Post-transplant Thrombotic Microangiopathy

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Abstract

Thrombotic microangiopathy (TMA) is a challenging and serious complication of kidney transplantation that significantly affects graft and patient survival, occurring in 0.8%–15% of transplant recipients. TMA is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ injury due to endothelial damage and microthrombi formation in small vessels. However, clinical features can range from a renal-limited form, diagnosed only on a kidney biopsy, to full-blown systemic manifestations, which include neurologic, gastrointestinal, and cardiovascular injury. TMA can arise because of genetic or acquired defects such as in complement-mediated TMA or can occur in the context of other conditions like infections, autoimmune diseases, or immunosuppressive drugs, where complement activation may also play a role. Recurrent TMA after kidney transplant is almost always complement-mediated, although complement overactivation may also play a role in *de novo* post-transplant TMAs associated with ischemia-reperfusion injury, immunosuppressive drugs, antibody-mediated rejection, viral infections, and relapse of autoimmune diseases, such as antiphospholipid antibody syndrome. Differentiating between a complement-mediated process and one triggered by other factors is often challenging but critical to minimize allograft damage because the former is nonresponsive to supportive therapy, needs long-term anticomplement therapy, and has a high risk of recurrence. Given the central role of complement and effect of genetic defects on the risk of recurrence in many forms of post-transplant TMA, genetic testing for complement disorders is key for proper diagnosis and management. Given that complement activation may also play a role in a subset of TMAs associated with other conditions, prompt recognition and timely initiation of anticomplement therapy is equally important. In addition, TMA associated with noncomplement genes, often part of a broader syndromic process with distinct clinical features, has also been described. Early identification and treatment are essential to prevent graft failure and other severe complications. This review explores the pathophysiologic mechanisms underlying various post-transplant TMAs.

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Introduction

Thrombotic microangiopathy (TMA) is a complex clinical and pathologic condition characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end-organ injury occurring because of endothelial damage and microthrombi in small vessels.[1] AKI is a prominent feature because of vulnerability of the glomerular circulation to endothelial damage.

TMA can present with varying degrees of severity and incomplete features; for instance, thrombocytopenia may be mild or absent in some patients. Others may present as renal-limited TMA without significant hematologic abnormalities.[2,3] Extrarenal manifestations may be seen and include strokes, seizures, and involvement of the cardiovascular, neurologic, pulmonary, or gastrointestinal systems.[4]

TMA can arise from various etiologies. In some cases, complement is central to the pathogenesis of disease, while in others it may only be a modifier or an innocent bystander. In addition, interactions among complement, neutrophils, and coagulation pathways are all involved in the complex pathophysiology of TMA. If a genetic or acquired defect in a complement protein is identified as the driver of disease, then the TMA is classified as a complement-mediated TMA or atypical hemolytic uremic syndrome (aHUS) or complement-mediated aHUS (because various terminologies have been used in the literature).[5] If TMA occurs in the context of another disease process, such as infection, autoimmune disease, malignancy, or medication-induced, further investigation should be undertaken to define whether the associated disease process is a trigger or driver of disease because the associated conditions may also activate the complement system, and genetic abnormalities in the complement may be identified in a subset of patients with these conditions.[6] This classification is in line with ongoing efforts to adopt a more etiology-based or mechanism-based classification.[5]

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In solid organ transplantation, TMA occurs in up to 15% of patients, presenting significant challenges because of multiple potential triggers, including infections, medications, ischemia-reperfusion injury, and antibody-mediated rejection (AMR).[7] Post-transplant TMA can be either recurrent or *de novo*. Recurrent TMA is typically complement-mediated, while *de novo* TMA may be complement-mediated (where complement dysregulation due to genetic mutations is the driver of disease) or driven by factors such as ischemia-reperfusion injury, calcineurin inhibitor (CNI) use, or viral infections (where complement activation may still play a role but may not be driving the disease). Distinguishing between a complement-mediated TMA and one associated with other factors is critical to minimize allograft damage because the former may require long-term complement-directed therapy and is often nonresponsive to supportive therapy alone. TMA driven by associated factors may also benefit from short-term complement treatment but may not require lifelong treatment. However, the precise role of complement and duration of therapy in each of these associated conditions has not been fully elucidated and needs more research.[8] If not recognized and treated timely, complement-mediated TMA has a high rate of recurrence. Therefore, a systematic approach to diagnosis and management is essential for tailoring effective treatment and improving outcomes. This review aims to elucidate the pathophysiologic mechanisms of post-transplant TMAs and provide a framework for the diagnostic workup of TMA in kidney transplant recipients.

Pathogenic Mechanisms Underlying Various Post-transplant TMAs

Complement-Mediated TMA

Complement-mediated TMA, also known as aHUS, results from dysregulation of the complement system.[5,9,10] This system is a tightly regulated network of proteins crucial for maintaining homeostasis and defending against disease, forming a key part of both the innate and humoral immune systems. The complement system is constantly active at low levels guarding our intravascular space, but it can become excessively activated by various triggers, such as apoptotic debris, pathogens, antibody-antigen complexes, and ischemia-reperfusion injuries associated with organ transplantation.[9]

The complement system can be activated through three main pathways: the classical pathway, the lectin pathway, and the alternative pathway[11,12] (Figure 1). To prevent self-damage, the complement system is tightly regulated by several complement-regulating proteins, such as factor H (FH), factor I (FI), membrane cofactor protein (MCP; CD46), and complement receptor 1 (CD35)[9] (Figure 2).

Dysregulation of the complement system, especially the alternative pathway, can lead to uncontrolled inflammation and tissue injury, resulting in endothelial damage and TMA[12] (Figure 3). The most common etiology of a dysregulated complement system in complement-mediated TMA is a heterozygous, loss-of-function mutation in a regulator of the alternative pathway (such as in FH, FI, or MCP; CD46) that leads to haploinsufficiency.[13,14] In these cases, the protein is generally not synthesized and/or not secreted into the bloodstream or secreted in normal amounts but is dysfunctional. In some cases, gain-of-function mutations in complement activators such as C3 or factor B may be found. Approximately, 10% of affected patients may carry more than one variant.

A majority of *CFH* mutations are located in C-terminal complement control repeats (CCPs) 19 and 20 and affect the binding to heparin, C3b, and endothelial cells, leading to inadequate control of complement activation at the glomerular endothelium.[15] Mutations in the *N*-terminal CCPs 1–4 lead to defective control of the alternative pathway both in the fluid phase and on cell surfaces. *CFI* mutations are found in both the catalytic serine protease domain (that affect cofactor activity) and the noncatalytic heavy chain domains.[16] Many of the mutations in the heavy chain domains cluster around calcium ions and are speculated to negatively affect calcium binding to FI, resulting in a structurally defective protein that either fails to be synthesized or is likely to be misfolded. Mutations in MCP are often found in the extracellular four CCP domains responsible for C3b and C4b binding and result in either a quantitative defect detected on flow cytometry or a qualitative defect resulting in a dysfunctional protein. Gain-of-function mutations in *C3* and *CFB* often lead to increased convertase formation and/or one that is resistant to decay by FH or decay-accelerating factor (DAF, CD55), thereby leading to increased complement deposition on endothelial cells.[17,18]

Complement-mediated TMA is characterized by incomplete penetrance, meaning not all family members with the same variant will manifest the disease; an environmental trigger is often required. Acquired deficiencies, such as FH autoantibodies, occur in about 5%–10% of patients, often associated with genetic predispositions, such as homozygous deletions in CFHR1 and CFHR3.[19,20]

Historically, transplantation was considered high risk in patients with complement-mediated TMA because of the potential for disease recurrence and early allograft loss. However, advances in the understanding of disease pathogenesis and availability of anticomplement therapies have allowed for successful kidney transplantation. A thorough pretransplant and post-transplant evaluation, including genetic testing, to predict and manage post-transplant TMA risk and prevent graft loss is key to successful kidney transplantation (Figure 4).[21]

Drug-Induced TMA

Drug-induced TMA can occur because of an immune-mediated process or direct toxicity.[22,23] In some cases, complement activation or ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) deficiency may play a role.

Immune-mediated TMA occurs because of reactive antibodies against a drug or its metabolites, which interact with endothelial cells, platelets, or circulating factors. This is suspected when severe systemic symptoms, typically AKI with anuria, emerge suddenly, usually within days (often <21 days) or hours, after drug exposure.

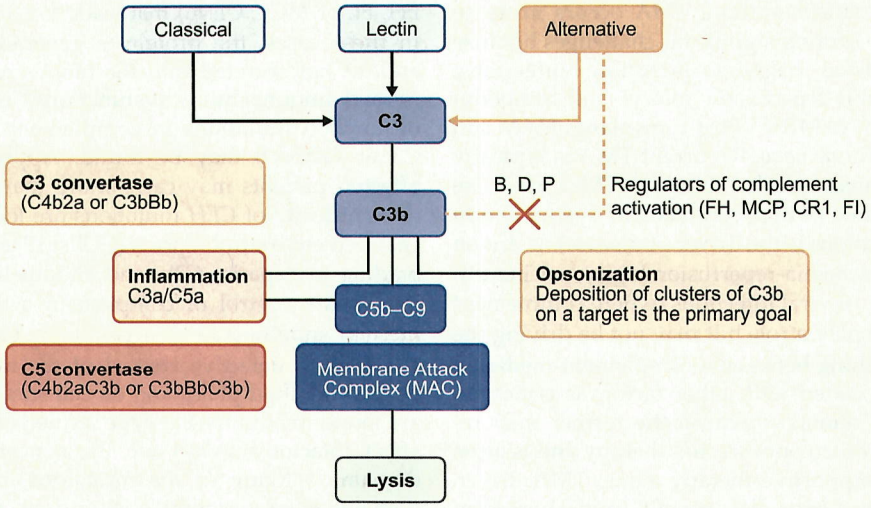

Figure 1. Pathways of complement activation. The complement system can be activated through three main pathways: the classical pathway, the lectin pathway, and the alternative pathway. The classical pathway is triggered when antibodies bind to foreign antigens, while the lectin pathway is activated when lectins, such MBL present on immune cells, bind to carbohydrate moieties on pathogens. The alternative pathway, which is constitutively active, can deposit on pathogens indiscriminately without prior exposure or memory. This pathway continuously generates small amounts of autoactivated C3 (C3[H_2O]) through a process known as C3 tickover. All three pathways aim to form C3 convertase, which cleaves the complement component C3 into C3a (an anaphylatoxin that recruits and activates effector cells) and C3b (which deposits on the cell surface). When C3b binds to a microbe or foreign debris, the system can amplify rapidly by engaging proteases like B and D, along with properdin, to create the powerful alternative pathway C3 convertase. This pathway includes an efficient feedback loop (tan dotted line) that generates large amounts of C3b for opsonization, leading to the recognition, engulfment, and destruction of pathogens by phagocytes. The addition of C3b to C3 convertase in any pathway forms C5 convertase, which activates the terminal complement pathway. Here, two types of C5 convertases (C4b2aC3b and C3bBbC3b) cleave C5 into C5a (an anaphylatoxin) and C5b, leading to the formation of the MAC (C5b-9). The MAC disrupts membrane bilayers, forming pores that cause cell swelling and lysis, while sublytic MAC may induce intracellular signaling and cell activation. B, factor B; CR1, complement receptor 1; D, factor D; FH, factor H; FI, factor I; MAC, membrane attack complex; MBL, mannose-binding lectin; MCP, membrane cofactor protein; P, properdin.

Direct toxicity-mediated TMA does not have a well-defined onset time after drug exposure. It is believed to result from a cumulative effect of the drug that directly damages the endothelium and disrupts various pathways, such as the vascular endothelial growth factor (VEGF) or mammalian target of rapamycin (mTOR). This damage may also stem from deregulation of transcription factors, such as NF kappa-B, which leads to increased production of proinflammatory and prothrombotic mediators, heightened oxidative stress, reduced nitric oxide levels, and decreased VEGF production, all contributing to widespread endothelial damage.

The anti-VEGF mAb bevacizumab was initially linked to TMA,[24] and this association has been extended to other

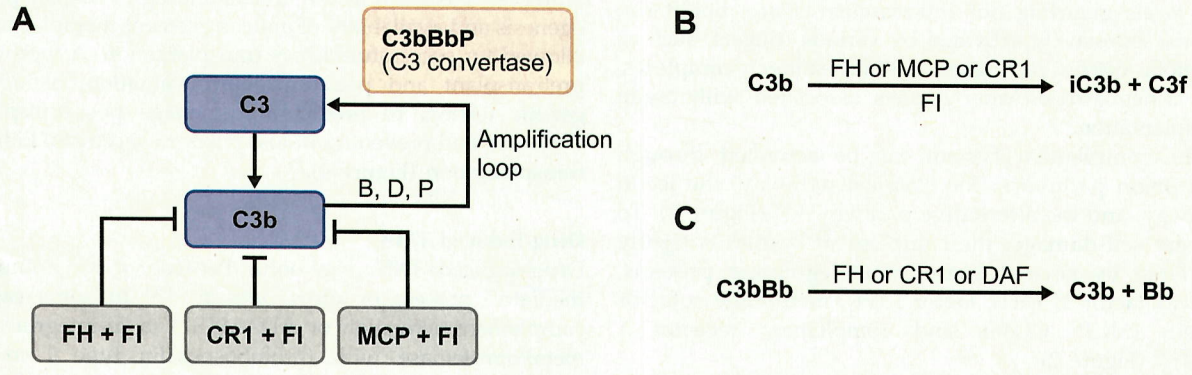

Figure 2. Regulation of alternative pathway. (A) Regulation of complement pathway is achieved by key regulators, FH, FI, MCP, and CR1, that interrupt the feedback loop. FH has both fluid-phase and cell-surface regulatory capacity. These functions are performed using binding sites for C3b (CCPs 1–4 and 19–20) as well as for polyanions, such as glycosaminoglycans (CCPs 6–8 and 19–20). Regulation occurs through two main mechanisms: cofactor activity and decay-accelerating activity (B). In cofactor activity, complement regulators like FH, along with serine protease FI, cleave complement fragments C3b and C4b. (C) In decay-accelerating activity, these regulators promote the dissociation of the catalytic domains of convertases, preventing the activation of the alternative pathway's feedback loop. CCP, complement control repeat; DAF, decay-accelerating factor.

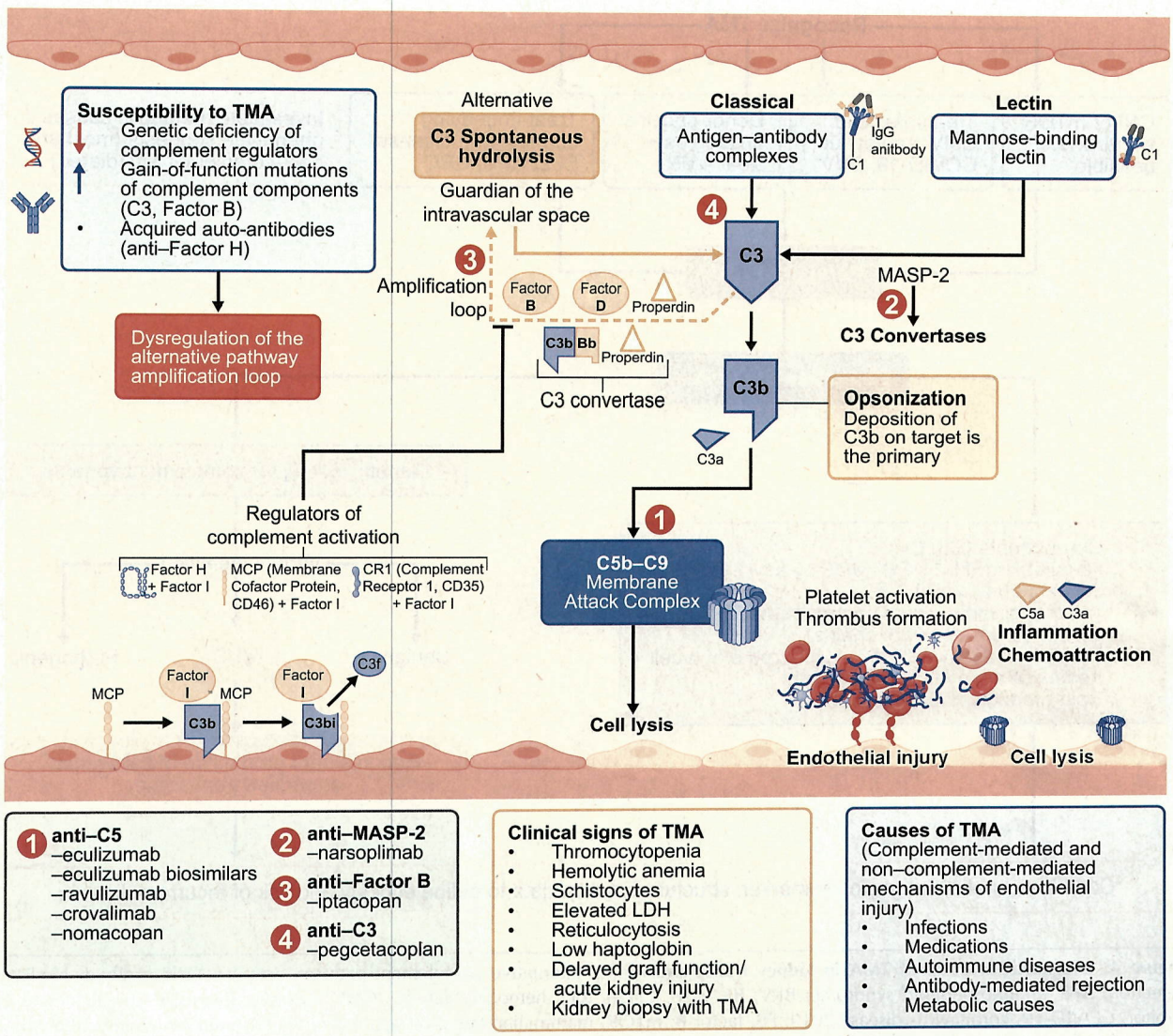

Figure 3. Etiopathogenesis of complement-mediated TMA. Loss-of-function mutations in complement regulators or gain-of-function mutations in components such as C3 or FB can lead to a dysregulated complement system and predispose to complement-mediated TMA. LDH, lactate dehydrogenase; MASP-2, Mannan-binding lectin serine protease 2; TMA, thrombotic microangiopathy. Figure made using BioRender.

VEGF inhibitors.[25] Causality was confirmed in an inducible podocyte-specific VEGF receptor a deletion mouse model. Similarly a whole-body knockout of the receptor-VEGF receptor 2 or vascular endothelial growth factor receptor 2 also developed a TMA.[26] VEGF is pivotal in maintaining the homeostasis of endothelial-podocyte complex. Inhibition of VEGF leads to altered downstream signaling pathways, which result in hypertension, proteinuria, and a TMA.[27] It has been hypothesized that at least some of this effect may be due to impaired local FH production with increased C3 deposition in mouse models.[28] Tyrosine kinase inhibitors inhibit many intracellular signaling pathways, including those of VEGF-VEGF receptor pathway, and these too have been associated with a TMA, albeit more commonly display a minimal change-like disease.[29]

Proteasome inhibitors such as bortezomib, which have been used to treat AMR, are also associated with drug-induced TMA through a toxic, dose-dependent mechanism.[30] These drugs exhibit antiangiogenic activity through decreased proliferation of endothelial cells, secretion of interleukin-6, and blockade of VEGF, resulting in endothelial injury and TMA.

Chronic high-dose IFN-β therapy has been causally associated with TMA.[31] In mouse models of type 1 IFN overexpression, a direct dose-dependent toxic effect on endothelium has been demonstrated.[32] In keeping with this, monogenic type 1 interferonopathies, such as biallelic mutations in *STAT2* with unrestrained IFNα/β activity, have been demonstrated to cause biopsy-proven TMA.[33] SLE is another condition with evidence of IFN dysregulation and features of TMA commonly seen on kidney biopsy.[34,35]

In the context of kidney transplantation, TMA has been reported after use of mTOR inhibitors or CNI.[36–38] The underlying mechanism involves arteriolar vasoconstriction and endothelial injury, which leads to release of vWf multimers. These multimers overwhelm ADAMTS13,

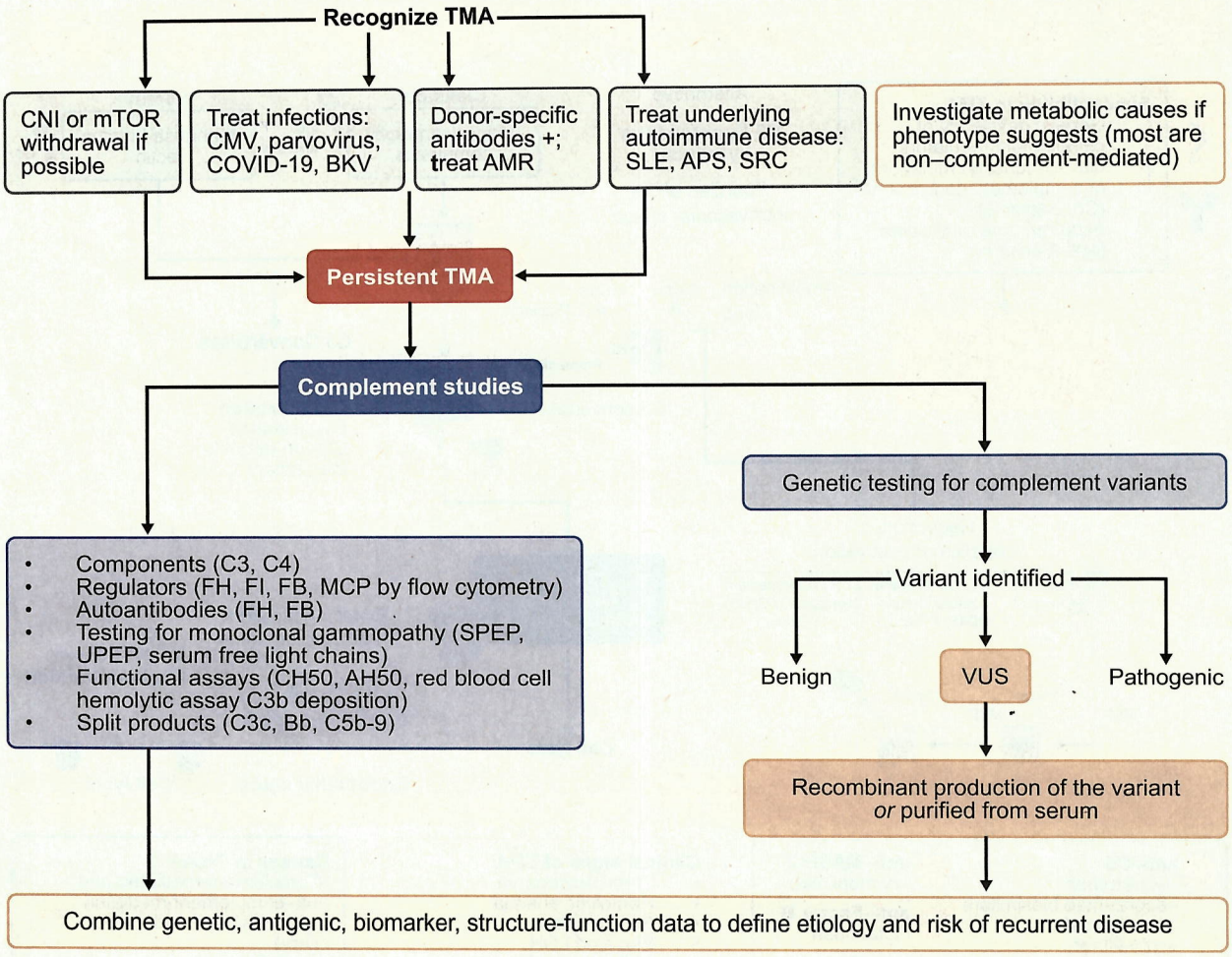

Figure 4. Diagnostic workup of TMA in kidney transplant. AH50, alternative complement pathway activity; AMR, antibody-mediated rejection; APS, antiphospholipid syndrome; BKV, BK virus; CH50, total hemolytic activity; CMV, cytomegalovirus; CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; FB, factor B; mTOR, mammalian target of rapamycin; SPEP, serum protein electrophoresis; SRC, scleroderma renal crisis; UPEP, urine protein electrophoresis; VUS, variant of uncertain significance.

causing platelet aggregation and complement activation because of interplay between complement and coagulation pathways.[23] In our experience, patients with CNI-associated TMA after kidney transplant are older and often experience longer cold ischemia times, suggesting that CNIs may exacerbate the risk of ischemia-reperfusion injury in the early post-transplant period.[21] More recently, complement dysregulation has been implicated in CNI therapy, specifically cyclosporine.[39] Cyclosporine may cause shedding of heparan sulfate side chains from the endothelial cell glycocalyx, reducing FH binding and cofactor activity. This mechanism may account for reports of drug-induced TMA responding to eculizumab, although most patients lack genetic variants.[40] Although these reports may indicate publication bias, because clinicians are more likely to report successful use of a treatment as opposed to therapeutic failures, a comprehensive evaluation, including ADAMTS13 and genetic testing, should be performed in cases unresponsive to holding the medication. CNI-sparing drugs such as belatacept that allow the minimization or discontinuation of CNIs and mTORs may be considered in select patients. However, anticomplement therapy may be considered for patients with worsening kidney injury or those considered at high risk of rejection if CNI is stopped.

Infection-Associated TMA

A variety of infections can induce TMA, with Shiga toxin–producing *Escherichia coli* being a prominent example.[41] Shiga toxin translocates through the intestinal epithelium and is believed to bind to leukocytes and circulate to the kidneys. The Shiga toxin then binds to and is internalized through the glycosphingolipid receptor (Gb3) on microvascular endothelial cells. The catalytic subunit A of the Shiga toxin/Gb3 complex is cleaved by the protease furin to release a fragment that translocates to the cytoplasm. This fragment inhibits ribosomal function and protein synthesis, leading to cell death; signaling pathways are also activated, inducing an inflammatory response. This cascade increases tissue factor and vWF levels, further contributing to the prothrombotic state.

Other mechanisms of infection-associated TMA include platelet activation, thrombin generation, and production of ADAMTS13 inhibitors. ADAMTS13 deficiency has been

particularly noted with influenza and HIV infections, although ADAMTS13-negative cases have also been detected where influenza unmasks an underlying complement defect.[42,43] In pneumococcal and influenza infections, neuraminidase production cleaves sialic residues from red blood cells and platelets, decreasing FH binding and disrupting complement regulation, which contributes to endothelial damage.[42,44] The pathogenesis of pneumococcal-associated TMA has also been attributed to the process of pneumococcal neuraminidase exposing the usually cryptic Thomsen-Friedenreich antigen (T-antigen) on red blood cells and glomeruli to which preformed IgM antibodies can bind, resulting in endothelial damage and TMA.[45]

Kidney transplant patients are at heightened risk for infections due to immunosuppression. Infections can induce TMA in the allograft in the presence of other factors that contribute to endothelial injury, such as CNIs, high panel-reactive antibody levels, and ischemia-reperfusion injury. These triggers enhance the ability of viruses and other infectious agents to induce microthrombi on damaged kidney microvasculature.

Notable pathogens include cytomegalovirus (CMV), parvovirus B19, and severe acute respiratory syndrome coronavirus 2.[46–48] Coronaviruses can activate multiple complement pathways.[48] The resultant complement activation, along with dysregulated neutrophilia, endothelial injury, and hypercoagulability, may lead to TMA. Some patients with coronavirus disease 2019 may also have a genetic predisposition related to complement dysregulation, just as with other infections.

For parvovirus B19, TMA is believed to result from endothelial damage due to circulating immune complexes or direct invasion of the endothelium.[46] The virus's tropism for endothelial cells is likely because of the presence of the P antigen (the receptor for B19) on these cells.

CMV has also been linked to post-transplant TMA.[47] CMV can cause direct endothelial damage and platelet adhesion by inducing the expression of adhesion molecules and releasing vWF. This endothelial damage can lead to microvascular thrombosis, explaining the association between CMV and TMA. However, quantitative CMV-PCR levels do not always correlate with kidney allograft pathology or the detection of CMV inclusions in kidney tissue. In addition, CMV can activate the classical complement pathway through C1q binding to infected cells, thereby unmasking underlying defects in the complement system, leading to membrane attack complex (MAC) formation and cellular lysis. Nonetheless, CMV evades the complement system by incorporating complement regulatory proteins (CD55 and CD59) into its virion.

BK hemorrhagic cystitis has been described as a risk factor for hematopoietic cell transplantation–associated TMA but sparingly reported as cause for TMA after a kidney transplant.[49–51] One case of a 52-year-old demonstrated widespread endothelial infection by a BK-related virus leading to microthrombotic events that caused tissue ischemia.[49] Although small vessels of the myocardium and skeletal muscle were chief targets of the viral infection, kidney-allograft biopsy also showed viral proteins in endothelial cells, along with endothelial injury.

AMR and TMA

AMR is considered a potential confounder for TMA and is associated with a high risk of premature graft loss. The TMA Banff working group has highlighted this as an area of controversy, noting the difficulty in distinguishing AMR from TMA.[52] It remains unclear whether AMR should be included in the differential diagnosis of TMA or whether it actually causes a TMA.

Concomitant AMR is believed to be a major driver of kidney failure, with aberrant humoral alloimmune response being a critical risk factor. Various mechanisms for antibody-mediated endothelial injury have been proposed.[53–56] The binding of donor-specific antibodies to endothelial antigens, such as HLA molecules, initiates complement activation, culminating in the formation of MACs. These complexes compromise endothelial cell membranes, inducing lysis and disrupting vascular integrity. Donor-specific antibody engagement also induces endothelial cell expression of adhesion molecules, including P-selectin, facilitating leukocyte recruitment. This promotes the adherence and transmigration of neutrophils and macrophages into graft tissues, exacerbating inflammation and tissue damage. Endothelial cell activation, triggered by antibody binding, leads to the secretion of proinflammatory cytokines, further amplifying immune responses and exacerbating tissue injury. In addition, antibodies exert direct cytotoxic effects by disrupting receptor signaling, inducing apoptosis, and impairing cellular function. Finally, antibody-mediated endothelial damage predisposes to platelet aggregation and microvascular thrombosis, impeding blood flow and tissue oxygenation within the graft, thereby contributing to TMA and graft failure.

Transplant glomerulopathy may represent a chronic, smoldering form of TMA. The use of anticomplement therapy in AMR and TMA has met with mixed success on the basis of several case series, likely because of both complement-mediated (including upstream complement activation) and non–complement-mediated mechanisms.[57–60]

Differentiating between an early AMR-associated TMA from drug-induced TMA or other forms of renal-limited TMAs may be challenging. There are no published guidelines or evidence on how to distinguish between these conditions and/or treat them. Therefore, recommendations are based on expert opinion. In such situations, treating the underlying rejection should be prioritized using center-specific protocols. Anticomplement therapy can be considered in addition to the standard immunosuppression and treating the associated trigger, without necessarily stopping the CNI. Alternatively, CNI-sparing drugs such as belatacept may be used as maintenance immunosuppression.

Metabolic Causes of a TMA

Inborn Error of B12 Metabolism

Methylmalonic aciduria and homocystinuria, cobalamin C type (MMACHC), is an inborn error of intracellular cobalamin (vitamin B12) metabolism linked to TMA, characterized by defects in two essential cobalamin coenzymes: methylcobalamin and adenosylcobalamin.[61] Biallelic loss-of-function mutations in the *MMACHC* gene result in the accumulation of methylmalonic acid

and homocysteine, alongside decreased methionine synthesis. Elevated homocysteine levels are speculated to cause endothelial toxicity, while impaired nitric oxide–mediated inhibition of platelet aggregation and hypomethioninemia may also play a role in small vessel injury.[62–64] Treatment includes parenteral hydroxocobalamin and betaine because C5 inhibitory therapies, such as eculizumab, have not demonstrated benefit.[65] Literature on MMACHC-mediated TMA after kidney transplantation is sparse, but there is a report of recurrent disease in the absence of hydroxocobalamin therapy, suggesting that circulating factors such as hyperhomocysteinemia or hypomethioninemia may be involved.[62]

Other inborn errors of metabolism associated with TMA include mutations in *MTR* and *MTHFD1*, although cases are rare and data are limited.[66–68]

Diacylglycerol Kinase Epsilon Mutations

Autosomal recessive mutations in diacylglycerol kinase epsilon (*DGKE*) can cause pleiotropic effects, leading to either TMA or mesangioproliferative GN. The incidence of DGKE-mediated TMA is extremely rare, at approximately 0.009 cases per million per year, and it usually presents within the first 2 years of life.[68]

DGKE is a lipid kinase that phosphorylates arachidonic acid–containing diacylglycerol. A deficiency in DGKE leads to reduction in phosphatidylinositol 4,5-bisphosphate, which impairs downstream signaling pathways of the VEGF-receptor 2. This disruption affects the induction of cyclooxygenase-2 and production of PG E2, contributing to the procoagulant state observed in TMA and causing alterations to the glomerular filtration barrier.[69]

Owing to this underlying pathophysiology, eculizumab is unlikely to be effective in DGKE-mediated TMA, and instances of disease relapse while on eculizumab support this.[70] The occurrence of *DGKE* mutations alongside rare variants in complement genes have only rarely been reported.[71] Management of DGKE-mediated TMA remains supportive.

Notably, five cases of DGKE-mediated TMA have undergone kidney transplantation, with no recurrence reported. This suggests that kidney transplantation may correct the underlying intracellular signaling defect and prevent recurrent disease.[70,72]

EXOSC3 Mutations

Biallelic pathogenic mutations in EXOSC3 have been linked to TMA.[68] This form of TMA is part of a syndrome associated with pontocerebellar hypoplasia. EXOSC3 is an essential subunit of the RNA exosome, a multiprotein complex responsible for RNA processing.[73] Without EXOSC3, the RNA exosome cannot properly process RNA, leading to the accumulation of multiple RNA species.[74] This accumulation disrupts ribosomal function and induces cellular stress.[75]

The precise mechanism by which ribosomal dysfunction leads to TMA is not well understood. However, the lack of response to eculizumab suggests that the TMA is not related to the terminal complement pathway activity. The severe neurologic manifestations associated with EXOSC3 mutations are often fatal at a young age, and there are no documented cases of kidney transplantation for this condition.

TSEN2 Mutations

TSEN2-mediated TMA is a childhood syndrome characterized by microcephaly, craniofacial malformations, and both growth and intellectual retardation.[68,76] TSEN2 is a subunit of the transfer RNA (tRNA) splicing endonuclease. While the exact mechanism underlying the disease is not fully understood, it is believed that recessive mutations in TSEN2 disrupt the composition of mature tRNAs essential for protein synthesis and may lead to the accumulation of pre-tRNAs, causing cellular stress.

Eculizumab has been used in several reported cases of TSEN2-mediated TMA, but all patients eventually progressed to kidney failure. Notably, one case involved a child who relapsed while on eculizumab, indicating that the disease mechanism might be independent of terminal complement pathway activation.

Kidney transplantation has been performed in two individuals with TSEN2-mediated TMA. In one case, TMA developed on the third day after transplantation and was treated with eculizumab.[76] Conversely, in the other case where eculizumab was not administered at the time of transplantation, no recurrence was observed.

Autoimmune Disease–Associated TMA

SLE

SLE is a multisystem disorder characterized by autoantibodies against various nuclear antigens, such as DNA and ribonucleoproteins. This autoimmune response leads to complement activation, inflammation, and tissue damage. TMA in SLE can arise through several mechanisms.[77] Notably, deficiencies or low gene copy numbers of early complement pathway components, such as homozygous mutations in C1q or C4 deficiencies because of low gene copy numbers, are strong genetic risk factors for SLE.[78] These factors are potential mechanisms for the generation of autoantibodies that bind to host proteins or deposit within tissues as a component of immune complexes and further trigger activation of the complement system.[79] In addition, genetic variants or polymorphisms in FH, FI, and factor B, along with FH autoantibodies and deletions in FH-related protein 1, have been reported in a small number of cases in TMA associated with SLE.[80,81] These findings suggest that genetic predispositions, combined with ongoing complement activation in SLE, contribute to TMA development.

It may seem paradoxical that both a deficiency of the complement system and its excessive activation are both associated with the pathophysiology of SLE. This can be reconciled by understanding that excess apoptotic debris from complement component deficiencies may provide nuclear autoantigens, leading to autoantibody formation. The resulting immune complexes are not efficiently cleared, triggering proinflammatory cytokine production and IFN-α secretion by plasmacytoid dendritic cells. Elevated IFN-α levels can stimulate the production of neutrophil extracellular traps (NETs), which are often associated with lupus nephritis and TMA.[82]

Table 1. Novel complement therapies in the pipeline

Name of the Drug	Target/Route	Mechanism of Action	ClinicalTrials.gov
Eculizumab	Anti-C5 humanized mAb; IV	Binds C5, inhibits cleavage of C5 and MAC generation	Approved; NCT03518203 (HSCT-TMA)
Ravulizumab	Anti-C5 humanized mAb. Engineered from eculizumab with extended half-life; IV	Binds C5, inhibits cleavage of C5 and MAC generation	Approved; NCT04543591 (adult HSCT-TMA), NCT04557735 (pediatric HSCT-TMA), NCT04570397 (COVID-19)
Iptacopan	Small molecule; oral	Factor B inhibitor preventing C3 and C5 convertase formation	Phase 3; NCT04889430 (adult aHUS); NCT05795140 (aHUS)
Crovalimab	SMART antibody; SC	Binds to the C5 β-chain and prevents cleavage by the C5 convertase; inhibits C5b6 deposition	Phase 3; NCT04861259 (adult aHUS), NCT04958265 (pediatric aHUS)
Narsoplimab OMS721	Humanized mAb; IV/SC	MASP-2 inhibitor	Phase 3; NCT03205995 (aHUS); NCT05855083 (pediatric HSCT-TMA)
Nomacopan	Small protein; SC	Inhibits terminal complement activation by binding to C5 and preventing C5a release and C5b-9 formation; inhibits leukotriene B4	Phase 3; NCT04784455 (pediatric HSCT-TMA)
Pegcetacoplan	Peptides conjugated to polyethylene glycol; SC	Binds C3 and C3b; inhibits C3 and C5 convertases of the classical, lectin, and alternative pathways	Phase 2; NCT05148299 (HSCT-TMA)

Ravulizumab has been engineered from eculizumab by changing four amino acids. This change preserves the binding of ravulizumab to C5 in serum but allows it to dissociate from C5 in the acidified endosome (pH 6.0). Additionally, these amino acid alterations also result in an increased efficiency of neonatal Fc receptor–mediated recycling of ravulizumab, thereby leading to an increased $t_{1/2}$ of approximately 52 days compared with approximately 11 days for eculizumab. Therefore, ravulizumab can be administered every 8 weeks versus eculizumab, which is given every 2 weeks. aHUS, atypical hemolytic uremic syndrome; COVID-19, coronavirus disease 2019; HSCT, hematopoietic stem cell transplant; IV, intravenous; MAC, membrane attack complex; MASP-2, Mannan-binding lectin serine protease 2; SC, subcutaneous; SMART, sequential mAb recycling technology; TMA, thrombotic microangiopathy.

The presence of TMA in patients with lupus nephritis is associated with a poor prognosis, with 80% of patients developing kidney failure within 5 years of diagnosis.[77]

Case reports of patients with kidney failure due to SLE who developed TMA after kidney transplantation have been described. In one report, a 27-year-old woman with SLE and kidney failure with documented TMA received a living-related kidney transplant and experienced a TMA recurrence.[83] She was initially treated with plasma exchange without success. However, she responded to eculizumab, which restored her kidney function. In two other cases, patients with SLE did not have TMA in their native kidneys but developed an early and aggressive form of the disease after kidney transplant. Genetic testing revealed mutations in FH in both these patients, indicating that the TMA was likely complement-mediated.[84]

Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is characterized by the presence of antiphospholipid antibodies that bind to endothelial cells and trigger thrombosis. This condition can affect nearly every organ system, leading to significant morbidity, including stroke, skin ulcerations, nephropathy, seizures, and cognitive decline.[85] Approximately 1% of patients with APS may develop catastrophic APS (CAPS), a severe form of the disease that often proves fatal.[86] CAPS is marked by small vessel thrombosis affecting three or more organs within a week.

In APS, antiphospholipid antibodies activate the complement cascade, causing cellular injury and promoting coagulation through various mechanisms.[87–89] Elevated levels of the MAC have been observed in patients with CAPS. Clinical improvement after eculizumab treatment has been associated with decreased MAC levels and normalization of serum C3 and C4, supporting the role of complement in APS. However, the precise mechanisms of complement activation in APS and its relationship to vascular events are not yet fully understood. In addition, NETs have been implicated in APS pathogenesis, potentially exacerbating thrombosis by activating the coagulation cascade and inhibiting anticoagulant factors.[90]

Kidney transplantation in patients with antiphospholipid antibodies has historically proven challenging because of higher risk for thrombosis and allograft failure. In some cases, TMA may be the sole manifestation of APS, and it is not fully understood why certain patients develop TMA rather than macrovascular thrombosis. While the standard treatment for APS involves anticoagulation and immunosuppression, variability in treatment effectiveness and recurring thrombosis indicate that anticomplement therapy may offer benefits for both prevention and treatment of TMA after kidney transplantation. [91–94]

Scleroderma Renal Crisis

Scleroderma renal crisis (SRC) is a severe complication of systemic sclerosis, marked by a sudden onset of hypertension, TMA, and AKI. The pathogenesis of SRC involves vascular damage, autoantibody production, and fibroblast dysfunction, with the complement system also playing a role. Impairment of the vascular endothelial

function can result in an increase in ultra-large vWF multimers beyond the amount that can be efficiently cleaved by ADAMTS13. Reports of renal deposition of complement components C1q, C4d, and C3b, along with reduced levels of C3 and factor B, suggest involvement of both the classical and alternative pathways of complement.[95–97] Emerging evidence indicates that, akin to APS and SLE, microparticles released from activated platelets may trigger neutrophil activation and NETosis, leading to high levels of NETs in patients with scleroderma.[98,99] TMA associated with SRC has been reported in a limited number of cases after transplant.[100] Early detection and aggressive treatment are essential to prevent loss of allograft and other complications. Efficacy of angiotensin-converting enzyme inhibitors on SRC survival has been provided by various retrospective and prospective studies.[101] Complement inhibitors could also offer a promising treatment for refractory TMA in SRC by directly targeting the underlying causes of the crisis. [92,101]

New Complement Therapies

There are two C5 inhibitors that are currently available and US Food and Drug Administration–approved for complement-mediated TMA after kidney transplant: eculizumab and ravulizumab[102,103] (Table 1). Biosimilars to eculizumab are also now available for use in some countries.[104,105] Several other drugs are in development (Table 1). Prospective, randomized controlled trials are required to investigate the utility of anticomplement therapies in TMA, to provide insights on which patients to treat and for how long. If patients are identified to have pathogenic complement mutations at the time of pretransplant evaluation or have lost a prior allograft to TMA (even in the absence of a genetic mutation), prophylactic anticomplement therapy may be indicated to avoid risk of recurrent TMA and allograft thrombosis and results in excellent graft survival.[106,107] These patients also need longer-term (sometime lifelong) treatment post-transplant. Retrospective studies suggest that eculizumab rescue therapy might be an alternative, with maintained graft function, provided treatment is started within 7 days after TMA onset[108] Patients who develop post-transplant TMA because of associated triggers/conditions, and where genetics are not indicative of a pathogenic mutation, may also be treated with anticomplement therapy, but the duration of treatment depends on individual risk factors.

The predominant concern with using anticomplement therapy is life-threatening infections with encapsulated organisms, such as *Neisseria meningitidis* (due to blockage of the terminal complement pathway). Meningococcal vaccination must be administered to everyone undergoing treatment with anticomplement drugs. Particularly relevant to transplant is that when anticomplement therapy needs to be initiated urgently, appropriate antibiotics should be used for at least 14 days after the meningococcal vaccine. This practice varies among transplant centers, with some opting to continue antibiotics as long as the patient is on anticomplement therapy because of the concern that immunosuppressed patients may not mount an adequate response to vaccination. More data are needed to clarify and establish a uniform best practice for prophylactic antibiotic use in the transplant population. Nevertheless, the future holds much promise for the further delineation of complement disease associations and for novel targeted therapeutic agents.

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Clinical Nephrology Insights

Strategies to Prevent Hemodialysis Catheter Dysfunction

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Abstract

Millions of patients with kidney failure rely on hemodialysis central venous catheters (CVCs) for their life-sustaining dialysis treatments. CVC dysfunction necessitates removal of up to 20% of CVCs and is an important problem for patients with kidney failure. Thrombosis and fibrin sheath formation are the most common mechanisms of CVC dysfunction beyond the first week after insertion. Factors such as female sex, left-sided CVC placement, and prior CVC dysfunction are associated with a higher risk of dysfunction. Patient-specific factors contribute substantially to variation in the number of CVC dysfunction events. Weekly thrombolytic locks have been shown to improve CVC blood flow rates, prevent infection, and reduce dysfunction requiring removal. However, routine administration may not be cost-effective in hemodialysis units with low infection rates, and targeted use among patients with established CVC dysfunction has not been studied. Concentrated heparin lock (*e.g.*, 5000 versus 1000 international unit/ml) has been associated with lower requirements for therapeutic CVC thrombolysis but greater systemic bleeding risks and costs. Citrate 4% was noninferior to standard heparin locks to prevent thrombosis, may cause less bleeding, and is less costly in some countries. Tunneled CVCs with a symmetrical tip have been associated with a lower risk of CVC dysfunction compared with those with a step tip. Multifaceted CVC care interventions can reduce the incidence of dysfunctional CVCs by 33% compared with usual care. Future research to identify patients at high risk of CVC dysfunction will inform individualized vascular access plans, targeted use of preventive strategies, and enrollment criteria for future clinical trials.

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Introduction

Hemodialysis is a life-sustaining treatment used by more than 3 million people with kidney failure worldwide and is projected to rise over the next two decades.[1] Maintaining a safe and reliable means of accessing the circulatory system for adequate hemodialysis is a perpetual challenge. Hemodialysis central venous catheters (CVCs) are used by most patients commencing long-term hemodialysis in the United Kingdom (60%), Australia (61%), New Zealand (80%), Canada (80%), and the United States (85%).[2–5] Their use is also common among prevalent patients receiving long-term hemodialysis in Australia (20%), the United States (25%), Canada (45%), New Zealand (45%), and Ireland (54%).[2,5–7] The incidence and prevalence of CVC use have increased among patients receiving incident and prevalent maintenance hemodialysis in some countries over the past decade (Figure 1).[2,5,8–10] The prevalence also varies widely among the long-term hemodialysis population globally. For example, in Japan, only 2% of prevalent patients receive long-term hemodialysis through a CVC, which highlights the complex array of individual, geographical, institutional, and sociocultural factors that ultimately influence an individual's modality of vascular access.[11,12]

Indications for Hemodialysis Catheters

CVCs are a reality for most patients who receive long-term hemodialysis, either temporarily while awaiting arteriovenous (AV) access (AV fistula or AV graft) creation or maturation, situational repair of alternative KRT modalities, or anticipated transplantation, or as a long-term option for vascular access. Over the past two decades, the preferred type of long-term hemodialysis access has shifted from a "fistula first, catheter last" paradigm to a more patient-centered approach that prioritizes vascular access options that are most appropriate to an individual's specific circumstances. This has led to the mantra of establishing "the right access for the right patient at the right time for the right reasons."[13] Contributing to this shift is the growing recognition that preferencing fistulas over catheters was premised on

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