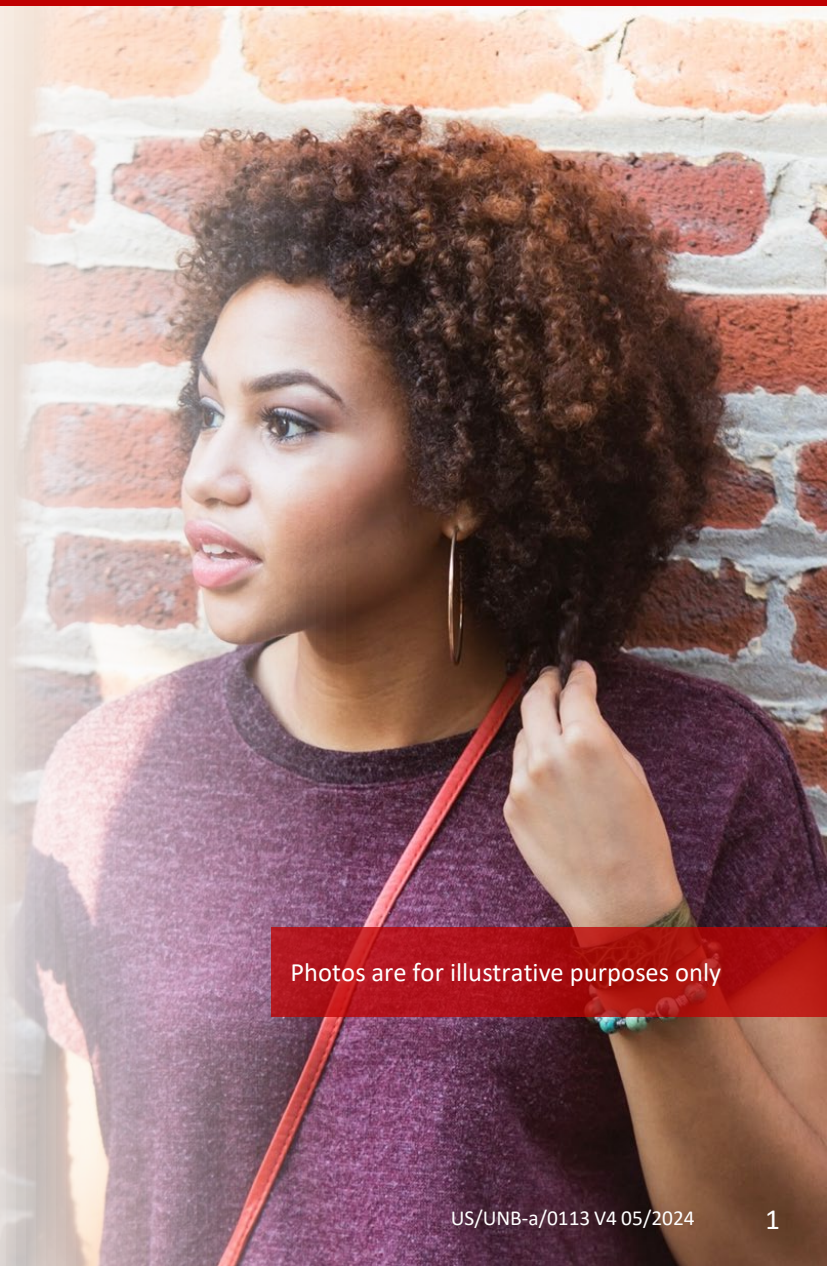
Exploring TMAs and atypical-HUS

Pathophysiology, differential diagnosis, and management

- [Speaker name]
- [Title]
- [Affiliation]



HUS, hemolytic uremic syndrome; TMA, thrombotic microangiopathy.

aHUS Source

ALEXION
AstraZeneca Rare Disease

This program is sponsored by Alexion, AstraZeneca Rare Disease.

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Program objectives

1. To review the clinical presentation, differential diagnosis, and management of thrombotic microangiopathies (TMAs) including atypical-HUS
2. To take an in-depth look into atypical-HUS
3. To examine some of the factors affecting the risk of recurrence of TMA

HUS, hemolytic uremic syndrome; TMA, thrombotic microangiopathy.

Clinical presentation of thrombotic microangiopathy (TMA)

Patients with TMA present with a "clinical triad" of laboratory signs and symptoms[1-3]

1 Thrombocytopenia

- Platelets <150 × 10^9/L or >25% decrease from baseline

2 Hemolytic anemia

- Elevated LDH and/or decreased hemoglobin and/or decreased haptoglobin and/or elevated reticulocyte count

Microangiopathic hemolytic anemia

- Schistocytes and hemolytic anemia

Note: Schistocytes may not appear on initial evaluation; daily review of blood smears is advised.[1]

Clinical triad

3 One or more signs and symptoms of organ damage*

Neurological symptoms

- Confusion, stroke, seizures, and/or other cerebral abnormalities

GI symptoms

- Diarrhea ± blood, nausea/vomiting, abdominal pain, and/or gastroenteritis/pancreatitis

Pulmonary symptoms

- Dyspnea, pulmonary hemorrhage, and/or pulmonary edema

Renal impairment

- Elevated creatinine levels, decreased eGFR, elevated blood pressure, and/or abnormal urinalysis

Cardiovascular symptoms

- MI, hypertension, arterial stenosis, and/or peripheral gangrene

Visual symptoms

- Pain and blurred vision, retinal vessel occlusion, and/or ocular hemorrhage

*Not all signs and symptoms may be present simultaneously.

eGFR, estimated glomerular filtration rate; GI, gastrointestinal; LDH, lactate dehydrogenase; MI, myocardial infarction; TMA, thrombotic microangiopathy.

1. Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14 suppl 11(11):2-15. **2.** Loirat C, Fremeaux-Bacchi V. *Orphanet J Rare Dis.* 2011;6:60. **3.** Campistol JM, et al. *Nefrologia*. 2015;35(5):421-447.

Understanding select TMA etiologies

DIC[1,2]

- Coagulation abnormality with elevated INR and aPTT

HUS[1,3]

- Shiga toxin–producing *E. coli*, *Shigella dysenteriae* type 1
- *Streptococcus pneumoniae*

Additional (genetic) causes[1]

- Cobalamin C genetic deficiency
- DGKE

TTP[1,3]

- ADAMTS13 activity <10%*
- Congenital TTP (cTTP, no autoantibodies)
- Acquired TTP (iTTP, ADAMTS13 autoantibodies)

External triggers[1-3]

- Autoimmune diseases (eg, SLE, APS, scleroderma)
- CAPS
- Drug therapies
- Glomerulopathy
- Infections
- Malignancy
- Malignant/severe hypertension
- Pregnancy (HELLP; preeclampsia)
- Sepsis
- Solid organ/bone marrow transplant
- STEC-HUS
- TTP

Atypical-HUS[1,4]

- ADAMTS13 activity >10%*
- With or without a genetic mutation
- Possible external triggers in 70% of cases

Atypical-HUS could be an additional or overlapping diagnosis for many of the TMAs listed here, particularly in the case of external triggers[1]

*Exact cut-off as specified by the laboratory and assay technique employed.[1]

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; APS, antiphospholipid syndrome; aPTT, activated partial thromboplastin time; CAPS, catastrophic antiphospholipid syndrome; DGKE, diacylglycerol kinase epsilon; DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzymes, low platelets; HUS, hemolytic uremic syndrome; INR, international normalized ratio; iTTP, immune-mediated TTP; SLE, systemic lupus erythematosus; STEC, Shiga toxin–producing *Escherichia coli*; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

1. Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14 suppl 11(11):2-15. **2.** Brocklebank V, et al. *Clin J Am Soc Nephrol.* 2018;13(2):300-317. **3.** Azoulay E, et al. *Chest.* 2017;152(2):424-434.
4. Noris M, et al. *Clin J Am Soc Nephrol.* 2010;5(10):1844-1859.

What tests would you order to determine the cause of TMA?

TMA, thrombotic microangiopathy.

Testing for TMA etiologies

DIC[1,2]

- PT/aPTT
- INR
- Fibrinogen
- D-dimer

STEC-HUS[1]

- Shiga toxin panels

Additional (genetic) causes[1,3]

- Cobalamin C deficiency:
  - Methylmalonic acid/methionine, homocysteine, vitamin B12
- DGKE testing

TTP[1,2,4-6]

- ADAMTS13 activity levels*
- PLASMIC score

External triggers[1-3,7-10]

- Autoimmune diseases:
  - SLE: ANA, anti-dsDNA
  - CAPS: antiphospholipids, lupus anticoagulant
  - SRC: Anti-Scl70, ACA RNA polymerase III
- Infections:
  - Chest X-ray, influenza A, HIV, COVID-19, hepatitis B and C
- Other tests:
  - Genetic mutation screening, echocardiogram, pregnancy

Atypical-HUS[1,2,11,12]

- Diagnosis of exclusion
- ADAMTS13 activity levels
- Complement testing (including complement components C3, C4, and sC5b-9)

*Exact cut-off as specified by the laboratory and assay technique employed.[1]

ACA RNA, anticentromere antibody ribonucleic acid; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; anti-dsDNA, anti-double-stranded deoxyribonucleic acid antibody; anti-Scl70, anti-topoisomerase I; aPTT, activated partial thromboplastin time; CAPS, catastrophic antiphospholipid syndrome; DGKE, diacylglycerol kinase epsilon; DIC, disseminated intravascular coagulation; HIV, human immunodeficiency virus; HUS, hemolytic uremic syndrome; INR, international normalized ratio; PT, prothrombin time; SLE-ANA, systemic lupus erythematosus antinuclear antibody; SRC, scleroderma renal crisis; STEC, Shiga toxin–producing *Escherichia coli*; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

1. Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14 suppl 11(11):2-15. **2.** Azoulay E, et al. *Chest.* 2017;152(2):424-434. **3.** Brocklebank V, et al. *Clin J Am Soc Nephrol.* 2018;13(2):300-317. **4.** Wynick C, et al. *Thromb Res.* 2020;196:335-339. **5.** Tufano A, et al. *Blood Transfus.* Published online August 9, 2022. doi:10.2450/2022.0082-22 **6.** Vincent JL, et al. *Crit Care*. 2018;22(1):158. **7.** Campistol JM, et al. *Nefrologia.* 2015;35(5):421-447. **8.** Mayo Clinic. Chest x-rays. Updated March 05, 2022. Accessed April 27, 2023. https://www.mayoclinic.org/tests-procedures/chest-x-rays/about/pac-20393494j **9.** Hanna RM, et al. *Adv Chronic Kidney Dis*. 2022;29(2):149-160.e1. **10**. Nayer A, Ortega LM. *J Nephropathol.* 2014;3(1):9-17. **11.** Cammett T, et al. *Mol Diag Ther.* 2023;27:61-74. **12.** Loirat C, et al. *Pediatr Nephrol.* 2016;31:15-39.

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ALEXION AstraZeneca Rare Disease

How often do you see TMAs?

A Less than once per year

B 1 or 2 times per year

C 3 or 4 times per year

D More than 4 times per year

TMAs may be more common than you think[1]

- Patients with TMAs do not always present with classical features of the disease[2,3]
  - Up to 20% of patients with atypical-HUS may present with normal platelet counts; this may still indicate a greater than 25% change from the patient's usual baseline[2]

HUS, hemolytic uremic syndrome; TMA, thrombotic microangiopathy.

1. Schaefer F, et al. *Kidney Int*. 2018;94(2):408-418. **2.** Vincent JL, et al. *Critical Care.* 2018;22(1):158. **3.** Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14 suppl 11(11):2-15.

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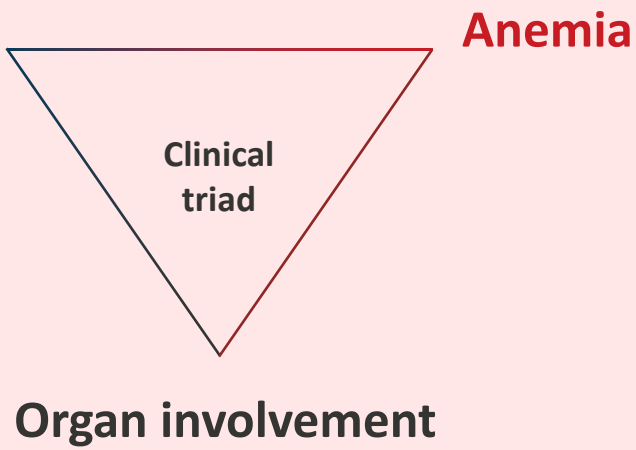
Differential diagnosis of atypical-HUS

Management needs differ for TTP and atypical-HUS; rapid recognition is crucial[1]

Step 1 | Step 2 | Step 3

Recognize TMA early

When you see the clinical triad of thrombocytopenia, anemia, and organ involvement[1-3] – think TMA!



HUS, hemolytic uremic syndrome; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

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Differential diagnosis of atypical-HUS

Management needs differ for TTP and atypical-HUS; rapid recognition is crucial[1]

Step 1 | **Step 2** | Step 3

Rapidly determine the cause of TMA

A Order an ADAMTS13 test immediately
(and with quick turnaround time, when possible)

Draw blood before initiating PE/PI[1]

While waiting for ADAMTS13 results

- A platelet count >30,000 mm^3 and/or serum creatinine level >1.7-2.3 mg/dL almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)[1]
- The PLASMIC score is a validated tool for predicting ADAMTS13 activity[2-4]
  - A PLASMIC score of 0 to 4 should trigger suspicion of atypical-HUS[3]

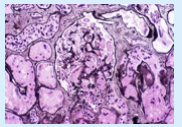
B Additional tests[1]

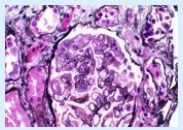
- CBC
- Blood smear to test for the presence of schistocytes (may require repeat testing)
- Shiga toxin/EHEC test to rule out STEC-HUS*

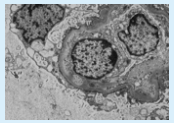
C Optional tests (if medically appropriate)[1,5]:

1. **Renal biopsy**
2. **Complement level testing**

Examples of renal biopsy findings[5]


Glomerular/ arteriolar thrombi


Basement membrane splitting


Basement membrane formation and early cellular interposition

Figures reproduced from Lusco MA, et al. 2016.[4]

*Shiga toxin/EHEC test is warranted with history/presence of GI symptoms.[1]

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; CBC, complete blood count; EHEC, enterohemorrhagic *Escherichia coli*; GI, gastrointestinal; HUS, hemolytic uremic syndrome; PE, plasma exchange; PI, plasma infusion; STEC, Shiga toxin–producing *Escherichia coli*; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

1. Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14 suppl 11(11):2-15. **2.** Wynick C, et al. *Thromb Res.* 2020;196:335-339. **3.** Tufano A, et al. *Blood Transfus.* 2022; doi:10.2450/2022.0082-224
4. Vincent JL, et al. *Crit Care.* 2018;22(1):158. **5.** Lusco MA, et al. *Am J Kidney Dis.* 2016;68(6):e33-e34.

Differential diagnosis of atypical-HUS

Management needs differ for TTP and atypical-HUS; rapid recognition is crucial[1]

Step 1	Step 2	Step 3

Atypical-HUS is a diagnosis of exclusion

5%-10% ADAMTS13 activity[1]*	>10% ADAMTS13 activity[1]	Shiga toxin/EHEC positive[1]
TTP	Seriously consider atypical-HUS	STEC-HUS

TIME CRITICAL

Atypical-HUS is a diagnosis of exclusion: time is critical
When STEC-HUS and TTP are ruled out, seriously consider atypical-HUS[1]

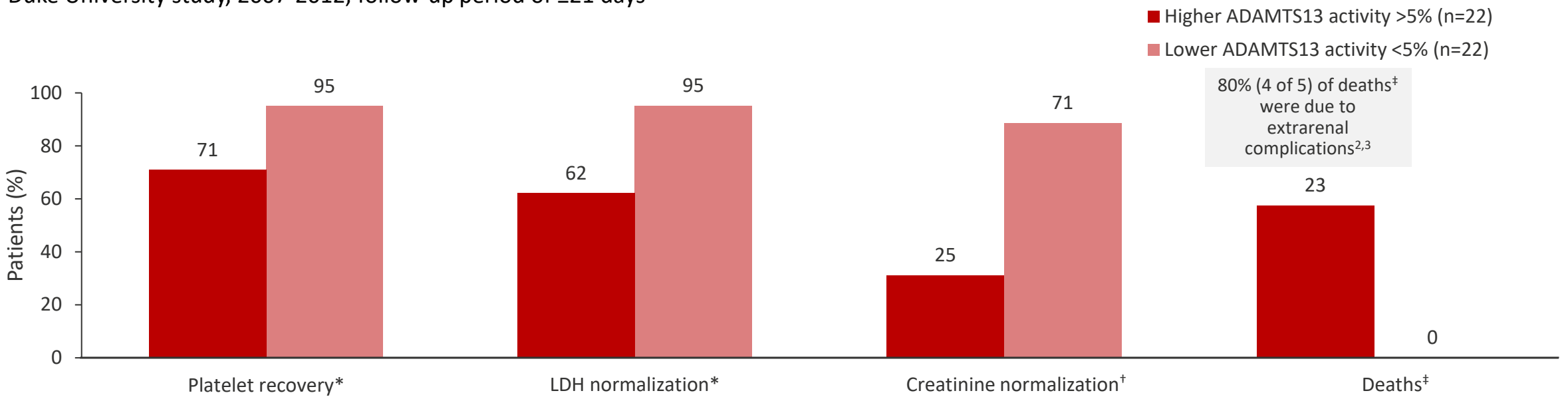
*Range found in published literature is <5%-10%.
ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; EHEC, enterohemorrhagic *Escherichia coli*; HUS, hemolytic uremic syndrome; STEC, Shiga toxin–producing *Escherichia coli*; TTP, thrombotic thrombocytopenic purpura.

1. Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14 suppl 11(11):2-15.

How quickly do you think a patient must be diagnosed in order to improve outcomes?

Management needs differ in patients with/without severe ADAMTS13 deficiency

Duke University study, 2007-2012, follow-up period of ≤21 days[1,2]



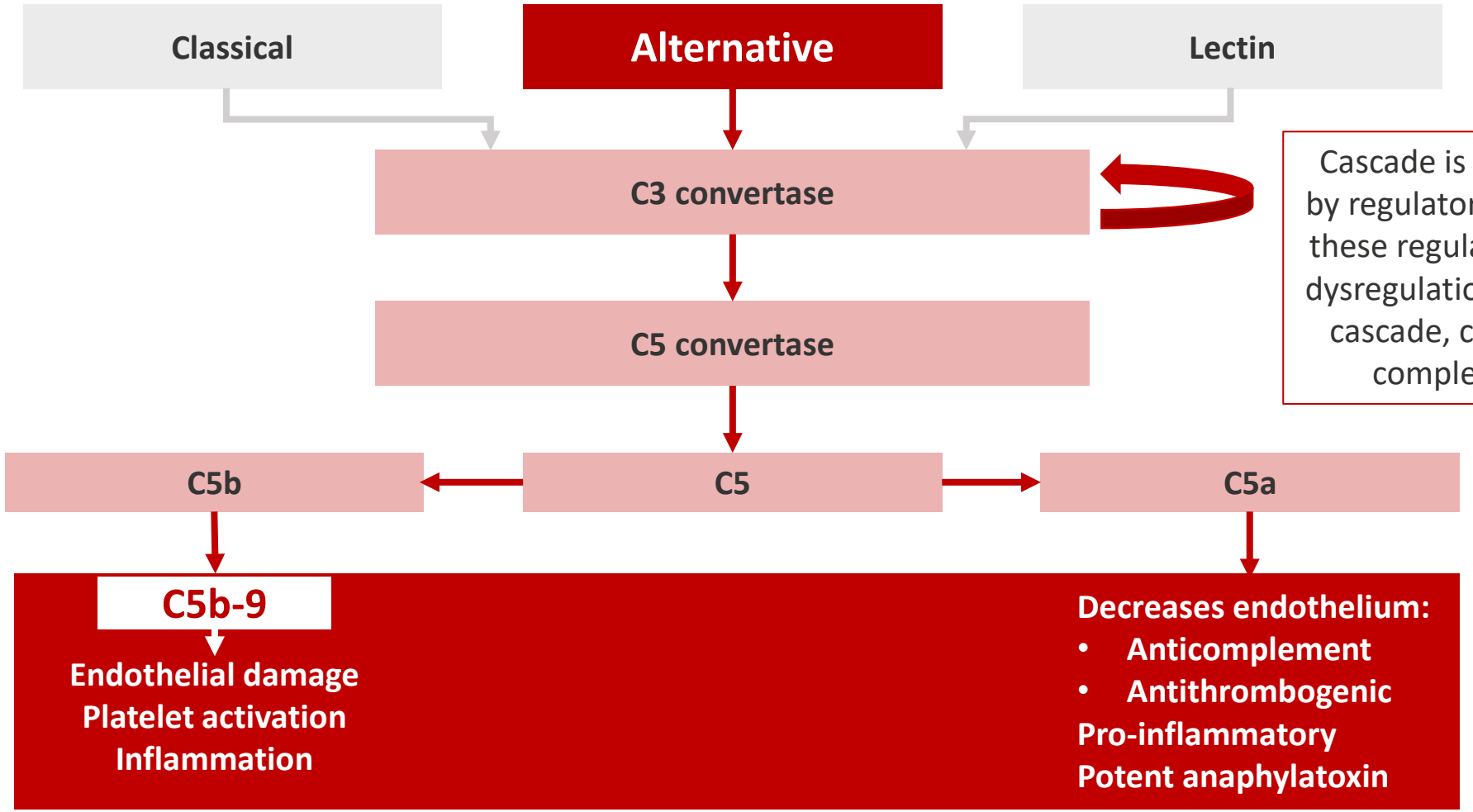
In this retrospective analysis, 23% of patients with ADAMTS13 >5% (potentially atypical-HUS) died in the acute phase of treatment despite extensive use of PE[1,2]

Note on endpoints: platelet count recovery: platelet count >150,000/µL by Day 21; LDH normalization: normal LDH by Day 21; renal function recovery: normal creatinine level by Day 21.[1,2]
*Of patients with available data.[1] †Of patients with abnormal creatinine level at baseline.[1] ‡Non-ST segment elevation MI/aspiration pneumonia, non-ST segment elevation MI/abdominal abscess, multiorgan failure, respiratory failure, sepsis.[2]
ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; HUS, hemolytic uremic syndrome; LDH, lactate dehydrogenase; MI, myocardial infarction; PE, plasma exchange.
1. Pishko AM, Arepally GM. *Blood*. 2014;124(21):4192. **2.** Pishko AM, Arepally GM. Poster presented at: 56th American Society of Hematology Annual Meeting and Exposition; December 6-9, 2014; San Francisco, CA. **3.** Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14 suppl 11(11):2-15.

A closer look at atypical-HUS

HUS, hemolytic uremic syndrome.

Terminal complement dysregulation leads to atypical-HUS[1-3]



Cascade is driven and managed by regulatory proteins. Defects in these regulatory proteins lead to dysregulation of the complement cascade, causing uncontrolled complement activation[1]

C, complement component; HUS, hemolytic uremic syndrome.

1. Noris M, et al. *Nat Rev Nephrol*. 2012;8(11):622-633. **2.** Merle NS, et al. *Front Immunol.* 2015;6:257. **3.** Klos A, et al. *Mol Immunol*. 2009;46(14):2753-2766.

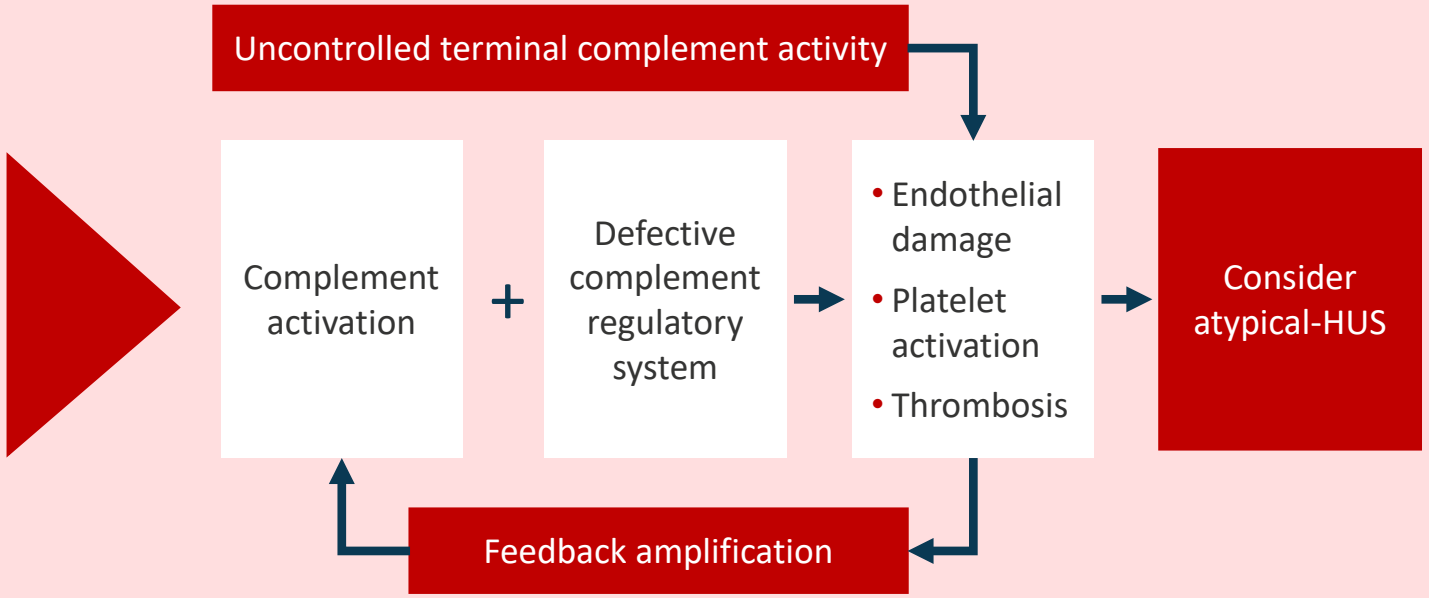
What is atypical-HUS?

Atypical-HUS is a rare, life-threatening disorder associated with continuous risk of complement-mediated TMA[1]

Complement-triggering conditions may unmask TMA in patients with atypical-HUS[1,4]

Triggers can include (but are not limited to)[1-3]:

- Infection
- Pregnancy, postpartum, HELLP, or preeclampsia
- Malignant hypertension or hypertensive emergency
- Transplantation
- Autoimmune disorders (eg, SLE, APS, scleroderma)
- Glomerulonephritis
- Malignancy
- Surgery or trauma
- Certain prescription medications or illicit drugs



Consider atypical-HUS when you see a TMA

Figure adapted from Laurence J, et al. 2016.[1]

APS, antiphospholipid syndrome; HELLP, hemolysis, elevated liver enzymes, low platelets; HUS, hemolytic uremic syndrome; SLE, systemic lupus erythematosus; TMA, thrombotic microangiopathy.

1. Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14 suppl 11(11):2-15. **2.** Azoulay E, et al. *Chest.* 2017;152(2):424-434. **3.** Asif A, et al. *J Nephrol.* 2017;30(3):347-362. **4.** Noris M, et al. *Nat Rev Nephrol*. 2012;8(11):622-633.

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How do you deal with possible atypical-HUS in a patient with a complement-triggering condition?

HUS, hemolytic uremic syndrome.

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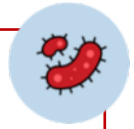
Complement-triggering conditions may lead to atypical-HUS in some patients

Complement activation by trigger occurs frequently and is not always apparent.[1] Triggers can include:

Infection[1-3]



Suspect atypical-HUS if:

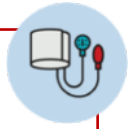
- Symptoms of TMA persist after treatment of infections including COVID-19, H1N1 influenza, adenovirus, cytomegalovirus, and *Streptococcus pneumoniae*

Pregnancy[1,4]

Suspect atypical-HUS if:

- Signs of TMA are present during complications from pregnancy (eg, preeclampsia or HELLP syndrome)
- Symptoms present postpartum
- Symptoms persist for >48 hours after delivery or termination

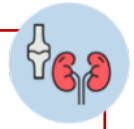
Malignant/severe hypertension[7]



Suspect atypical-HUS if:

- TMA persists despite hypertension management

Post transplant[1,2,5,6]



- Atypical-HUS can be unmasked in the posttransplant setting, and its recurrence is associated with graft loss and severe, systemic end-organ damage

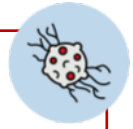
Autoimmune disorders (eg, SLE, APS, scleroderma)[7]

- TMA can occur due to a vicious cycle of endothelial damage and increased complement activity

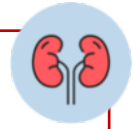
Drug therapy[1,5,8]

- TMAs may be related to the use of certain drugs, including immunosuppressants, chemotherapies, and anti-inflammatories
- Suspect atypical-HUS if TMA does not resolve following drug withdrawal

Malignancy[1]



Glomerulonephritis[1]



Surgery or trauma[1]

Various conditions involving multiple organ systems can trigger atypical-HUS. Rapid diagnosis and early management of atypical-HUS are time critical

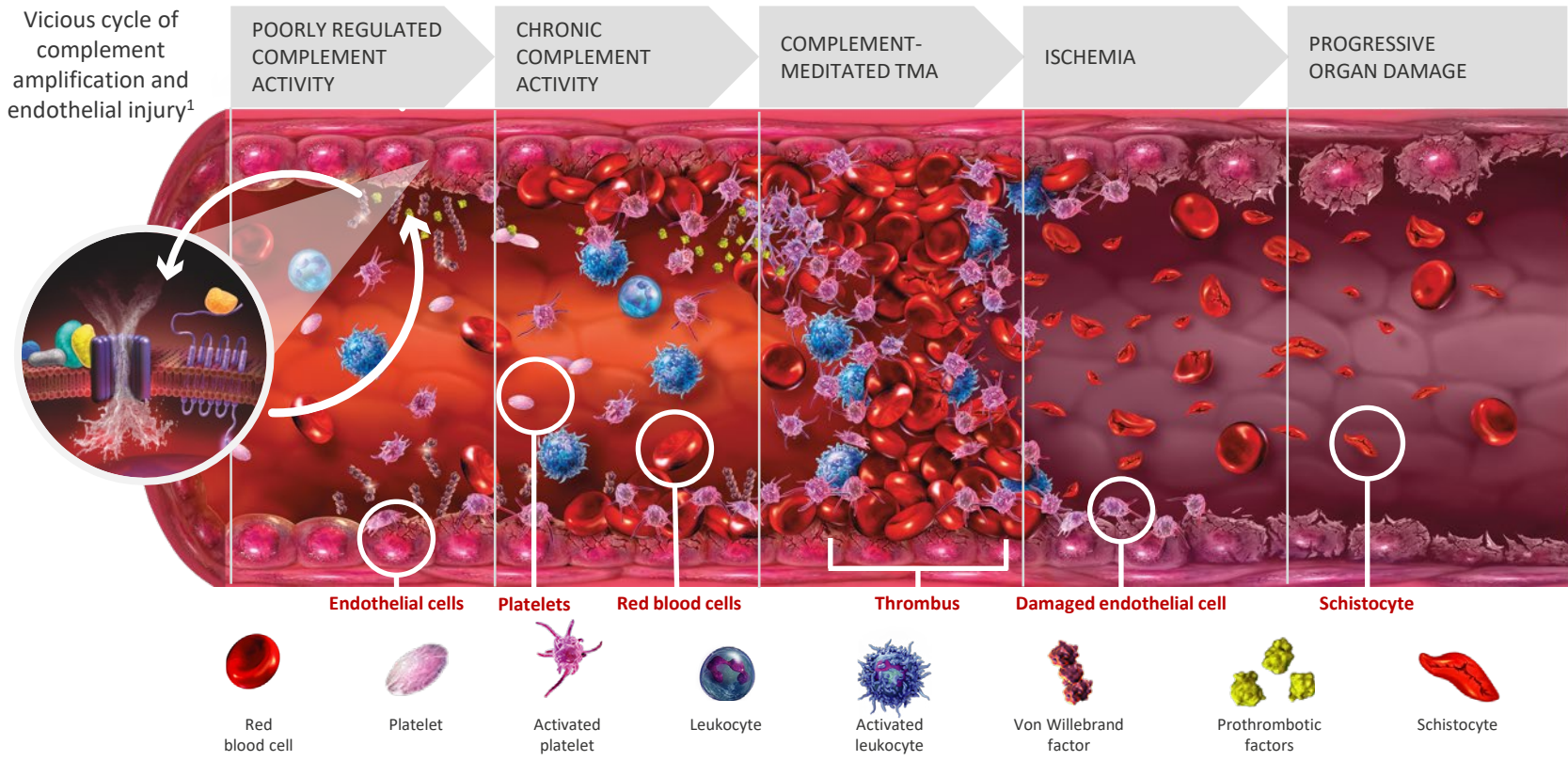
APS, antiphospholipid syndrome; HELLP, hemolysis, elevated liver enzymes, low platelets; HUS, hemolytic uremic syndrome; TMA, thrombotic microangiopathy.

1. Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14 suppl 11(11):2-15. **2.** Azoulay E, et al. *Chest.* 2017;152(2):424-434. **3.** Kaufeld J, et al. *Kidney Int Rep*. 2021;6(10):2709-2712.
4. Sibai BM, et al. *Am J Obstet Gynecol*. 1993;169:1000-1006. **5.** Kavanagh D, et al. *Semin Nephrol*. 2013;33(6):508-530. **6.** Gonzalez Suarez ML, et al. *J Clin Med*. 2019;8(7):919.
7. Asif A, et al. *J Nephrol*. 2017;30(3):347-362. **8.** Noris M, et al. Genetic atypical hemolytic-uremic syndrome. Updated September 23, 2021. Accessed April 27, 2023. https://www.ncbi.nlm.nih.gov/books/NBK1367

Atypical-HUS is a life-threatening condition leading to ongoing endothelial injury, organ damage, and potential death[1-3]

- In atypical-HUS, the risk of TMA complications is lifelong[3,4]
- Onset can be sudden or gradual, can be life-threatening, and can occur at any age[3-5]

- Increased uncontrolled complement activity leads to a vicious cycle of ongoing vascular endothelial damage and complement amplification[1,6,7]
- This can lead to microvascular occlusions, reduced blood flow, and ischemic organ damage[1,6,7]



For illustrative purposes only; objects are not to scale.

HUS, hemolytic uremic syndrome; TMA, thrombotic microangiopathy.

1. Azoulay E, et al. *Chest*. 2017;152(2):424-434. **2.** Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14 suppl 11(11):2-15. **3.** Fremeaux-Bacchi V, et al. *Clin J Am Soc Nephrol*. 2013;8(4):554-562. **4.** Campistol JM, et al. *Nefrologia*. 2015;35(5):421-447. **5.** Laurence J. *Clin Adv Hematol Oncol*. 2020;18(4):221-230. **6.** Noris M, et al. *Nat Rev Nephrol*. 2012;8(11):622-633. **7.** Loirat C, Frémeaux-Bacchi V. *Orphanet J Rare Dis*. 2011;6:60.

Atypical-HUS signs and symptoms

Patients with atypical-HUS are at ongoing risk of systemic, life-threatening, and sudden complications[1-6]*

UP TO 33%

experience cardiovascular symptoms, including[4]:

- Arterial thrombosis[5,14]
- Hypertension[7,8]
- Vascular stenosis[7]
- Myocardial infarction[5]
- Sudden death[5]

UP TO 83%

have acute renal failure at presentation, including[9]:

- Elevated creatinine[10]
- Proteinuria[8]
- Decreased eGFR[10,11]

More than **50%** of adult patients with atypical-HUS are **at risk for ESRD and death** at 5 years[1]

UP TO 25%

experience neurological symptoms, including[4]:

- Confusion[5,10]
- Stroke[5]
- Encephalopathy[5,7]
- Seizure[10]

UP TO 20%

experience pulmonary symptoms, including[4]:

- Pulmonary hemorrhage[6]
- Dyspnea[6]
- Pulmonary edema[6]

UP TO 47%

experience GI symptoms, including[4]:

- Colitis[5]
- Nausea/vomiting[5]
- Abdominal pain[5,10]
- Gastroenteritis[2]
- Pancreatitis[5]
- Diarrhea[2,10]

Other macrovascular complications[12]:

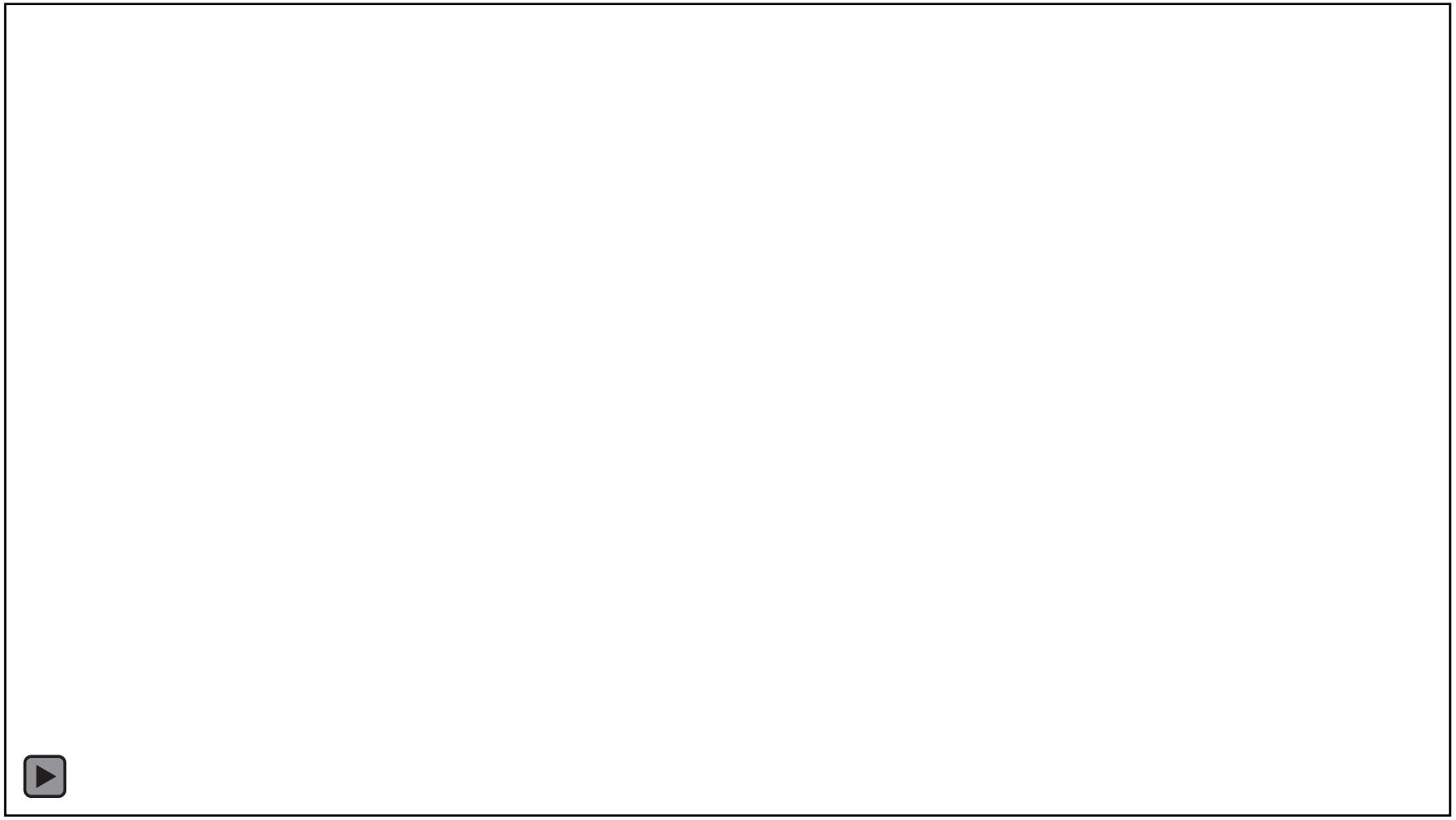
- Peripheral arterial disease[13]
- Phalangeal gangrene[12]

Early diagnosis of atypical-HUS may reduce the risk of organ injury and improve patient outcomes[1,6]
TMA may be more common than you think[6]

Actor portrayal. *The organ-specific symptoms associated with atypical-HUS are reported from published literature and are not limited to only those listed above. The percentage for each organ system listed is the high range for either the pediatric or adult population based on the references cited. eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GI, gastrointestinal; HUS, hemolytic uremic syndrome; TMA, thrombotic microangiopathy.

1. Azoulay E, et al. *Chest.* 2017;152(2):424-434. **2.** Goodship THJ, et al. *Kidney Int.* 2017;91(3):539-551. **3.** Fremeaux-Bacchi V, et al. *Clin J Am Soc Nephrol.* 2013;8(4):554-562. **4.** Schaefer F, et al. *Kidney Int.* 2018;94(2):408-418. **5.** Campistol JM, et al. *Nefrologia.* 2015;35(5):421-447. **6.** Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14(11)(suppl 11):2-15. **7.** Hofer J, et al. *Front Pediatr.* 2014;2:97. **8.** Krishnappa V, et al. *Ther Apher Dial.* 2018;22(2):178-188. **9.** Sellier-Leclerc AL, et al. *J Am Soc Nephrol.* 2007;18(8):2392-2400. **10.** Jamme M, et al. *PLoS One.* 2017;12(5):e0177894. **11.** Legendre CM, et al. *N Engl J Med.* 2013;368(23):2169-2181. **12.** Noris M, Remuzzi G. *Nat Rev Nephrol.* 2014;10(3):174-180. **13.** Brunelli SM, et al. *J Nephrol.* 2015;28(3):361-367. **14.** Noris M, Remuzzi G. *Am J Kidney Dis.* 2015;66(2):359-375.

Patient Story: Donnan



TMA recurrence: Risk factors and considerations

TMA, thrombotic microangiopathy.

Certain risk factors may increase the risk of recurrence of atypical-HUS*

Clinical history of TMA[1-3]

- Multiple TMA manifestations suggest high risk for subsequent TMA in the presence of complement-triggering conditions.

Pediatric onset[4]

- High risk due to the increased frequency of complement-activating events (eg, infections and vaccinations)

Family history of TMA or renal disease[5-7]

- Patients with a family history of TMA or renal disease have a higher rate of disease progression with a reported rate of ESRD or death between 50% and 80%

History of renal transplant[8]

- TMA recurrence following transplantation has been reported to range from 20% to >90% at 3 to 5 years, depending on the presence of a specific genetic mutation

Extrarenal manifestations of atypical-HUS or severe disease[9]

Identified genetic mutation[1-4,10]

- Unmanaged patients with atypical-HUS are at continuous risk for TMA relapse, and the risk is approximately 2 to 3 times higher in patients with a genetic pathogenic variant

Complement biomarkers[2]

- Increased plasma sC5b-9 levels in unmanaged patients with atypical-HUS have been associated with a higher risk of relapse

*This is not a comprehensive list but is intended to provide examples of factors that may increase risk for TMA, including atypical-HUS. Anything that amplifies complement is a risk factor for TMA.
C5, complement component 5; ESRD, end-stage renal disease; HUS, hemolytic uremic syndrome; TMA, thrombotic microangiopathy.

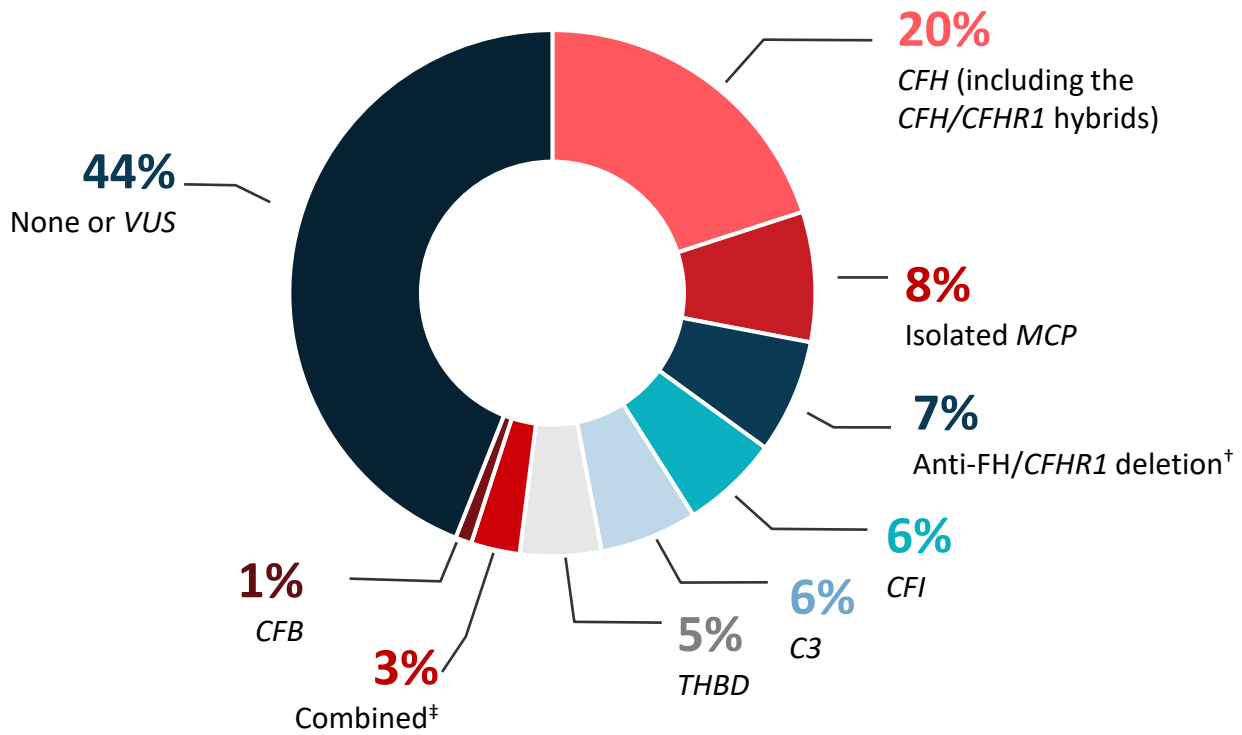
1. Menne J, et al. *BMC Nephrol.* 2019;20(1):125. **2.** Fakhouri F, et al. *Blood*. 2021;137(18):2438-2449. **3.** Fakhouri F, et al. *Clin J Am Soc Nephrol*. 2017;12(1):50-59. **4.** Macia M, et al. *Clin Kidney J*. 2017;10(3):310-319. **5.** Laurence J, et al. *Clin Adv Hematol Oncol*. 2016;14(11)(suppl 11):2-15. **6.** Noris M, Remuzzi G. *N Engl J Med*. 2009;361(17):1676-1687. **7**. Ariceta G, et al. *Kidney Int*. 2021;100(1):225-237. **8.** Campistol JM, et al. *Nefrologia*. 2015;35(5):421-447. **9.** Laurence J. *Clin Adv Hematol Oncol*. 2020;18(4):221-230. **10.** Neto ME, et al. *J Nephrol*. 2021;34:1373-1380.

Approximately 30%-40% of patients with atypical-HUS do not have an identifiable mutation[1]

Pathologic gene mutations and related autoantibodies that contribute to underlying complement activation are identified in approximately **60%-70%** of patients with atypical-HUS[1-4]

As **30%-40%** of patients with atypical-HUS do not carry an identified genetic mutation, **genetic testing is limited in its usefulness for diagnosis of atypical-HUS[1]**

Genetic mutations identified in patients with atypical-HUS[1,4-6]*



*Data from Noris M, et al. 2010 (N=273). All other data from Bresin E, et al. 2013 (N=795).[4,6] †90% (9 of 10) of patients with CFH autoantibodies have complete deficiency of FH-related proteins secondary to a CFHR1-3 gene deletion, suggesting a genetic basis for complement dysregulation in patients with CFH autoantibodies.[1,6] ‡Patients with ≥2 genetic abnormalities.[4]

Anti-FH, anti-complement factor H antibody; C, complement component; CF, complement factor; CFHR1, complement factor H–related protein 1; FH, factor H; HUS, hemolytic uremic syndrome; MCP, membrane cofactor protein; THBD, thrombomodulin; VUS, variant of unknown significance.

1. Loirat C, et al. *Pediatr Nephrol*. 2016;31(1):15-39. **2.** Fremeaux-Bacchi V, et al. *Clin J Am Soc Nephrol*. 2013;8(4):554-562. **3.** Fakhouri F, et al. *Clin J Am Soc Nephrol*. 2017;12(1):50-59. **4.** Bresin E, et al. *J Am Soc Nephrol*. 2013;24(3):475-486. **5.** Schaefer F, et al. *Kidney Int*. 2018;94(2):408-418. **6.** Noris M, et al. *Clin J Am Soc Nephrol*. 2010;5(10):1844-1859. **7.** Asif A, et al. *J Nephrol*. 2017;30:347-362. **8.** Noris M, et al. *Clin J Am Soc Nephrol*. 2010;5(10):1844-1859.

Genetic testing may provide prognostic value

Certain genetic mutations put some patients at high risk for poor outcomes[1-3]

Genetic testing is not required to diagnose atypical-HUS[4]

- Approximately 30%-40% of patients with atypical-HUS do not have an identifiable mutation[5]
- The prevalence of genetic mutations can differ in different populations and by country[6,7]
- As mutations continue to be discovered, more patients with atypical-HUS may be found to have a genetic component to their condition[4]

Once a diagnosis has been confirmed, **genetic testing can identify mutations** that are associated with a **higher risk** of[2]:

- TMA recurrence (after discontinuation of therapy)
- TMA recurrence post renal transplant
- ESRD progression, or death ≤12 months after first episode

The risk of TMA recurrence is approximately 2 to 3 times higher in patients with certain genetic mutations[2]

ESRD, end-stage renal disease; HUS, hemolytic uremic syndrome; TMA, thrombotic microangiopathy.

1. Tsai HM. *Transfus Med Rev*. 2014;28(4):187-197. **2.** Campistol JM, et al. *Nefrologia*. 2015;35(5):421-447. **3.** Abbas F, et al. *World J Transplant*. 2018;8(5):122-141. **4.** Laurence J. *Clin Adv Hematol Oncol*. 2012;10(10 suppl 17):1-12. **5.** Loirat C, et al. *Pediatr Nephrol*. 2016;31(1):15-39. **6.** Palma LMP, et al. *Clin Kidney J*. 2021;14(4):1126-1135. **7.** Fujisawa M, et al. *Clin Exper Nephrol*. 2018;22(5):1088-1099.

Atypical-HUS can occur both with and without triggers, and with or without identified genetic mutations

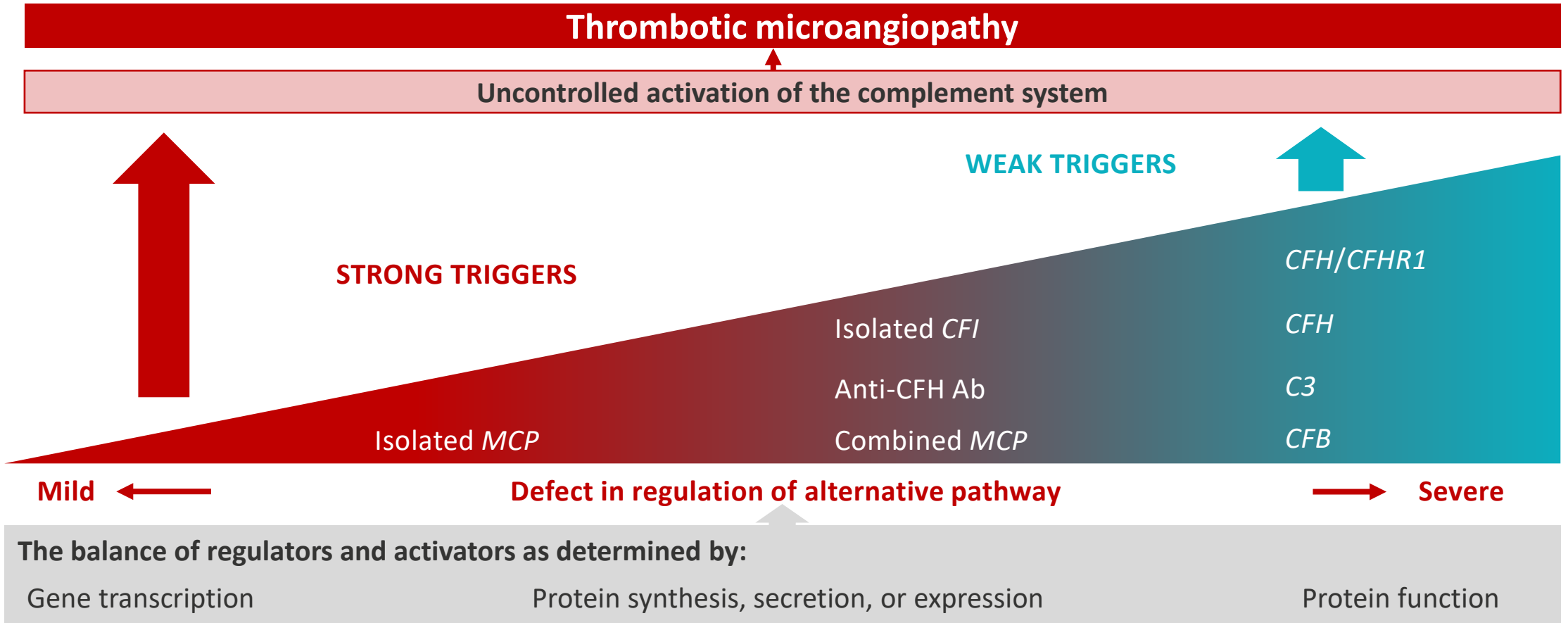


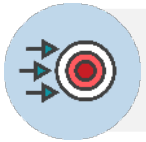
Figure adapted from Tsai HM. 20141 and Zuber J, et al. 2013.2
Ab, antibody; C3, complement component 3; CF, complement factor; CFHR1, complement factor H–related protein 1; HUS, hemolytic uremic syndrome; MCP, membrane cofactor protein.

1. Tsai HM. *Transfus Med Rev*. 2014;28(4):187-197. **2.** Zuber J, et al. *Transplant Rev (Orlando).* 2013;27(4):117-125.

Wrap-up

Summary

TMA is a serious, time-sensitive, and potentially fatal medical condition characterized by thrombocytopenia, microangiopathic hemolysis, organ damage, and early mortality[1,2]



Rapid diagnosis is essential to differentiate atypical-HUS from TTP, STEC-HUS, and other TMA etiologies in order to properly manage the disease[1]

Atypical-HUS is caused by dysregulation of the complement system[1]

Triggers may unmask and coincide with atypical-HUS. Some triggers include pregnancy, organ transplantation, autoimmune disease, glomerulopathy, lupus, malignant/severe hypertension, and infection[1]

Early diagnosis and management may help to protect your patients' kidneys and other organ systems from further damage[3]

Learn more about TMAs and atypical-HUS at:
aHUSSource.com/physician

HUS, hemolytic uremic syndrome; STEC, Shiga toxin–producing *Escherichia coli*; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

1. Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14 suppl 11(11):2-15. **2.** Fremeaux-Bacchi, et al. *Clin J Am Soc Nephrol.* 2013;8:554-562. **3.** Azoulay E, et al. *Chest*. 2017;152(2):424-434.

aHUS Source

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