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Acute Kidney Injury

Management of Atypical Haemolytic Uraemic Syndrome With Triggers: Diagnostic and Treatment Algorithms From an Asia-Pacific Perspective

Hee Gyung Kang[1] | Danny Hsu[2] | Noritoshi Kato[3] | Jin Seok Kim[4] | Masayoshi Okumi[5] | Min-Hua Tseng[6] | Kun-Hua Tu[7] | Desmond Yat Hin Yap[8] | Wai H. Lim[9,10,11]

[1]Division of Pediatric Nephrology, Department of Pediatrics, Seoul National University Children's Hospital & Seoul National University College of Medicine, Seoul, South Korea | [2]Haematology Department, Liverpool Hospital, Liverpool, NSW, Australia | [3]Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan | [4]Yonsei University College of Medicine, Severance Hospital, Seoul, South Korea | [5]Department of Urology, Kyoto Prefectural University of Medicine, Kyoto, Japan | [6]Department of Pediatrics, Chang-Gung Memorial Hospital, Taoyuan, Taiwan | [7]Kidney Research Center, Department of Nephrology, Chang-Gung Memorial Hospital, Taoyuan, Taiwan | [8]Division of Nephrology, Department of Medicine, The University of Hong Kong, Pokfulam, Hong Kong | [9]Department of Renal Medicine, Sir Charles Gairdner Hospital, Nedlands, WA, Australia | [10]Medical School, University of Western Australia, Perth, WA, Australia | [11]School of Health and Medical Sciences, Edith Cowan University, Perth, WA, Australia

Correspondence: Wai H. Lim (wai.lim@health.wa.gov.au)

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ABSTRACT

Complement-amplifying events/conditions associated with thrombotic microangiopathy (TMA) include pregnancy/postpartum period, severe hypertension, autoimmune diseases, drug exposures, infections and organ transplantation. Some of these 'triggers' may exist comorbidly with atypical haemolytic uraemic syndrome (aHUS; a complement-mediated form of TMA), unmask previously undiagnosed aHUS, or occur secondary to aHUS, thus creating a considerable diagnostic challenge. A major goal in patients presenting with TMA is to differentiate complement-mediated aHUS from other causes of TMA such that appropriate targeted treatment with complement 5 (C5) inhibitors can be initiated rapidly to avoid irreversible end-organ damage. To this end, nephrologists and haematologists from Australia, Hong Kong, Japan, Korea and Taiwan met virtually to discuss the management of TMA/aHUS in the presence of trigger conditions, focusing on the role of C5 inhibitors. To assist primary healthcare physicians and specialists from other disciplines in identifying and managing aHUS in the presence of triggers, the panel developed diagnostic and treatment algorithms as the main meeting output. Individual algorithms are presented for the settings of pregnancy, hypertension, autoimmune diseases, drug exposures, and kidney transplant. The algorithms combine clinical evidence with the panel's collective expertise to provide practical steps to differentiate aHUS and can be refined by local experts to reflect respective healthcare systems, approval and reimbursement procedures, resources and access to treatments for aHUS in any Asia-Pacific country.

1 | Introduction

Atypical haematolytic uraemic syndrome (aHUS), a form of thrombotic microangiopathy (TMA) caused by complement dysregulation, can manifest in the presence or absence of complement-amplifying conditions or events associated with its development [1–7]. aHUS is characterised by the triad of microangiopathic haemolytic anaemia (MAHA), thrombocytopenia,

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Summary at a Glance

Atypical haemolytic uraemic syndrome (aHUS) is challenging to diagnose and manage. Nephrologists and haematologists from the Asia-Pacific region have developed diagnostic and treatment algorithms for thrombotic microangiopathy/aHUS with triggers. These best practice recommendations, informed by systematic literature review and clinical expertise, aim to help primary care physicians and specialists identify and manage aHUS with triggers.

and end-organ dysfunction in the form of acute kidney injury [8, 9]. Its pathology involves endothelial damage, formation of microvascular thrombi, and occlusion of glomerular capillaries [1, 2, 8, 9]. Early recognition of aHUS and prompt initiation of targeted treatment are essential to prevent evolution to progressive end-organ damage and kidney failure [10].

Atypical HUS arises from genetic or acquired abnormalities that can cause uncontrolled activation of the terminal complement pathway [8, 9]. Current treatment aims to prevent the formation of membrane attack complex and downstream osmotic lysis of endothelial cells, through use of humanised monoclonal antibodies that bind to complement factor 5 (C5) [11]. Clinically available C5 inhibitors approved to treat aHUS include eculizumab [12] and ravulizumab [13].

Conditions/events known to be associated with TMA occurrence include pregnancy/postpartum period, severe hypertension, autoimmune diseases, drug exposures, infections and solid organ transplantation [9, 10, 14–17]. These conditions/events can act as 'triggers' that activate the complement system directly, enhance coexisting complement activation or independently induce endothelial injury [9]. Triggers can exist comorbidly with aHUS, unmask previously undiagnosed aHUS or occur secondary to aHUS [15].

A recent practice-changing Global aHUS Registry analysis, which evaluated a large population of patients presenting with triggers or associated conditions, emphasised the need to consider aHUS as a diagnosis in the presence of trigger conditions [7]. Initial management of TMA may therefore need to address more than one aetiological factor, including the possibility of underlying aHUS. A diagnostic objective is to identify individuals who may benefit from complement inhibition. However, in the absence of an objective tool to differentiate aHUS from other causes of TMA in the presence of triggers, prompt diagnosis continues to be a clinical challenge.

To understand diagnostic and management considerations unique to the Asia-Pacific (APAC) region, nephrologists and haematologists from Australia, Hong Kong, Japan, Korea and Taiwan met virtually in 2023 to discuss the management of TMA/aHUS, focusing on the role of C5 inhibitors. Meeting objectives were to identify key challenges in recognising aHUS in the presence of acute trigger conditions and to potentially formulate an overall strategy for the APAC region.

2 | Methods

Source materials for the virtual meeting were extracted independently by panel members from a database of published clinical studies and case reports maintained by the sponsor, Alexion, AstraZeneca Rare Disease. To identify any additional relevant materials, systematic searches were conducted of the PubMed database using the search terms 'atypical haemolytic uraemic syndrome', 'C5 inhibitor', 'real world evidence', 'genetic testing', 'clinical practice' and 'kidney transplantation' (and their variants). Limits/filters were applied for publication date (last 10 years) and language (English). Evidence was tabulated separately for each trigger condition and presented at the meeting as the basis for discussion. Evidence tables are provided in Tables S1–S5.

As the primary meeting output, the expert panel independently developed diagnostic and treatment algorithms with the goal of assisting primary healthcare physicians and specialists from other disciplines to identify and manage TMA/aHUS in the presence of triggers. The algorithms combine published clinical evidence with the collective expertise of the panel members, and present practical steps to determine the possibility of aHUS as the diagnosis in patients presenting with TMA, including considerations for genetic testing and use of C5 inhibitors. These 'generic' algorithms can be tailored to reflect respective healthcare systems, approval and reimbursement procedures, resources and access to treatments for aHUS within the APAC region.

3 | General Considerations

For definitions of terms used in this publication, see Table 1.

During the meeting, several general considerations emerged with respect to a best-practice approach for managing patients who present with TMA in the presence of triggers. In practice, treatment decisions are also guided by country-specific guidelines.

A general approach to differentiating TMA in the presence of a trigger is to manage the associated condition/event. Clinical features and investigations that may raise suspicion of aHUS as the diagnosis include the patient's family and personal medical history of TMA or aHUS, a kidney biopsy showing evidence of TMA, and an abnormal complement protein blood test (a low plasma C3 level/normal C4 level is indicative of potential alternative pathway activation). If TMA resolves after appropriate management of the

TABLE 1 | Terms and definitions used in this publication.

- "TMA" is a clinical syndrome characterised by the triad of MAHA, thrombocytopenia and end-organ dysfunction
- "aHUS" is a complement-mediated form of TMA (Note: in some publications aHUS is referred to as "complement-mediated TMA" or "CM-TMA")
- A "trigger" is a complement-amplifying condition or event associated with the development of TMA/aHUS

Abbreviations: aHUS, atypical haematolytic uraemic syndrome; MAHA, microangiopathic haemolytic anaemia; TMA, thrombotic microangiopathy.

trigger, the patient can be monitored and reassessed in the event of new manifestations or symptoms, especially if TMA recurs. The optimal time to wait for TMA resolution depends on the patient's clinical presentation and response to treatment of the precipitating trigger. If TMA persists despite appropriate management of the associated condition(s), a clinical diagnosis of aHUS can be made after excluding thrombotic thrombocytopenic purpura (TTP) and Shiga-like toxin-producing *Escherichia coli* haemolytic uraemic syndrome (STEC-HUS). The diagnostic hallmark of TTP is severe deficiency (<10%) of A Disintegrin and Metalloproteinase with Thrombospondin motifs, member 13 (ADAMTS13) activity [18]. As test results may not be immediately available at all centres, modified French and modified PLASMIC scoring systems incorporating proteinuria (Table 2) can be used for clinical prediction of severe ADAMTS13 deficiency [19]. A STEC-HUS diagnosis typically requires identification of STEC serotypes or toxins by culture and non-culture methods such as polymerase chain reaction ± serological testing for anti-STEC antibody [20].

TABLE 2 | PLASMIC, French and modified PLASMIC and French scores to differentiate TTP from aHUS [19].

Item	PLASMIC score	French score
Creatinine		
<2.0 mg/dL or <177 μmol/L	1	1
<2.273 mg/dL or <200 μmol/L		
Platelet count <30 g/L	1	1
Haemolysis variable[a]	1	—
No active cancer	1	—
No history of solid organ or stem cell transplant	1	—
MCV <90 per μm^3	1	—
INR <1.5	1	—
Modified score:		
Proteinuria <1.2 g/g of creatinuria	+1	+1
Interpretation[b]		
Unmodified score	≥6: high risk ≤5: low/ intermediate risk	2: high risk ≤1: low risk
Modified score	≥7: high risk ≤6: low/ intermediate risk	3: high risk ≤2: low risk

Abbreviations: aHUS, atypical haemolytic uraemic syndrome; INR, international normalised ratio; MCV, mean corpuscular volume; TTP, thrombotic thrombocytopenic purpura.
[a]Reticulocyte count >2.5%, or haptoglobin undetectable, or indirect bilirubin >2.0 mg/dL.
[b]Risk for TTP.
Adapted from Fage et al. [19], licensed under CC BY (https://creativecommons.org/licenses/by/4.0/).

As kidney function recovery is superior with a shorter interval between TMA occurrence and treatment start, C5 inhibitor therapy should be initiated within 3–5 days or earlier upon suspicion of aHUS and immediately upon a clinical diagnosis of aHUS. The panel suggests initial treatment for 6 months, focusing on achieving a stable haematological and kidney response. After 6 months, the decision to continue C5 inhibitor therapy and treatment duration should take into consideration the patient's aHUS individual risk profile (see Section 3.3).

3.1 | Vaccination Requirements

Inhibition of the terminal complement pathway predisposes individuals to heightened risk for meningococcal infection with encapsulated organisms such as *Neisseria meningitidis*. Patients should be vaccinated at least 2 weeks prior to initiating C5 inhibitor therapy. Vaccines against serogroups A, C, Y, W135 (and B where available) are strongly recommended. Prophylactic antibiotics (typically penicillin) for at least 2 weeks after vaccination are strongly recommended for patients commenced on C5 inhibitor therapy less than 2 weeks after receiving a meningococcal vaccine [21, 22]. Ongoing antimicrobial prophylaxis may also be recommended. Booster vaccines should be considered every 3–5 years, according to vaccine type and local label, in patients on long-term C5 inhibitor therapy.

3.2 | Genetic Testing

Genetic testing panels may include one or more genes known to be associated with aHUS: complement factor H (*CFH*), complement factor H-related (*CFHR*) proteins 1–5, complement factor I (*CFI*), *CD46* (membrane co-factor protein [*MCP*]), *C3*, complement factor B (*CFB*), thrombomodulin and diacylglycerol kinase epsilon [23]. Sequence analysis detects variants that are benign, likely benign, variants of unknown significance, likely pathogenic, or pathogenic; and may include small intragenic deletions/insertions and missense, nonsense, and splice-site variants. Gene-targeted analysis detects intragenic deletions or duplications. Multiplex ligation-dependent probe amplification screens for the *CFH* hybrid gene and copy number variation in *CFH* and *CFHR*s. Anti-CFH autoantibody testing detects antibodies that bind to the C terminal region of *CFH* [23]. As gene panel test availability and methods vary by country in the APAC region, algorithms can be tailored accordingly.

Because up to half of aHUS cases have no identifiable causative pathogenic gene variants [23, 24], and turnaround time for genetic or molecular diagnostic studies is typically 1–3 months, aHUS remains a clinical diagnosis. Nevertheless, genetic testing has several other important contributions to the management of aHUS [23–29]:

- To establish a definitive diagnosis in the case of a pathogenic gene variant(s).
- To establish the risk of relapse and progression to kidney failure.
- To inform the treatment plan (including decisions about discontinuing C5 inhibitor therapy).

- To inform decisions to transplant or identify donors (note: live-related donors are typically not considered regardless of genetic testing results)
- To inform genetic counselling for family members (recommended for pregnancy or organ donation only).

Candidates for genetic screening and molecular diagnostics include:

- All patients with severe TMA or complicated situations (e.g., not responding to appropriate and adequate treatment of the trigger).
- All patients with confirmed aHUS to assess risk for relapse.
- All patients being considered for C5 inhibitor treatment (although results are not required for aHUS diagnosis or treatment initiation).
- Prior to kidney transplant in all patients with a clinical suspicion or history of TMA/aHUS.
- In certain situations for patients on the transplant waitlist without a known aHUS diagnosis:
  - A red flag in the patient's medical history (e.g., history of malignant hypertension leading to kidney failure).
  - Kidney failure of uncertain cause in paediatric patients.
  - Family history of TMA/aHUS.
  - Evidence of TMA on kidney biopsy without a clear aetiology.
  - Presence of certain types of glomerulonephritides such as C3 glomerulonephritis and dense deposit disease.

Interpreting genetic test results is the most complex aspect of the diagnostic process. Identifying a complement gene variant does not establish its pathogenicity or how it translates to clinical presentation or subsequent relapse. This is particularly challenging in the transplant setting since genetic test results may be used to inform kidney transplant waitlists and patient management during the peri-transplant period. Where available, the panel recommends involvement of an experienced geneticist and genetic counsellor who specialise in kidney disease as this allows patients and families to make informed decisions about whether to proceed with genetic testing, facilitates cascade testing among family members, ensures understanding of the results and disease risk (detection of pathogenic variants, variants of unknown significance and no variants), and assists with family planning [30].

3.3 | Duration of C5 Inhibitor Therapy

There is currently no global consensus or guideline for optimal duration of C5 inhibitor therapy. A general recommendation is a minimum treatment period of 6 months after the acute phase of an aHUS diagnosis, irrespective of the nature of the triggering episodes, including at least 3 months' treatment after stabilisation or recovery of kidney function [31–33].

Discontinuing C5 inhibitor therapy can be considered after 6 months' treatment, taking into account the potential for recurrence according to a patient's individual risk profile. Factors to consider are the presence of complement abnormalities, including genetic variants (*CFH*, *C3*, *CFB*, *CFI* and *MCP*), history of prior TMA episodes or family history of aHUS, prior disease relapse, presence of severe extra-kidney manifestations, *CFH* autoantibodies, age at onset, and kidney transplantation. Prior to discontinuation, irrespective of the reason, it is necessary to establish the feasibility of rapid re-institution of C5 inhibitor therapy and to monitor the patient for signs of relapse. Monitoring involves regular evaluation of blood pressure, clinical features, and urinalysis for haemato-proteinuria, and laboratory investigations for MAHA (e.g., haemoglobin, platelet count, serum lactate dehydrogenase concentrations, haptoglobin and reticulocyte count). The frequency of monitoring is not clearly established but should be more frequent (weekly to fortnightly) in the early phase after treatment discontinuation, then at least every 3 months (in higher risk patients based on genetics/clinical risk factors) to 6 months for life. Patients can be advised to self-monitor at home using a urine dipstick (to detect haematuria and/or proteinuria), and to report any clinical symptoms or signs of relapse to clinicians, particularly during potential triggering events such as infections, vaccinations, surgery, and pregnancy. In the event of clinical relapse, rapid re-institution of C5 inhibition is essential.

4 | Pregnancy-Associated TMA/aHUS

4.1 | Overview of Available Literature

Pregnancy or its complications can trigger TMA and aHUS onset, often in patients with a genetic predisposition, but also in those without identified complement gene abnormalities [34]. The differential diagnosis of pregnancy-associated TMA includes TTP, other secondary TMAs, haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, pre-eclampsia/eclampsia and aHUS [35, 36]. TTP and severe pre-eclampsia/HELLP are more common in the second and third trimesters of pregnancy. TMA that occurs in the peripartum/postpartum period is suggestive of complement-mediated aHUS, although pregnancy-associated aHUS can occur in any trimester [36, 37]. Cohort studies have reported complement gene variants in 41%–56% of pregnant women with aHUS involving mainly the *CFH* gene [38–40]. Kidney outcomes in pregnancy-associated aHUS are better with than without C5 inhibitor therapy (Table S1) [34, 39–44]. Prompt initiation of C5 inhibitor therapy upon clinical suspicion of aHUS (ideally within 24 h) is associated with a higher likelihood of kidney recovery [31, 42, 43]. Clinical uncertainties with pregnancy-associated aHUS include its actual incidence, optimal duration of C5 inhibitor therapy (especially in patients with identifiable pathogenic gene variants), and risk of recurrence with subsequent pregnancies. Although safety data for C5 inhibitors in pregnancy are limited, eculizumab is generally regarded as safe, with no detection in breast milk and no documented adverse effect on complement levels in the newborn [45].

4.2 | Diagnosis and Management of Pregnancy-Associated TMA

A general algorithm for management of pregnancy-associated TMA is shown in Figure 1 [19, 31, 32, 34, 36, 38, 40–44, 46].

The first step is to exclude other causes of TMA. If appropriate investigations yield negative results or TMA continues post-delivery in patients with HELLP syndrome or pre-eclampsia/eclampsia, a diagnosis of aHUS must be considered. Serum levels of soluble fms-like tyrosine kinase receptor-1 (flt-1)/placental growth factor (PlGF) ratio may assist in assessing the risk of pre-eclampsia and differentiating it from aHUS [47].

5 | Hypertension-Associated TMA

5.1 | Overview of Available Literature

The prevalence of malignant hypertension reported in aHUS populations ranges from 6% to 54% [24, 48–50], which may be an overestimation given that aHUS/kidney disease often causes hypertension. Up to half (range: 0%–51.3%) of patients with TMA/aHUS and malignant hypertension and severe kidney disease have complement gene variants [24, 48, 49, 51–53] or other signs of complement involvement (e.g., C5b9 deposits in endothelial cells) [52, 54, 55]. Kidney outcomes in hypertension-associated aHUS are better with eculizumab relative to plasmapheresis or no treatment (Table S2) [48–50, 56].

5.2 | Diagnosis and Management of Hypertensive Emergency and TMA

A general algorithm for management of hypertensive emergency and TMA is shown in Figure 2 [26, 31, 32, 48–56].

The priority in patients presenting with TMA and hypertension is to control the blood pressure. An aHUS diagnosis can be suspected in patients with refractory hypertension or those with well-controlled blood pressure but persistent TMA. If investigations have excluded other causes of TMA, hypertension-associated aHUS can be diagnosed. In hypertensive emergencies where adequate control of blood pressure is difficult to achieve, especially in the presence of severe end-organ manifestations, concurrent use of a C5 inhibitor with escalation of antihypertensive treatment can be considered to reduce the risk of irreversible end-organ damage.

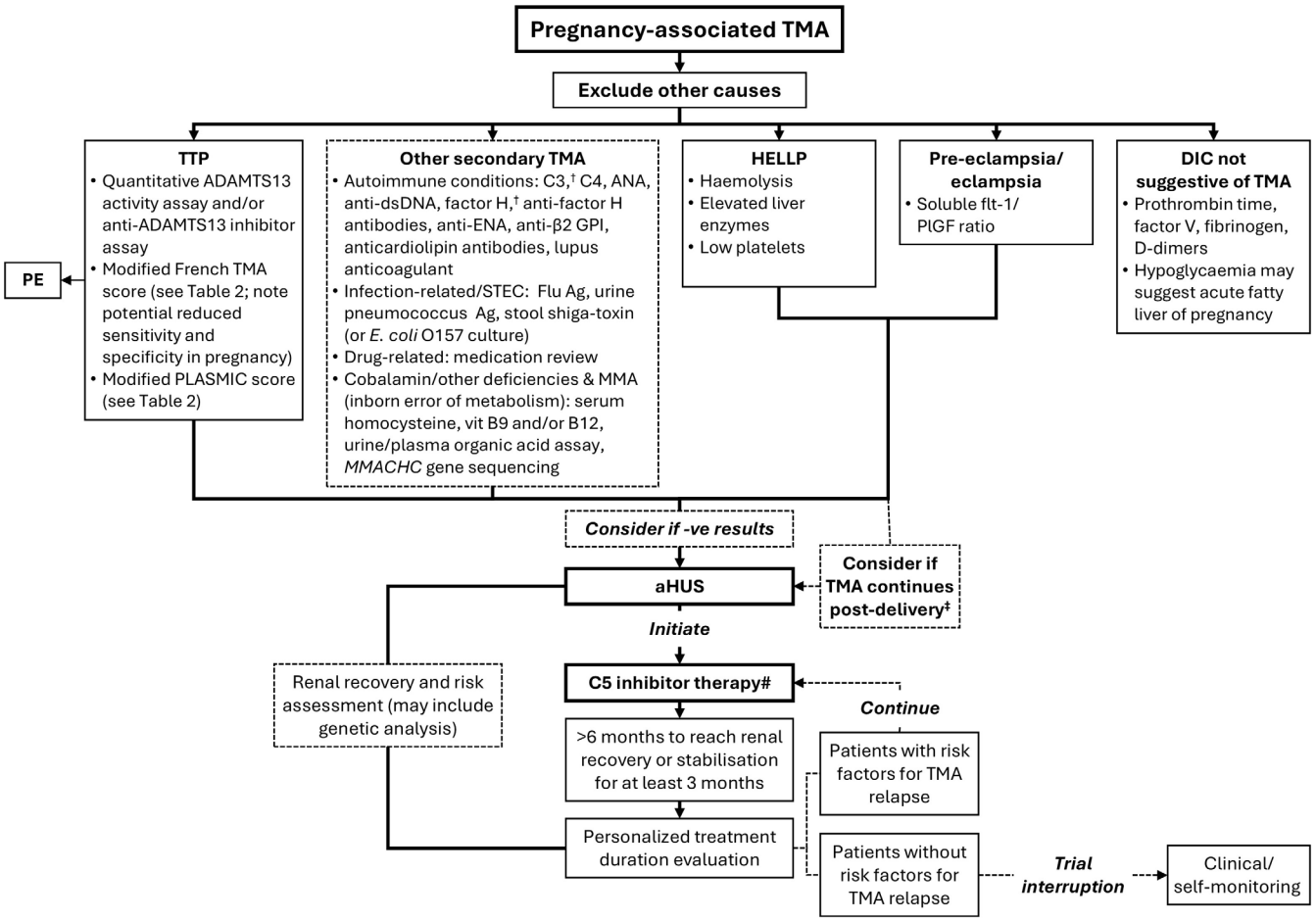

FIGURE 1 | Management of pregnancy-associated TMA [19, 31, 32, 34, 36, 38, 40–44, 46]. †Low C3 and/or low factor H or I plasma levels are suggestive of complement-mediated aHUS. ‡Kidney biopsy may be considered in cases with acceptable risk to confirm diagnosis (e.g., IgA-associated TMA, C3 glomerulopathy). #An aHUS genetic panel should be considered. ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; Ag, antigen; aHUS, atypical haemolytic uraemic syndrome; ANA, antinuclear antibody; anti-dsDNA, anti-double-stranded DNA; anti-ENA, anti-extractable nuclear antigen; C3, complement 3; C4, complement 4; C5, complement 5; DIC, disseminated intravascular coagulopathy; flt-1/PlGF, fms-like tyrosine kinase 1/placental growth factor; GPI, glycoprotein I; HELLP, haemolysis, elevated liver enzymes, low platelets; IgA, immunoglobulin A; MMA, methylmalonic acidaemia; PE, plasma exchange; STEC, Shiga toxin-producing *Escherichia coli*; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

6 | Autoimmune Disease-Associated TMA

6.1 | Overview of Available Literature

Precipitating factors for autoimmune-associated TMA/aHUS include catastrophic presentations of antiphospholipid syndrome (APS), systemic lupus erythematosus (SLE)/lupus nephritis, scleroderma and others [10, 14, 15, 57]. Autoimmune conditions refractory to conventional treatment may have an underlying pathophysiology of complement dysregulation [58]. Retrospective studies or systematic reviews of eculizumab in this setting have reported favourable outcomes in most patients (Table S3) [58–62]. However, the findings must be interpreted with caution as C5 inhibitor was used as add-on/rescue treatment in patients with autoimmune disease complicated by TMA and, as such, does not allow for direct comparisons of efficacy between C5 inhibitor therapy and other treatments such as plasma exchange.

6.2 | Diagnosis and Management of Autoimmune-Associated TMA

A general algorithm for management of autoimmune-associated TMA is shown in Figure 3 [1, 19, 31, 58–64].

A diagnosis of aHUS triggered by an autoimmune disease can be considered when other causes of TMA have been excluded and TMA persists despite conventional treatment of the autoimmune condition. The timeframe to initiate C5 inhibitor therapy depends on the type and severity of autoimmune disease at presentation and its response to treatment, although typically it is less than 1 week after initial presentation. Specific clinical examples for use of C5 inhibitor therapy include:

- Add-on treatment in patients with catastrophic APS who have not responded to plasma exchange and immunosuppression.
- Add-on treatment in patients presenting with SLE/lupus nephritis who have not responded to immunosuppressive therapy after 72–120 h, particularly those with evidence of central nervous system or cardiac involvement.
- Adjunctive treatment in patients with scleroderma who have failed frontline angiotensin-converting enzyme inhibitor therapy and have evidence of progressive kidney failure.

C5 inhibitor therapy in autoimmune-associated TMA should be continued at least until clinical and laboratory manifestations of TMA/MAHA have resolved. Continued administration of C5 inhibitor therapy should be considered carefully in patients for whom pathogenic gene variant(s) are identified.

7 | Drug-Induced TMA

7.1 | Overview of Available Literature

Drugs reported to induce TMA/aHUS include calcineurin inhibitors (tacrolimus, cyclosporin), mammalian target of rapamycin inhibitors (sirolimus, everolimus) and anti-cancer therapies such as carfilzomib, docetaxel + doxorubicin, gemcitabine, mitomycin and angiogenesis inhibitors (e.g., bevacizumab). As the patient population with drug-induced TMA is more heterogeneous relative to other trigger conditions, estimates of the true prevalence of aHUS and outcomes following C5 inhibitor therapy remain poorly defined. As per available literature, pathogenic gene mutations were identified in some patients with drug-induced TMA; however, in most cases, genetic studies were not reported or performed (Table S4) [59, 65–73].

7.2 | Diagnosis and Management of Drug-Induced TMA

A general algorithm for management of drug-induced TMA is shown in Figure 4 [15, 59, 65–73].

Initial management of drug-induced TMA involves withdrawing the offending agent and managing any underlying concurrent trigger (if present). If TMA persists despite withdrawal of the suspected drug (for at least 1–2 weeks or 3–5 drug half-lives) and exclusion of other causes of TMA, a diagnosis of aHUS can be considered. Although most patients with drug-induced aHUS respond to C5 inhibitor therapy, treatment should be considered only when TMA persists despite drug withdrawal.

8 | Infection-Triggered TMA

8.1 | Overview of Available Literature

As a result of immune system activation, TMA can be induced by various bacteria and viruses, including COVID-19. Infection-triggered TMA is more common in paediatric populations. Although severe infections can damage the endothelium directly, infection-triggered aHUS is more likely to occur in susceptible patients with complement gene abnormalities. In the setting of severe systemic infection, infection-related disseminated intravascular coagulation must be ruled out since it has a similar presentation but a different pathogenesis to aHUS [74]. Single-patient case studies have reported benefit with eculizumab in many, but not all, patients with infection-triggered aHUS. Genetic abnormalities in complement-related factors that predispose to aHUS were identified in about half of cases reported in the literature (Table S5) [75–86].

8.2 | Diagnosis and Management of Infection-Triggered TMA

Infection-triggered TMA is managed by treating the underlying infection and monitoring the patient for persistent TMA activity. An aHUS diagnosis can be considered in cases with recurrent TMA, especially following resolution of infective episodes; genetic analysis might be performed for these cases. C5 inhibitor therapy is generally not considered necessary for infection-triggered TMA since evidence for its efficacy is limited, although it needs to be considered in patients with

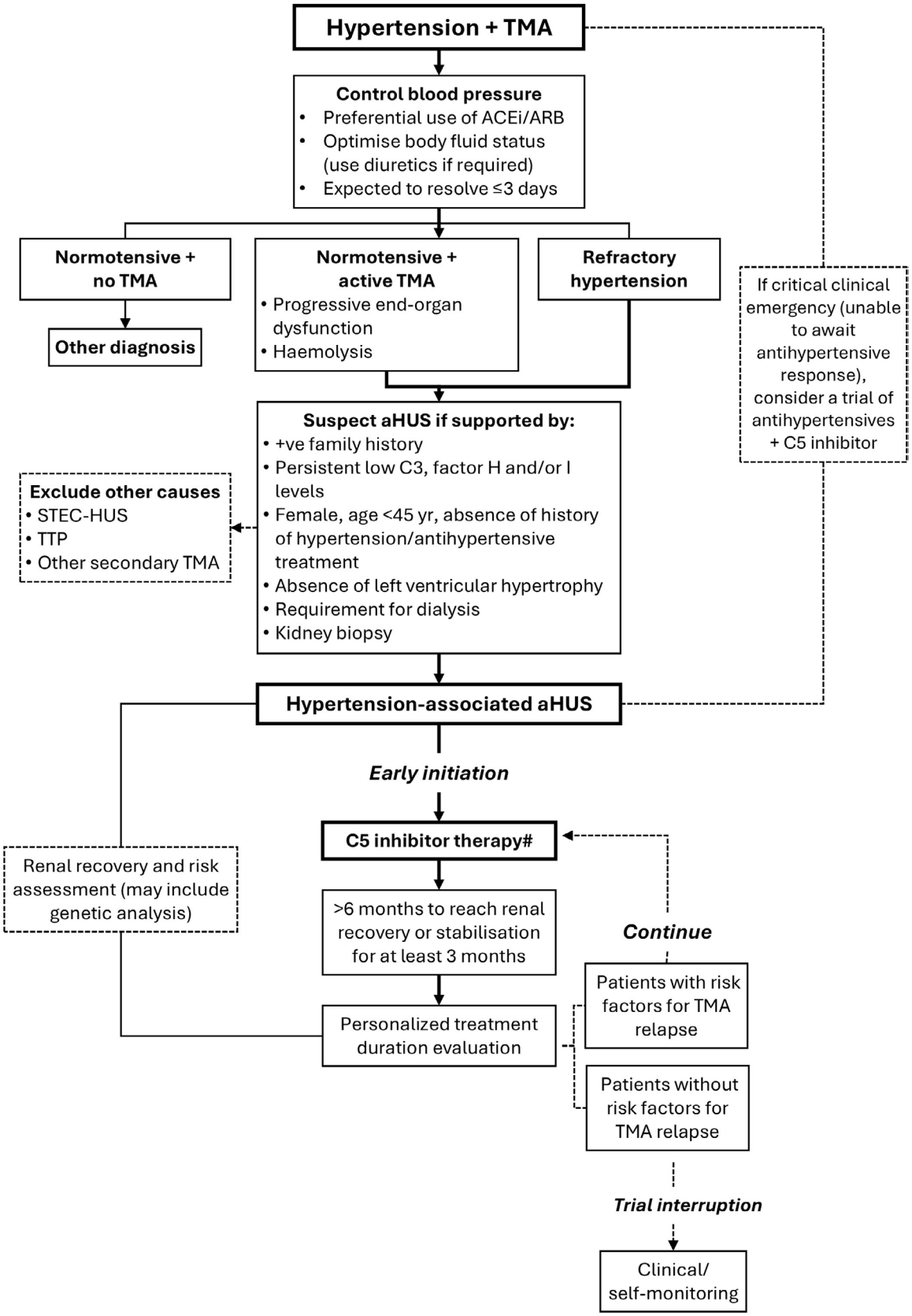

FIGURE 2 | Management of hypertensive emergency and TMA [26, 31, 32, 48–56]. #An aHUS genetic panel should be considered. ACEI, angiotensin converting enzyme inhibitor; aHUS, atypical haemolytic uraemic syndrome; ARB, angiotensin II receptor blocker; C3, complement 3; C5, complement 5; STEC, Shiga toxin-producing *Escherichia coli*; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

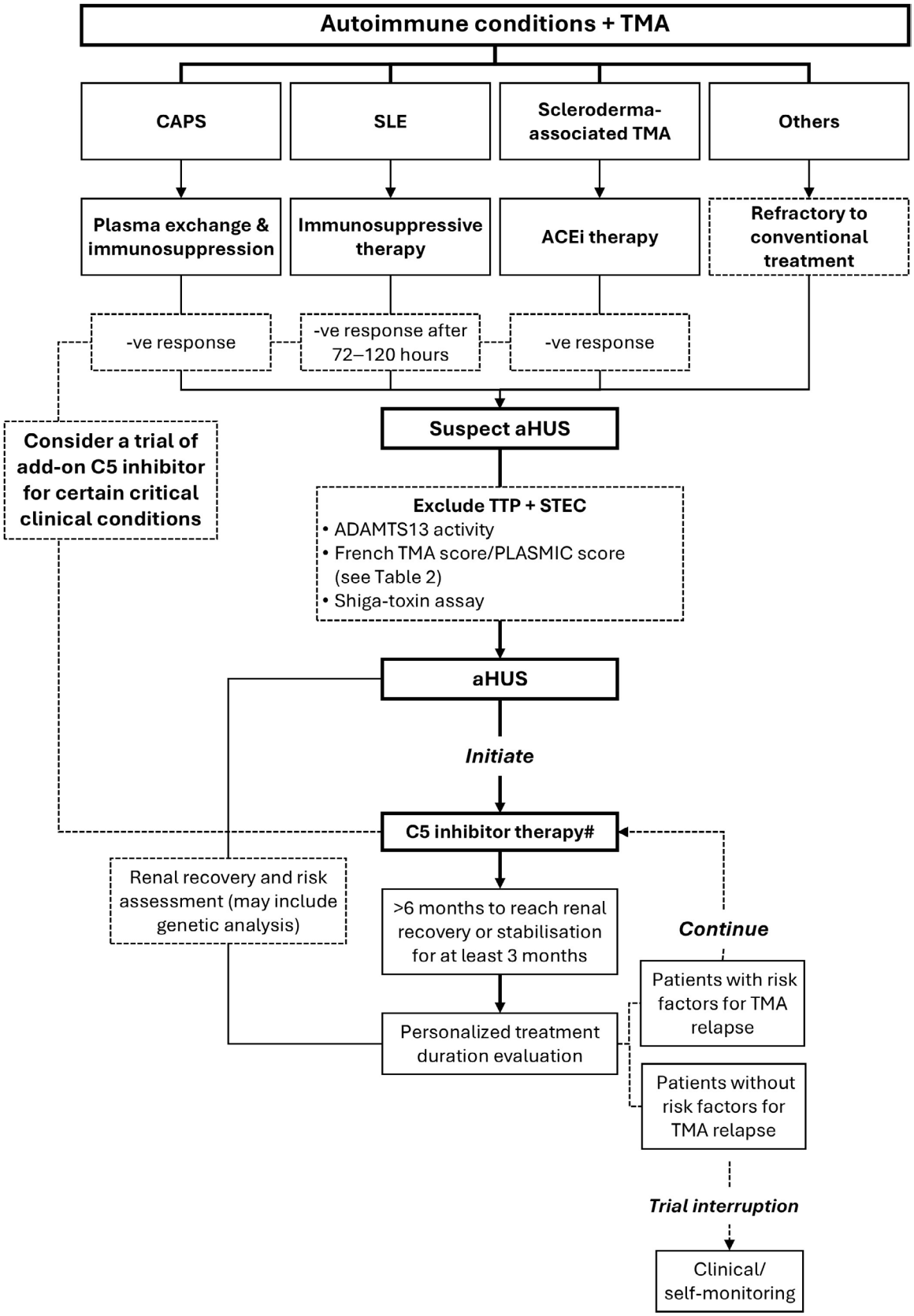

FIGURE 3 | Management of autoimmune disease-associated TMA [1, 19, 31, 58–64]. #An aHUS genetic panel should be considered. ACEI, angiotensin converting enzyme inhibitor; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS, atypical haemolytic uraemic syndrome; CAPS, catastrophic antiphospholipid syndrome; C5, complement 5; SLE, systemic lupus erythematosus; STEC, Shiga toxin-producing *Escherichia coli*; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

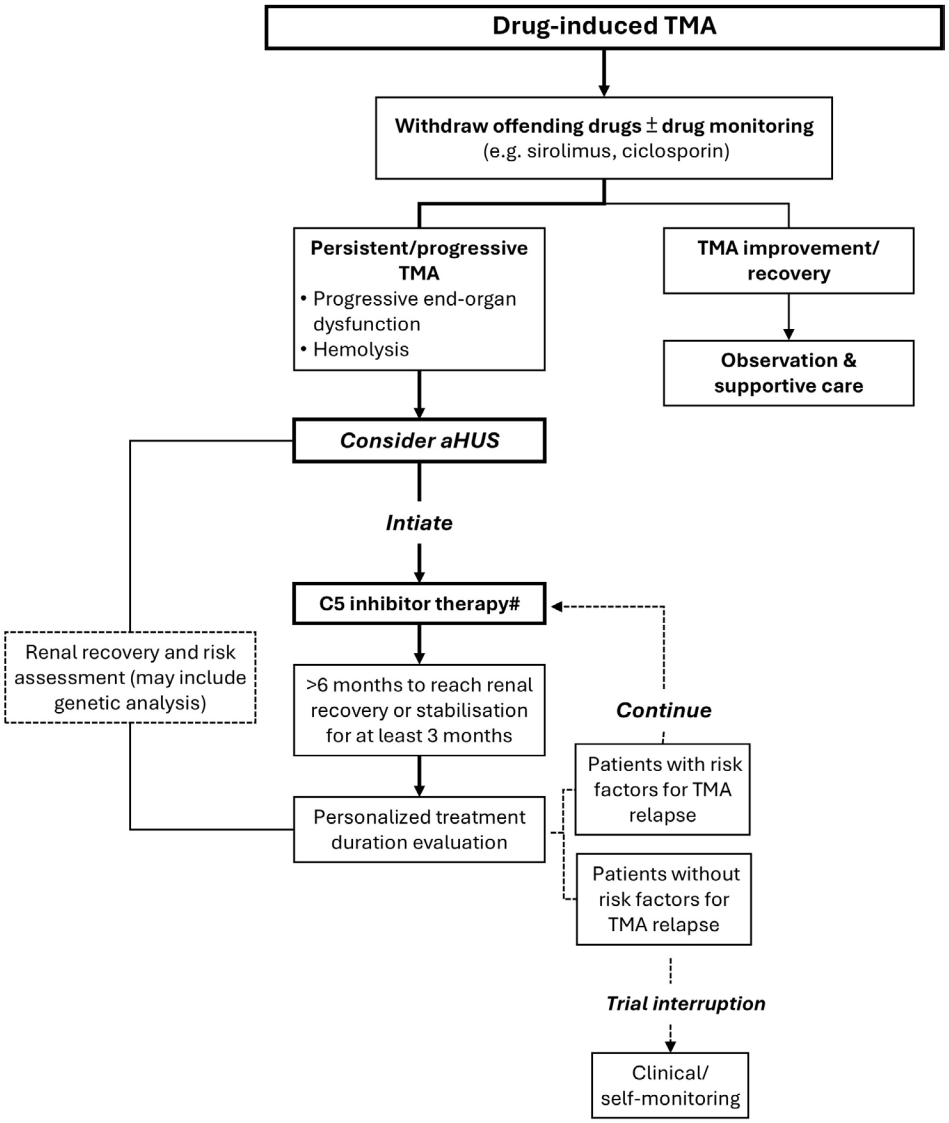

FIGURE 4 | Management of drug-induced TMA [15, 59, 65–73]. #An aHUS genetic panel should be considered. aHUS, atypical haemolytic uraemic syndrome; C5, complement 5; TMA, thrombotic microangiopathy.

persistent or recurrent TMA despite resolution of the infective event. Even though STEC-HUS must be excluded to establish the diagnosis of aHUS, there are reports that STEC can trigger the presentation of aHUS [86]. In certain countries (e.g., Korea) evidence of infection is an exclusion criterion for prescribing C5 inhibitor therapy.

9 | Kidney Transplant-Associated TMA

9.1 | Overview of Available Literature

TMA that occurs after kidney transplant may be disease recurrence in a patient whose primary condition is aHUS, or new onset and previously unrecognised aHUS, or post-transplant TMA associated with organ transplant. Transplant-specific factors such as ischaemia/reperfusion injury, acute rejection, infection, and immunosuppressive drugs can trigger an acute TMA event or disease recurrence in patients with known aHUS. Pathogenic variants are common (60%–80%) in the kidney transplant population [87–90]. Mutations in *CFH*, *CFI* and *CFB* genes are particularly associated with poor kidney transplant survival [91, 92]. Graft survival rates of 65%–100% were reported when eculizumab was used therapeutically for post-transplant aHUS recurrence [88, 93, 94].

9.2 | Management of Kidney Transplant-Associated TMA

A general algorithm for management of kidney transplant-associated TMA is shown in Figure 5 [1, 64, 91–96].

Patients with known aHUS under consideration for kidney transplantation should undergo mandatory genetic profiling to establish risk for post-transplant TMA recurrence. Those at moderate or high risk of recurrence (e.g., mutations in *CFH/I/B* genes or prior allograft failure from recurrence) should receive C5 inhibitor therapy up to and including the day of surgery or an initial dose prior to reperfusion. Lifelong C5 inhibitor

therapy after transplantation is generally advised for patients with pathogenic gene mutations known to cause recurrence and those who have experienced life-threatening disease or prior allograft failure from recurrent aHUS. Irrespective of the perceived risk for disease recurrence, post-transplant monitoring for TMA should be undertaken. Although the ideal frequency of clinical and self-monitoring remains uncertain, monitoring is especially critical if a decision has been taken to discontinue C5 inhibitor treatment or the patient experiences episode(s) of trigger events such as acute rejection or infections (even in patients maintained on a C5 inhibitor).

10 | Summary Tables

Table 3 summarises access to and turnaround times for essential diagnostic assays and genetic testing, and reimbursement criteria for C5 inhibitor therapy, in APAC countries where C5 inhibitors are in use.

Table 4 summarises characteristics and outcomes of aHUS in the presence of triggers, based on clinical studies/case reports presented in Tables S1–S5, the kidney transplant literature [87–90, 93, 94], and the collective expertise of the panel members.

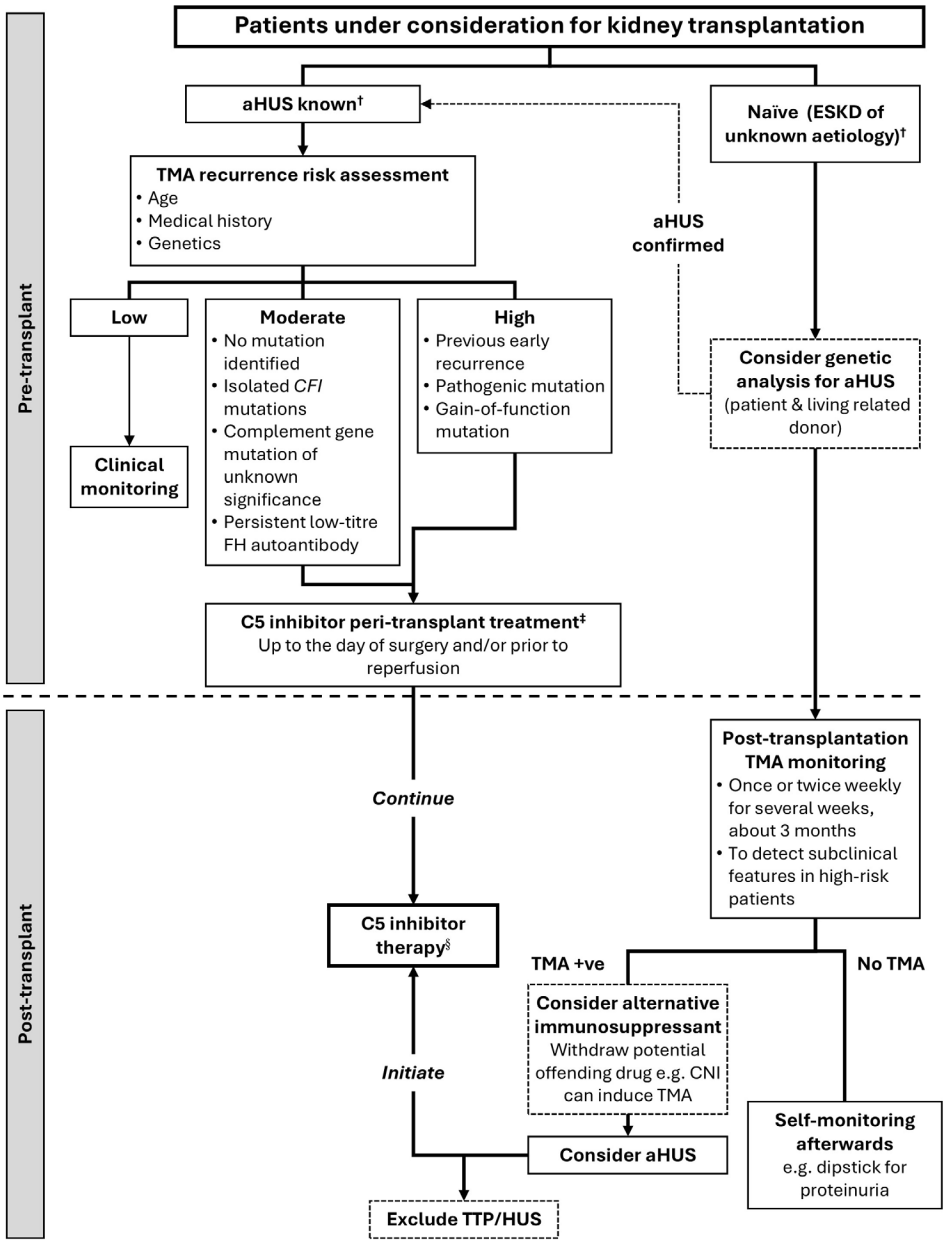

FIGURE 5 | Management of kidney-transplant-associated TMA [1, 64, 91–96]. †In South Korea, TMA that occurs in kidney transplant recipients with aHUS or CKD of unknown origin is an indication for C5 inhibitors in the absence of other causes. ‡In the APAC region, the feasibility of C5 inhibitor prophylaxis depends on country-specific approval procedures and whether prophylactic use is funded. §Discontinuation requires extreme caution in patients with CKD stages G3b–G5 and kidney transplant recipients. aHUS, atypical haemolytic uraemic syndrome; APAC, Asia-Pacific; C5, complement 5; CFI, complement factor I; CKD, chronic kidney disease; CNI, calcineurin inhibitor; ESKD, end stage kidney disease; FH, factor H; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

TABLE 3 | Country-specific availability of, and turnaround times for, essential diagnostic assays and genetic testing, and reimbursement criteria for C5 inhibitor therapy in APAC countries where C5 inhibitors are in use.

Country	Testing for ADAMTS13 activity (turnaround time)	Detection of Shiga toxin (turnaround time)	aHUS genetic panel (turnaround time)	Reimbursement of C5 inhibitor therapy (initial approved duration)	Established treatment criteria for reimbursement (list)
Australia	Widely available (< 1–3 days)	Widely available (< 1–3 days)	Selected sites (> 3 months)	Yes (6 months)	Yes (excluded TTP and STEC-HUS)
Hong Kong	Widely available (< 1–7 days)	Widely available (< 1–7 days)	Selected sites (2–4 weeks)	Yes (at physician's discretion, but usually 12 months and subject to renewal)	Yes (excluded secondary HUS[a])
Japan	Selected sites (< 1–3 days)	Widely available (< 1–3 days)	Selected sites (> 1–2 months)	Yes (not defined)	Yes (complement-mediated TMA)
South Korea	Selected sites (< 1–3 days) About 2 weeks for sites using a central laboratory	Widely available (< 1–3 days)	Selected sites (> 1–2 months)	Yes (approval needed from HIRA; additional approval needed every 6 months)	Yes (confirmed diagnosis of aHUS and evidence of active, progressing TMA; excluded STEC-HUS)
Taiwan	Selected sites (< 1–3 days)	Widely available (< 1–3 days)	Selected sites (within 1 month)	Yes (approval needed from NHIA; additional approval needed every 6 months)	Yes (excluded TTP and other secondary TMA[a])

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with thrombospondin motifs, member 13; aHUS, atypical haemolytic uraemic syndrome; APAC, Asia-Pacific; HIRA, Health Insurance Review & Assessment; HUS, haemolytic uraemic syndrome; NHIA, National Health Insurance Administration; STEC-HUS, Shiga-like toxin-producing *Escherichia coli* haemolytic uraemic syndrome; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

[a]Refers to non-complement-mediated TMA or HUS syndromes.

TABLE 4 | Characteristics and outcomes of aHUS in the presence of triggers.

Trigger type	Initial treatment before suspicion of aHUS	Likelihood of aHUS	Prevalence of pathogenic gene variants	Kidney biopsy consideration	Response to C5 inhibitor therapy (survival)
Pregnancy	Delivery/blood pressure control, or Supportive care for postpartum complications	Post-partum occurrence	41%–56% [38–40]	Rarely reported; diagnosis is mainly clinical	Yes (improved survival and renal outcomes; complete renal recovery rates up to 88% if treated early) [39, 42, 43]
Hypertension	Blood pressure control	Persistent TMA/MAHA despite adequate blood pressure control	35%–56% [48–50, 56]	Not commonly done; diagnosis is based on clinical criteria and response	Yes (improved renal survival; up to 100% 5-year survival) [48–50, 56]
Autoimmune disease	Immunosuppressants or corticosteroids for APS/SLE	Persistent TMA/MAHA despite targeted treatment of underlying autoimmune disease	Reported in 6 of 10 [58] and in 1 of 4 [59] patients tested	More likely due to differential diagnosis with lupus nephritis/TMA	Yes (favourable haematologic and kidney responses; renal recovery rates > 70%) [58, 60, 61]
Drugs	Drug discontinuation	Diagnosis after exclusion and poor response to drug withdrawal	Often not tested; some cases reported with *CFH/CFHR3-1* deletions [68, 72, 73]	Sometimes used; TMA findings can support diagnosis	Variable (haematologic remission common, kidney recovery varies; among 17 aHUS cases with clearly reported kidney outcomes, 5 had complete kidney recovery, 6 had partial kidney improvement; 6 had no kidney recovery) [59, 65–67, 69–73]

(Continues)

TABLE 4 | (Continued)

Trigger type	Initial treatment before suspicion of aHUS	Likelihood of aHUS	Prevalence of pathogenic gene variants	Kidney biopsy consideration	Response to C5 inhibitor therapy (survival)
Infection	Antibiotics and supportive therapy	Based on TMA features after infection resolution or failure of supportive therapy	Heterogeneous: reports of *CFH/C3/MCP* mutations or risk haplotypes; *CFHR1/CFHR3* and *CFHR1–CFHR4* gene deletions and anti-CHF antibodies [76–78, 80, 82, 85, 86]	Occasionally considered but not standard	High rates of haematologic remission; kidney outcomes variable (among 10 aHUS cases with clearly reported kidney outcomes, 3 had complete kidney recovery, 4 had partial kidney improvement; 3 had no kidney recovery) [77, 79–86]
Kidney transplant	Exclude acute rejection and consider changing to alternative CNI or CNI-free regimen	TMA in kidney allograft (biopsy) with no evidence of acute rejection	60%–80% [87–90]	Biopsy often used to differentiate from antibody-mediated rejections or recurrence	Yes. 65%–100% graft survival when used therapeutically after recurrence [88, 93, 94]

Abbreviations: aHUS, atypical haemolytic uraemic syndrome; APS, antiphospholipid syndrome; CNI, calcineurin inhibitors; MAHA, microangiopathic haemolytic anaemia; SLE, systemic lupus erythematosus; TMA, thrombotic microangiopathy.

11 | Discussion

Substantial progress in understanding the pathophysiology of aHUS has led to improved identification and diagnosis of patients with aHUS, including in the APAC region. The availability of complement inhibitors has dramatically improved patient outcomes by preventing or slowing progression to kidney failure and improving survival. Wider availability of genetic testing for pathogenic variants, alongside greater characterisation and understanding of the underlying predisposition to aHUS, and the role of triggering events in the development of TMA/aHUS, is a cornerstone of personalised medicine for patients presenting with TMA. Nevertheless, knowledge gaps remain (e.g., validated biomarkers to predict disease recurrence); and some APAC countries face the ongoing challenge of gaining timely access to C5 inhibitor therapy.

Due to the rarity of aHUS and associated diagnostic challenges, many clinicians have minimal experience managing patients with this disease. Our aim was to provide a clinically relevant and practical framework, including the role of C5 inhibitor therapy, that primary healthcare providers and clinicians in other specialties can apply when managing patients presenting with TMA in the context of various triggers. The diagnostic and treatment algorithms present best clinical practice across the APAC region as informed by published clinical evidence and the expertise of panel members. The algorithms are not designed to be a definitive treatment plan but are clinical guides that can be refined to reflect country-specific variations in patient presentation, management approaches, and prescription of C5 inhibitor therapy.

Author Contributions

All authors contributed to manuscript preparation, accept responsibility for the entire content of this manuscript, have consented to its submission to the journal and reviewed the results and approved the final version of the manuscript.

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Conflicts of Interest

H.G.K. has received grants from Amgen, Apellis Pharmaceuticals, AstraZeneca, Bayer, Boehringer Ingelheim and Kyowa Kirin outside the submitted work; has received consulting fees from Bayer and Kyowa Kirin outside the submitted work; has received honoraria from Alexion, AstraZeneca, Handok and Kyowa Kirin outside the submitted work and has participated on an Advisory Board for Bayer outside the submitted work. D.H. has received speaker's fees and fees for advisory boards from Alexion, AstraZeneca, Novartis and Sobi outside the submitted work. N.K. and W.H.L. have received honoraria from Alexion. J.S.K. has received honoraria from AstraZeneca, Handok and Novartis outside the submitted work; has received fees for advisory boards from AstraZeneca, Handok, Novartis and Roche outside the submitted work. M.O. and M.-H.T. have received honoraria and advisory role fees from Alexion. K.-H.T. and D.Y.H.Y. have no conflicts of interest to declare.

Data Availability Statement

The source materials (published clinical studies and case reports) presented during the meeting and used to develop diagnostic and treatment algorithms are available in Tables S1–S5.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** nep70116-sup-0001-Supinfo.docx.