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ILLUSTRATED REVIEW

Thrombotic microangiopathies: An illustrated review

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Abstract

The thrombotic microangiopathies (TMAs) are a heterogenous group of disorders with distinct pathophysiologies that cause occlusive microvascular or macrovascular thrombosis, and are characterized by microangiopathic hemolytic anemia, thrombocytopenia, and/or end-organ ischemia. TMAs are associated with significant morbidity and mortality, and data on the management of certain TMAs are often lacking. The nomenclature, classification, and management of various TMAs is constantly evolving as we learn more about these rare syndromes. Thorough clinical and laboratory evaluation is essential to distinguish various TMAs and arrive at an accurate diagnosis, which is key for appropriate management. In this illustrated review, we focus on thrombotic thrombocytopenic purpura (TTP), Shiga toxin–associated hemolytic uremic syndrome, complement-mediated hemolytic uremic syndrome, hematopoietic cell transplant-associated TMA, and drug-induced TMA, and describe their incidence, pathophysiology, diagnosis, and management. We also highlight emerging complement-directed therapies under investigation for the management of complement-mediated TMAs.

KEYWORDS
atypical hemolytic uremic syndrome, hemolytic uremic syndrome, management, pathophysiology, thrombotic microangiopathies, thrombotic thrombocytopenic purpura

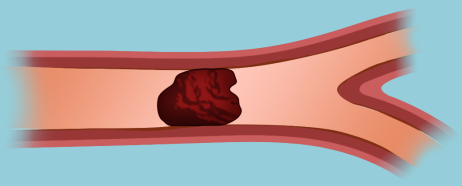
Essentials

- Thrombotic microangiopathies (TMAs) are a diverse group of rare, life-threatening disorders.
- We review the incidence, pathophysiology, evaluation, and management of various TMAs.
- Thorough evaluation is essential to distinguish TMAs, as management relies on accurate diagnosis.
- Several complement-directed therapies are emerging in the treatment of complement-mediated TMAs.

Definition & Characteristics

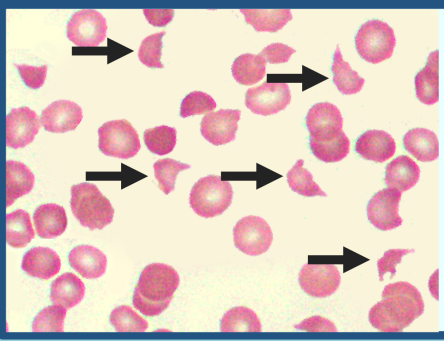
Thrombotic Microangiopathy (TMA)

is an overarching term that encompasses a highly diverse group of disorders with unique pathophysiologies.



- Describes occlusive microvascular or macrovascular disease, often with intraluminal thrombus formation [1,2], characterized by:

Microangiopathic Hemolytic Anemia (MAHA)



Classically characterized by many of the following:

↑ Lactate dehydrogenase
↑ Indirect bilirubin
- Negative direct antiglobulin test
↓ Haptoglobin
↑ Reticulocytes

- **Microangiopathy:** fragmented red blood cells seen on peripheral smear (schistocytes)

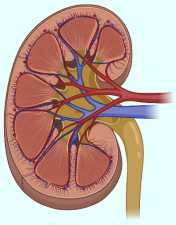
and

Non-Immune Thrombocytopenia

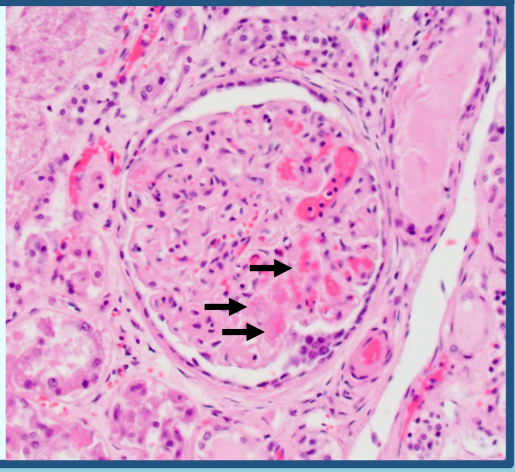
and/or

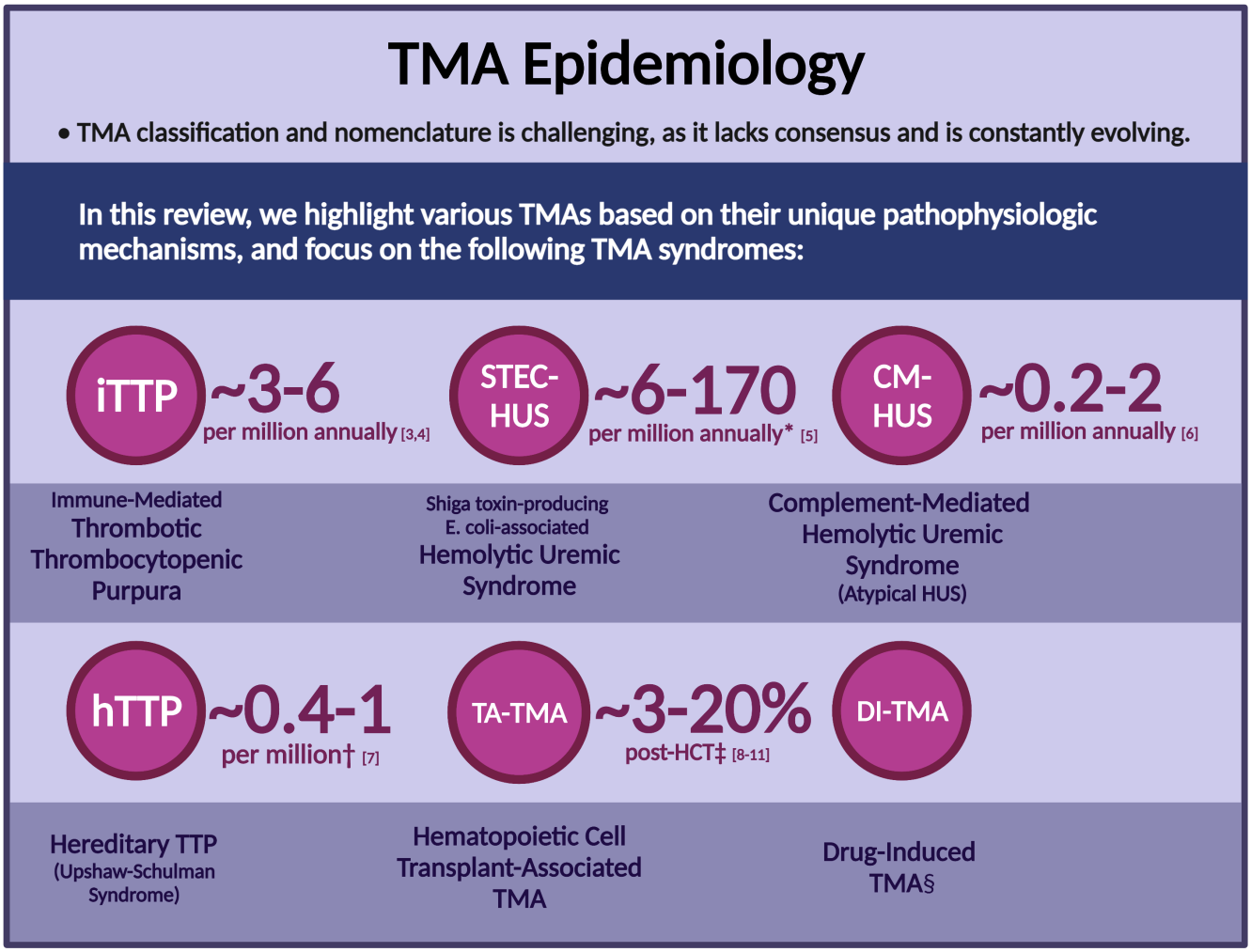
End-Organ Ischemia

- Varying degrees of organ ischemia/infarction (e.g. brain, heart, kidneys), often associated with high morbidity or mortality



- Focal TMA refers to microvascular thrombosis seen histologicaly, without peripheral MAHA or thrombocytopenia





* varies by age and geographic location
† worldwide genetic prevalence. Prevalence may be higher in certain geographic locations [12]
‡ available studies vary in their definition of TA-TMA and report cumulative incidence over different follow-up durations
§ incidence is unknown and varies with drug type

Diagnostic Evaluation

Initial Evaluation

- History, physical, and careful medication review
- Complete blood count with differential
- Reticulocyte count
- Peripheral blood film
- Renal and hepatic function
- Direct & indirect bilirubin
- Haptoglobin
- Lactate dehydrogenase
- Direct antiglobulin test (if hemolysis is present)
- Fibrinogen, D-dimer, PT, PTT
- Imaging studies/additional work-up as indicated

Thrombotic Microangiopathy

identified based on presence of MAHA, thrombocytopenia +/- end-organ involvement*

- Send ADAMTS13 activity

TTP

PLASMIC score
A score of ≥ 6 confers high pre-test probablity of TTP [13]. It takes into account:

Kidney injury is mild or absent, vs other TMAs (severe)

Coagulopathic findings are absent, their presence may suggest DIC

ADAMTS13 activity
Severe deficiencies (<10%) are characteristic of TTP [14]

Mild/moderate deficiencies can be seen in other TMAs

- **ADAMTS13 inhibitor or antibody** — A positive test highly suggests immune TTP
- **Genetic testing** — evaluates for hereditary TTP

STEC-HUS

Stool shiga-toxin
confirms diagnosis

Other infections, such as **Streptococcus Pneumoniae** can cause infection-induced HUS

CM-HUS

Clinical diagnosis
of exclusion

Genetic Testing
(CFH, CFI, CFB, MCP, C3) evaluates for hereditary causes

CFH antibody
may identify autoimmune cause when suspected. CFI antibodies have been reported, but their significance is unclear [15]

Serum complement levels
(CH50, C5b-9 C3, C4) are neither sensitive nor specific

TA-TMA

- **Hypertension** is a common presenting finding
- **Kidney involvement** is a hallmark of TA-TMA, other organs may be involved
- TMA may be **focal** (absent peripheral MAHA) [16], and may overlap with DI-TMA

Clinical diagnosis

Several **diagnostic criteria** have been developed to aid in diagnosis [16,17], as well as a recently developed **prognostic model** [18]

DI-TMA

Clinical Diagnosis

- **Based on clinical features and temporal relationship with known causative drug, after excluding other causes**
- Certain drugs may cause iTTP [20-22], which may be confused with DI-TMA. In DI-TMA, severe ADAMTS13 deficiency is absent.

Immune
- Onset is usually acute [19]
- **Drug-dependent antibody** testing may help identify culprit drug, but does not rule out diagnosis [1]

Non-immune
- Onset is usually gradual and dose-dependent [1]

Other TMAs

The following diseases and syndromes can cause TMA:

- **DIC**
- **Hypertensive Crisis**
- **Infections** (e.g. HIV, HCV, CMV, COVID19)
- **Neoplastic** (e.g. MDS, PCD, solid tumors)
- **Rheumatologic** (e.g. antiphospholipid syndrome, SLE, systemic sclerosis, vasculitis, connective tissue disease)
- **Pregnancy-associated** (e.g. preeclampsia, HELLP)
- **Metabolism-mediated TMA** (e.g. defective B12 metabolism, due to *MMACHC* gene mutation)
- **Coagulation-mediated TMA** (e.g. genetic mutations in DGKE, thrombomodulin, plasminogen)

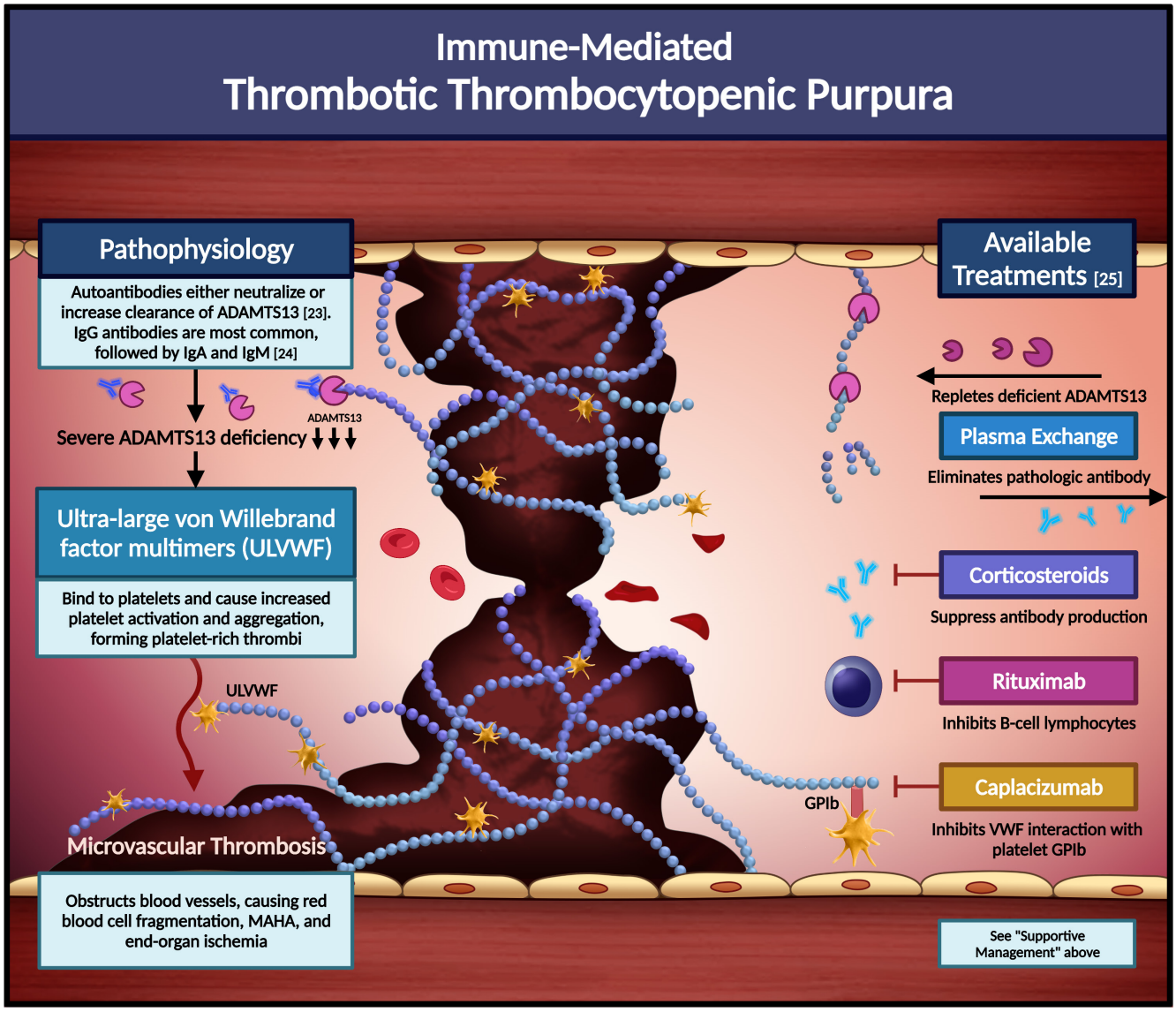
Supportive Management

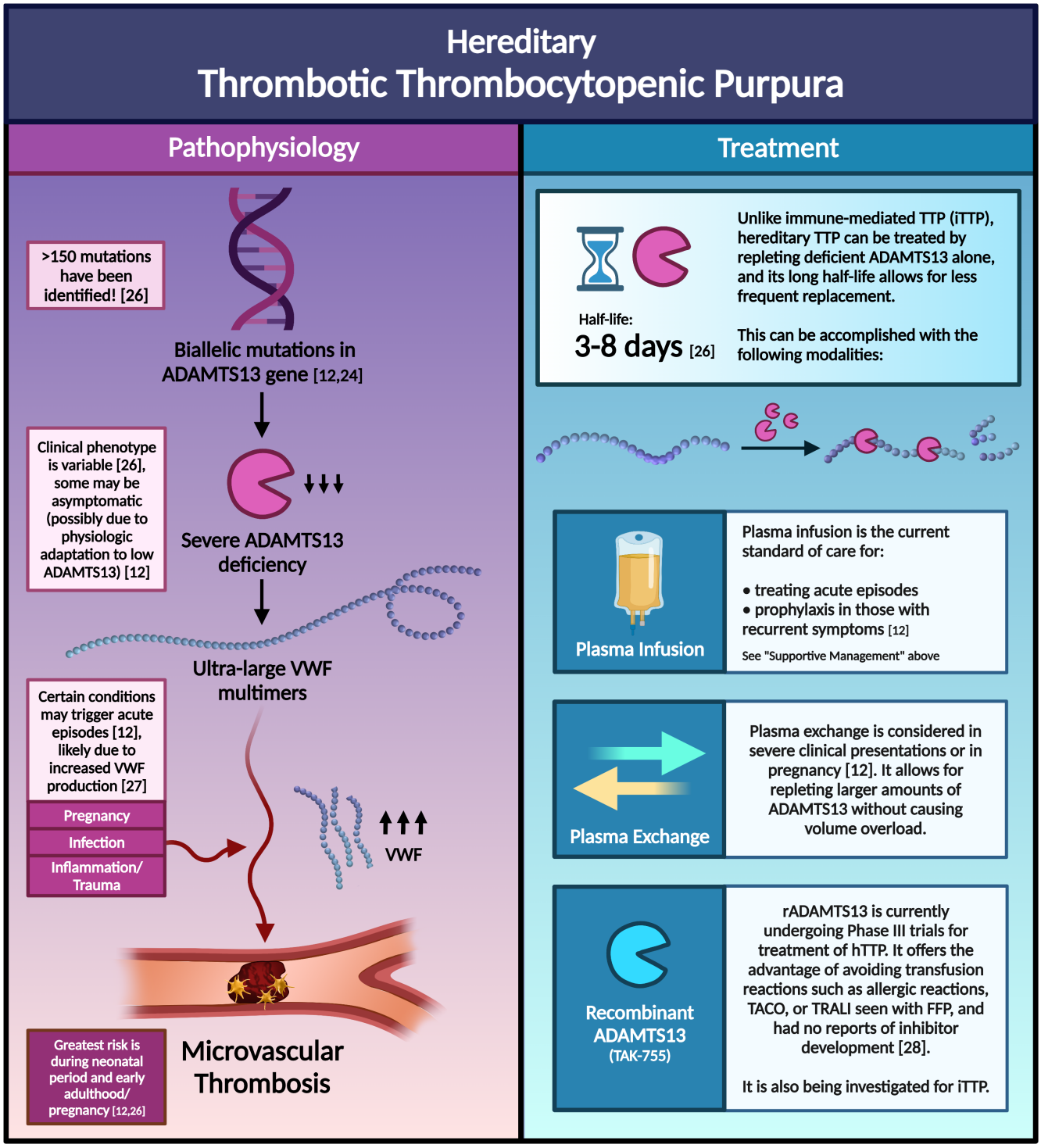
We discuss the pathophysiology and management of individual TMAs in detail below.
General principles of initial supportive management apply to most TMAs, regardless of pathophysiology:

- Support renal function with careful management of blood pressure, fluids, and electrolytes, and RRT as needed.
- Support erythropoiesis with hematinics (e.g. folic acid), and ESAs in cases of severe renal dysfunction.
- RBC transfusions as needed. Platelet transfusions may be considered for limb/organ/life-threatening bleeding.
- PLEX is initiated whenever iTTP is suspected, and can be considered in select cases of other TMAs (discussed separately)

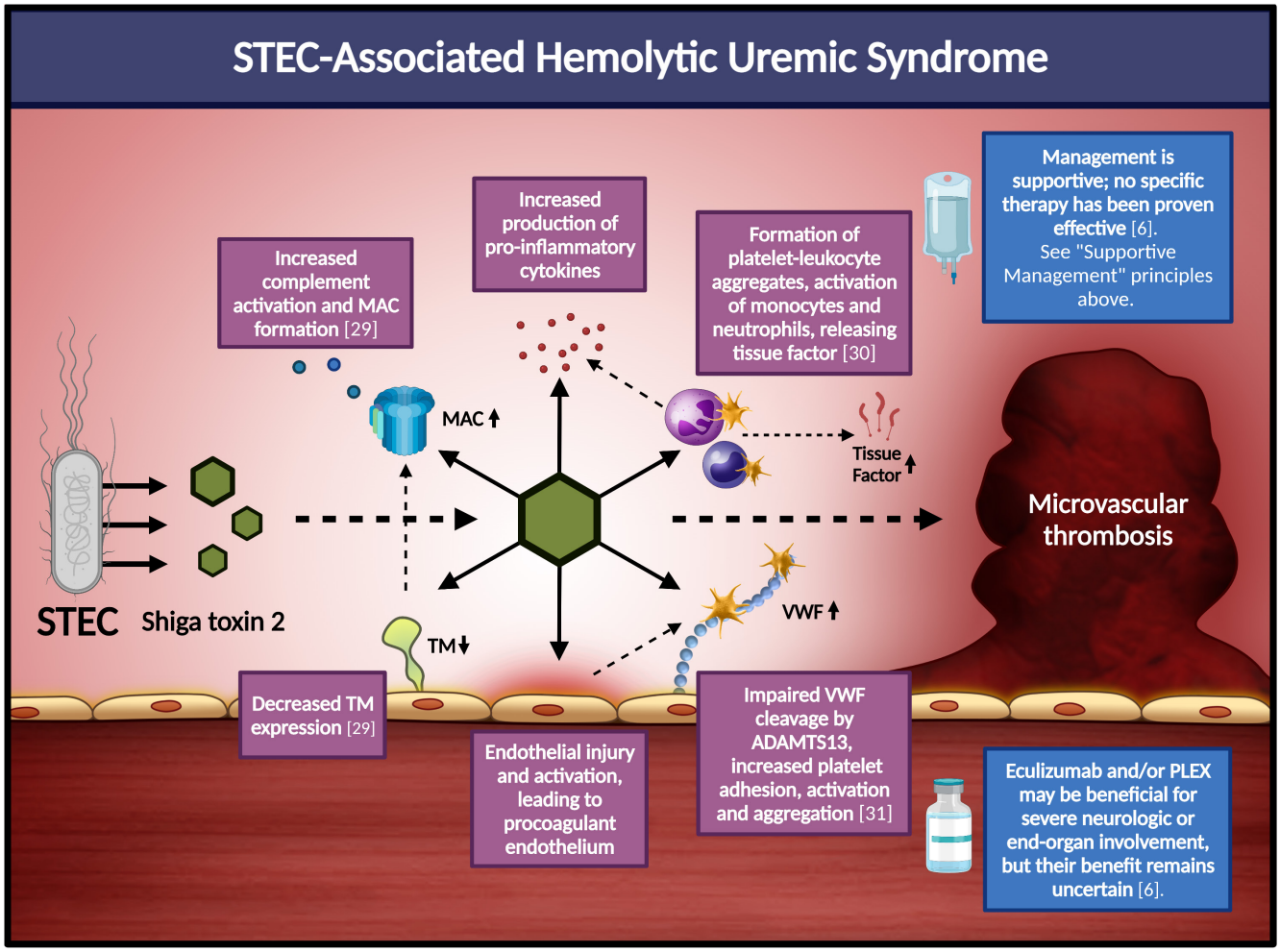
*See "Definition & Characteristics" above

CFH, complement factor H; CFI, complement factor I; DIC, disseminated intravascular coagulation; CM-TMA, complement-mediated hemolytic uremic syndrome; DI-TMA, drug-induced thrombotic microangiopathy; ESA, erythropoietin-stimulating agent; HELLP, hemolysis, elevated liver enzymes and low platelets; MAHA, microangiopathic hemolytic anemia; MDS, myelodysplastic syndrome; PCD, plasma cell dyscrasias; PLEX, plasma exchange; RBC, red blood cell; RRT, renal replacement therapy; SLE, systemic lupus erythematosus; STEC-HUS, Shiga toxin-producing E. coli-associated hemolytic uremic syndrome; TA-TMA, hematopoietic cell transplant-associated thrombotic microangiopathy; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura

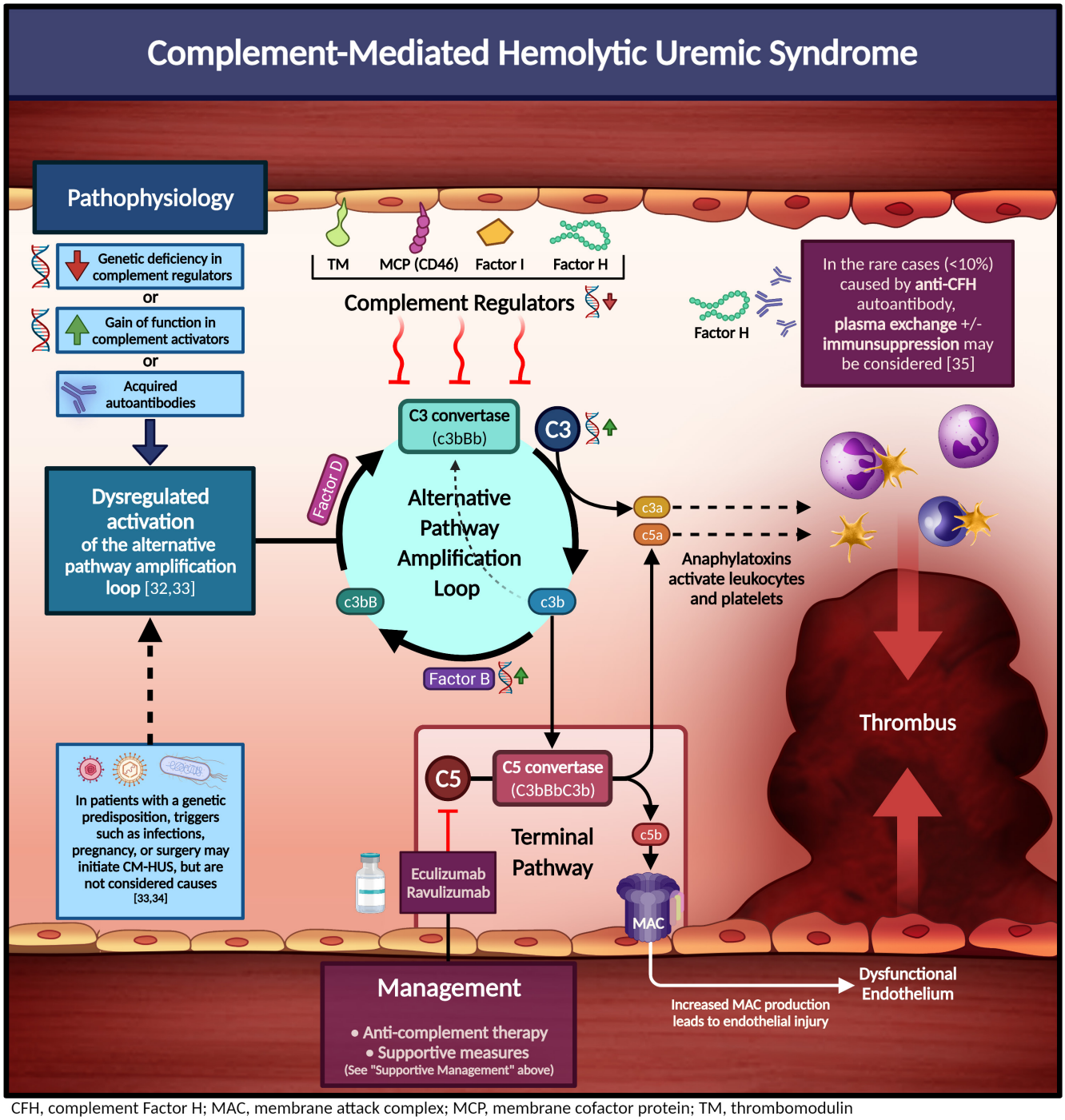

Immune-Mediated
Thrombotic Thrombocytopenic Purpura
Pathophysiology
Autoantibodies either neutralize or increase clearance of ADAMTS13 [23]. IgG antibodies are most common, followed by IgA and IgM [24]
ADAMTS13
Severe ADAMTS13 deficiency
Ultra-large von Willebrand factor multimers (ULVWF)
Bind to platelets and cause increased platelet activation and aggregation, forming platelet-rich thrombi
ULVWF
Microvascular Thrombosis
Obstructs blood vessels, causing red blood cell fragmentation, MAHA, and end-organ ischemia
Available Treatments [25]
Repletes deficient ADAMTS13
Plasma Exchange
Eliminates pathologic antibody
Corticosteroids
Suppress antibody production
Rituximab
Inhibits B-cell lymphocytes
GPIb
Caplacizumab
Inhibits VWF interaction with platelet GPIb
See "Supportive Management" above



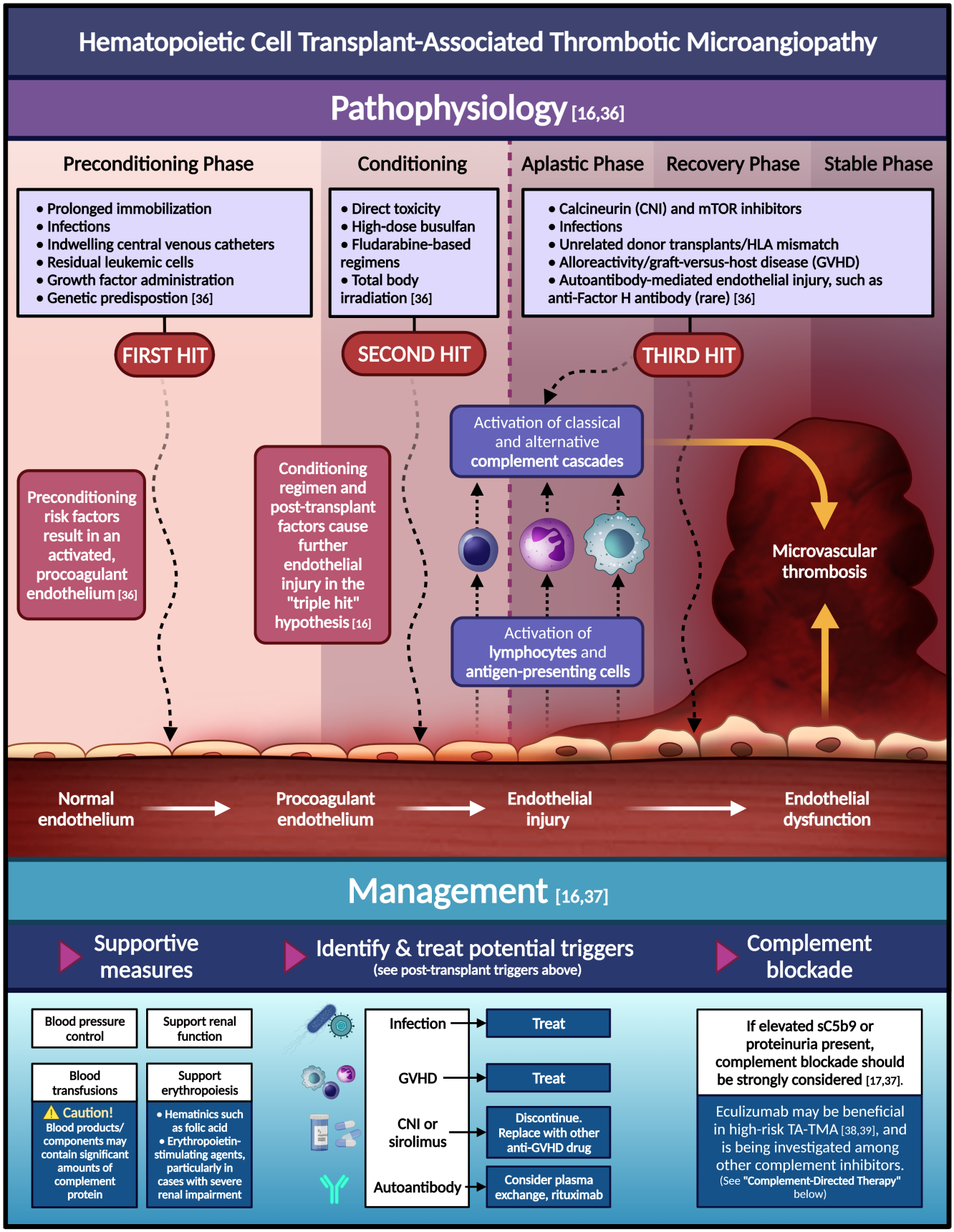
FFP, fresh frozen plasma; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury; VWF, von Willebrand factor



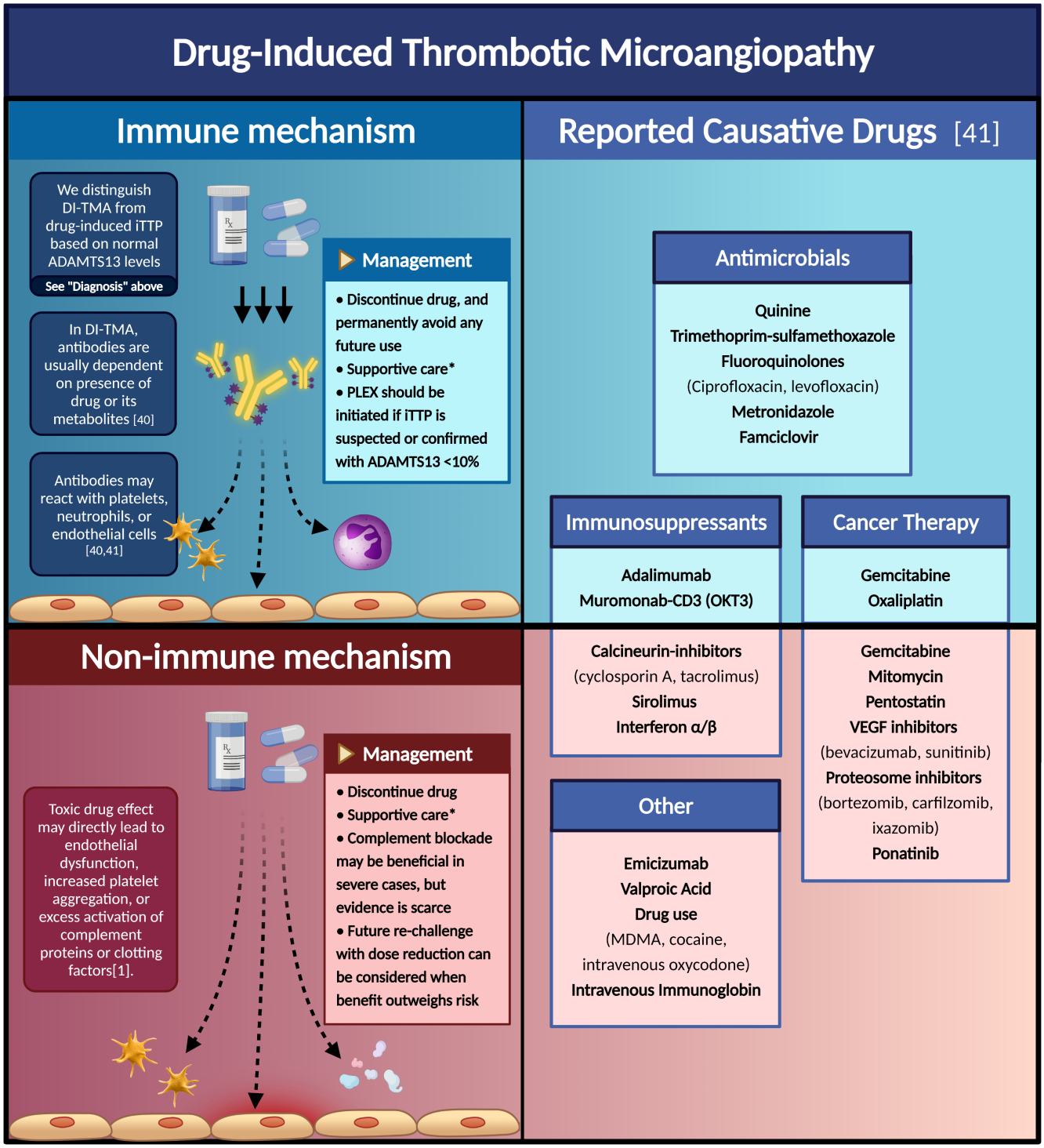
MAC, membrane attack complex; PLEX, plasma exchange; STEC, shiga toxin-producing E. coli; TM, thrombomodulin; VWF, von Willebrand factor



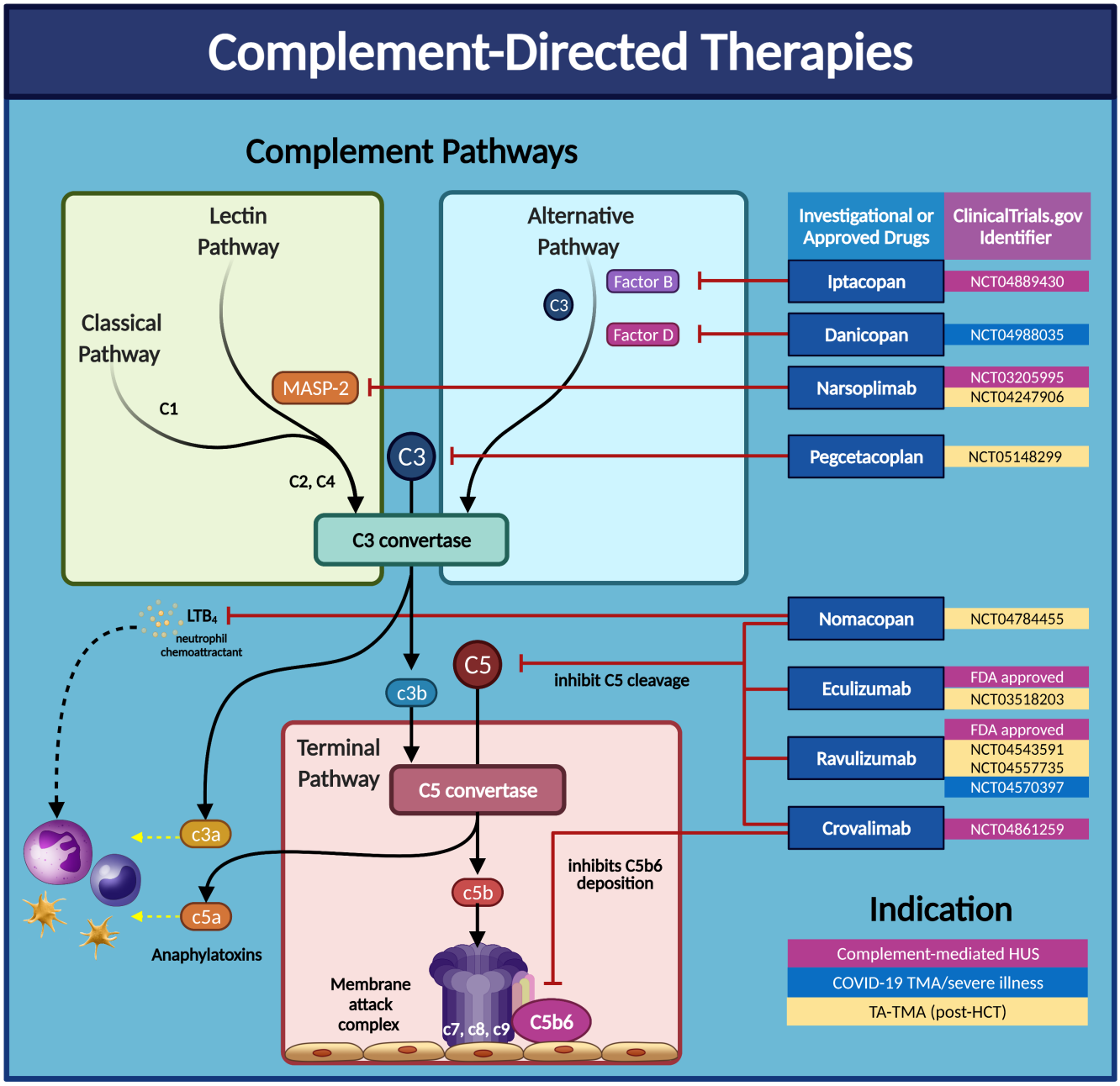
CFH, complement Factor H; MAC, membrane attack complex; MCP, membrane cofactor protein; TM, thrombomodulin



Pathophysiology mechanisms adapted from Dvorak et al. [16] and Khosla et al. [36]



* See "Supportive Management" principles above
iTTP, immune-mediated thrombotic thrombocytopenic purpura; PLEX, plasma exchange



HCT, hematopoietic cell transplant; HUS, hemolytic uremic syndrome; LTB_4, Leukotriene B_4; TMA, thrombotic microangiopathy; TA-TMA, hematopoietic cell transplant-associated thrombotic microangiopathy

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RELATIONSHIP DISCLOSURE

The authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

MYA created all illustrations. MYA, SK, DCS, LN, and SA contributed to the scientific content and revised the manuscript.

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