Complement-Mediated Disorders in Oncology: aHUS, TMA & PNH

Michael Jaglal MD, MS
Senior Member
Moffitt Cancer Center
Professor of Medicine
Morsani College of Medicine
University of South Florida

The Complement System — Overview

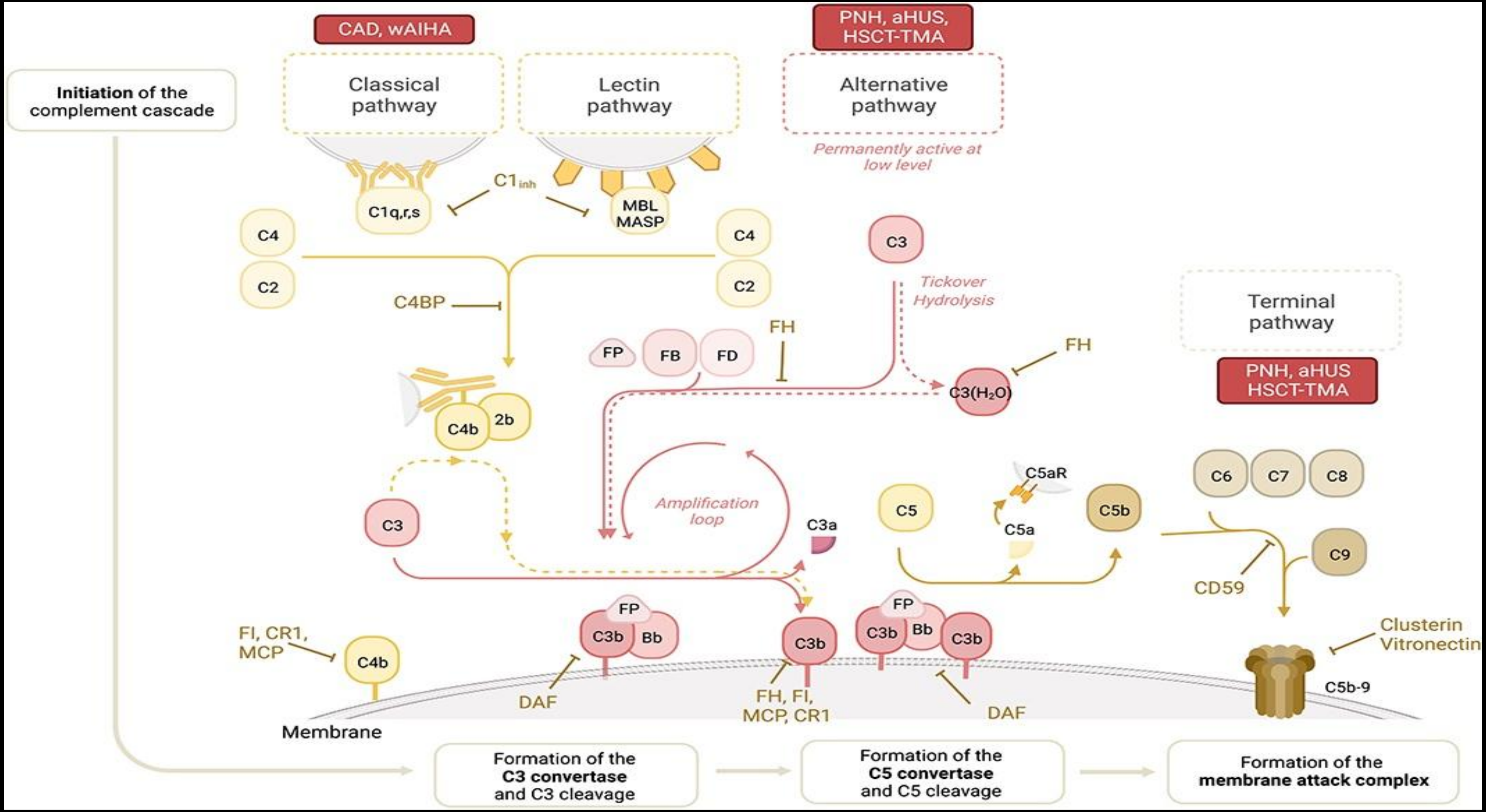
The complement system is an elaborate cascade of innate immunity comprising three activation pathways: Classical, Lectin, and Alternative

All three converge on a common terminal pathway → formation of the membrane attack complex (MAC, C5b-9)

Tight regulation by Factor H, Factor I and membrane-bound (CD55, CD59, MCP/CD46) inhibitors prevents self-damage

Dysregulation - via genetic variants, autoantibodies, or acquired defects -leads to uncontrolled complement activation and end-organ injury

Brodsky RA. Blood. 2015;126(22):2459-65; Schmidt et al Blood. 2022;139(13):1954-1972



. Duval A, Frémeaux-Bacchi V.Review Complement biology for hematologists.
American Journal of Hematology. 2023

Complement Disease Associations

Pathway	Key Components	Associated Diseases
Classical	C1q, C1r, C1s, C4, C2	Cold agglutinin disease (CAD), warm AIHA
Lectin	MBL, MASP	HSCT-TMA
Alternative	C3, Factor B, Factor D, Properdin	PNH, aHUS, HSCT-TMA
Terminal	C5, C6–C9 → MAC	All complement-mediated hemolytic/thrombotic disorders

- **Amplification loop** (C3b → C3 convertase → more C3b) is central to disease pathogenesis
- Loss of regulation at the amplification step → explosive complement activation

Duval et al. Complement biology for hematologists. American Journal of Hematology. 2023;98 Suppl 4:S5-S19

Pathogenesis of TTP, typical HUS and atypical HUS

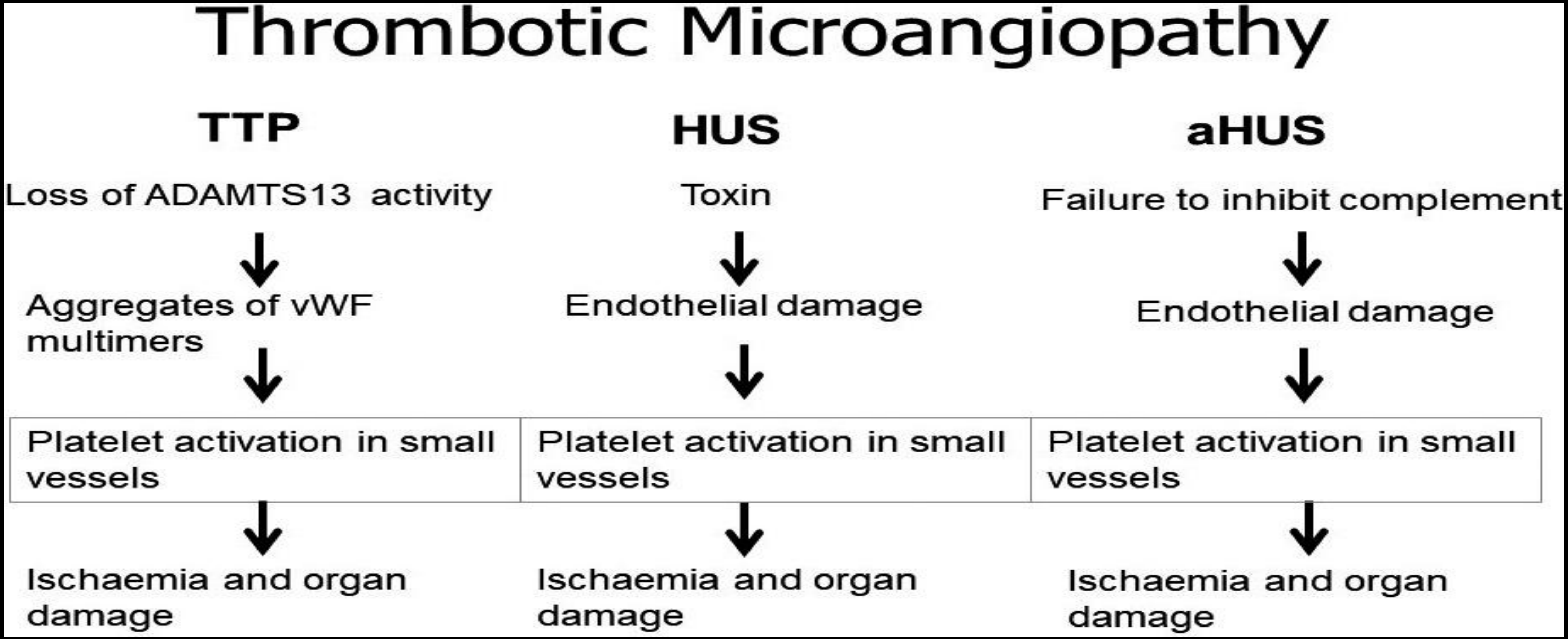


Figure 1. Illustration of the pathogenesis of TTP, typical HUS and atypical HUS

Genomic investigation of inherited thrombotic microangiopathy—aHUS and TTP. Int J Lab Hematol. May 31, 2020.

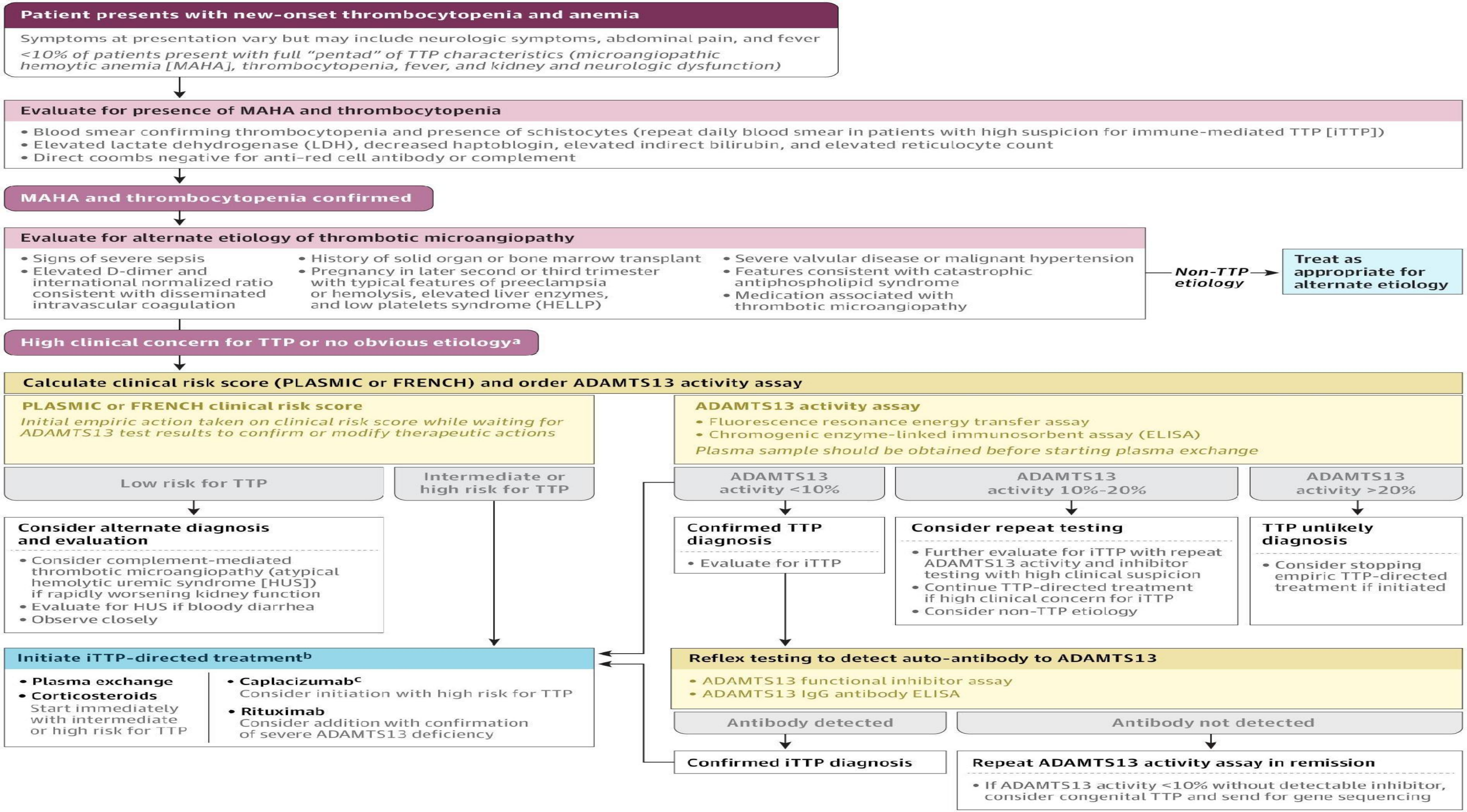


Figure 2. Initial Diagnostic Workflow for Patients With Suspected Thrombotic Thrombocytopenic Purpura, Immune Thrombotic Thrombocytopenic Purpura. JAMA. August 11, 2025.

Clinical presentation

- A 28-year-old woman presents to the emergency department with 3 days of fatigue, pallor, decreased urine output, and bilateral lower extremity edema. She reports a mild upper respiratory infection 10 days prior that resolved spontaneously. She has no significant past medical history. She is not pregnant and takes no medications.

Physical

- **Vital Signs**
- Blood pressure: 168/102 mmHg Heart rate: 104 bpm
- Temperature: 37.2°C Respiratory rate: 18/min
- SpO2: 98% on room air

- **Physical Examination**
- General: Pale, fatigued-appearing woman
- Skin: Petechiae on bilateral lower extremities; no purpura or rash
- Cardiovascular: Tachycardic, regular rhythm, no murmurs
- Abdomen: Soft, mildly tender in flanks bilaterally
- Extremities: 2+ pitting edema bilaterally

Labs

Test	Result	Reference Range

Atypical hemolytic uremic syndrome (aHUS)

- aHUS is a complement-mediated thrombotic microangiopathy (TMA)
- Characterized by the classic triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury.
- 10% of all HUS cases, with an estimated incidence of ~1 in 500,000 per year in the United States.
- Present at any age, from the neonatal period through adulthood.

Fakhouri F, Schwotzer N, Frémeaux-Bacchi V. How I Diagnose and Treat Atypical Hemolytic Uremic Syndrome. Blood. 2023.

aHUS -Complement Dysregulation

- Results from uncontrolled activation of the alternative complement pathway, driven by a "two-hit" mechanism
- Hit 1 (susceptibility): Germline mutations in complement regulatory genes (CFH, CFI, CD46/MCP, C3, CFB, THBD) or acquired anti-Factor H autoantibodies (~10% of pediatric cases)
- Hit 2 (trigger): Environmental triggers — infections, pregnancy, drugs, transplantation, surgery — provoke endothelial perturbation and complement activation that cannot be self-limited in susceptible individuals
- This leads to excessive C5b-9 (membrane attack complex) formation → endothelial injury → platelet activation → microvascular thrombosis → organ damage.

- Sridharan M, Go RS, Willrich MAV. Atypical Hemolytic Uremic Syndrome: Review of Clinical Presentation, Diagnosis and Management. Journal of Immunological Methods. 2018.

AHUS-**Clinical Presentation**

- Onset ranges from neonatal period to adulthood; many patients present after an identifiable trigger [3]
- **Renal:** AKI progressing to ESRD in ~50% of untreated patients; hypertension
- **Hematologic:** Schistocytes on smear, elevated LDH, low haptoglobin, thrombocytopenia
- **Extrarenal involvement:** CNS (seizures, encephalopathy), cardiac, GI, pulmonary in some cases
- Pregnancy-associated aHUS typically presents postpartum and must be distinguished from HELLP/preeclampsia

Sridharan M, Go RS, Willrich MAV. Atypical Hemolytic Uremic Syndrome: Review of Clinical Presentation, Diagnosis and Management. Journal of Immunological Methods. 2018.

Treatment of AHUS

- Complement C5 blockade is the cornerstone of aHUS treatment
- Eculizumab: Anti-C5 monoclonal antibody; IV every 2 weeks after loading dose
- Ravulizumab: Long-acting anti-C5; dosing every 8 weeks; approved for adults and pediatric patients ≥1 month

- Key treatment principles:
- Initiate early — do not wait for genetic results; early treatment improves renal recovery even in dialysis-dependent patients.
- Meningococcal vaccination is mandatory before or concurrent with complement inhibitor initiation (risk of Neisseria meningitidis infection)

- Fakhouri F, Schwotzer N, Frémeaux-Bacchi V. How I Diagnose and Treat Atypical Hemolytic Uremic Syndrome. Blood. 2023.

Long-Term Management and Prognosis

- Lifelong C5 blockade is no longer a universal paradigm — increasingly individualized based on genotype and clinical course
- Patients with CFH mutations have the highest relapse risk; those with MCP/CD46 mutations may have milder courses and may be candidates for treatment discontinuation with close monitoring
- Transplantation: High recurrence risk post-kidney transplant, especially with CFH, C3, CFB mutations; peri-transplant eculizumab is effective for prevention
- Anti-Factor H antibody–associated aHUS may respond to immunosuppression in addition to complement blockade

- Fakhouri F, Schwotzer N, Frémeaux-Bacchi V. How I Diagnose and Treat Atypical Hemolytic Uremic Syndrome. Blood. 2023.

Clinical Presentation

- A 44-year-old woman presents with a 6-month history of progressive fatigue, intermittent episodes of dark-colored urine most prominent in the early morning, and exertional dyspnea. She also reports episodic abdominal pain and dysphagia. She has no significant past medical history and takes no medications. She denies any family history of hematologic disorders.

- **Physical Examination**
- Vital signs: HR 102 bpm, BP 118/72 mmHg, RR 16, SpO_2 98% on room air, Temp 37.0°C
- General: Pale-appearing, fatigued
- HEENT: Conjunctival pallor, scleral icterus
- Cardiovascular: Tachycardic, regular rhythm, grade II/VI systolic flow murmur at the left sternal border
- Abdomen: Mild diffuse tenderness without hepatosplenomegaly
- Extremities: No edema, no petechiae

Labs

Test	Result	Reference Range

Paroxysmal Nocturnal Hemoglobinuria (PNH) Pathophysiology

- Clonal hematopoietic stem cell disorder caused by somatic mutation in the *PIGA* gene
- Loss of GPI-anchored complement regulators CD55 and CD59 on blood cell surfaces
- CD59 deficiency → failure to inhibit MAC → intravascular hemolysis
- CD55 deficiency → impaired C3 convertase decay → C3 opsonization → extravascular hemolysis
- Clinical triad: hemolytic anemia, thrombosis, bone marrow failure
- Estimated prevalence: 1.04–3.81 per 100,000

- Brodsky RA. How I Treat Paroxysmal Nocturnal Hemoglobinuria. Blood. 2021;137(10):1304-1309

PNH -Diagnosis

- **Flow cytometry** is the gold standard: FLAER (fluorescent aerolysin) + GPI-anchored protein markers on granulocytes, monocytes, and RBCs
- Suspect PNH in patients with:

  - Unexplained Coombs-negative hemolytic anemia
  - Thrombosis at unusual sites (hepatic, cerebral, dermal veins)
  - Cytopenias with elevated LDH, low haptoglobin, hemoglobinuria

- - **PNH clones are common in bone marrow failure syndromes**: detected in ~53% of aplastic anemia and ~14% of MDS patients

- - Small PNH clones predict better response to immunosuppressive therapy and favorable prognosis in AA/MDS

- Ishiyama K, Yonemura Y, Kawaguchi T, et al. A Longitudinal Analysis of Paroxysmal Nocturnal Haemoglobinuria-Type Cells in Patients With Bone Marrow Failure: Results of a Prospective Multi-Centre Study in Japan British Journal of Haematology. 2023;203(3):468-476.
- Fattizzo B, Ireland R, Dunlop A, et al. Clinical and Prognostic Significance of Small Paroxysmal Nocturnal Hemoglobinuria Clones in Myelodysplastic Syndrome and Aplastic Anemia. Leukemia. 2021;35(11):3223-3231

PNH — Treatment Landscape

Agent	Target	Route	Dosing Interval	FDA Approved
Eculizumab	C5	IV	Every 2 weeks	2007
Ravulizumab	C5 (long-acting)	IV	Every 8 weeks	2018
Crovalimab	C5	SC	Every 4 weeks	2024
Pegcetacoplan	C3	SC	Every 3 days or pump	2021
Iptacopan	Factor B	Oral	Twice daily	2023
Danicopan	Factor D	Oral	Add-on to C5 inhibitor	2024

Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria. The New England Journal of Medicine. 2021;384(11):1028-1037. Padilla Kelley T, King HL, Malhotra A, et al. Advancement in Complement Inhibition for PNH and Primary Complement Mediated Thrombotic Microangiopathy Blood Advances. 2025;:bloodadvances.

PNH & Malignancy — AA/MDS/AML

- PNH, aplastic anemia (AA), and MDS share immune-mediated bone marrow failure
- 15–20% of AA patients and 2–6% of PNH patients develop secondary MDS/AML by 10 years
- Clonal hematopoiesis (CH) is nearly ubiquitous in AA; PIGA mutations coexist with myeloid driver mutations (DNMT3A, ASXL1, BCOR)
- Risk factors for malignant transformation: longer disease duration, telomere attrition, adverse mutations (ASXL1, U2AF1), high allelic burden
- NCCN MDS Guidelines recommend flow cytometry for PNH clone as part of additional testing in MDS workup

- Sun L, Babushok DV. Secondary Myelodysplastic Syndrome and Leukemia in Acquired Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria Blood. 2020;136(1):36-49.
- Gurnari C, Pagliuca S, Prata PH, et al. Clinical and Molecular Determinants of Clonal Evolution in Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology. 2023;41(1):132-142

Questions