Patients with **atypical-HUS** can be at continuous risk of the life-threatening consequences of unpredictable complement-mediated TMA\(^1\)

Chronic, uncontrolled complement activity in atypical-HUS leads to ongoing endothelial injury, organ damage, and potential death\(^1,2\)

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HUS, hemolytic uremic syndrome; TMA, thrombotic microangiopathy.

The information in this presentation is intended as educational information for healthcare professionals. It does not replace a healthcare professional’s judgment or clinical diagnosis.
What Is Thrombotic Microangiopathy?

TMA manifests as thrombocytopenia, microangiopathic hemolysis, and organ involvement.

TMAs present with similar signs and symptoms, but have distinct underlying causes.

When you suspect TMA

- Rapidly take a sample to test for ADAMTS13 activity PRIOR TO intervention to ensure accurate test results.
- Confirm negative for Shiga toxin/EHEC.
- Get medical history including previous TMA and other potential causes.
- Obtain family history of TMA or renal impairment.

TMA Diagnostic Pathway

A clinical diagnosis of atypical-HUS in a patient with signs and symptoms of TMA requires exclusion of other underlying causes.

Differential diagnosis for TMAs: Atypical-HUS, TTP, and STEC-HUS.

Other Signs and Symptoms

Pulmonary symptoms
- Dyspnea and/or Pulmonary hemorrhage
- Pulmonary edema

Visual symptoms
- Pain and blurred vision
- Ocular hemorrhage

Evaluate ADAMTS13 activity and Shiga toxin/EHEC test.

While ADAMTS13 results are awaited, a platelet count >30 × 10⁹/L and/or sCr >1.7 to 2.3 mg/dL almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP).

5% ADAMTS13 activity
- Shiga toxin/EHEC positive

TMA can also manifest in the presence of clinical conditions such as the following

- Pregnancy-postpartum
- Malignant/severe hypertension
- Solid organ transplantation

- Autoimmune disease (eg, SLE, scleroderma)
- Hematopoietic stem cell transplantation

Early identification of atypical-HUS allows for rapid disease management.
Pathophysiology of Atypical-HUS

Atypical-HUS results from chronic, uncontrolled complement activity that may lead to progressive and life-threatening complications.

Genetic mutations, polymorphisms, and autoantibodies lead to chronic, uncontrolled complement activity.

The number of new genetic abnormalities discovered in patients with atypical-HUS continues to increase over time.

45% of patients with atypical-HUS have an identifiable genetic mutation or anti-complement factor H antibody.

Regardless of whether or not a mutation is identified, patients with atypical-HUS have similarly devastating outcomes.

High morbidity and mortality regardless of mutation identification.

ESRD, estimated glomerular filtration rate; CFH, complement factor H; HUS, hemolytic uremic syndrome.
Chronic, uncontrolled complement activity can result in continuous endothelial damage and ongoing risk of TMA\textsuperscript{2,3,18}

Individual with atypical-HUS

- The assembly of multiple C5b-9 complexes on the surface of endothelial cells causes endothelial injury and platelet activation\textsuperscript{2,19-21}
- Binding of C5a to the C5a receptor results in a decrease in the endothelium's anticomplement and antithrombogenic properties\textsuperscript{2,20,22,23}
- Disrupted endothelial cells
  - Release complement-activating microparticles, resulting in a vicious cycle of endothelial activation, complement amplification, and ongoing endothelial injury\textsuperscript{2,24}
  - Release prothrombotic coagulation proteins, activate platelets, and recruit leukocytes, resulting in the formation of thrombi in small blood vessels throughout the body\textsuperscript{2}

- Uncontrolled complement activity causes ongoing vascular endothelial injury, resulting in TMA lesions and progressive organ damage\textsuperscript{1,18,25}
- Biomarkers of complement activation, inflammation, endothelial cell activation and damage, coagulation, and renal damage (eg, Ba, sTNFR1, sVCAM-1, D-dimer, U-Cystatin C) are similarly elevated among patients with atypical-HUS receiving or not receiving plasma exchange or plasma infusion\textsuperscript{26}

TMA lesions from repeated endothelial injury can progress toward irreversible tissue damage\textsuperscript{1,18,25}

HUS, hemolytic uremic syndrome; TMA, thrombotic angiopathy; vWF, von Willebrand factor.
Patients with atypical-HUS are at ongoing risk of systemic, life-threatening, and sudden complications. Atypical-HUS patients can show involvement in more than one organ system.

- **Neurological symptoms**: Confusion, stroke, encephalopathy, seizure
- **GI symptoms**: Colitis, abdominal pain, pancreatitis, diarrhea, nausea, vomiting, gastroenteritis
- **Cardiovascular symptoms**: Arterial thrombosis, arterial stenosis, hypertension, cardiomyopathy, myocardial infarction, arterial thrombosis, vascular stenosis, hypertension
- **Renal symptoms**: Elevated creatinine, decreased eGFR, proteinuria
- **Cardiac symptoms**: Stroke, seizure, cardiomyopathy, myocardial infarction
- **Vascular complications**: Peripheral arterial disease, phalangeal gangrene, arterial thrombosis, vascular stenosis, hypertension
- **Other complications**: Myocardial infarction, hypertension, stroke, seizure, cardiomyopathy, myocardial infarction

Approximately 50% of adult patients with atypical-HUS are at risk for ESRD and death. Pediatric patients have a lower risk of developing ESRD compared with adult patients (adjusted hazard ratio 0.55 [95% CI, 0.41–0.73]); sex, race, family history of atypical-HUS, time from initial presentation to diagnosis, and potential complement-activating conditions were not associated with ESRD risk.
Complement-Amplifying Conditions May Unmask Atypical-HUS

Ongoing complement activity

- Complement-amplifying conditions
  - Infection
  - Malignant/severe hypertension
  - Surgery/trauma
  - Pregnancy-associated
  - Transplant (renal/bone marrow)
  - Autoimmune diseases
  - Certain medications
  - Other

Uncontrolled Complement Amplification

- Defective Complement Regulatory Proteins
  - Endothelial damage
  - Platelet activation
  - Thrombosis
- TMA

Feedback Amplification

TMAs associated with complement-amplifying conditions

- Infection
- Malignant/severe hypertension
- Surgery/trauma
- Pregnancy-associated
- Transplant (renal/bone marrow)
- Autoimmune diseases
- Certain medications
- Other


- 70% of patients (191/273) with atypical-HUS presented their first clinical manifestations while experiencing a complement-amplifying condition

Ongoing complement activity

- Complement-amplifying conditions place patients with atypical-HUS at high risk for TMA manifestations

Examples of complement-amplifying conditions include

- Persistent TMA despite hypertension management should raise suspicion for atypical-HUS unmasked by MHT or severe hypertension

Infection

- Suspect atypical-HUS if symptoms of TMA persist after treatment of infection

Pregnancy

- A high clinical suspicion for atypical-HUS should be raised if signs of TMA present postpartum or persist more than 48 hours after delivery/termination

Atypical-HUS is commonly unmasked in the postpartum setting

NOTE: The diagram is for illustrative purposes only; disease areas are not drawn to proportional scale and are not meant to reflect relative incidence.

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; HUS, hemolytic uremic syndrome; STEC-HUS, Shiga toxin-producing E. coli-hemolytic uremic syndrome; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

If the signs and symptoms of TMA do not rapidly resolve in response to management of the triggering condition, evaluate for atypical-HUS by assessing for STEC-HUS and ADAMTS13 deficiency

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Certain medications used in transplant

- Suspect atypical-HUS if TMA symptoms persist after the associated drug (such as calcineurin inhibitors) has been discontinued

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Study Description: A retrospective analysis of 19 patients who experienced clinical manifestations of atypical-HUS, and 21 patients who experienced clinical manifestations of TTP, during pregnancy or postpartum. Patients with aHUS were referred between 2000 and 2008 to the laboratory of immunology at Hôpital Européen Georges-Pompidou (Paris, France), a reference center for the evaluation of complement disorders. A diagnosis of atypical-HUS was defined by the coexistence of hemolytic anemia, thrombocytopenia, and acute renal failure. Patients with ADAMTS13 deficiency-associated TTP were identified from previously published cases.

*Defined as complement dysregulation TMA.
Potential exposure to any complement-amplifying condition may lead to TMA manifestations in patients with atypical-HUS\textsuperscript{4,9,12,16}

Examples of factors that may increase risk for TMA manifestations in patients with atypical-HUS include\textsuperscript{7,36,a}

**History of renal transplant**\textsuperscript{1,37}
- The risk of atypical-HUS recurrence following transplantation has been reported to range from 20% to more than 80% depending on the presence of a specific genetic mutation\textsuperscript{38}
- Risk for TMA is also deemed high in patients without a genetic mutation who have received a renal transplant\textsuperscript{1,37}
- Risk for allograft loss is high in patients with atypical-HUS\textsuperscript{12,17,39}

**Age of patient**\textsuperscript{6}
- Children are considered to be at high risk for recurrent TMA due to the frequency of common events that lead to complement activation in this age group\textsuperscript{6}

**Identified genetic mutation**\textsuperscript{12,27,40}
- Clinical studies show that mutations in complement genes are associated with higher risk of TMA\textsuperscript{12,27,40}

**Pregnancy/Postpartum**\textsuperscript{9,35,41,42}
- Patients with atypical-HUS are at risk for TMA manifestations during the pregnancy/postpartum period\textsuperscript{9,41,42} due to factors such as infection, hemorrhage, and HELLP syndrome\textsuperscript{9,41}

**Clinical history or family history of TMA**\textsuperscript{36,40,43,44}
- Multiple TMA manifestations suggests high risk for subsequent TMA in the presence of complement-amplifying conditions\textsuperscript{36,40}
- Patients with family history of disease have a higher rate of disease progression; rate of ESRD has been reported to be between 50-80%\textsuperscript{12,44}

\(\text{This is not a comprehensive list, but is intended to provide examples of factors that may increase risk for TMA. Anything that amplifies complement is a risk factor for TMA.} \)


**Mortality outcomes differed in patients receiving PE with and without severe ADAMTS13 deficiency**\textsuperscript{45}

**Rates of Renal Recovery and Premature Mortality in Patients With Severe or Nonsevere ADAMTS13 Activity Undergoing PE/PI for the Treatment of TMA**\textsuperscript{45} (Follow-up Period up to 21 Days)

- **Hematological Improvements**
  - Platelet Count Recovery\textsuperscript{a}
  - LDH Normalization\textsuperscript{a}
- **Renal Function Recovery**
  - Creatinine Normalization\textsuperscript{b}
- **Deaths**
  - Premature Mortality

- ADAMTS13 activity >5% (n = 22)
- ADAMTS13 activity <5% (n = 22)

\(\text{80\% (4 of 5) of deaths}^e\text{ were due to extrarenal complications}^e\)

**TTP and atypical-HUS are driven by different pathophysiologic processes and have different management goals**

**Patients with atypical-HUS remain at risk of impaired renal function and death, regardless of hematologic improvement after PE/PI**\textsuperscript{8}
**Factors to Consider for Long-term Management of Atypical-HUS**

When developing a management plan for an atypical-HUS patient, risk assessment for TMA manifestations, the patient’s unique clinical situation, and an understanding of the unpredictable nature of atypical-HUS should be considered. Factors that may increase risk for TMA complications in patients with atypical-HUS:

- **History of renal transplant**
- **Ongoing renal dysfunction**
- **Age of patient**
- **Pregnancy/postpartum**
- **Genetic mutation**
- **Clinical or family history of TMA**

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**References**

Atypical-HUS is a chronic, unpredictable, genetic disease that can be life threatening\textsuperscript{1,3,4}

Patients with TMA require rapid differential diagnosis to make appropriate management decisions\textsuperscript{3}

Persistent TMA in patients with complement-amplifying conditions may suggest atypical-HUS\textsuperscript{8}

The role of PE/PI is limited in management of atypical-HUS\textsuperscript{8}

HUS, hemolytic uremic syndrome; PE/PI: plasma exchange/plasma infusion; TMA, thrombotic microangiopathy.