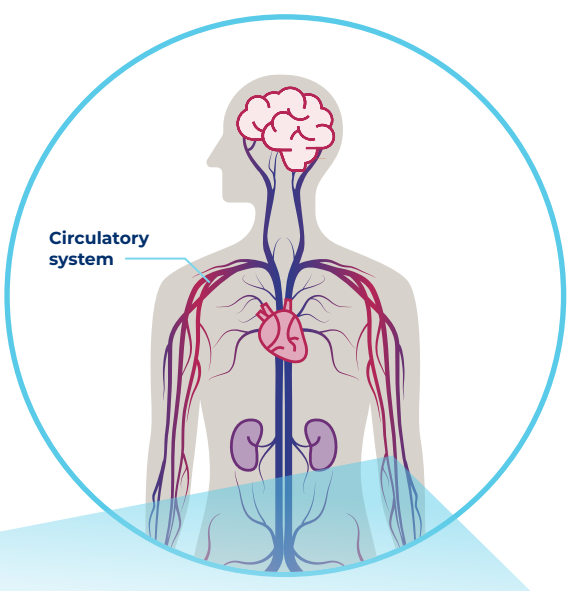
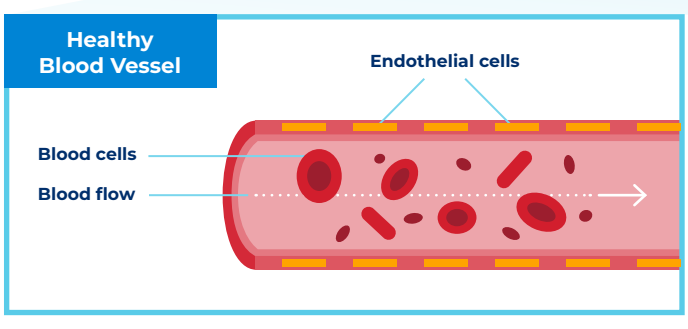
Atypical Hemolytic Uremic Syndrome (aHUS)

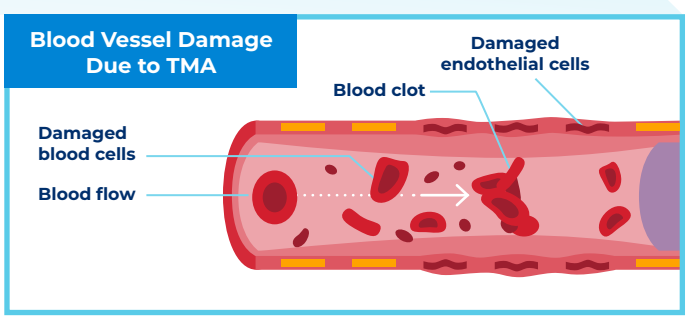
WHAT ARE TMAs?

Thrombotic microangiopathies (TMAs) are a **group of severe and potentially life-threatening rare disorders that cause blood clots and damage** to the walls of the smallest blood vessels (capillaries and small arteries). The blood clots can cause **injury to organs**, that may lead to organ failure and death.[1-4]

In some cases, overactivation or dysregulation of the **complement system** can drive or worsen development of TMA.[2,4] This overactivation **fuels inflammation and an attack on organs and cells in the body**, including endothelial cells that line blood vessels.[2,5]







Signs, symptoms and complications of TMA include:

- Organ damage, including kidneys, brain and heart[3,4]
- Shortness of breath[5,6]
- High blood pressure[4,6,7]
- Thrombosis (blood clots)[8]
- Low platelet count[1]
- Anemia[1]
- Fatigue[5]
- Confusion[9,10]
- Bruising[5]

WHAT IS aHUS?

aHUS is a type of TMA caused by a combination of genetic and/or environmental factors resulting in **dysregulation of the complement system**.

aHUS may appear in the presence or absence of a "trigger" or co-existing condition. aHUS is a **progressive, chronic condition with relapses**.[11-14]

HOW IS aHUS DIAGNOSED?[15]

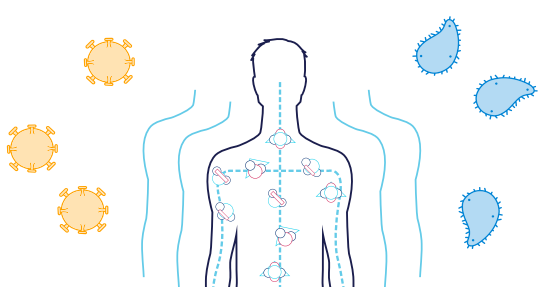
There are no specific diagnostic tests for aHUS, which often leads to a significant delay in diagnosis.

aHUS is ultimately considered based on an **evaluation of laboratory tests**, including blood cell counts and renal function, symptoms and family history.

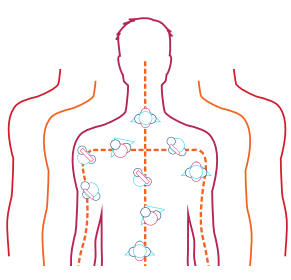
Because the prognosis of aHUS can be poor if not recognized early, a **timely and accurate diagnosis—in addition to treatment—is critical to improving patient outcomes**.

There remains a need for continued innovation to advance scientific understanding, increase awareness and simplify diagnosis of aHUS.

THE COMPLEMENT SYSTEM



The complement system is a part of the immune system and is **essential to the body's defense against infection**.[16]



When the system is **thrown out of balance**, or dysregulated, these proteins can **trigger a dangerous, uncontrolled cascade of reactions** that attack cells and tissues resulting in **harmful inflammation** and the **destruction of healthy cells**.[17]

WHAT ROLE DOES COMPLEMENT INHIBITION PLAY IN TREATING aHUS?

In aHUS, immediate, complete and sustained **terminal complement inhibition** (by blocking the C5 protein) is the proven standard of care to **treat aHUS and its life-threatening complications**.

Alexion's leadership in complement inhibition has set the course for the continued study and development of innovative treatments for certain rare complement-mediated diseases, including aHUS.

WHAT TREATMENT APPROACH IS BEING STUDIED BY ALEXION?

In addition to developing the **first approved therapy for aHUS**, Alexion continues to explore new ways to **improve the patient experience**, including **additional treatment options and delivery choices for those impacted** by this devastating disease.

Alexion continues to **advance scientific research in aHUS** and accelerate the **development of life-changing therapies**.

References

1. Arnold D, Patriquin C, Nazy I. Thrombotic microangiopathies: a general approach to diagnosis and management. *Canadian Medical Association Journal*. 2017. 189 (4):153-159.
2. Blasco M, Guillén-Olmos E, et al. Complement Mediated Endothelial Damage in Thrombotic Microangiopathies. *Frontiers in Medicine*. 2022. 9:1-12.
3. Barbour T, John S, Cohney S, et al. Thrombotic microangiopathy and associated renal disorders. *Nephrology Dialysis Transplantation*. 2012. 27(7):2673–2685.
4. Blasco M, Guillèn E, et. al. Thrombotic microangiopathies assessment: mind the complement. Clinical Kidney Journal. 2020. 14(4):1055-1066.
5. Greenbaum L, Licht C, Nikolaou V, et al. Functional Assessment of Fatigue and Other Patient-Reported Outcomes in Patients Enrolled in the Global aHUS Registry. *Kidney International Reports*. 2020. 5:1161-1171.
6. Timmermans S, Abdul-Hamid M, et al. Patients with hypertension-associated thrombotic microangiopathy may present with complement abnormalities. *Kidney International*. 2017. 91(6): 1420-1425.
7. Thomas M, Robinson S, Scully M. How we manage thrombotic microangiopathies in pregnancy. *British Journal of Haematology*. 2016. 173(6) 821-830.
8. Meri S. Complement activation in diseases presenting with thrombotic microangiopathy. *European Journal of Internal Medicine*. 2013. 24(6):496-502.
9. Sridharan M, Abraham R, Amer H, et al. Atypical Hemolytic Uremic Syndrome-Clinical Presentation, Treatment, and Short Term Outcomes: The Mayo Clinic Experience.
10. Timmermans S, Abdul-Hamid M, et al. Patients with hypertension-associated thrombotic microangiopathy may present with complement abnormalities. *Kidney International*. 2017. 91(6): 1420-1425.
11. Jokiranta, TS. HUS and atypical HUS. Clinical Platelet Disorders. 2017. 129(21).
12. Asif, A., Nayer, A. & Haas, C.S. Atypical hemolytic uremic syndrome in the setting of complement-amplifying conditions: case reports and a review of the evidence for treatment with eculizumab. *J Nephrol*. 2017. 30, 347–362.
13. Afshar-Kharghan, V. Atypical hemolytic uremic syndrome. *Hematology Am Soc Hematol Educ Program*. 2016 (1): 217–225.
14. Brambilla, M, Ardissino, G, Paglialonga, F, et al. Haemoglobinuria for the early identification of aHUS relapse: data from the ItalKId-HUS Network. *J Nephrol*. 2022. 35, 279–284.
15. Laurence J, Haller H, Mannucci P, Nangaku M, et al. Atypical hemolytic uremic syndrome (ahus): essential aspects of an accurate diagnosis. *Clinical Advances in Hematology and Oncology*. 2016. Nov;14(11).
16. Merle, N. S., et al. Complement System Part II: Role in immunity. *Frontiers of Immunology*. 2015. 6:257.
17. Garred, P., Tenner, A. J., & Mollnes, T. E. Therapeutic Targeting of the Complement System: From Rare Diseases to Pandemics. *Pharmacological Reviews*. 2021. 73(2):792-827