: 1611–1619
96. Mele C *et al*. Characterization of a new DGKE intronic mutation in genetically unsolved cases of familial atypical hemolytic uremic syndrome. *Clin J Am Soc Nephrol* 2015; 10: 1011–1019
97. Westland R *et al*. Phenotypic expansion of DGKE-associated diseases. *J Am Soc Nephrol* 2014; 25: 1408–1414
98. Tati R *et al*. Complement activation associated with ADAMTS13 deficiency in human and murine thrombotic microangiopathy. *J Immunol* 2013; 191: 2184–2193
99. Ruiz-Torres MP *et al*. Complement activation: the missing link between ADAMTS-13 deficiency and microvascular thrombosis of thrombotic microangiopathies. *Thromb Haemost* 2005; 93: 443–452
100. Cao W *et al*. Human neutrophil peptides and complement factor Bb in pathogenesis of acquired thrombotic thrombocytopenic purpura. *Haematologica* 2016; 101: 1319–1326
101. Reti M *et al*. Complement activation in thrombotic thrombocytopenic purpura. *J Thromb Haemost* 2012; 10: 791–798
102. Westwood JP *et al*. Complement and cytokine response in acute Thrombotic Thrombocytopenic Purpura. *Br J Haematol* 2014; 164: 858–866
103. Wu TC *et al*. Complement activation and mortality during an acute episode of thrombotic thrombocytopenic purpura. *J Thromb Haemost* 2013; 11: 1925–1927
104. Fan X *et al*. Genetic variations in complement factors in patients with congenital thrombotic thrombocytopenic purpura with renal insufficiency. *Int J Hematol* 2016; 103: 283–291
105. Noris M *et al*. Complement factor H mutation in familial thrombotic thrombocytopenic purpura with ADAMTS13 deficiency and renal involvement. *J Am Soc Nephrol* 2005; 16: 1177–1183
106. Chapin J *et al*. Eculizumab in the treatment of refractory idiopathic thrombotic thrombocytopenic purpura. *Br J Haematol* 2012; 157: 772–774
107. Tsai E *et al*. Use of eculizumab in the treatment of a case of refractory, ADAMTS13-deficient thrombotic thrombocytopenic purpura: additional data and clinical follow-up. *Br J Haematol* 2013; 162: 558–559
108. Pecoraro C *et al*. Treatment of congenital thrombotic thrombocytopenic purpura with eculizumab. *Am J Kidney Dis* 2015; 66: 1067–1070
109. Schwartz J *et al*. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the seventh special issue. *J Clin Apher* 2016; 31: 149–162
110. Scully M *et al*. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. *Blood* 2011; 118: 1746–1753
111. Clark WF *et al*. A phase-II sequential case-series study of all patients presenting to four plasma exchange centres with presumed relapsed/refractory thrombotic thrombocytopenic purpura treated with rituximab. *Br J Haematol* 2015; 170: 208–217
112. Benhamou Y *et al*. Efficacy of a rituximab regimen based on B cell depletion in thrombotic thrombocytopenic purpura with suboptimal response to standard treatment: Results of a phase II, multicenter non-comparative study. *Am J Hematol* 2016
113. Peyvandi F *et al*. Caplacizumab for acquired thrombotic thrombocytopenic purpura. *N Engl J Med* 2016; 374: 511–522
114. Fakhouri F *et al*. Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations. *J Am Soc Nephrol* 2010; 21: 859–67
115. Ardissino G *et al*. Eculizumab for atypical hemolytic uremic syndrome in pregnancy. *Obstet Gynecol* 2013; 122 (2 Pt 2): 487–489
116. Zschiedrich S, Prager EP, Kuehn EW. Successful treatment of the postpartum atypical hemolytic uremic syndrome with eculizumab. *Ann Intern Med* 2013; 159: 176
117. Scully M *et al*. Thrombotic thrombocytopenic purpura and pregnancy: presentation, management, and subsequent pregnancy outcomes. *Blood* 2014; 124: 211–219
118. Vaught AJ *et al*. Direct evidence of complement activation in HELLP syndrome: A link to atypical hemolytic uremic syndrome. *Exp Hematol* 2016; 44: 390–398
119. Haeger M, Unander M, Bengtsson A. Enhanced anaphylatoxin and terminal C5b-9 complement complex formation in patients with the syndrome of hemolysis, elevated liver enzymes, and low platelet count. *Obstet Gynecol* 1990; 76: 698–702
120. Derzsy Z *et al*. Activation of the complement system in normal pregnancy and preeclampsia. *Mol Immunol* 2010; 47: 1500–1506
121. He Y *et al*. Expression of the complement system's activation factors in plasma of patients with early/late-onset severe pre-eclampsia. *Am J Reprod Immunol* 2016; 76: 205–211
122. Ari E *et al*. Human serum complement C3 and factor H in the syndrome of hemolysis, elevated liver enzymes, and low platelet count. *Am J Reprod Immunol* 2009; 62: 238–242
123. Fakhouri F *et al*. Factor H, membrane cofactor protein, and factor I mutations in patients with hemolysis, elevated liver enzymes, and low platelet count syndrome. *Blood* 2008; 112: 4542–4545

124. Crovetto F *et al*. The genetics of the alternative pathway of complement in the pathogenesis of HELLP syndrome. *J Matern Fetal Neonatal Med* 2012; 25: 2322–2325
125. Salmon JE *et al*. Mutations in complement regulatory proteins predispose to preeclampsia: a genetic analysis of the PROMISSE cohort. *PLoS Med* 2011; 8: e1001013
126. Kelly RJ *et al*. Eculizumab in pregnant patients with paroxysmal nocturnal hemoglobinuria. *N Engl J Med* 2015; 373: 1032–1039
127. Servais A *et al*. Atypical haemolytic uraemic syndrome and pregnancy: outcome with ongoing eculizumab. *Nephrol Dial Transplant* 2016
128. Burwick RM, Feinberg BB. Eculizumab for the treatment of preeclampsia/HELLP syndrome. *Placenta* 2013; 34: 201–203
129. Beck BB *et al*. Renal thrombotic microangiopathy in patients with cblC defect: review of an under-recognized entity. *Pediatr Nephrol* 2016
130. Bouts AH *et al*. CD46-associated atypical hemolytic uremic syndrome with uncommon course caused by cblC deficiency. *Pediatr Nephrol* 2010; 25: 2547–2548
131. Guigonis V *et al*. Late-onset thrombocytic microangiopathy caused by cblC disease: association with a factor H mutation. *Am J Kidney Dis* 2005; 45: 588–595
132. Cornec-Le Gall E *et al*. Adult-onset eculizumab-resistant hemolytic uremic syndrome associated with cobalamin C deficiency. *Am J Kidney Dis* 2014; 63: 119–123
133. Morigi M *et al*. Alternative pathway activation of complement by Shiga toxin promotes exuberant C3a formation that triggers microvascular thrombosis. *J Immunol* 2011; 187: 172–180
134. Ozaki M *et al*. Human mannose-binding lectin inhibitor prevents Shiga toxin-induced renal injury. *Kidney Int* 2016; 90: 774–782
135. Locatelli M *et al*. Shiga toxin promotes podocyte injury in experimental hemolytic uremic syndrome via activation of the alternative pathway of complement. *J Am Soc Nephrol* 2014; 25: 1786–1798
136. Orth D *et al*. Shiga toxin activates complement and binds factor H: evidence for an active role of complement in hemolytic uremic syndrome. *J Immunol* 2009; 182: 6394–6400
137. Poolpol K *et al*. Interaction of Shiga toxin 2 with complement regulators of the factor H protein family. *Mol Immunol* 2014; 58: 77–84
138. Stahl AL, Sartz L, Karpman D. Complement activation on platelet-leukocyte complexes and microparticles in enterohemorrhagic Escherichia coli-induced hemolytic uremic syndrome. *Blood* 2011; 117: 5503–5513
139. Arvidsson I *et al*. Shiga toxin-induced complement-mediated hemolysis and release of complement-coated red blood cell-derived microvesicles in hemolytic uremic syndrome. *J Immunol* 2015; 194: 2309–2318
140. Ahlenstiel-Grunow T *et al*. Systemic complement activation and complement gene analysis in enterohaemorrhagic *Escherichia coli*-associated paediatric haemolytic uraemic syndrome. *Nephrol Dial Transplant* 2016; 31: 1114–1121
141. Ferraris JR *et al*. Activation of the alternative pathway of complement during the acute phase of typical haemolytic uraemic syndrome. *Clin Exp Immunol* 2015; 181: 118–125
142. Thurman JM *et al*. Alternative pathway of complement in children with diarrhea-associated hemolytic uremic syndrome. *Clin J Am Soc Nephrol* 2009; 4: 1920–1924
143. Alberti M *et al*. Two patients with history of STEC-HUS, posttransplant recurrence and complement gene mutations. *Am J Transplant* 2013; 13: 2201–2206
144. Caillaud C *et al*. CFH gene mutation in a case of Shiga toxin-associated hemolytic uremic syndrome (STEC-HUS). *Pediatr Nephrol* 2016; 31: 157–161
145. Challis RC *et al*. A de novo deletion in the regulators of complement activation cluster producing a hybrid complement factor H/complement factor H-related 3 gene in atypical hemolytic uremic syndrome. *J Am Soc Nephrol* 2016; 27: 1617–1624
146. Westra D *et al*. Serological and genetic complement alterations in infection-induced and complement-mediated hemolytic uremic syndrome. *Pediatr Nephrol* 2016
147. Kielstein JT *et al*. Best supportive care and therapeutic plasma exchange with or without eculizumab in Shiga-toxin-producing E. coli O104:H4 induced haemolytic-uraemic syndrome: an analysis of the German STEC-HUS registry. *Nephrol Dial Transplant* 2012; 27: 3807–3815
148. Menne J *et al*. Validation of treatment strategies for enterohaemorrhagic Escherichia coli O104:H4 induced haemolytic uraemic syndrome: case-control study. *BMJ* 2012; 345: e4565
149. Lapeyraque AL *et al*. Eculizumab in severe Shiga-toxin-associated HUS. *N Engl J Med* 2011; 364: 2561–2563
150. Spinale JM *et al*. Long-term outcomes of Shiga toxin hemolytic uremic syndrome. *Pediatr Nephrol* 2013; 28: 2097–2105
151. Greinacher A *et al*. Treatment of severe neurological deficits with IgG depletion through immunoadsorption in patients with Escherichia coli O104:H4-associated haemolytic uraemic syndrome: a prospective trial. *Lancet* 2011; 378: 1166–1173
152. Michael M *et al*. Interventions for hemolytic uremic syndrome and thrombotic thrombocytopenic purpura: a systematic review of randomized controlled trials. *Am J Kidney Dis* 2009; 53: 259–272
153. Loos S *et al*. An outbreak of Shiga toxin-producing Escherichia coli O104:H4 hemolytic uremic syndrome in Germany: presentation and short-term outcome in children. *Clin Infect Dis* 2012; 55: 753–759
154. Quin LR *et al*. In vivo binding of complement regulator factor H by Streptococcus pneumoniae. *J Infect Dis* 2005; 192: 1996–2003
155. Johnson S, Waters A. Is complement a culprit in infection-induced forms of haemolytic uraemic syndrome? *Immunobiology* 2012; 217: 235–243
156. Gilbert RD, Nagra A, Haq MR. Does dysregulated complement activation contribute to haemolytic uraemic syndrome secondary to Streptococcus pneumoniae? *Med Hypotheses* 2013; 81: 400–403
157. Szilagyi A *et al*. The role of complement in *Streptococcus pneumoniae*-associated haemolytic uraemic syndrome. *Nephrol Dial Transplant* 2013; 28: 2237–2245
158. Kavanagh D, Goodship TH, Richards A. Atypical haemolytic uraemic syndrome. *Br Med Bull* 2006; 77–78: 5–22
159. Jin A *et al*. Thrombotic microangiopathy and human immunodeficiency virus in the era of eculizumab. *Clin Kidney J* 2016; 9: 576–579
160. Alpers CE. Light at the end of the TUNEL: HIV-associated thrombotic microangiopathy. *Kidney Int* 2003; 63: 385–396
161. Peraldi MN *et al*. Acute renal failure in the course of HIV infection: a single-institution retrospective study of ninety-two patients and sixty renal biopsies. *Nephrol Dial Transplant* 1999; 14: 1578–1585

Clinical Kidney Journal
ckj

162. Becker S *et al*. HIV-associated thrombotic microangiopathy in the era of highly active antiretroviral therapy: an observational study. *Clin Infect Dis* 2004; 39: S267–S275
163. Java A *et al*. Cytomegalovirus-induced thrombotic microangiopathy after renal transplant successfully treated with eculizumab: case report and review of the literature. *Transpl Int* 2015; 28: 1121–1125
164. Kim CH *et al*. Conditioning for hematopoietic transplantation activates the complement cascade and induces a proteolytic environment in bone marrow: a novel role for bioactive lipids and soluble C5b-C9 as homing factors. *Leukemia* 2012; 26: 106–116
165. Kwan WH *et al*. Antigen-presenting cell-derived complement modulates graft-versus-host disease. *J Clin Invest* 2012; 122: 2234–2238
166. Mii A *et al*. Renal thrombotic microangiopathy associated with chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Pathol Int* 2011; 61: 518–527
167. Sakamoto K *et al*. Hematopoietic stem cell transplantation-associated thrombotic microangiopathy accompanied by renal arteriolar C4d deposition. *Pediatr Transplant* 2015; 19: E97–E100
168. Jodele S *et al*. Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults. *Blood* 2014; 124: 645–653
169. Hale GA *et al*. Hemolytic uremic syndrome after bone marrow transplantation: clinical characteristics and outcome in children. *Biol Blood Marrow Transplant* 2005; 11: 912–920
170. Jodele S *et al*. Abnormalities in the alternative pathway of complement in children with hematopoietic stem cell transplant-associated thrombotic microangiopathy. *Blood* 2013; 122: 2003–2007
171. Jodele S *et al*. The genetic fingerprint of susceptibility for transplant-associated thrombotic microangiopathy. *Blood* 2016; 127: 989–996
172. Jodele S *et al*. New approaches in the diagnosis, pathophysiology, and treatment of pediatric hematopoietic stem cell transplantation-associated thrombotic microangiopathy. *Transfus Apher Sci* 2016; 54: 181–190
173. de Fontbrune FS *et al*. Use of eculizumab in patients with allogeneic stem cell transplant-associated thrombotic microangiopathy: a study from the SFGM-TC. *Transplantation* 2015; 99: 1953–1959
174. Jodele S *et al*. Eculizumab therapy in children with severe hematopoietic stem cell transplantation-associated thrombotic microangiopathy. *Biol Blood Marrow Transplant* 2014; 20: 518–525
175. Chapin J *et al*. Hematopoietic transplant-associated thrombotic microangiopathy: case report and review of diagnosis and treatments. *Clin Adv Hematol Oncol* 2014; 12: 565–573
176. Peffault de Latour R *et al*. Successful use of eculizumab in a patient with post-transplant thrombotic microangiopathy. *Br J Haematol* 2013; 161: 279–280
177. Okano M *et al*. Recovery from life-threatening transplantation-associated thrombotic microangiopathy using eculizumab in a patient with very severe aplastic anemia. *Bone Marrow Transplant* 2014; 49: 1116–1118
178. Sevindik OG *et al*. Renal and neurological response with eculizumab in a patient with transplant associated thrombotic microangiopathy after allogeneic hematopoietic progenitor cell transplantation. *Case Rep Hematol* 2015; 2015: 425410
179. Fernandez C *et al*. Eculizumab treatment in a patient with hematopoietic stem cell transplantation-associated thrombotic microangiopathy and steroid-refractory acute graft versus host disease. *Hematol Rep* 2015; 7: 6107
180. Vasu S *et al*. Eculizumab therapy in adults with allogeneic hematopoietic cell transplant-associated thrombotic microangiopathy. *Bone Marrow Transplant* 2016; 51: 1241–1244
181. Ho VT *et al*. Blood and marrow transplant clinical trials network toxicity committee consensus summary: thrombotic microangiopathy after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2005; 11: 571–575
182. Elsallabi O *et al*. Hematopoietic stem cell transplant-associated thrombotic microangiopathy. *Clin Appl Thromb Hemost* 2016; 22: 12–20
183. Worel N *et al*. ABO-incompatible allogeneic hematopoietic stem cell transplantation following reduced-intensity conditioning: close association with transplant-associated microangiopathy. *Transfus Apher Sci* 2007; 36: 297–304
184. Au WY *et al*. Successful treatment of thrombotic microangiopathy after haematopoietic stem cell transplantation with rituximab. *Br J Haematol* 2007; 137: 475–478
185. Carella AM *et al*. Rituximab for allo-SCT-associated thrombotic thrombocytopenic purpura. *Bone Marrow Transplant* 2008; 41: 1063–1065
186. Zhang C *et al*. Complement 5a receptor mediates angiotensin II-induced cardiac inflammation and remodeling. *Arterioscler Thromb Vasc Biol* 2014; 34: 1240–1248
187. Zhang C *et al*. Antagonist of C5aR prevents cardiac remodeling in angiotensin II-induced hypertension. *Am J Hypertens* 2014; 27: 857–864
188. Engstrom G *et al*. Plasma levels of complement C3 is associated with development of hypertension: a longitudinal cohort study. *J Hum Hypertens* 2007; 21: 276–282
189. Gan W *et al*. Associations of CFH polymorphisms and CFHR1-CFHR3 deletion with blood pressure and hypertension in Chinese population. *PLoS One* 2012; 7: e42010
190. Akimoto T *et al*. Clinical features of malignant hypertension with thrombotic microangiopathy. *Clin Exp Hypertens* 2011; 33: 77–83
191. Khanal N *et al*. Differentiating malignant hypertension-induced thrombotic microangiopathy from thrombotic thrombocytopenic purpura. *Ther Adv Hematol* 2015; 6: 97–102
192. Deguchi I *et al*. Malignant hypertension with reversible brainstem hypertensive encephalopathy and thrombotic microangiopathy. *J Stroke Cerebrovasc Dis* 2012; 21: 915 e17–e20
193. Chapin J *et al*. Complement factor H mutations are present in ADAMTS13-deficient, ticlopidine-associated thrombotic microangiopathies. *Blood* 2013; 121: 4012–4013
194. Tada K *et al*. Clopidogrel-induced thrombotic microangiopathy in a patient with hypocomplementemia. *Intern Med* 2016; 55: 969–973
195. Faguer S *et al*. Eculizumab and drug-induced haemolytic-uraemic syndrome. *Clin Kidney J* 2013; 6: 484–485
196. Starck M, Wendtner CM. Use of eculizumab in refractory gemcitabine-induced thrombotic microangiopathy. *Br J Haematol* 2013
197. Al Ustwani O *et al*. Eculizumab therapy for gemcitabine induced hemolytic uremic syndrome: case series and concise review. *J Gastrointest Oncol* 2014; 5: E30–E33
198. Turner JL *et al*. Gemcitabine-associated thrombotic microangiopathy: response to complement inhibition and reinitiation of gemcitabine. *Clin Colorectal Cancer* 2016

199. Yui JC *et al*. Proteasome inhibitor associated thrombotic microangiopathy. *Am J Hematol* 2016; 91: E348–E352
200. Tsai HM *et al*. Antibody inhibitors to von Willebrand factor metalloproteinase and increased binding of von Willebrand factor to platelets in ticlopidine-associated thrombotic thrombocytopenic purpura. *Ann Intern Med* 2000; 132: 794–799
201. Gore EM, Jones BS, Marques MB. Is therapeutic plasma exchange indicated for patients with gemcitabine-induced hemolytic uremic syndrome? *J Clin Apher* 2009; 24: 209–214
202. Qaqish I *et al*. Carfilzomib: A cause of drug associated thrombotic microangiopathy. *Transfus Apher Sci* 2016; 54: 401–404
203. Francis KK *et al*. Disseminated malignancy misdiagnosed as thrombotic thrombocytopenic purpura: A report of 10 patients and a systematic review of published cases. *Oncologist* 2007; 12: 11–19
204. Lesesne JB *et al*. Cancer-associated hemolytic-uremic syndrome: analysis of 85 cases from a national registry. *J Clin Oncol* 1989; 7: 781–789
205. Oberic L *et al*. Cancer awareness in atypical thrombotic microangiopathies. *Oncologist* 2009; 14: 769–779
206. Wang Y *et al*. Amelioration of lupus-like autoimmune disease in NZB/WF1 mice after treatment with a blocking monoclonal antibody specific for complement component C5. *Proc Natl Acad Sci USA* 1996; 93: 8563–8568
207. Barilla-Labarca ML, Toder K, Furie R. Targeting the complement system in systemic lupus erythematosus and other diseases. *Clin Immunol* 2013; 148: 313–321
208. Zhao J *et al*. Association of genetic variants in complement factor H and factor H-related genes with systemic lupus erythematosus susceptibility. *PLoS Genet* 2011; 7: e1002079
209. Bermea RS *et al*. Use of eculizumab in atypical hemolytic uremic syndrome, complicating systemic lupus erythematosus. *J Clin Rheumatol* 2016; 22: 320–323
210. Coppo R *et al*. Dramatic effects of eculizumab in a child with diffuse proliferative lupus nephritis resistant to conventional therapy. *Pediatr Nephrol* 2015; 30: 167–172
211. El-Husseini A *et al*. Thrombotic microangiopathy in systemic lupus erythematosus: efficacy of eculizumab. *Am J Kidney Dis* 2015; 65: 127–130
212. Pickering MC *et al*. Eculizumab as rescue therapy in severe resistant lupus nephritis. *Rheumatology (Oxford)* 2015; 54: 2286–2288
213. Raufi AG *et al*. Atypical hemolytic uremic syndrome secondary to lupus nephritis, responsive to eculizumab. *Hematol Rep* 2016; 8: 6625
214. Hamasaki K *et al*. Systemic lupus erythematosus and thrombotic thrombocytopenic purpura: a case report and literature review. *Clin Rheumatol* 2003; 22: 355–358
215. Seshan SV *et al*. Role of tissue factor in a mouse model of thrombotic microangiopathy induced by antiphospholipid antibodies. *Blood* 2009; 114: 1675–1683
216. Girardi G *et al*. Complement C5a receptors and neutrophils mediate fetal injury in the antiphospholipid syndrome. *J Clin Invest* 2003; 112: 1644–1654
217. Thurman JM *et al*. A novel inhibitor of the alternative complement pathway prevents antiphospholipid antibody-induced pregnancy loss in mice. *Mol Immunol* 2005; 42: 87–97
218. Romay-Penabad Z *et al*. Complement C5-inhibitor rEV576 (coversin) ameliorates in-vivo effects of antiphospholipid antibodies. *Lupus* 2014; 23: 1324–1326
219. Canaud G *et al*. Eculizumab improves posttransplant thrombotic microangiopathy due to antiphospholipid syndrome recurrence but fails to prevent chronic vascular changes. *Am J Transplant* 2013; 13: 2179–2185
220. Oku K *et al*. Complement activation in patients with primary antiphospholipid syndrome. *Ann Rheum Dis* 2009; 68: 1030–1035
221. Sinico RA *et al*. Renal involvement in primary antiphospholipid syndrome: retrospective analysis of 160 patients. *Clin J Am Soc Nephrol* 2010; 5: 1211–1217
222. Foltyn Zadura A *et al*. Factor H autoantibodies in patients with antiphospholipid syndrome and thrombosis. *J Rheumatol* 2015; 42: 1786–1793
223. Barratt-Due A *et al*. Complement activation is a crucial pathogenic factor in catastrophic antiphospholipid syndrome. *Rheumatology (Oxford)* 2016; 55: 1337–1339
224. Kronbichler A *et al*. Efficacy of eculizumab in a patient with immunoadsorption-dependent catastrophic antiphospholipid syndrome: a case report. *Medicine (Baltimore)* 2014; 93: e143
225. Shapira I *et al*. Brief report: induction of sustained remission in recurrent catastrophic antiphospholipid syndrome via inhibition of terminal complement with eculizumab. *Arthritis Rheum* 2012; 64: 2719–2723
226. Wig S *et al*. A case of relapsing and refractory catastrophic anti-phospholipid syndrome successfully managed with eculizumab, a complement 5 inhibitor. *Rheumatology (Oxford)* 2016; 55: 382–384
227. Strakhan M *et al*. 36-year-old female with catastrophic antiphospholipid syndrome treated with eculizumab: a case report and review of literature. *Case Rep Hematol* 2014; 2014: 704371
228. Zikos TA *et al*. Eculizumab induces sustained remission in a patient with refractory primary catastrophic antiphospholipid syndrome. *J Clin Rheumatol* 2015; 21: 311–313
229. Hadaya K *et al*. Eculizumab in acute recurrence of thrombotic microangiopathy after renal transplantation. *Am J Transplant* 2011; 11: 2523–2527
230. Bakhtar O *et al*. A case of thrombotic microangiopathy associated with antiphospholipid antibody syndrome successfully treated with eculizumab. *Transplantation* 2014; 98: e17–e18
231. Lonze BE *et al*. Eculizumab prevents recurrent antiphospholipid antibody syndrome and enables successful renal transplantation. *Am J Transplant* 2014; 14: 459–465
232. Rodriguez-Pinto I *et al*. Catastrophic antiphospholipid syndrome (CAPS): Descriptive analysis of 500 patients from the International CAPS Registry. *Autoimmun Rev* 2016
233. Canaud G *et al*. Inhibition of the mTORC pathway in the antiphospholipid syndrome. *N Engl J Med* 2014; 371: 303–312
234. Edey M *et al*. Is complement factor H a susceptibility factor for IgA nephropathy? *Mol Immunol* 2009; 46: 1405–1408
235. Endo M *et al*. Glomerular deposition of mannose-binding lectin (MBL) indicates a novel mechanism of complement activation in IgA nephropathy. *Nephrol Dial Transplant* 1998; 13: 1984–1990
236. Matsuda M *et al*. Deposition of mannan binding protein and mannan binding protein-mediated complement activation in the glomeruli of patients with IgA nephropathy. *Nephron* 1998; 80: 408–413
237. Hisano S *et al*. Mesangial IgA2 deposits and lectin pathway-mediated complement activation in IgA glomerulonephritis. *Am J Kidney Dis* 2001; 38: 1082–1088
238. Roos A *et al*. Glomerular activation of the lectin pathway of complement in IgA nephropathy is associated with more severe renal disease. *J Am Soc Nephrol* 2006; 17: 1724–1734

Clinical Kidney Journal
ckj

239. Wyatt RJ *et al*. Partial H (beta 1H) deficiency and glomerulonephritis in two families. *J Clin Immunol* 1982; 2: 110–117
240. Gharavi AG *et al*. Genome-wide association study identifies susceptibility loci for IgA nephropathy. *Nat Genet* 2011; 43: 321–327
241. Zhai YL *et al*. Rare variants in the complement factor h-related protein 5 gene contribute to genetic susceptibility to IgA nephropathy. *J Am Soc Nephrol* 2016; 27: 2894–2905
242. Ring T *et al*. Use of eculizumab in crescentic IgA nephropathy: proof of principle and conundrum? *Clin Kidney J* 2015; 8: 489–491
243. Rosenblad T *et al*. Eculizumab treatment for rescue of renal function in IgA nephropathy. *Pediatr Nephrol* 2014; 29: 2225–2228
244. Schreiber A *et al*. C5a receptor mediates neutrophil activation and ANCA-induced glomerulonephritis. *J Am Soc Nephrol* 2009; 20: 289–298
245. Xiao H *et al*. Alternative complement pathway in the pathogenesis of disease mediated by anti-neutrophil cytoplasmic autoantibodies. *Am J Pathol* 2007; 170: 52–64
246. Xiao H *et al*. C5a receptor (CD88) blockade protects against MPO-ANCA GN. *J Am Soc Nephrol* 2014; 25: 225–231
247. Fukui S *et al*. Antineutrophilic cytoplasmic antibody-associated vasculitis with hypocomplementemia has a higher incidence of serious organ damage and a poor prognosis. *Medicine (Baltimore)* 2016; 95: e4871
248. Manenti L *et al*. Association of serum C3 concentration and histologic signs of thrombotic microangiopathy with outcomes among patients with ANCA-associated renal vasculitis. *Clin J Am Soc Nephrol* 2015; 10: 2143–2151
249. Hilhorst M *et al*. Complement in ANCA-associated glomerulonephritis. *Nephrol Dial Transplant* 2015
250. Jones RB *et al*. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; 363: 211–220
251. Geetha D *et al*. Rituximab versus cyclophosphamide for ANCA-associated vasculitis with renal involvement. *J Am Soc Nephrol* 2015; 26: 976–985
252. Ma H, Sandor DG, Beck LH Jr. The role of complement in membranous nephropathy. *Semin Nephrol* 2013; 33: 531–542
253. Endo M *et al*. Glomerular deposition and urinary excretion of complement factor H in idiopathic membranous nephropathy. *Nephron Clin Pract* 2004; 97: c147–c153
254. Segawa Y *et al*. IgG subclasses and complement pathway in segmental and global membranous nephropathy. *Pediatr Nephrol* 2010; 25: 1091–1099
255. Nangaku M, Shankland SJ, Couser WG. Cellular response to injury in membranous nephropathy. *J Am Soc Nephrol* 2005; 16: 1195–1204
256. Jha V *et al*. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. *J Am Soc Nephrol* 2007; 18: 1899–1904
257. McDonald DT, Roy LP. Micro-angiopathic haemolysis, thrombocytopenia and nephrotic syndrome associated with membranous nephropathy in a Vietnamese boy. *Aust Paediatr J* 1988; 24: 311–313
258. Manenti L *et al*. Atypical haemolytic uraemic syndrome with underlying glomerulopathies. A case series and a review of the literature. *Nephrol Dial Transplant* 2013; 28: 2246–2259
259. Koulova L *et al*. Rituximab for the treatment of refractory idiopathic thrombocytopenic purpura (ITP) and thrombotic thrombocytopenic purpura (TTP): report of three cases. *Am J Hematol* 2005; 78: 49–54
260. Kuppachi S, Chander P, Yoo J. Membranous nephropathy and thrombotic thrombocytopenic purpura treated with rituximab. *J Nephrol* 2009; 22: 561–564
261. Thurman JM *et al*. Complement activation in patients with focal segmental glomerulosclerosis. *PLoS One* 2015; 10: e0136558
262. Zhang YM *et al*. Clinical significance of IgM and C3 glomerular deposition in primary focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol* 2016; 11: 1582–1589
263. Challis RC *et al*. Thrombotic microangiopathy in inverted formin 2-mediated renal disease. *J Am Soc Nephrol* 2016
264. Batal I *et al*. Renal biopsy findings predicting outcome in scleroderma renal crisis. *Hum Pathol* 2009; 40: 332–340
265. Scambi C *et al*. The local complement activation on vascular bed of patients with systemic sclerosis: a hypothesis-generating study. *PLoS One* 2015; 10: e0114856
266. Devresse A *et al*. Complement activation and effect of eculizumab in scleroderma renal crisis. *Medicine (Baltimore)* 2016; 95: e4459
267. Thomas CP *et al*. Eculizumab for rescue of thrombotic microangiopathy in PM-Scl antibody-positive autoimmune overlap syndrome. *Clin Kidney J* 2015; 8: 698–701
268. Woodworth TG *et al*. Scleroderma renal crisis and renal involvement in systemic sclerosis. *Nat Rev Nephrol* 2016
269. Cozzi F *et al*. Prognosis of scleroderma renal crisis: a long-term observational study. *Nephrol Dial Transplant* 2012; 27: 4398–4403
270. Pickering MC *et al*. Prevention of C5 activation ameliorates spontaneous and experimental glomerulonephritis in factor H-deficient mice. *Proc Natl Acad Sci USA* 2006; 103: 9649–9654
271. Servais A *et al*. Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. *Kidney Int* 2012; 82: 454–464
272. Iatropoulos P *et al*. Complement gene variants determine the risk of immunoglobulin-associated MPGN and C3 glomerulopathy and predict long-term renal outcome. *Mol Immunol* 2016; 71: 131–142
273. Bomback AS *et al*. Eculizumab for dense deposit disease and C3 glomerulonephritis. *Clin J Am Soc Nephrol* 2012; 7: 748–756
274. Radhakrishnan S *et al*. Eculizumab and refractory membranoproliferative glomerulonephritis. *N Engl J Med* 2012; 366: 1165–1166
275. Brackman D *et al*. Thrombotic microangiopathy mimicking membranoproliferative glomerulonephritis. *Nephrol Dial Transplant* 2011; 26: 3399–3403
276. Gurkan S *et al*. Eculizumab and recurrent C3 glomerulonephritis. *Pediatr Nephrol* 2013; 28: 1975–1981
277. Kersnik Levart T *et al*. Severe active C3 glomerulonephritis triggered by immune complexes and inactivated after eculizumab therapy. *Diagn Pathol* 2016; 11: 94
278. Tran CL *et al*. Discontinuation of dialysis with eculizumab therapy in a pediatric patient with dense deposit disease. *Pediatr Nephrol* 2016; 31: 683–687
279. Vivarelli M, Pasini A, Emma F. Eculizumab for the treatment of dense-deposit disease. *N Engl J Med* 2012; 366: 1163–1165
280. Rousset-Rouviere C *et al*. Rituximab fails where eculizumab restores renal function in C3nef-related DDD. *Pediatr Nephrol* 2014; 29: 1107–1111
281. Payette A *et al*. A case of C3 glomerulonephritis successfully treated with eculizumab. *Pediatr Nephrol* 2015; 30: 1033–1037

Clinical Kidney Journal
ckj

282. Daina E, Noris M, Remuzzi G. Eculizumab in a patient with dense-deposit disease. *N Engl J Med* 2012; 366: 1161–1163
283. Inman M *et al*. Eculizumab-induced reversal of dialysis-dependent kidney failure from C3 glomerulonephritis. *Clin Kidney J* 2015; 8: 445–448
284. Le Quintrec M *et al*. Eculizumab for treatment of rapidly progressive C3 glomerulopathy. *Am J Kidney Dis* 2015; 65: 484–489
285. Oosterveld MJ *et al*. Eculizumab in pediatric dense deposit disease. *Clin J Am Soc Nephrol* 2015; 10: 1773–1782
286. Ozkaya O *et al*. Eculizumab therapy in a patient with dense-deposit disease associated with partial lipodystropy. *Pediatr Nephrol* 2014; 29: 1283–1287
287. McCaughan JA, O'Rourke DM, Courtney AE. Recurrent dense deposit disease after renal transplantation: an emerging role for complementary therapies. *Am J Transplant* 2012; 12: 1046–1051
288. Sanchez-Moreno A *et al*. Eculizumab in dense-deposit disease after renal transplantation. *Pediatr Nephrol* 2014; 29: 2055–2059
289. Kurosawa S, Stearns-Kurosawa DJ. Complement, thrombotic microangiopathy and disseminated intravascular coagulation. *J Intensive Care* 2014; 2: 65
290. Loirat C *et al*. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. *Pediatr Nephrol* 2016; 31: 15–39
291. Kavanagh D, Smith-Jackson K. Eculizumab in children with hemolytic uremic syndrome. *Kidney Int* 2016; 89: 537–538
292. Wong E *et al*. Patient stratification and therapy in atypical haemolytic uraemic syndrome (aHUS). *Immunobiology* 2016; 221: 715–718
293. Kavanagh D *et al*. Transplantation in atypical hemolytic uremic syndrome. *Semin Thromb Hemost* 2010; 36: 653–659
294. Reynolds JC *et al*. Thrombotic microangiopathy after renal transplantation in the United States. *Am J Kidney Dis* 2003; 42: 1058–1068
295. Ponticelli C, Banfi G. Thrombotic microangiopathy after kidney transplantation. *Transpl Int* 2006; 19: 789–794
296. Zuber J *et al*. Targeted strategies in the prevention and management of atypical HUS recurrence after kidney transplantation. *Transplant Rev (Orlando)* 2013; 27: 117–125
297. Verbiest A, Pirenne J, Dierickx D. De novo thrombotic microangiopathy after non-renal solid organ transplantation. *Blood Rev* 2014; 28: 269–279
298. Satoskar AA *et al*. De novo thrombotic microangiopathy in renal allograft biopsies-role of antibody-mediated rejection. *Am J Transplant* 2010; 10: 1804–1811
299. Haas M. The Revised (2013) Banff Classification for antibody-mediated rejection of renal allografts: update, difficulties, and future considerations. *Am J Transplant* 2016; 16: 1352–1357
300. Ozaltin F *et al*. DGKE variants cause a glomerular microangiopathy that mimics membranoproliferative GN. *J Am Soc Nephrol* 2013; 24: 377–384
301. Noris M, Mescia F, Remuzzi G. STEC-HUS, atypical HUS and TTP are all diseases of complement activation. *Nat Rev Nephrol* 2012; 8: 622–633
302. Bruel A, Kavanagh D, Noris M *et al*. Hemolytic uremic syndrome in pregnancy and postpartum. *Clin J Am Soc Nephrol* 2017
303. Fakhouri F. Pregnancy-related thrombotic microangiopathies: Clues from complement biology. *Transfus Apher Sci* 2016; 54: 199–202
304. George JN. The association of pregnancy with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Curr Opin Hematol* 2003; 10: 339–344
305. Fakhouri F, Vercel C, Fremeaux-Bacchi V. Obstetric nephrology: AKI and thrombotic microangiopathies in pregnancy. *Clin J Am Soc Nephrol* 2012; 7: 2100–2106
306. Steegers EA *et al*. Pre-eclampsia. *Lancet* 2010; 376: 631–644
307. Hughes AK *et al*. Molecular basis for high renal cell sensitivity to the cytotoxic effects of shigatoxin-1: upregulation of globotriaosylceramide expression. *J Am Soc Nephrol* 2002; 13: 2239–2245
308. Obrig TG. Escherichia coli Shiga toxin mechanisms of action in renal disease. *Toxins (Basel)* 2010; 2: 2769–2794
309. Richards A, Kavanagh D. Pathogenesis of thrombotic microangiopathy: insights from animal models. *Nephron Exp Nephrol* 2009; 113: e97–e103
310. Pape L *et al*. Eculizumab in typical hemolytic uremic syndrome (HUS) with neurological involvement. *Medicine (Baltimore)* 2015; 94: e1000
311. Trachtman H *et al*. Renal and neurological involvement in typical Shiga toxin-associated HUS. *Nat Rev Nephrol* 2012; 8: 658–669
312. Banerjee R *et al*. Streptococcus pneumoniae-associated hemolytic uremic syndrome among children in North America. *Pediatr Infect Dis J* 2011; 30: 736–739
313. Lee CS *et al*. Invasive pneumococcal pneumonia is the major cause of paediatric haemolytic-uraemic syndrome in Taiwan. *Nephrology (Carlton)* 2012; 17: 48–52
314. Prestidge C, Wong W. Ten years of pneumococcal-associated haemolytic uraemic syndrome in New Zealand children. *J Paediatr Child Health* 2009; 45: 731–735
315. Waters AM *et al*. Hemolytic uremic syndrome associated with invasive pneumococcal disease: the United Kingdom experience. *J Pediatr* 2007; 151: 140–144
316. Blaum BS *et al*. Structural basis for sialic acid-mediated self-recognition by complement factor H. *Nat Chem Biol* 2015; 11: 77–82
317. Lopes da Silva R. Viral-associated thrombotic microangiopathies. *Hematol Oncol Stem Cell Ther* 2011; 4: 51–59
318. Segerer S *et al*. Cellular injury associated with renal thrombotic microangiopathy in human immunodeficiency virus-infected macaques. *J Am Soc Nephrol* 2002; 13: 370–378
319. Dhakal P, Bhatt VR. Is complement blockade an acceptable therapeutic strategy for hematopoietic cell transplant-associated thrombotic microangiopathy? *Bone Marrow Transplant* 2016
320. van den Born BJ *et al*. Microangiopathic hemolysis and renal failure in malignant hypertension. *Hypertension* 2005; 45: 246–251
321. van den Born BJ, Koopmans RP, van Montfrans GA. The renin-angiotensin system in malignant hypertension revisited: plasma renin activity, microangiopathic hemolysis, and renal failure in malignant hypertension. *Am J Hypertens* 2007; 20: 900–906
322. Amraoui F *et al*. Long-term renal outcome in patients with malignant hypertension: a retrospective cohort study. *BMC Nephrol* 2012; 13: 71
323. Van Laecke S, Van Biesen W. Severe hypertension with renal thrombotic microangiopathy: what happened to the usual suspect? *Kidney Int* 2017; 91: 1271–1274
324. Timmermans S *et al*. Patients with hypertension-associated thrombotic microangiopathy may present with complement abnormalities. *Kidney Int* 2017; 91: 1420–1425

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325. Shavit L, Reinus C, Slotki I. Severe renal failure and microangiopathic hemolysis induced by malignant hypertension–case series and review of literature. *Clin Nephrol* 2010; 73: 147–152
326. Al-Nouri ZL *et al*. Drug-induced thrombotic microangiopathy: a systematic review of published reports. *Blood* 2015; 125: 616–618
327. Kavanagh D *et al*. Type I interferon causes thrombotic microangiopathy by a dose-dependent toxic effect on the microvasculature. *Blood* 2016
328. Hunt D *et al*. Thrombotic microangiopathy associated with interferon beta. *N Engl J Med* 2014; 370: 1270–1271
329. Eremina V *et al*. VEGF inhibition and renal thrombotic microangiopathy. *N Engl J Med* 2008; 358: 1129–1136
330. Izzedine H, Perazella MA. Thrombotic microangiopathy, cancer, and cancer drugs. *Am J Kidney Dis* 2015; 66: 857–868
331. Antman KH *et al*. Microangiopathic hemolytic anemia and cancer: a review. *Medicine (Baltimore)* 1979; 58: 377–384
332. George JN. Systemic malignancies as a cause of unexpected microangiopathic hemolytic anemia and thrombocytopenia. *Oncology (Williston Park)* 2011; 25: 908–914
333. Amornsiripanitch N *et al*. Complement factor H autoantibodies are associated with early stage NSCLC. *Clin Cancer Res* 2010; 16: 3226–3231
334. Benz K *et al*. Thrombotic microangiopathy as a complication in a patient with focal segmental glomerulosclerosis. *Pediatr Nephrol* 2007; 22: 2125–2128
335. Bokenkamp A *et al*. Recurrent haemolytic uraemic syndrome in a boy with focal and segmental glomerulosclerosis. *Eur J Pediatr* 1992; 151: 791–792
336. Noris M, Mele C, Remuzzi G. Podocyte dysfunction in atypical haemolytic uraemic syndrome. *Nat Rev Nephrol* 2015; 11: 245–252
337. Caletti MG, Gallo G, Gianantonio CA. Development of focal segmental sclerosis and hyalinosis in hemolytic uremic syndrome. *Pediatr Nephrol* 1996; 10: 687–692
338. Chang A *et al*. A clinicopathologic study of thrombotic microangiopathy in the setting of IgA nephropathy. *Clin Nephrol* 2006; 66: 397–404
339. El Karoui K *et al*. A clinicopathologic study of thrombotic microangiopathy in IgA nephropathy. *J Am Soc Nephrol* 2012; 23: 137–148
340. Wuttke M, Kottgen A. Insights into kidney diseases from genome-wide association studies. *Nat Rev Nephrol* 2016; 12: 549–562
341. Chen SF *et al*. Clinicopathologic characteristics and outcomes of renal thrombotic microangiopathy in antineutrophil cytoplasmic autoantibody-associated glomerulonephritis. *Clin J Am Soc Nephrol* 2015; 10: 750–758
342. Dische FE, Culliford EJ, Parsons V. Haemolytic uraemic syndrome and idiopathic membranous glomerulonephritis. *Br Med J* 1978; 1: 1112–1113
343. Friedlander MA, Jacobs GH. Recurrent thrombotic thrombocytopenic purpura associated with membranous glomerulopathy. *Am J Kidney Dis* 1991; 17: 83–85
344. Wong EK *et al*. Characterization of a factor H mutation that perturbs the alternative pathway of complement in a family with membranoproliferative GN. *J Am Soc Nephrol* 2014; 25: 2425–2433
345. Malik TH *et al*. A hybrid CFHR3-1 gene causes familial C3 glomerulopathy. *J Am Soc Nephrol* 2012; 23: 1155–1160
346. Licht C *et al*. Deletion of Lys224 in regulatory domain 4 of Factor H reveals a novel pathomechanism for dense deposit disease (MPGN II). *Kidney Int* 2006; 70: 42–50
347. Goodship TH *et al*. Factor H autoantibodies in membranoproliferative glomerulonephritis. *Mol Immunol* 2012; 52: 200–206
348. Gale DP *et al*. Identification of a mutation in complement factor H-related protein 5 in patients of Cypriot origin with glomerulonephritis. *Lancet* 2010; 376: 794–801
349. Boyer O *et al*. Complement factor H deficiency and posttransplantation glomerulonephritis with isolated C3 deposits. *Am J Kidney Dis* 2008; 51: 671–677
350. Lorcy N *et al*. Three kidneys, two diseases, one antibody? *Nephrol Dial Transplant* 2011; 26: 3811–3813
351. Cooper M *et al*. Familial mesangio-capillary glomerulonephritis with initial presentation as haemolytic uraemic syndrome. *Nephrol Dial Transplant* 2004; 19: 230–233
352. Barrera-Vargas A *et al*. Renal thrombotic microangiopathy in proliferative lupus nephritis: risk factors and clinical outcomes: a case-control study. *J Clin Rheumatol* 2016; 22: 235–240
353. Barber C *et al*. Evaluation of clinical outcomes and renal vascular pathology among patients with lupus. *Clin J Am Soc Nephrol* 2012; 7: 757–764
354. Hernandez-Molina G *et al*. Thrombotic microangiopathy and poor renal outcome in lupus patients with or without antiphospholipid syndrome. *Clin Exp Rheumatol* 2015; 33: 503–508
355. Ghossein C, Varga J, Fenves AZ. Recent developments in the classification, evaluation, pathophysiology, and management of scleroderma renal crisis. *Curr Rheumatol Rep* 2016; 18: 5
356. National Institute for Health and Care Excellence. Highly specialised technologies: Eculizumab for treating atypical haemolytic uraemic syndrome. NICE 2015, p. 7