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Diagnosis and treatment of complement-mediated thrombotic microangiopathies: consensus of the Genetic Diseases Committee of the Chilean Society of Nephrology

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Abstract

Thrombotic microangiopathy (TMA) is a clinical-pathological syndrome defined by microangiopathic hemolytic anemia, thrombocytopenia, and organ dysfunction, commonly affecting the kidneys. The etiologies are diverse and include genetic disorders (affecting complement proteins or other pathways, such as cobalamin metabolism), infections, autoimmune diseases, malignancies, transplantation, pregnancy, and drugs. Differentiating these causes is essential, as treatment strategies and prognoses vary widely. This consensus document, developed by a multidisciplinary group of clinicians and geneticists, provides a structured approach for evaluating TMA, with particular focus on complement-mediated TMA (C-TMA). C-TMA should be considered when TMA features persist after resolution or exclusion of secondary causes. Diagnostic confirmation relies on clinical judgment, histopathology, and a favorable response to C5 complement inhibitors, such as eculizumab or ravulizumab. This therapeutic response is considered both diagnostic and prognostic. Complement gene variants (e.g., *CFH*, *CFI*, *MCP/CD46*, and others) and copy number variations (e.g., CFHR1-5 deletions) are found in up to 50–60% of patients, but their absence does not rule out C-TMA. Early complement inhibition may prevent irreversible organ damage and should not be delayed by pending genetic results. Genetic counseling is advised for all patients, regardless of variant status, to assess familial risk and guide long-term follow-up. A consensus aims to outline scenarios in which treatment initiation is strongly recommended, including severe or relapsing disease, chronic kidney dysfunction, among others. In Chile and Latin America, TMA remains underdiagnosed due to limited access to specialized diagnostic tools and delays in recognizing clinical subtypes. The availability of molecular testing and complement studies is restricted, often delaying targeted therapies. Treatment still relies heavily on plasma exchange, with limited access to complement inhibitors. This consensus aims to standardize care, improve early recognition, and support rational use of targeted therapies in C-TMA, particularly in regions with limited access to specialized testing or complement inhibitors.

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Clinical trial number
Not applicable.

Key learning points

What was known

- C-TMA is caused by dysregulation of the alternative complement pathway, with genetic variants identified in up to 60% of patients.
- Before complement inhibitors, outcomes were poor, with high rates of mortality, dialysis dependence, and post-transplant recurrence.
- In Chile, C-TMA remained underdiagnosed due to limited access to molecular diagnostics and complement-targeted therapy, highlighting the need for national consensus.

This study adds

- This is the first Chilean consensus providing a structured diagnostic and therapeutic algorithm for C-TMA across adult and pediatric settings.
- It establishes practical recommendations for early initiation and rational use of C5 inhibitors, adapted to a resource-limited healthcare context.
- It highlights the importance of genetic counseling and multidisciplinary care to improve outcomes and reduce inequities in access to treatment.

Potential impact

- Standardizing C-TMA diagnosis and management may reduce delays, improve survival, and preserve kidney function.
- The consensus facilitates equitable access to targeted therapy by guiding clinical decision-making even when genetic results are pending.
- Adoption of these recommendations could influence national policies, ensure rational use of high-cost therapies and promoting earlier recognition of rare kidney diseases.

Keywords Complement system, Genetic variants, Thrombotic microangiopathy, Kidney disease

Introduction

Thrombotic microangiopathies (TMA) are a group of disorders characterized by severe endothelial damage and thrombus formation in the microvasculature, leading to structural and functional alterations in organs and tissues. On histological examination, thickening of arterioles and capillaries, endothelial swelling / detachment, subendothelial accumulation of proteins, cell debris and platelet thrombi obstruct vessel lumina are observed. These lesions typically affect the kidney, but several parenchymal tissues (brain, heart, lungs and gastrointestinal tract) may be involved too [1].

In clinical practice, we approach TMA through a diagnostic triad: microangiopathic hemolytic anemia, reduction of platelet count, and organ damage. TMA frequently occurs as a consequence of various underlying conditions, which will be addressed in this review. However, in the absence of an evident cause to explain its development, an alteration in the alternative pathway of the complement system should be suspected.

Originally, hemolytic uremic syndrome (HUS) was described in pediatric patients who developed signs of TMA following a diarrheal episode secondary to Shiga toxin produced by Escherichia coli (STEC-HUS). However, some HUS cases were identified as not preceded by diarrhea and/or presented with a different clinical characteristics or evolution. They were defined as atypical HUS (aHUS). aHUS is characterized by uncontrolled activation of the alternative complement pathway, resulting in endothelial damage and platelet activation [1] (Fig. 1).

Several pathogenic mechanisms have been established in the pathophysiology of TMA, either complement-mediated (C-TMA), antibody-mediated, or non-complement-mediated (NC-TMA), leading in last years to a continuous review and transition in aHUS nomenclature. In this context, the consensus group decided to designate HUS as TMA in this article, to underscore the wide range of pathogenic mechanisms and clinical presentations involved.

It has been described that C-TMA has a genetic origin in up to 60% of cases affecting both adult and pediatric populations. Their annual incidence is estimated at 0.5 cases per million inhabitants, though it is likely underestimated due to a low level of suspicion of disease or diagnosis, which may vary among different geographical populations [2]. Currently, there is no epidemiological data for C-TMA in Chile.

Prior to the drug development of complement system inhibitors, the mortality and/or dialysis-dependence rates were 40% at onset and 65% after one year follow-up, with a 90% recurrence rate post-kidney transplant [3]. Early C-TMA identification and treatment with C5

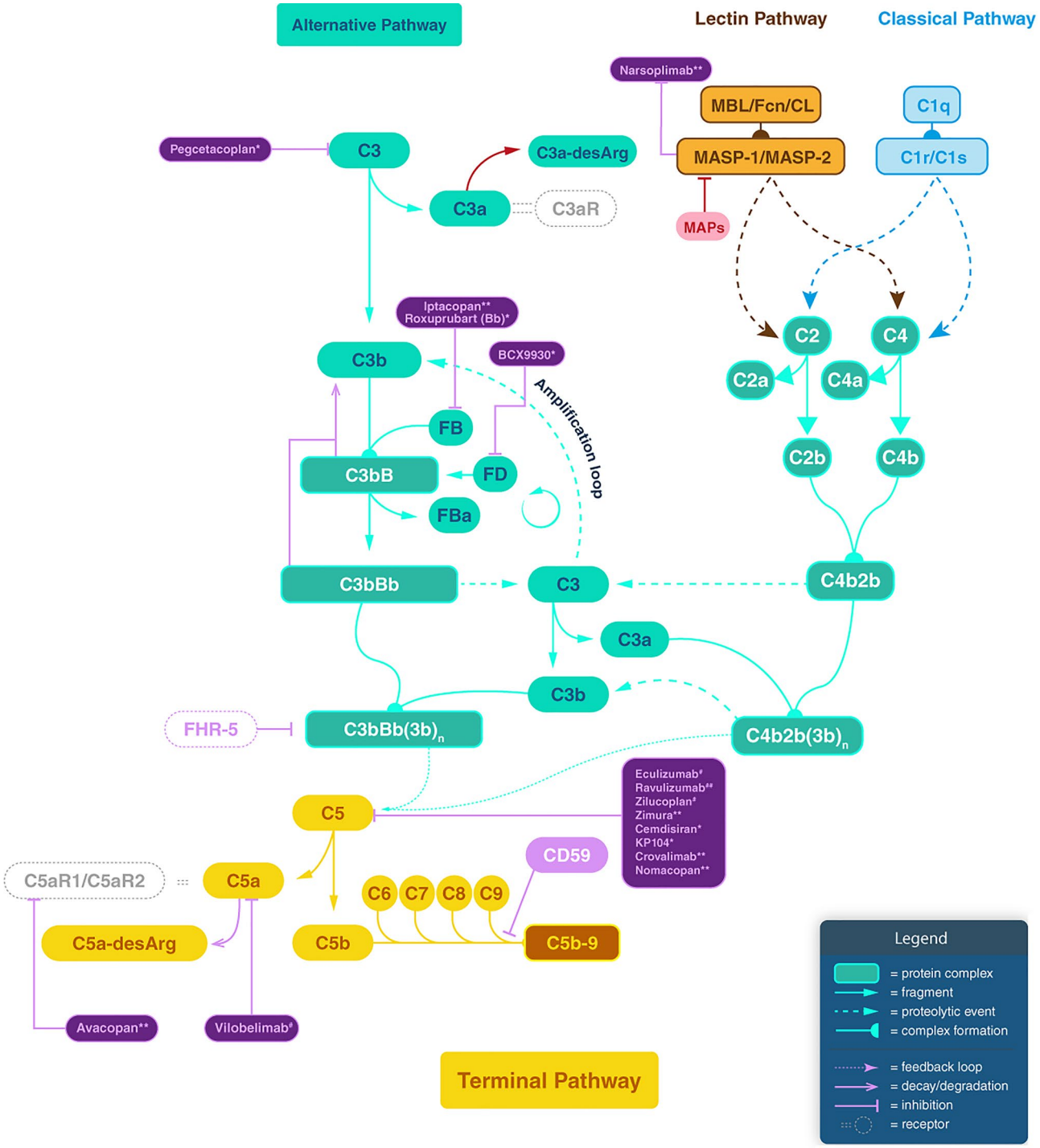

Fig. 1 Complement cascade, amplification loop, and therapeutic targets relevant to C-TMA. The complement system can be initiated through three pathways—classical (blue), lectin (orange), and alternative (turquoise)- all converging on C3 and culminating in the formation of the membrane-attack complex (MAC, C5b-9, yellow). The diagram highlights pharmacologic inhibitors currently approved or in clinical trials (purple rectangles). * phase study 2; ** phase study 3

complement inhibitors improved the prognosis of this disease, by reducing significantly morbidity and mortality [4].

In many countries, C-TMA remains significantly under recognized due to limited access to timely complement diagnostics. Molecular testing is not always promptly available, delaying differentiation from other diagnosis.

Access to targeted therapy is restricted and often requires case-by-case approval, leading to treatment delays.

The aim of this consensus is to raise awareness about C-TMA, improving the suspicion and precision of diagnosis, as well as access to specific treatment, and the unification of clinical criteria and protocols to promote high-quality care of patients with C-TMA based on scientific evidence.

Methodology

In May 2023, the Genetic Diseases Committee of the Chilean Society of Nephrology was established with the purpose of addressing the diagnosis and management of genetic kidney diseases. During the initial stage, priority was given to C-TMA, given the lack of a national consensus ensuring the rational use of C5 inhibitors tailored to the Chilean context. To this end, pediatric nephrologists, adult nephrologists, and genetic experts with recognized expertise in this condition were convened, holding both in-person and virtual meetings.

A comprehensive literature review was undertaken, encompassing major databases (MEDLINE, EBSCO, ProQuest, SciELO) in both English and Spanish, in order to perform a narrative synthesis aimed at developing management recommendations for C-TMA applicable to the Chilean setting.

The development of recommendations followed an iterative process of analysis, discussion, and feedback, structured according to the Delphi method, which allowed the formulation of consensus-based guidelines. After six months of work, the committee designed an algorithm intended to provide practical recommendations for clinical management, with the overarching goals of facilitating early diagnosis and guiding the rational use of complement inhibitors.

Consensus

Suspicion of TMA

TMA is a histological diagnosis characterized by thickening and swelling arteriole and capillary walls, detached endothelial cells, and platelet thrombi occluding the vascular lumen. Clinically, TMA may present as shown in Fig. 2[a] [5].

- Non-immune microangiopathic hemolytic anemia (presence of > 1% schistocytes in smear, LDH > 1.5 times the upper normal limit of the laboratory, undetectable or age-adjusted decreased haptoglobin, elevated free hemoglobin in plasma, and negative direct Coombs test).
- Thrombocytopenia (< 150,000/mm^3 or a 25% reduction from baseline value).
- Target organ damage secondary to microvascular occlusion, such as brain and kidney. Attention should be drawn to the fact that approximately 25% of patients with C-TMA may present with renal-limited TMA and a kidney biopsy is essential for early detection. Renal-limited TMA is associated with less severe renal dysfunction and a lower risk of death compared to cases with hematological involvement. The effect of anti-C5 therapy in renal-limited TMA remains unclear [4].

In the critically ill patient setting, it is essential to rule out the diagnosis of disseminated intravascular coagulation, confirmed by elevated levels of D-dimer and PT-INR; and fibrinogen and platelet consumption. Another condition that must be ruled out is cyanocobalamin deficit, since it is a condition that can be effectively corrected with appropriate supplementation.

When TMA is clinically suspected, differential diagnosis study should be conducted on potential underlying causes (Fig. 2b).

Differential diagnosis of TMA

TMA represents a severe condition that raises a significant clinical challenge requiring the coordinated intervention of a multidisciplinary team to improve its clinical outcomes. The main etiologies of TMA are described below. A primary alteration of the alternative complement pathway should be suspected if TMA manifestations do not improve within a few days of starting treatment for the suspected cause (Fig. 2b). In such cases, a therapeutic test with C5 inhibitors should be considered [6].

Thrombotic thrombocytopenic purpura (TTP)

The first diagnosis to rule out is TTP due to its high morbidity and mortality. It is characterized by a severe deficiency of the ADAMTS13 metalloprotease [7]. This can occur by genetic defects or autoantibodies, promoting the formation of microthrombi and damage of vital organs. The clinical presentation includes thrombocytopenia, microangiopathic hemolytic anemia, and often neurological symptoms, kidney failure, and fever [8]. ADAMTS13 deficiency is defined by an activity < 10%, with or without the presence of an inhibitor. In adults, a clinical approach to the diagnosis of TTP can be made using the PLASMIC score [9]. A score ≥ 6 suggests a severe deficiency of ADAMTS13, and early starting of plasma exchange therapy with fresh frozen plasma treatment should be considered [10]. A recent study assessed the applicability of the PLASMIC score in C-TMA. A score ≤ 5 demonstrated high sensitivity and an excellent positive predictive value for identifying probable C-TMA, but its low negative

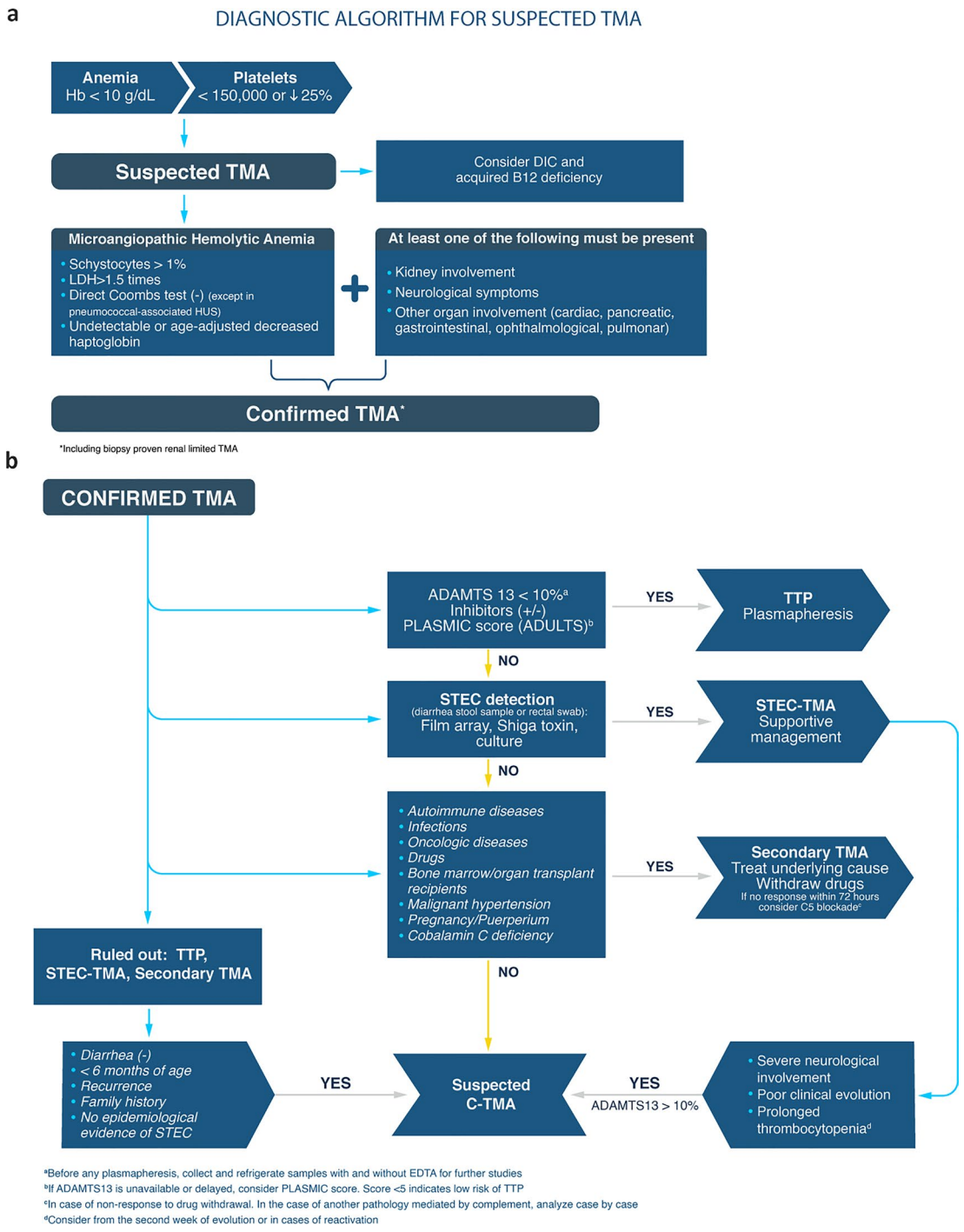

Fig. 2 **a**. Diagnostic algorithm for suspected TMA. Diagnostic algorithm for suspected TMA, outlining initial laboratory findings, exclusions and criteria for confirming TMA based on microangiopathic hemolytic anemia and organ involvement. TMA: Thrombotic Microangiopathy; Hb: Hemoglobin; LDH: Lactate Dehydrogenase; DIC: Disseminated Intravascular Coagulation., PNH: Paroxysmal nocturnal hemoglobinuria. **b.** Differential Diagnosis of TMA. Comprehensive workflow for confirmed TMA, guiding differential diagnosis (TTP, STEC-HUS, secondary TMA, C-TMA), and specifying further investigations, specialist consultations, and tailored treatment approaches for each TMA subtype. TMA: Thrombotic Microangiopathy; ICU: Intensive Care Unit; TTP: Thrombotic Thrombocytopenic Purpura; C-TMA: Complement-mediated Thrombotic Microangiopathy; HUS: Hemolytic Uremic Syndrome; STEC: Shiga Toxin-producing Escherichia coli; ADAMTS13: A Disintegrin And Metalloproteinase with Thrombospondin type 1 Motifs member 13. PLASMIC: Clinical score to predict ADAMTS13 deficiency in TTP. **C.** Treatment of C-TMA. Management protocol for suspected C-TMA, detailing the initiation of C5 blockade therapy, necessary pre-treatment evaluations, and subsequent therapeutic pathways based on genetic, antibody, or enzymatic findings. C-TMA: Complement-Mediated Thrombotic Microangiopathy; CFB: Complement Factor B; CFH: Complement Factor H; CFI: Complement Factor I; IV CFM: Intravenous Cyclophosphamide; MMF: Mycophenolate Mofetil; TMA: Thrombotic Microangiopathy; VUS: Variant of Uncertain Significance; CD46: Cluster of Differentiation 46 (Complement Regulatory Protein)

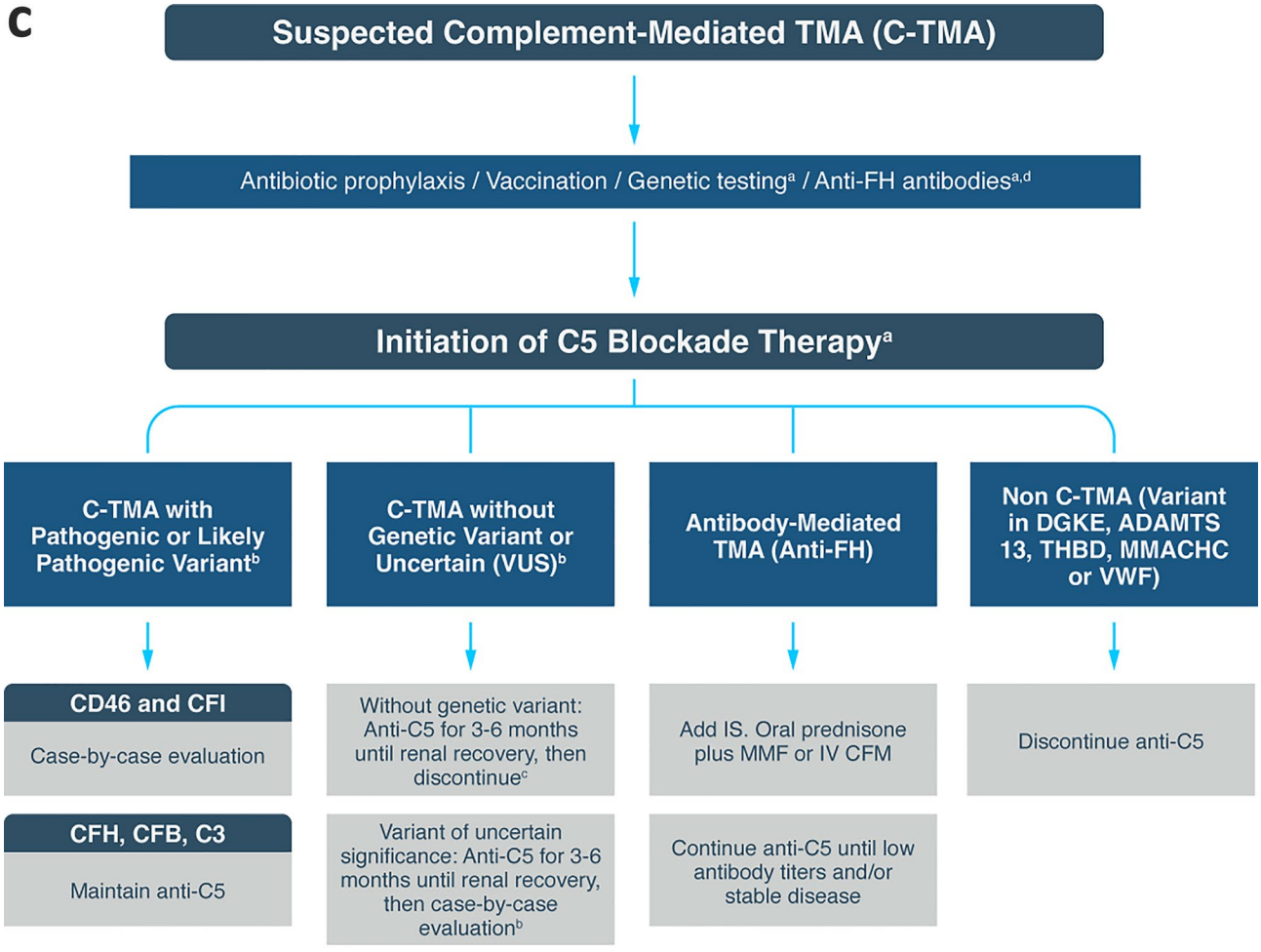

Fig. 2 (continued)

predictive value (55.6%) limits the PLASMIC score's reliability in excluding aHUS [11]. In addition, new evidence suggests that incorporating the urine protein/creatinine ratio as an additional variable can enhance the diagnostic accuracy of established clinical scores for distinguishing TTP from C-TMA [12].

Infections

In the pediatric population, the main differential diagnosis is Shiga toxin-producing *Escherichia coli*-associated TMA, (STEC-TMA, formerly known as STEC-HUS). STEC-TMA typically begins after the ingestion of food or water contaminated with feces containing the bacteria [13]. The diagnosis of STEC-TMA requires a combination of clinical examination and laboratory tests. Patients typically present with a prodrome of profuse diarrhea, often bloody, occurring 2 to 5 days after STEC infection. Confirmation of the infection is achieved through feces sample analysis using bacterial cultures or, ideally, molecular biology tests to detect Shiga toxin genes. In the absence of diarrhea, STEC-TMA should also be ruled out and rectal swabs can be performed [14].

Regarding other infections, TMA development has been linked to herpes viruses, influenza, human immunodeficiency virus, SARS-CoV-2, Dengue, Coxsackie. In these cases, the management was primarily supportive and focused on eradicating the infectious agent [15, 16]. Infection by neuraminidase-producing pathogens (Influenza virus and *Streptococcus pneumoniae*) can induce systemic TMA with severe kidney, neurological, and respiratory involvement, often carrying a very poor prognosis. It should be noted that the direct Coombs test can be positive secondary to T-antigen activation by pneumococcal neuraminidase activity [17].

Autoimmune diseases

In adult patients with TMA, an autoimmune workup is recommended, particularly to evaluate for conditions associated with autoantibodies against the endothelium and/or phospholipids, such as systemic sclerosis, antiphospholipid syndrome, and systemic lupus erythematosus. A blood sample should be taken prior to plasmapheresis if performed, to avoid the removal of potential autoantibodies that may indicate an underlying autoimmune disease. Treating the underlying disease, along with supportive management, should reverse the condition; however, in case of refractory patients, the treatment with complement inhibitors has been reported [18, 19].

Pregnancy and puerperium

The main TMA conditions associated with pregnancy include severe preeclampsia and hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP syndrome); less frequently TTP, C-TMA and catastrophic antiphospholipid syndrome. These conditions require a multidisciplinary approach, prioritizing the stabilization of the mother. HELLP syndrome typically develops in the third trimester, and its definitive management is based on pregnancy termination [20]. A primary alteration of the alternative complement pathway should be suspected if TMA manifestations do not improve 48–72 h postpartum [7].

Neoplasms

In cancer patients, TMA may be directly related to the underlying malignancy—either as an initial manifestation or during disease progression—or may occur secondary to cancer treatment. In the first case, TMA is secondary to systemic microvascular metastases [21]. Most cases are associated with solid tumors, primarily gastric, lung, breast, and prostate adenocarcinomas. Hematological cancers represent 8% of cases [22].

Additionally, monoclonal gammopathy has been increasingly recognized as another potential cause of C-TMA. In a series from the Mayo Clinic, monoclonal gammopathy was identified in 13.7% of adults with TMA, suggesting that monoclonal immunoglobulins may contribute to complement dysregulation and endothelial injury [23].

Drugs

Certain drugs are associated with the development of TMA through two mechanisms: direct endothelial damage (dose-dependent) or the induction of autoantibodies (idiosyncratic, dose-independent) [24–26]. If a drug or medication is suspected as the causal agent of TMA, the first step is to discontinue it and initiate supportive treatment. If endothelial toxicity is suspected, the drug may be reintroduced at a reduced dose with close monitoring of clinical and laboratory response. Table 1 lists the drugs that have been associated with the development of TMA [27, 28].

Transplantation

Hematopoietic stem cell transplants and solid organ transplants share several mechanisms that predispose to the development of TMA, primarily through endothelial damage. In both types of transplantation, immunosuppression can cause endothelial damage and increase susceptibility to infections, including viral (CMV, EBV, BK virus) and bacterial pathogens [15, 29]. In solid organ transplantation, ischemia–reperfusion and antibody-mediated rejection induce endothelial injury and complement activation. In hematopoietic transplantation, graft-versus-host disease must be ruled out.

In the kidney transplantation setting, biopsy is a key tool to rule out antibody-mediated rejection associated with TMA. A primary alteration of the alternative complement pathway should be suspected if TMA signs persist after ruling out and/or correcting secondary causes.

Table 1 Drug-induced thrombotic microangiopathy

Drug classification	Name
Chemotherapy drug	Docetaxel, Doxorubicin, Mitomycin, DCR-MYC, Gemcitabine, Cisplatin, Oxaliplatin, Pentostatin, Vincristine, Cytarabine; Carboplatin + Etoposide + Melfalan; Cyclophosphamide + Thiotepa
Proteasome inhibitors	Bortezomib, Carfilzomib, Ixazomib.
VEFG, kinases and immune checkpoint inhibitors	Alentuzumab, Bevacizumab, Ramucirumab, Cetuximab, Imatinib, Ipilimumab, Pazopanib, Ponatinib, Palbociclib, Ruxolitinib, Sunitinib.
Monoclonal antibodies	Adalimumab, Certolizumab Pegol, Emicizumab + aPCC, Golimumab, OKT3, Ustekinumab, Moxetumomab Pasudotox
Others immunosuppressive drugs	Cyclosporine, Rapamycin, Tacrolimus, Hydroxychloroquine, Interferon Beta 1-A/1-B, Alemtuzumab, Fingolimod
Opioids and Drugs of Abuse	Cocaine, Ecstasy, Oxymorphone, Oxycodone, Polyethylene oxide
Anticonvulsant	Valproic acid
Antimicrobial	Ciprofloxacin, Levofloxacin, Metronidazole, Penicillin, Vancomycin, Rifampin, Trimethoprim -Sulfamethoxazole, Tenofovir/Emtricitabine
Others	Clopidogrel, Simvastatin, Bupropion, Estrogen /Progesterone, Quetiapine, Quinine, Ticlopidine, Alendronate, Captopril, Hydrochlorothiazide, Primidone

In such cases, initiating treatment with a C5 inhibitor is recommended if no improvement is observed within the first 4 days [30].

Malignant hypertension

Malignant hypertension can occur as a consequence of any untreated or uncontrolled etiology of arterial hypertension and can cause endothelial damage and, secondarily, TMA. Similarly, kidney-predominant TMA usually leads to severe hypertension [31]. TMA secondary to malignant hypertension occurs in only approximately 2% of cases of primary malignant hypertension; therefore, alternative etiologies—most notably C-TMA, drug-induced TMA, glomerulopathies, and systemic diseases—should be strongly considered [32]. The treatment should focus on aggressive blood pressure control. When it does not occur, C-TMA should be considered and treatment with complement inhibitors initiated. TMA is more common in malignant hypertension secondary to drug-induced hypertension, systemic diseases and IgA nephropathy.

Genetic non-complement mediated TMA

Cobalamin deficiency, both acquired and congenital, must be ruled out as it is a treatable cause of TMA. The diagnosis is more common in pediatric patients and is based on identifying elevated homocysteinemia, low methioninemia, and high urinary methylmalonic acid, along with normal or low vitamin B12 levels. Treatment involves parenteral administration of hydroxocobalamin [33].

There are genetic variants of other proteins that can cause TMA, including DGKE, thrombomodulin, plasminogen, and INF2, which should be ruled out alongside those related to the complement cascade, as they have different prognosis and treatments [34].

Antibody-mediated TMA

Up to 25% of the causes of C-TMA are due to the presence of anti-Factor H (FH) antibodies, with a significant percentage associated with deletions in the genes of FH regulatory proteins (CFHR1-CFHR3). This deletion is found in 5–36% of the general population and acts through a gain-of-function mechanism that impairs FH regulation. Measuring anti-FH antibodies at the onset of TMA is important, as it can support treatment with therapeutic plasma exchange and immunosuppression. However, this test is currently not available in many countries to confirm the diagnosis [35].

Diagnosis of C-TMA

There is no confirmatory diagnostic test for C-TMA. The diagnosis is based on clinical features and by exclusion after ruling out the secondary causes mentioned previously. The determination of complement factors or functional tests (C3, C4, AH50, CH50) has low sensitivity and specificity, and they do not distinguish whether the deficit is due to consumption or low synthesis. A decrease in the C3 fraction is present only in 36% of cases [36]. On the other hand, many fragments released during complement activation increase when there is kidney failure. Genetic testing and anti-CFH autoantibody are useful in confirming the complement mediated etiology.

Clinical evaluation

Traditionally, clinical evaluation by exclusion has been the most used diagnostic method for C-TMA, and there are some specific features that can suggest its presence:

- It is a TMA that predominantly affects the kidneys due to their vulnerability to complement-mediated damage [37–40].
- It tends to have an acute presentation, driven by the "C3 amplification loop" which causes exponential activation of this factor (Fig. 1).
- C-TMA is characterized by genetic susceptibility; therefore, there may be a personal or family history of TMA. Of note, the absence of these findings does not rule out a genetic cause of TMA.

Histopathological study

Histopathological studies can confirm TMA and provide insights into its origin, particularly in cases of diagnostic uncertainty, which is crucial for kidney transplant patients with graft dysfunction. However, kidney biopsy carries a high risk of bleeding, especially in patients with thrombocytopenia, and histopathologic features alone are not sufficiently specific to determine the underlying etiology. Consequently, in most TMA cases, biopsy is often avoided, and diagnosis is frequently established by clinical and laboratory findings, which has important implications for diagnostic algorithms and therapeutic decision-making.

A prompt kidney biopsy, performed once the patient is hematologically stable, is essential. Beyond confirming the diagnosis of TMA, it allows for the distinction between acute and irreversible damage. This histopathological evaluation provides critical information for prognosis and guides the intensity of therapeutic interventions. Early biopsy should therefore be highlighted as a key component of optimal patient management.

"Diagnostic-therapeutic" test

The "diagnostic-therapeutic" test with C5 inhibitors is a key tool in approaching the diagnosis of C-TMA.

These agents block endothelial injury and intracapillary hemostatic activity, leading to a rapid increase in platelet counts, confirming disease control. By halting the formation of microthrombi, the tissue reperfusion and the regeneration of damaged parenchyma it is promoted [3, 30]. The parameters for clinical response will be described in the treatment section.

Genetic study

Since the results of genetic studies are not immediately available, the treatment should be initiated without waiting for confirmation in a patient with suspected C-TMA. However, once the genetic analysis is concluded, the results can guide therapeutic decisions and define prognosis. Genetic variants in complement-related proteins are responsible for 30% to 60% of C-TMA cases. In the remaining cases, pathogenic variants are not detected, but this does not exclude deregulation of the alternative complement pathway. Notably, 16% of cases are familial forms [41, 42].

Variants related to C-TMA can cause a loss of function in complement regulatory factors (CFH, CFI, MCP/CD46, CFH/CFHR rearrangements) or a gain of function in components of the C3 convertase (C3, CFB), leading to increased complement activity that exceeds the capacity for complement activation control. Most patients identified with anti-factor H antibodies have a homozygous deletion in CFHR1 and/or CFHR3. The genes involved in the phenotype determine the severity of the disease, prognosis, response to treatment [43] (Table 2).

Of note, variants of uncertain significance (VUS) are frequently identified due to the rarity of C-TMA and the infrequent analysis of complement genes. A VUS is a genetic variant for which, at the time of analysis, there is insufficient or conflicting evidence to classify it as either benign or pathogenic. Importantly, VUS are not considered clinically actionable and should not guide patient management unless additional evidence becomes available. Basing decision on a VUS risks either prematurely stopping effective therapy in a patient with a true underlying defect or unnecessarily prolonging expensive treatment in another patient. Discussion of VUS in the context of clinical history, within a multidisciplinary team including clinicians and geneticist, is essential to evaluate whether further evidence could lead to a more definitive classification, such as likely benign or likely pathogenic. However, many VUS remain in this category. For this reason, re-analysis of VUS after 6 to 12 months is recommended.

Treatment oF C-TMA

Supportive therapy

Patients with C-TMA should be managed in specialized referral centers with a multidisciplinary approach involving nephrology, intensive care, hematology, nutrition, clinical genetics, infectious diseases, neurology, psychology, and social assistance specialists. Acute kidney injury and its complications must be treated. Red blood cell transfusion is indicated in cases of severe (Hb < 7 g/dL) or symptomatic anemia. Platelet transfusions should be avoided as they exacerbate thrombotic events, except in cases of active bleeding or the need for surgical intervention with a platelet count < 30,000/μL (Fig. 2c) [36, 48].

C5 inhibitors

C5 inhibitors are the first-line therapy for C-TMA. Eculizumab and Ravulizumab are humanized monoclonal hybrid antibodies (IgG2 and IgG4) that block the terminal complement pathway [49]. Their mechanism of action involves binding to the C5 component of the complement system and preventing its cleavage into C5a and C5b, thereby inhibiting the formation of the membrane attack complex (C5b-9) [50] (Fig. 1).

Early initiation of anti-C5 therapy has dramatically changed the prognosis of C-TMA by substantially improving survival and reducing progression to

Table 2 Genes discovered in association with C-TMA

Gene	Protein function	Frequency (%) [44–46]	Average age of presentation (years) [46]	5-Year Survival Rate Free of ESKD, without C5 Blockade (%) [47]	5-Year Survival Rate Free of ESKD, with C5 Blockade (%)[47]	Transplant recurrence without C5 inhibition (%) [44, 47]
CFH	Inhibition of C3 convertase with FH cofactor	20–30	19.8	17	78	80–90
CFI	Inhibition of C3b & C4b in the present of FI, MCP, THBD	4–10	35.9	16	83.5	70–80
MCP/CD46	FI cofactor for C3b & C4b cleavage on cellular surface	10–15	5.3	87.5	95.6	15–20
C3	Component of C3 & C5 convertase	5–10	22.4	25	80	40–50
CFB	It binds to C3 to form C3 convertase	1–4	6.0			100
Anti-FH	Modification of FH function	24 < 18 yrs 19 > o = 18 yrs	13.1			Depend on antibody titer

Table 3 Recommended doses of Eculizumab for C-TMA

Patient Body Weight	Induction	Maintenance
40 kg and over	900 mg weekly x 4 doses	1,200 mg at week 5; then 1,200 mg every 2 weeks
30 kg to less than 40 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg to less than 20 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 3 weeks

Table 4 Recommended doses of ravulizumab for C-TMA

Weight	Loading dose	Maintenance dose (starting 2 weeks after the loading dose)	Maintenance Interval
5 to < 10 kg	600 mg	300 mg	Every 4 weeks
10 to < 20 kg	600 mg	600 mg	
20 to < 30 kg	900 mg	2,100 mg	Every 8 weeks
30 to < 40 kg	1,200 mg	2,700 mg	
40 to < 60 kg	2,400 mg	3,000 mg	
60 to < 100 kg	2,700 mg	3,300 mg	
≥ 100 kg	3,000 mg	3,600 mg	

end-stage kidney disease from 50 to 60% to 10–15% [51]. Its use is recommended as early as possible, ideally within the first 24 h after diagnostic suspicion, due to better kidney outcomes [3].

Eculizumab was the first terminal complement pathway inhibitor available for effective C-TMA block treatment. It has an estimated half-life of 11 to 12 days, and infusions are repeated every 2 weeks to maintain optimal complement blockade [36, 49]. Ravulizumab was developed by incorporating two structural changes to Eculizumab, aimed to extend its elimination half-life, so infusion frequency is every 4–8 weeks [52].

Both Eculizumab and Ravulizumab are approved by the FDA and EMA for C-TMA. Ravulizumab is the only C5 inhibitor currently approved by the Chilean regulatory agency. In the public sector, access depends on each hospital's resources; in many cases, initial doses may be locally funded, but continuation of therapy often requires legal processes to secure ongoing treatment. In the private healthcare system, access tends to be somewhat easier, although it still involves insurance authorization and administrative procedures. Over recent years, our committee has made continuous efforts to incorporate anti-C5 therapy into the Chilean High-Cost Law to improve patient access.

Both drugs have safety and efficacy studies in both adult and pediatric populations [3, 51, 53–55]. Tables 3 and 4 detail the recommended doses based on weight of Eculizumab and Ravulizumab, respectively [3, 56].

A) Response Evaluation

The C-TMA response to C5 blockade is assessed based on the following criteria: normalization of platelet counts within the first 10 days of therapy, reduction of LDH levels to less than twice the upper normal limit, and > 25% decrease in serum creatinine or withdrawal from dialysis. Renal function recovery may be slower or even absent in a minority of cases, particularly in patients who initially require dialysis. In cases of no response, a kidney biopsy would help exclude differential diagnoses or confirm irreversible chronic kidney damage [57].

B) Duration of Therapy

Currently, one of the most debated topics is the duration of treatment with complement inhibitors due to the risks of infections, high costs, and the lack of evidence supporting permanent complement activation, even in patients who are carriers of pathogenic variants.

During treatment, it is important to consider an acute phase, aimed at rapidly blocking complement to reverse TMA, and a maintenance phase, where management can be individualized, and complement blockade can be discontinued based on risk assessment [56]. During the acute phase of C-TMA, treatment with C5 inhibitors is suggested to continue for 3 to 6 months [57]. In patients with a favorable hematologic response who persist with severe kidney dysfunction or dialysis dependence, a kidney biopsy should be considered to evaluate irreversible chronic damage and to guide the safe discontinuation of treatment. Extrarenal relapses, mainly hematological, are rare under these conditions.

The decision to discontinue or continue complement inhibitors during the maintenance phase must be personalized and is primarily based on the assessment of relapse risk after treatment discontinuation. Other factors are also considered, such as the patient's age, partial or complete recovery of kidney function, whether C-TMA affects a native or transplanted kidney, the presence of severe extrarenal manifestations, the patient's willingness to stop or continue treatment, genetic study results [58], history of relapses, and the detection of elevated anti-FH antibody titers.

C-TMA without a detected pathogenic variant or with a variant of uncertain significance with a relapse risk < 5% is considered a low-risk condition for recurrence. In such cases, discontinuing C5 blockade is recommended once kidney function is stable [59]. Treatment discontinuation requires close patient monitoring and immediate access to C5

inhibitors in the event of a documented recurrence [57].

If a pathogenic variant is detected, the relapse risk will depend on the altered gene. Indefinite treatment is advised for those associated with CFH, CFB, and C3. For other variants, the decision to discontinue C5 blockade should be discussed on case-by-case of disease [56]. If a variant in DGKE, THBD OR MMAHCH is identified, anti-C5 therapy should be discontinued.

It is essential to educate patients about the early symptoms of TMA so they can seek medical attention promptly. Regular monitoring should also be conducted to detect signs of TMA, including evaluation of proteinuria and hemoglobinuria with test strips, complete blood count (hemoglobin, platelets), creatinine, and LDH [60].

C) Kidney Transplant Considerations

Regarding transplant recipients with a history of C-TMA as the cause of chronic kidney diease should be stratified into high, intermediate, or low risk for post-transplant recurrence based on complement gene mutations, the presence of anti-CFH antibodies, and any prior history of recurrence in previous grafts (Table 2) [61].

For patients at high or intermediate risk (CFH, CFI, C3, or CFB, or with anti-CFH antibodies) prophylactic complement inhibition is recommended starting perioperatively and continued post-transplant. In patients with isolated MCP/CD46 mutations, the risk of recurrence is low, and kidney transplantation without prophylactic complement inhibition is generally considered safe, although rare recurrences have been reported. For patients with no identified genetic defect, the risk of post-transplant recurrence is intermediate, and individualized assessment is required [62].

D) Additional Complementary Recommendations

- **Infectious Risk**: Due to their mechanism of action, C5 inhibitors increase the risk of infections caused by encapsulated microorganisms, particularly, *Neisseria meningitidis*. Therefore, all patients should receive tetravalent meningococcal vaccines (ACWY) and serotype B vaccines 14 days prior to starting treatment or as soon as possible [63, 64], in parallel to antibiotic prophylaxis. It has been observed that even after vaccination, the risk of invasive disease persists. Consequently, there are protocols that extend the use of antibiotic prophylaxis with penicillin/amoxicillin, macrolides [52], or ciprofloxacin [64] for up to 60 days after discontinuing eculizumab infusions [52]. Vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B is also recommended. Additionally, sexually active patients should be educated about the risk of disseminated gonococcal infections [36, 64].
- **Anti-FH Antibody Measurement**: Although the measurement of anti–FH antibodies is recommended in the international literature, this assay is not yet available in our setting. We recommend, before initiating plasma therapy—particularly in pediatric patients—collecting a plasma sample to test for anti-FH antibodies and storing it at − 80 °C until analysis. Anti-FH antibody-associated C-TMA is more frequent in children (10–24%) and in CFHR1-CFHR3 deletions [65], but it is also described in the adult population. Detection is important for therapy choice and its follow-up.
- **Genetic Study**: Genetic testing for complement variants is not required to initiate therapy with C5 inhibitors. Delaying treatment for genetic testing is not recommended, benefits in the acute phase have been observed with or without genetic variants detection [41].

Plasma therapy

If C5 inhibitors are not available, plasma therapy (preferably therapeutic plasma exchange or plasma infusion) is considered a temporary second-line management option until the complement inhibitor becomes accessible. In C-TMA, the outcomes of plasma therapy are variable and associated with complications, particularly in pediatric populations, such as allergic reactions, vascular access issues, and hemodynamic complications [51].

C-TMA associated with anti-FH antibodies

There is no universally accepted therapeutic approach, but specific therapy to reduce antibody titers is considered necessary. Therapeutic alternatives include a combination of C5 blockade and immunosuppressants, corticosteroids plus mycophenolate mofetil, cyclophosphamide, or rituximab, or therapeutic plasma exchange with immunosuppressants. C5 blockade can be highly effective in managing the acute phase, especially in cases with severe extrarenal manifestations. Once clinical stability is achieved, discontinuation of C5 blockade should be considered, maintaining immunosuppression for at least 1 year after anti-FH antibody titers have decreased below a certain threshold [31, 51, 57]. Monitoring antibody titers every 3 to 6 months helps to detect early relapses [65].

Complement inhibitors in clinical research

Currently, new complement system inhibition therapies acting in several target molecules belonging to its

pathway activation are under study in clinical trials. Figure 1 outlines the principal drugs, its molecular target and the clinical trial phase. These drugs have the potential to become new therapeutic options in C-TMA and other pathologies related to abnormal complement system activation [66].

Conclusion

The Genetic Diseases Committee aims to strengthen the approach to C-TMA by developing and spreading a consensus guideline tailored to the healthcare context. Key priorities include enhancing clinician education, improving access to specialized diagnostics, and fostering inter-institutional collaboration—efforts that seek to optimize care and reduce inequities. These recommendations are intended as a practical guide for physicians, who, in coordination with multidisciplinary teams, will determine the most appropriate treatment for each patient. Currently, new molecules targeting the alternative complement pathway at different levels are under study and could become therapeutic options for this condition in the future, offering meaningful benefits to affected individuals and their families (Fig. 1).

This work is based on a narrative review and expert consensus rather than a systematic review. Therefore, it may be subject to selection bias and does not provide the same level of evidence as a systematic methodology. Nevertheless, it reflects the best available evidence combined with local expert opinion, which is particularly relevant given the limited data on the management of C-TMA in Chile and Latin America.

Author contributions

All the authors reviewed the literature, drafted the consesus, prepared figures and tables, and read and approved the final manuscript.

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Data availability

All data generated during the consensus process are included within the article and supplementary files.

Declarations

Ethical approval

Not applicable, as this is not original research involving patients or human participants.

Consent to participate and consent to publish

Not applicable.

Standards or norms observed

This work is based on a structured literature review and expert discussion; it does not involve interventions in humans. Hence, specific research ethics standards (e.g., Declaration of Helsinki) do not apply. All data generated during the consensus process are included within the article and supplementary files.

Competing interests

The authors declare no competing interests.

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