aHUS Solving the Puzzle

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History

- 45 y/o male
- PMH: HTN, Family Hx of ESRD

Clinical presentation

- CKD bl cr 2 [2019 -2021]
- Severe HTN Emergency
- RFT deteriorated rapidly (cr 3 >> 8)

Labs

- Hb 8.8 (NN) , plt normal
- LDH 445 , U.ACR 0.9 g/day
- ANA, Anti dsDNA negative, C3 & C4 normal

Renal Biopsy

Chronic Thrombotic Microangiopathy with Focal Dominant C3 Deposits

Renal Biopsy;

Light Microscopic and Immunoperoxidase Findings are Compatible with:

- Chronic Thrombotic Microangiopathy with Focal Dominant C3 Deposits. See Comment

- Additional Features: Focal Global Glomerulosclerosis (35%), Mild Interstitial fibrosis and tubular atrophy (15%), Mild Arteriosclerosis and Moderate Arteriolar Hyalinosis

Light Microscopy: Examination of serial sections prepared from the biopsy received revealed renal cortical and corticomedullary tissue.

Twelve (12) glomeruli were seen, in serial sections examined, out of which 4 were globally sclerosed. The glomeruli showed mild to moderate mesangial matrix increase with mild hypercellularity, focal few intracapillary leucocytes and frequent mild capillary basement membrane thickening with segmental peripheral duplication.

Tubules showed patchy mild atrophic changes.

Interstitium showed focal mild fibrosis (15% of submitted tissue).

Arteries showed mild intimal sclerosis. Arterioles showed moderate hyalinosis.

Congo red: Examination of congo red stained sections viewed under polarized light revealed no amyloid deposits.

Immunohistochemistry: Serial sections on charged slides were treated for anti IgA, IgG, kappa and lambda and C3 antibodies.

IgA: negative IgG: negative

C3: Focal segmental mesangial and GBM deposits (+2-3)

Kappa and Lambda: negative

Genetic analysis report

Indication Renal disease; focal C3 deposits, rapid development to end stage renal disease

Order Sequence analysis: *CFH* gene

RESULTS

- **Detection of a likely pathogenic variant in gene *CFH*, which is associated with complement factor H deficiency and consistent with your patient's symptoms assuming autosomal dominant inheritance.**

Gene	Variant	Zygosity	Heredity	MAF (%)	Classification
CFH	c.3531T>G; p.Tyr1177*	het.	AD, AR	-	likely pathogenic

CFH, c.3531T>G; p.Tyr1177* (het.), NM_000186.4

OMIM / Reference	Phenotype	Heredity
609814	Complement factor H deficiency	AD, AR
235400	{Hemolytic uremic syndrome, atypical, susceptibility to, 1}	AD, AR
126700	Basal laminar drusen	AD
610698	{Macular degeneration, age-related, 4}	AD

33y, female, ACR 4 gm, S.Cr 2.3 mg/dl, UA: RBCs 60-70, +ve ANA, -ve ADNA, C3: 75

Light Microscopy: Examination of serial sections prepared from the biopsy received revealed renal corticomedullary tissue.
Nine (9) glomeruli were seen, not represented in all serial sections examined, out of which 2 were globally sclerosed. The patent glomeruli showed thickened capillary basement membranes with segmental peripheral duplication, focal endocapillary hypercellularity and focal mild mesangial proliferation. Four (4) glomeruli showed cellular crescents. Two (2) glomeruli showed segmental tuft sclerosis.
Tubules showed mild injury.
Interstitium showed moderate lymphocytic infiltrate.
Arteries and arterioles were unremarkable.
Congo red: Examination of congo red stained sections viewed under polarized light revealed no amyloid deposits.

Immunohistochemistry: Serial sections on charged slides were treated for anti IgA, IgG and C3 antibodies. Examination revealed:
IgA: negative. IgG: negative.
C3: GBM and mesangial deposits (2+).

Electron Microscopy: Ultrastructural examination revealed diffuse thickening of glomerular capillary basement membranes with extensive subendothelial electron-dense deposits as well as frequent subepithelial humps. The overlying podocytes showed widespread foot process effacement. The mesangial areas showed expansion by the same deposits. The endothelium showed injury.

Diagnosis:

Renal Biopsy;

Membranoproliferative Glomerulonephritis with 40% Crescents; Consistent with C3 Dominant Glomerulonephritis

CLINICAL INFORMATION

Abnormal renal morphology; Acute kidney injury; Anemia; Chronic kidney disease; Glomerular C3 deposition; Hemolytic anemia; Proteinuria
(Clinical information indicated above follows HPO nomenclature.)

Family history: Unknown.
Consanguineous parents: No.

RISK FACTOR IDENTIFIED

INTERPRETATION

By NGS-CNV analysis and MLPA confirmation, a homozygous disease-associated deletion encompassing the entire *CFHR1* and *CFHR3* genes was identified. **The increased genetic susceptibility to atypical hemolytic uremic syndrome is confirmed.**

No further clinically relevant variant was identified.

RECOMMENDATIONS

- Clinical evaluation to assess the phenotypic overlap with the detected variants is recommended.
- For broader genetic testing, proceeding to exome or genome sequencing can be considered.
- Genetic counselling is recommended.

MAIN FINDINGS

COPY NUMBER VARIATIONS				
CNV DESCRIPTION*	SIZE (KB)	GENE COUNT**	INTERPRETATION***	RELATED DISORDER
seq[GRCh37] 1q31.3(196743986_196801129)x0	57 kb	2	Pathogenic	Hemolytic uremic syndrome, atypical, susceptibility to

* according to ISCN 2020; ** genes are listed below; *** according to ACMG 2020, modified

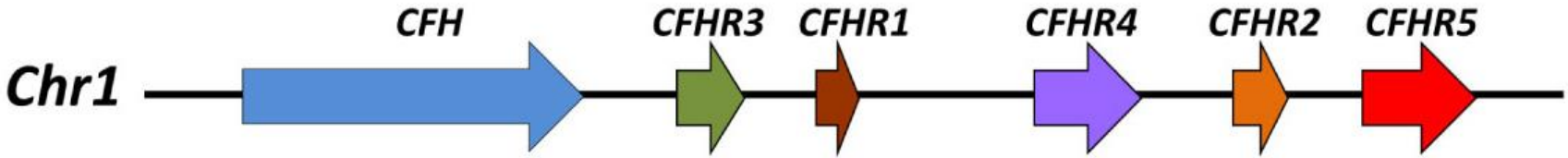
GENES INCLUDED IN THE DETECTED CNVs:

CNV DESCRIPTION*	RefSeq GENES
seq[GRCh37] 1q31.3(196743986_196801129)x0	*CFHR1, CFHR3*

* according to ISCN 2020

GENE (TRANSCRIPT, METHOD)	OUTCOME
CFHR1 (NM_002113.3; MLPA)	one-copy loss encompassing entire gene
CFHR3 (NM_021023.6; MLPA)	one-copy loss encompassing entire gene

- The most important regulator of the alternative pathway is factor H (CFH)



The CFHR genes arose as a result of genomic duplication and because of the high sequence homology, the region is prone to non-allelic homologous recombination, a process that can result in gene deletion, duplication and rearrangement.

Genetic variant occurring in over 1% of the population are termed 'polymorphisms'

SEVERAL INHERITED AND ACQUIRED ABNORMALITIES CAUSE C3G/HUS

- Genetic causes include pathogenetic mutations in complement-related genes, such as C3, CFB, CFH, CFI, and CFHR
- Acquired abnormalities are associated with development of autoantibodies against complement proteins and complexes; for example, C3 nephritic factor (C3NeF) that targets C3 convertase, C5NeF that targets C5 convertase, anti-CFH autoantibodies, and anti-CFB autoantibodies

Complement mediated kidney disease

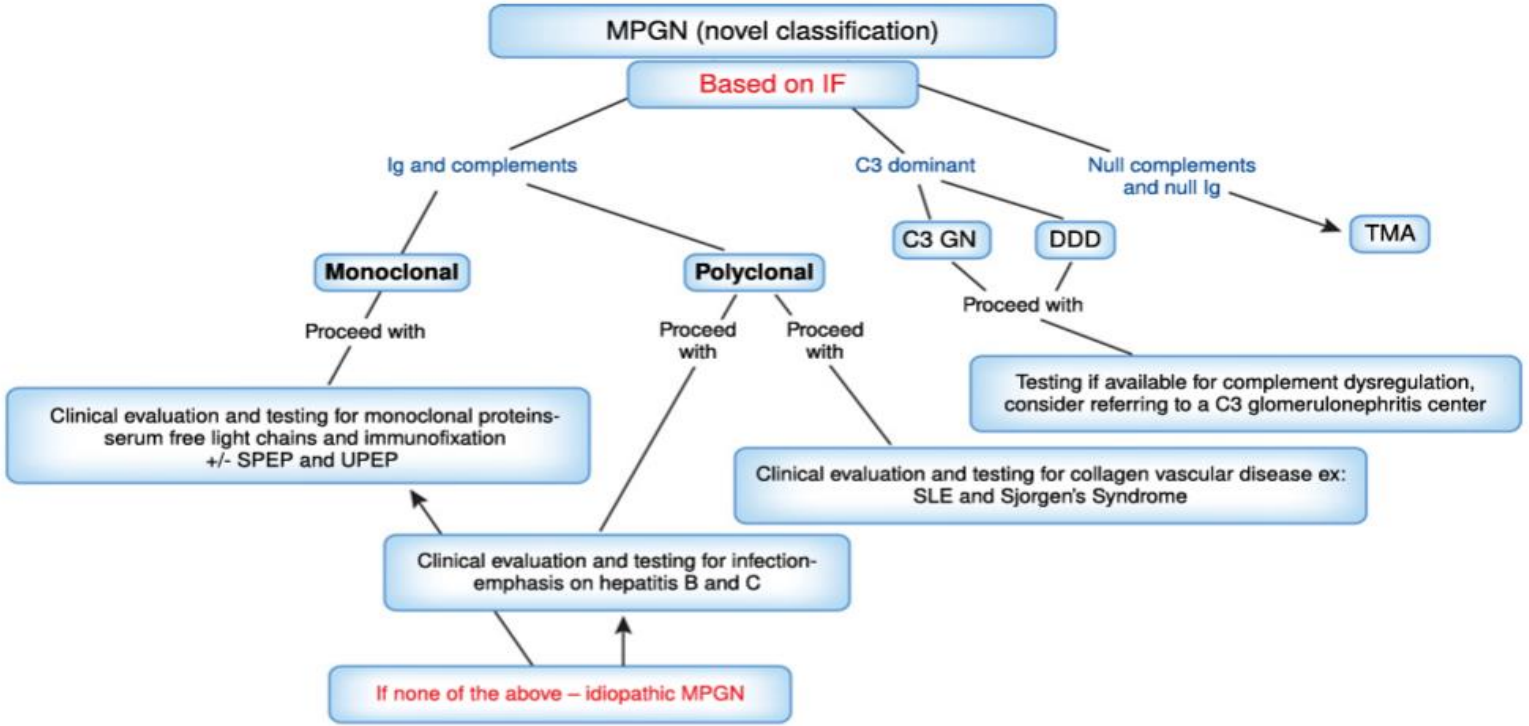


Figure 2. | Simplistic breakdown of the new MPGN classification using immunofluorescence as the basis and an approach to evaluation when the kidney biopsy indicated MPGN. DDD, dense deposit disease; IF, immunofluorescence; SPEP, serum protein electrophoresis; TMA, thrombotic microangiopathy; UPEP, urine protein electrophoresis.

TABLE 22.1 Causes of a Membranoproliferative Pattern of Glomerular Injury

Immune complex mediated, monoclonal immunoglobulin mediated	Deposition of immune complexes as a result of an infection	Viral: hepatitis B and C Bacterial: endocarditis, infected ventriculoatrial shunt, visceral abscesses, leprosy, meningococcal meningitis Protozoa/other infections: malaria, schistosomiasis, mycoplasma, leishmaniasis
	Deposition of immune complexes as a result of an autoimmune disease	Systemic lupus erythematosus Sjögren syndrome Rheumatoid arthritis
	Deposition of monoclonal immunoglobulin as a result of a monoclonal gammopathy	Plasma cell or B-cell disorder
Complement-mediated (C3 glomerulonephritis and dense deposit disease)	Mutations in complement-regulating proteins CFH, CFI, CFHR5	
	Antibodies to complement regulating proteins C3/C4 nephritic factor, antibodies against CFH, CFI, or CFB	
	Mutations in complement factors C3, CFB	
	Monoclonal gammopathy	
Non–immunoglobulin mediated, non–complement mediated	Healing phase of HUS/TTP Antiphospholipid (anticardiolipin) antibodies syndrome POEMS syndrome Radiation nephritis Nephropathy associated with bone marrow transplantation Drug-associated thrombotic microangiopathies Sickle cell anemia and polycythemia Dysfibrinogenemia and other prothrombotic states Transplant glomerulopathy	
Idiopathic	None of the conditions previously mentioned present	

Complement mediated kidney disease

Table 1 | Atypical haemolytic–uraemic syndrome and C3 glomerulopathy

Parameter	aHUS[203]	C3G[204]
Clinical course	Acute	Chronic
Incidence	0.2–1.9/million/year[205]	1–3/million/year[206]
Associated infectious disease	Shiga toxin-producing *Escherichia coli* infection associated with haemolytic–uraemic syndrome	Post-infectious glomerulonephritis
Complement activation phase	Endothelial cell and/or glycocalyx	Fluid phase and/or glomerular basement membrane
Triggers	Autoimmunity, transplantation, pregnancy, infections, drugs and metabolic disease[207]	Infection[65,208]
Kidney failure	60–70% without complement inhibition; 10–15% with complement inhibition[203,209]	50% at 10 years[67]
Post-transplant recurrence	Variable; depends on genetic risk factors[210]	Very high[204]
Extrarenal manifestations	Systemic thrombotic microangiopathy; retinal drusen are rare	Partial lipodystrophy[211], retinal drusen[212]
C3 levels	Low in 30–50% of patients[213]	Low in up to 75% of patients[67,214]
Acquired drivers	Anti-factor H autoantibodies[215]	Nephritic factors[216], anti-factor H autoantibodies[215], monoclonal immunoglobulin[53,217]

aHUS, atypical haemolytic–uraemic syndrome; C3G, C3 glomerulopathy.

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- aHUS Complications and Prognosis
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OVERVIEW OF aHUS

aHUS, atypical hemolytic uremic syndrome.

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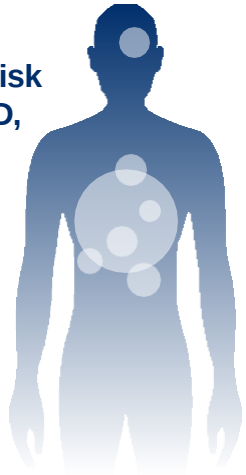
WHAT IS aHUS?[1-11]

aHUS is caused by genetic abnormalities that result in chronic, uncontrolled complement activation, leading to complement-mediated TMA in the presence or absence of an identified trigger[1-3]

Patients with aHUS may be at continual risk of subsequent TMA manifestations, ESRD, and/or death without a timely diagnosis and appropriate management[4-6]

Extrarenal manifestations may occur in patients with aHUS, including signs and symptoms of the CV, GI, visual, central nervous, and pulmonary systems[7-9]



A clinical diagnosis is required for aHUS, using diagnostic tests available for other causes of TMA[10,11]

Involvement of a multidisciplinary team for diagnosis is advantageous to identify the various signs and symptoms of aHUS rapidly and provide patient-centric management and monitoring[3,5]

aHUS, atypical hemolytic uremic syndrome; **CV,** cardiovascular; **ESRD,** end-stage renal disease; **GI,** gastrointestinal; **TMA,** thrombotic microangiopathy.

1. Noris M, Remuzzi G. *N Engl J Med.* 2009;361(17):1676-1687. **2.** Riedl M, et al. *Semin Thromb Hemost.* 2014;40(4):444-464. **3.** Goodship TH, et al. *Kidney Int.* 2017;91(3):539-551. **4.** Fremeaux-Bacchi V, et al. *Clin J Am Soc Nephrol.* 2013;8(4):554-562. **5.** Gordon CE, et al. *Am J Kidney Dis.* 2017;70(5):715-721. **6.** Schaefer F, et al. *Kidney Int.* 2018;94(2):408-418. **7.** Zheng X, et al. *J Pediatr Ophthalmol Strabismus.* 2014;51:e62-e65. **8.** Sallée M. *Nephrol Dial Transplant.* 2010;25(6):2028-2032. **9.** Jamme M, et al. *PLoS One.* 2017;12(5):e0177894. doi:10.1371/journal.pone.0177894 **10.** Campistol JM, et al. *Nefrologia.* 2015;35(5):421-447. **11.** Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14(11)(suppl 11):2-15.

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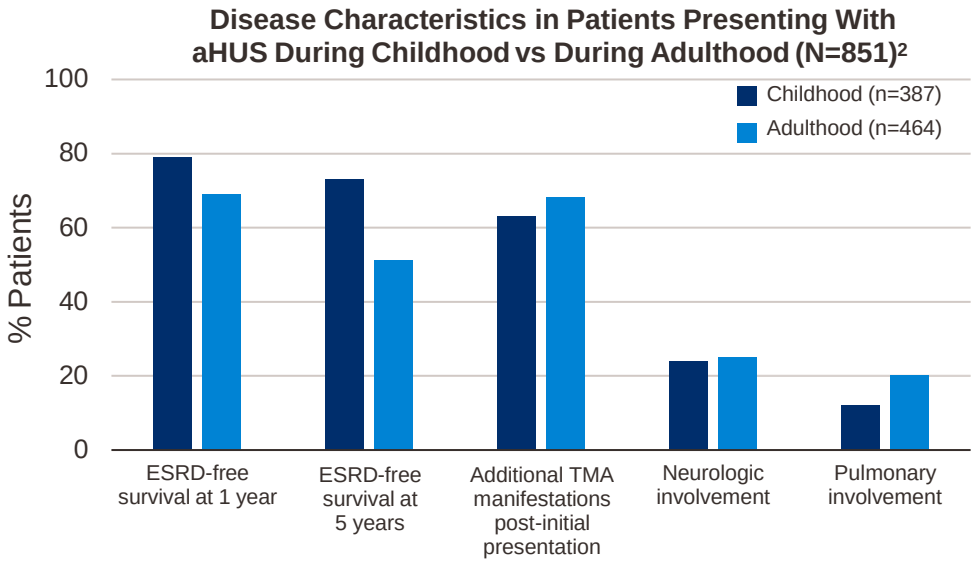
THE GLOBAL aHUS REGISTRY[1-4]

- The Global aHUS Registry, initiated in April 2012, is an observational, noninterventional, multicenter registry designed to prospectively collect demographic characteristics, medical and disease history, treatment effectiveness, and safety outcomes data for patients with aHUS[1]
- Both adults and children diagnosed with aHUS have been enrolled[1]
- Extrarenal manifestations were more frequent in patients who were in the initial presenting phase (19%-38%) compared with those in the chronic phase (12%-23%)[2]

As of January 2020, 351 clinical sites in 23 countries had enrolled 1858 patients in the Global aHUS Registry[3,4]



Graph recreated from Schaefer F, et al. *Kidney Int.* 2018;94(2):408-418.

aHUS, atypical hemolytic uremic syndrome; **ESRD,** end-stage renal disease; **TMA,** thrombotic microangiopathy.

1. Licht C, et al. *BMC Nephrol.* 2015;16:207. doi:10.1186/s12882-015-0195-1 **2.** Schaefer F, et al. *Kidney Int.* 2018;94(2):408-418. **3.** Fakhouri F, et al. *J Nephrol.* 2021;34(5):1581-1590. **4.** aHUS Registry. Alexion Pharmaceuticals, Inc. Accessed September 9, 2021. http://www.ahusregistry.com/library.html#top

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THE COMPLEMENT SYSTEM IN THE PATHOPHYSIOLOGY OF aHUS

aHUS, atypical hemolytic uremic syndrome.

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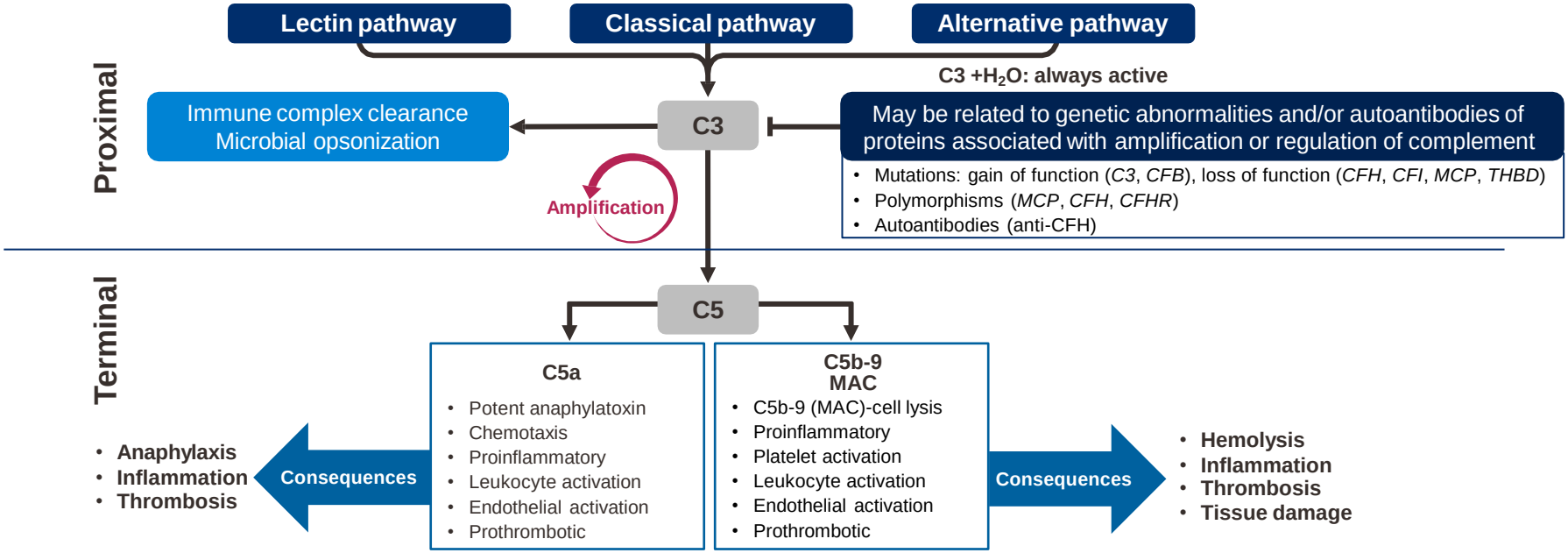
UNCONTROLLED COMPLEMENT ACTIVATION IN aHUS[1-7]



aHUS, atypical hemolytic uremic syndrome; **MAC,** membrane attack complex; **MCP**, membrane cofactor protein; **THBD**, thrombomodulin.

1. Walport MJ. *N Engl J Med.* 2001;344(14):1058-1066. **2.** Holers VM. *Immunol Rev.* 2008;223:300-316. **3.** Noris M, et al. *Nat Rev Nephrol.* 2012;8(11):622-633.
4. Noris M, et al. *Clin J Am Soc Nephrol.* 2010;5(10):1844-1859. **5.** Noris M, Remuzzi G. *N Engl J Med.* 2009;361(17):1676-1687.
6. Legendre CM, et al. *N Engl J Med.* 2013;368(23):2169-2181. **7.** Campistol JM, et al. *Nefrologia.* 2015;35(5):421-447.

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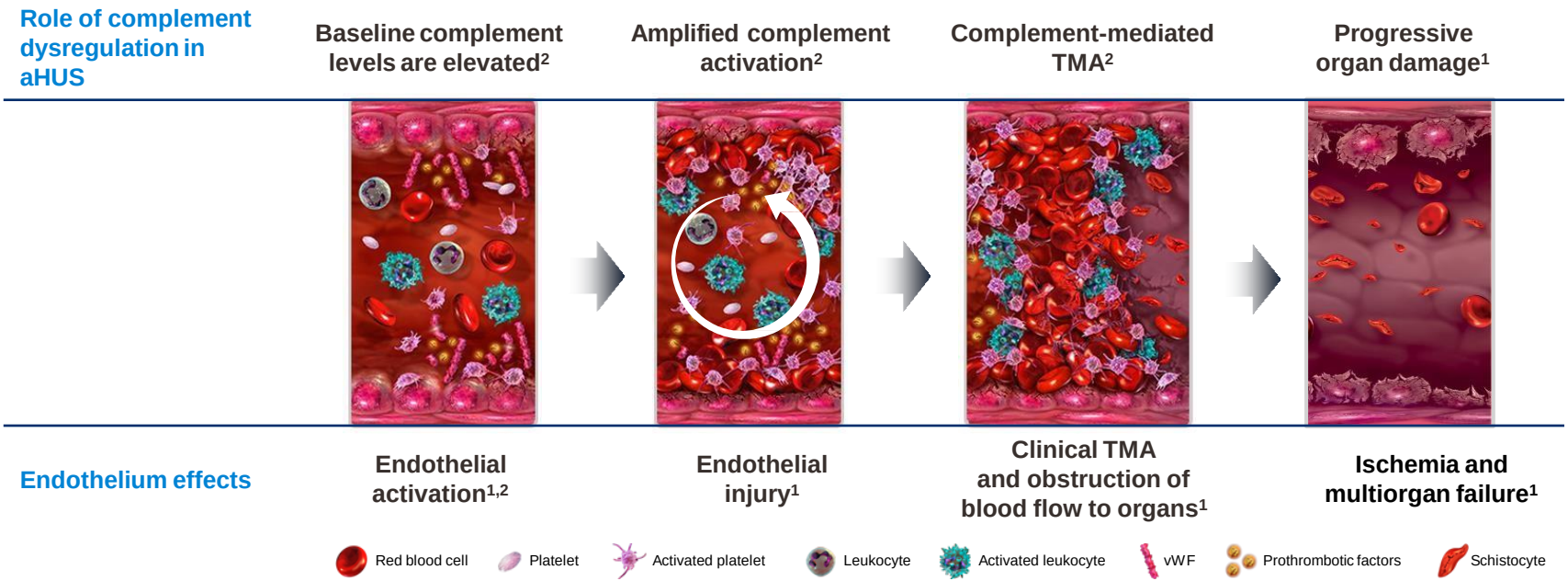
VASCULAR INJURY IN PATIENTS WITH aHUS[1]



aHUS, atypical hemolytic uremic syndrome; **TMA,** thrombotic microangiopathy; **vWF,** von Willebrand factor.

1. Noris M, et al. *Nat Rev Nephrol*. 2014;10(3):174-180. **2.** Cofiell R, et al. *Blood*. 2015;125(21):3253-3262.

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DIFFERENTIAL DIAGNOSIS OF aHUS

aHUS, atypical hemolytic uremic syndrome.

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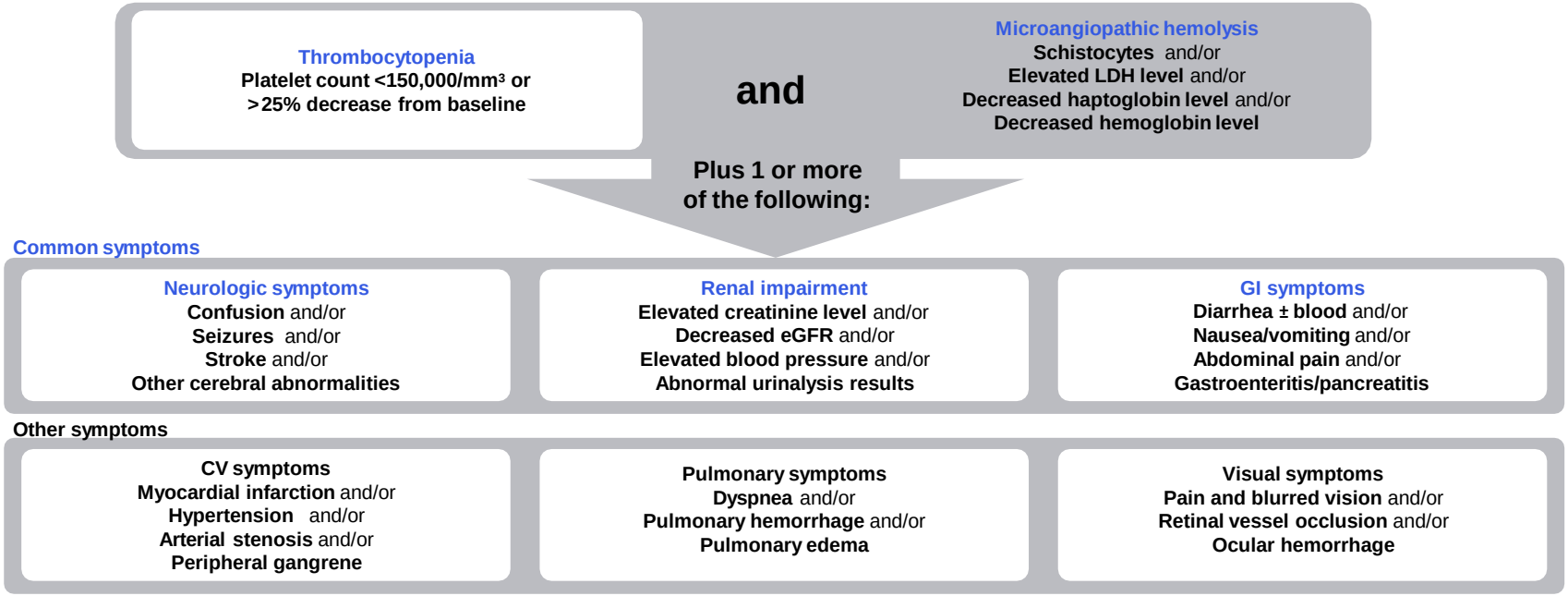
THROMBOCYTOPENIA, MICROANGIOPATHIC HEMOLYSIS, AND ORGAN DYSFUNCTION IN TMA[1-4]



CV, cardiovascular; **eGFR,** estimated glomerular filtration rate; **GI,** gastrointestinal; **LDH,** lactate dehydrogenase; **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(11)(suppl 11):2-15. **3.** Frémeaux-Bacchi V, et al. Supplementary appendix. *Clin J Am Soc Nephrol*. 2013;8(4):554-562. Accessed October 12, 2021. https://cjasn.asnjournals.org/content/clinjasn/suppl/2013/01/09/CJN.04760512.DCSupplemental/CJN04760512SupplementaryData.pdf

4. Jamme M, et al. *PLoS One*. 2017;12(5):e0177894. doi:10.1371/journal.pone.0177894

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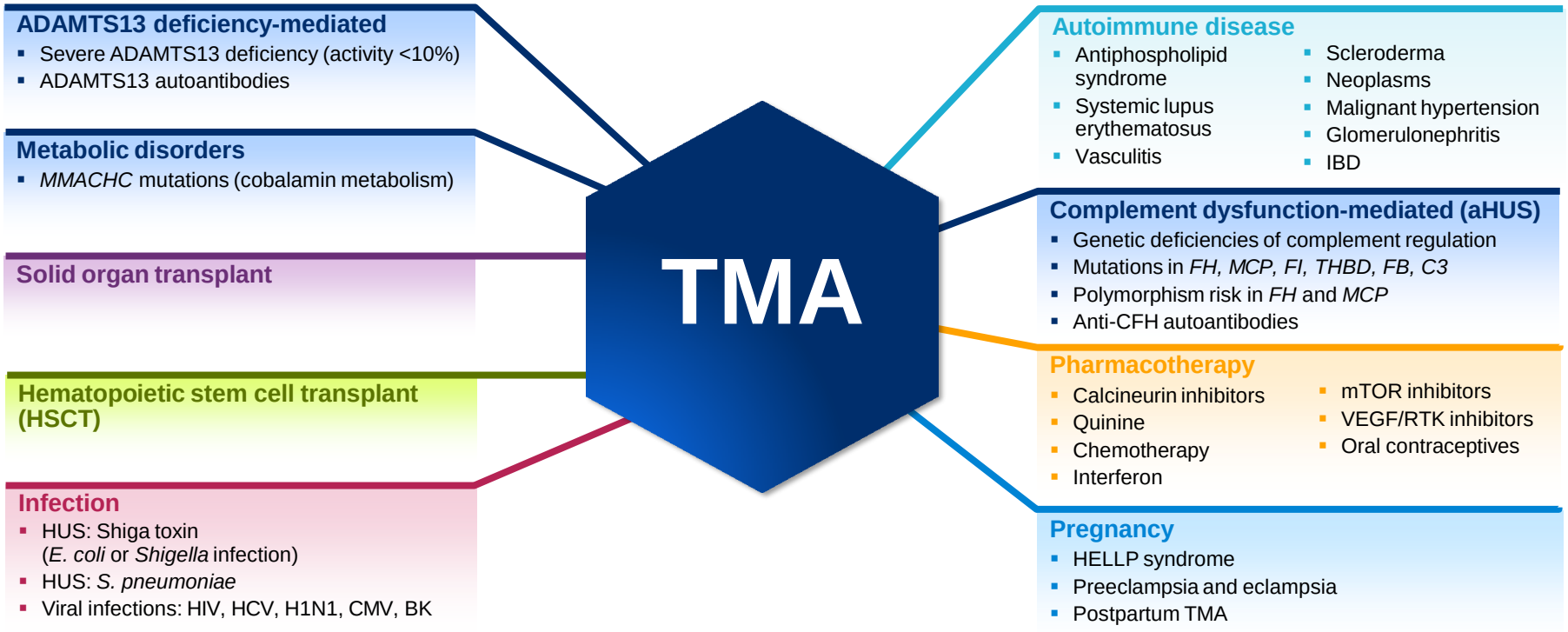
POTENTIAL CAUSES OF TMA[1-4]



ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13**; aHUS,** atypical hemolytic uremic syndrome**; BK,** BK polyomavirus; **C3**, complement component 3; **CFH**, complement factor H; **CMV,** cytomegalovirus; **FB,** complement factor B; **FH,** complement factor H; **FI,** complement factor I; **HCV,** hepatitis C virus**; HELLP,** hemolysis, elevated liver enzymes, low platelets**; HIV**, human immunodeficiency virus; **H1N1**, influenza A virus; **HUS,** hemolytic uremic syndrome; **IBD,** inflammatory bowel disorder; **MCP,** membrane cofactor protein**; *MMACHC,*** methylmalonic aciduria and homocystinuria type C; **mTOR,** mammalian target of rapamycin**; RTK,** receptor tyrosine kinase; **THBD,** thrombomodulin**; TMA,** thrombotic microangiopathy; **VEGF,** vascular endothelial growth factor.

1. Campistol JM, et al. *Nefrologia.* 2015;35(5):421-447. **2.** Nester CM, et al. *Mol Immunol.* 2015;67(1):31-42. **3.** Asif A, et al. *J Nephrol.* 2017;30(3):347-362. **4.** Brocklebank V, et al. *Clin J Am Soc Nephrol.* 2018;13(2):300-317.

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aHUS, TTP, AND STEC-HUS ARE RARE CONDITIONS WITH UNIQUE MECHANISMS OF DISEASE[1]

TTP[2-4]

Insufficient ADAMTS13 activity leaves vWF intact[2-4]

vWF

Severe deficiency in ADAMTS13 activity (<10%)

Fully unfolded vWF aggregates with platelets

Lesions found throughout multiple organ systems
Platelet- and vWF-rich microthrombi

Incidence in the US is estimated to be[4]:

- 0.37/100,000 people/year
- 2.9/million adults/year
- 0.1/million children/year

aHUS[1,5,6]

Chronic uncontrolled complement activation leads to endothelial cell damage and thrombosis[1,5,6]

Gain of function

and/or

Loss of function

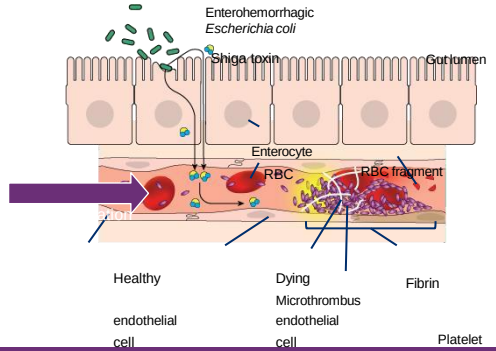
Uncontrolled complement activation leads to endothelial damage , platelet activation and inflammation

Lesions predominantly in the kidneys but may be found in other organ systems Fibrin-rich microthrombi

- **Incidence in the US is estimated to be** 2 cases per million people per year[7,8]
- **Studies in Europe have reported an incidence** of 0.11 to 0.23 cases per million people/year[9,10]

STEC-HUS[1,11,12]

Endothelial damage resulting from bacterial toxins[1,11,12]



Lesions predominantly in the kidneys Fibrin-rich microthrombi

- **Incidence in the UK is estimated** at 7.1/million people/year[4]
- Higher incidence during periods related to **EHEC outbreaks[4]**

Patients who experience TMA because of a concomitant condition likely have other underlying risk factors, and pathogenic mechanisms are likely to be multifactorial[4]

aHUS, atypical hemolytic uremic syndrome; **ADAMTS13,** a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; **EHEC,** enterohemorrhagic *Escherichia coli*; **RBC,** red blood cell; **STEC-HUS,** Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrom
TTP, thrombotic thrombocytopenic purpura; **vWF,** von Willebrand factor.

1. Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14(11)(suppl 11):2-15. **2.** Tsai HM. *Int J Hematol.* 2010;91(1):1-19. **3.** Sadler JE. *Blood.* 2008;112(1):11-18. **4.** Brocklebank V, et al. *Clin J Am Soc Nephrol.* 2018;13(2):300-317.
5. Noris M, et al. *Nat Rev Nephrol.* 2012;8(11):622-633. **6.** Bommer M, et al. *Ditsch Arztebl Int.* 2018;115(19):327-334. **7.** Yoshida Y, et al. *Ren Replace Ther.* 2017;3:5. doi: 10.1186/s41100-016-0088-1 **8.** Constantinescu AR, et al. *Am J Kidney Dis.* 2004;43(6):976-982.
9. Fremeaux-Bacchi V, et al. *Clin J Am Soc Nephrol.* 2013;8(4):554-562. **10.** Campistol JM, et al. *Nefrologia.* 2015;35(5):421-447. **11.** Barbour T, et al. *Nephrol Dial Transplant.* 2012;27(7):2673-2685. **12.** Razzaq S. *Am Fam Physician.* 2006;74(6):991-996.

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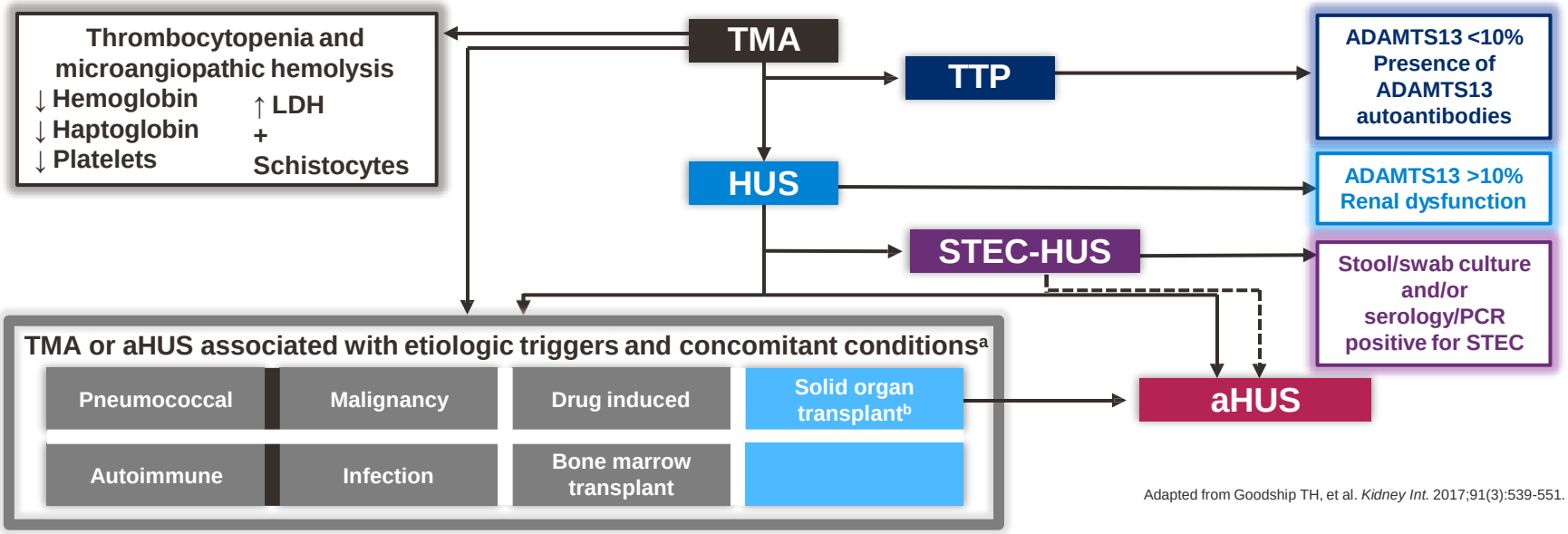
CLINICAL AND LABORATORY ASSESSMENTS AND THE ETIOLOGY OF TMA[1-3]



Adapted from Goodship TH, et al. *Kidney Int.* 2017;91(3):539-551.

[a]Including complement-mediated TMA.[4] [b]Owing to the high prevalence of complement abnormalities in these subgroups, genetic testing is recommended.[1]

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; **aHUS,** atypical hemolytic uremic syndrome; **HUS,** hemolytic uremic syndrome; **LDH,** lactate dehydrogenase; **PCR,** polymerase chain reaction; **STEC-HUS,** Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome; **TMA**, thrombotic microangiopathy; **TTP,** thrombotic thrombocytopenic purpura.

1. Goodship TH, et al. *Kidney Int.* 2017;91(3):539-551. **2.** Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14(11)(suppl 11):2-15.
3. Brocklebank V, et al. *Clin J Am Soc Nephrol.* 2018;13(2):300-317. **4.** Palma LMP, et al. *Kidney Int Rep.* 2021;6(1):11-23. doi:10.1016/j.ekir.2020.10.009

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LABORATORY VALUES AND DIAGNOSIS OF TTP[1,2]

Association Between Patient Characteristics and ADAMTS13 Deficiency Using Multivariate Analysis[1]

Patient characteristic	Adjusted odds ratio	95% CI	*P* value
SCr level ≤200 µmol/L (2.26 mg/dL)	23.4	8.8-62.5	<0.001
Platelet count ≤30 × 10^9/L	9.1	3.4-24.2	<0.001

Adapted from Coppo P, et al. *PLoS One*. 2010;5(4):e10208.

These patient characteristics are associated with a diagnosis of TTP[1]

While waiting for other test results, return to your laboratory values to help eliminate a diagnosis of TTP[1,2]

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; **CI,** confidence interval; **SCr,** serum creatinine; **TTP,** thrombotic thrombocytopenic purpura.

1. Coppo P, et al. *PLoS One*. 2010;5(4):e10208. doi:10.1371/journal.pone.0010208 **2.** Laurence J, et al. *Clin Adv Hematol Oncol*. 2016;14(11)(suppl 11):2-15.

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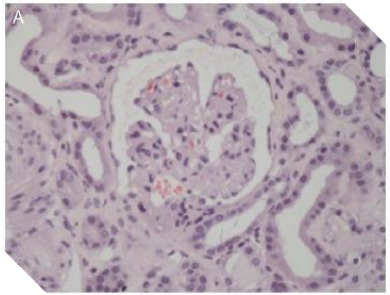
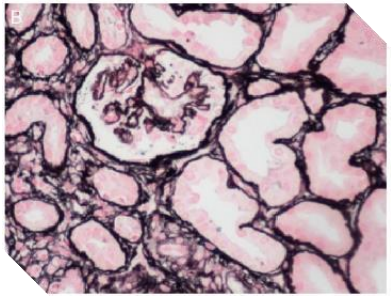
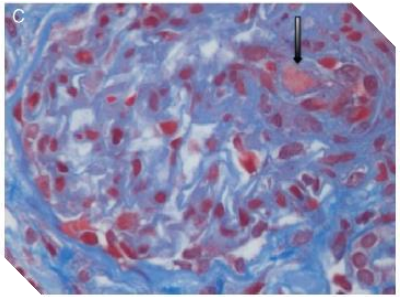
RENAL BIOPSY IN THE DIAGNOSIS OF TMA[1,2]



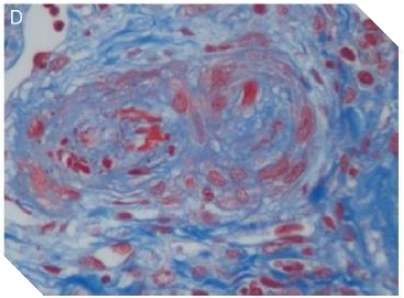
Ischemic and retracted glomeruli[1]



Mesangiolysis[1]



Thrombi in glomerular capillaries (arrow)[1]



Artery occluded by platelet thrombi[1]

Figures from Campistol JM, et al. *Nefrologia*. 2015;35(5):421-447.

- TMA describes a histologic lesion of the arterioles and capillaries resulting in[1]
  - Thickened and swollen vessel walls
  - Detachment of endothelial cells
  - Widening of subendothelial space caused by the buildup of proteins and cell lysis materials
  - The presence of platelet thrombi obstructing vascular lumen
- Renal biopsy findings may indicate TMA, but biopsy alone cannot differentiate between aHUS and STEC-HUS[2]
- Renal biopsy is NOT required for diagnosis of aHUS[2]

aHUS, atypical hemolytic uremic syndrome; **STEC-HUS,** Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome; **TMA**, thrombotic microangiopathy.

1. Campistol JM, et al. *Nefrologia*. 2015;35(5):421-447. **2.** Laurence J, et al. *Clin Adv Hematol Oncol*. 2016;14(11)(suppl 11):2-15.

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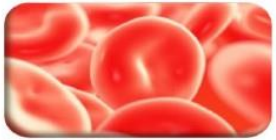
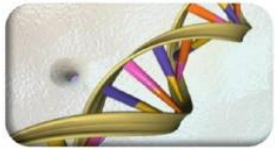
Important features of aHUS Diagnosis



Incomplete triad

In the French aHUS registry, 13% (14/107) of adults with aHUS had a normal platelet count at presentation[1]



Mutation

Today, known mutations are identified in only 50% to 70% of patients with aHUS. A diagnosis of aHUS does not require identification of a mutation[2–5]

Complement

In one study, C3 was found to be normal in up to 80% of patients with aHUS, and CFH protein levels were normal in 87% of patients with aHUS with a *CFH* mutation[4]

Incomplete penetrance

50% of family members are carrying the same complement mutation will have the disease; 20% to 30% of all patients have a familial occurrence of aHUS[3,4,6]

[no notes on this page]

aHUS, atypical hemolytic uremic syndrome; C3, complement component 3; CFH, complement factor H; CFI, complement factor I.

1. Sallée M *et al. BMC Nephrol* 2013;14:3. **2.** Noris M *et al. N Engl J Med* 2009;361:1676–87. **3.** Fremeaux-Bacchi V *et al. Clin J Am Soc Nephrol* 2013:8:554–62. **4.** Noris M *et al. Clin J Am Soc Nephrol* 2010;5:1844–59. **5.** Laurence J *et al. Clin Adv Hematol Oncol* 2016;14(11 suppl 11):2–15. **6.** Loirat C *et al. Pediatr Nephrol* 2016;31:15–39.

aHUS DIAGNOSIS[1]

Lack of a definitive biomarker for aHUS[2]

No single test can positively diagnose aHUS; complement gene variants are not detected in 40%-60% of patients with aHUS with currently available tests

Overlapping clinical features[3]

Clinical features of aHUS, such as thrombocytopenia and hemolytic anemia, are characteristic of other conditions as well

Underlying conditions that trigger aHUS[3]

aHUS may be triggered by underlying conditions with overlapping symptoms, which may mask aHUS and complicate diagnosis

Progressive onset[4]

Patients may have a progressive onset, with subclinical or fluctuating laboratory values and a gradual increase in SCr that can eventually result in CKD

A clinical diagnosis is required for aHUS, using diagnostic tests available for other causes of TMA[1,3]

aHUS is a diagnosis of exclusion and a condition that may lead to irreversible organ damage[1]

aHUS, atypical hemolytic uremic syndrome; **CKD**, chronic kidney disease; **SCr,** serum creatinine; **TMA,** thrombotic microangiopathy.

1. Campistol JM, et al. *Nefrologia*. 2015;35(5):421-447. **2.** Fakhouri F, Frémeaux-Bacchi V. *Nat Rev Nephrol*. 2021;17(8):543-553.
3. Laurence J, et al. *Clin Adv Hematol Oncol*. 2016;14(11)(suppl 11):2-15. **4.** Loirat C, Frémeaux-Bacchi V. *Orphanet J Rare Dis*. 2011;6:60. doi:10.1186/1750-1172-6-60

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GENETICS OF COMPLEMENT REGULATION IN aHUS

aHUS, atypical hemolytic uremic syndrome.

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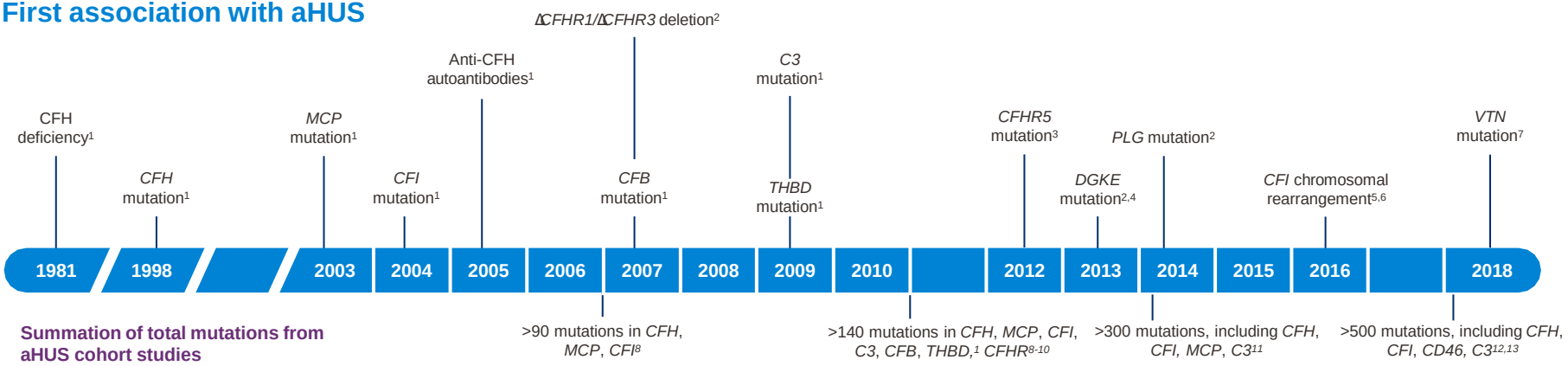
CONTINUOUS DISCOVERY OF NEW GENETIC ABNORMALITIES IN PATIENTS WITH aHUS[1-13]

First association with aHUS



Identification of new genetic variants in aHUS leads to a better understanding of the relationship between genetic mutations and disease outcome[2]

aHUS, atypical hemolytic uremic syndrome; **C3,** complement component 3; **CD46,** cluster of differentiation 46; **CFB,** complement factor B; **CFH,** complement factor H; **CFI,** complement factor I; **DGKE,** diacylglycerol kinase epsilon; **MCP,** membrane cofactor protein; **PLG,** plasminogen; **THBD,** thrombomodulin; **VTN,** vitronectin.

1. Le Quintrec M, et al. *Semin Thromb Hemost.* 2010;36(6):641-652. **2.** Rodriguez de Córdoba S, et al. *Semin Thromb Hemost.* 2014;40(4):422-430. **3.** Westra D, et al. *J Hum Genet.* 2012;57(7):459-464.
4. Lemaire M, et al. *Nat Genet.* 2013;45(5):531-536. **5.** Brocklebank V, et al. *Kidney Int.* 2017;92(5):1261-1271. **6.** Gleeson PJ, et al. *Immunobiology.* 2016;221(10):1124-1130.
7. Bu F, et al. *J Am Soc Nephrol.* 2018;12(29):2809-2819. **8.** Caprioli J, et al. *Blood.* 2006;108(4):1267-1279. **9.** Noris M, et al. *Clin J Am Soc Nephrol.* 2010;5(10):1844-1859.
10. Moore I, et al. *Blood.* 2010;115(2):379-387. **11.** Rodriguez E, et al. *Biosci Rep.* 2014;34(5):e00146. doi:10.1042/BSR20140117
12. Osborne AJ, et al. *J Immunol.* 2018;200(7):2464-2478. **13.** Ji RR, et al. *J Rare Dis Res Treat.* 2018;4(1):13-51.

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GENETIC ABNORMALITIES IN PATIENTS WITH aHUS[1-10]

Genetic Mutations Identified in Patients With aHUS[1,2]

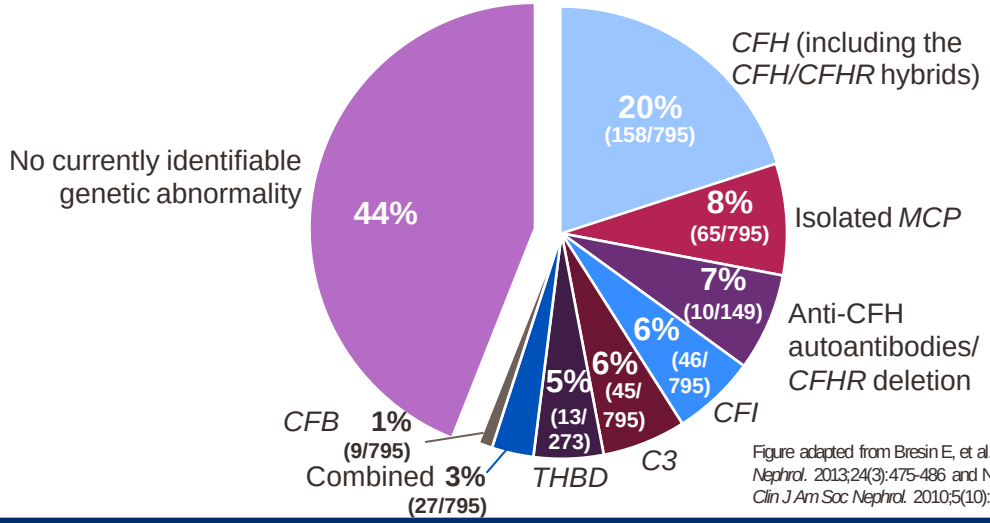

Figure adapted from Bresin E, et al. *J Am Soc Nephrol.* 2013;24(3):475-486 and Noris M, et al. *Clin J Am Soc Nephrol.* 2010;5(10):1844-1859.

- ***DGKE* mutations** have been identified in 5% (4 of 83) to 41% (9 of 22) of patients aged ≤2 years[3,4]
- ***VTN* mutations** have also been implicated in aHUS pathophysiology[5]
- **Variants of unknown significance** have also been identified in patients with aHUS[6]
  - Study of a sufficiently large population needed[7]
  - Clinical impact not known until functional assay is performed[6,7]
  - Bioinformatic tools are available for predicting pathogenicity of these and other variants but should be used with caution[6,7]

Mutations in genes encoding proteins that are not exclusively associated with the complement pathway, including *DGKE* (cell metabolism), *PLG* (coagulation and fibrinolysis), and *VTN* (coagulation and fibrinolysis), have been identified in patients with aHUS[5,8-10]

aHUS, atypical hemolytic uremic syndrome; **DGKE,** diacylglycerol kinase epsilon; **MCP,** membrane cofactor protein; **PLG,** plasminogen; **THBD,** thrombomodulin; **VTN,** vitronectin.

1. Bresin E, et al. *J Am Soc Nephrol.* 2013;24(3):475-486. **2.** Noris M, et al. *Clin J Am Soc Nephrol.* 2010;5(10):1844-1859. **3.** Lemaire M, et al. *Nat Genet.* 2013;45(5):531-536. **4.** Sánchez Chinchilla D, et al. *Clin J Am Soc Nephrol.* 2014;9(9):1611-1619. **5.** Bu F, et al. *J Am Soc Nephrol.* 2018;12(29):2809-2819. **6.** Vieira-Martins P, et al. *Transfus Apher Sci.* 2016;54(2):212-219. **7.** Richards S, et al. *Genet Med.* 2015;17(5):405-424. **8.** Rodriguez de Córdoba S, et al. *Semin Thromb Hemost.* 2014;40(4):422-430. **9.** Feitz WJC, et al. *Med Genet.* 2018;30(4):400-409. **10.** Leavesley DI, et al. *IUBMB Life.* 2013;65(10):807-818.

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GENETIC AND ENVIRONMENTAL FACTORS IN THE DEVELOPMENT OF aHUS[1-5]

- Etiologic triggers may unmask aHUS, including[1,2]

- Polymorphisms/risk haplotypes and additional genetic abnormalities can increase predisposition to aHUS[1,2]
- 3% (27/795)-6% (8/144) of patients with aHUS may carry combined mutations in more than 1 gene[3-5]

aHUS, atypical hemolytic uremic syndrome.

1. Rodríguez de Córdoba S, et al. *Semin Thromb Hemost.* 2014;40(4):422-430. **2.** Goodship TH, et al. *Kidney Int.* 2017;91(3):539-551. **3.** Bresin E, et al. *J Am Soc Nephrol.* 2013;24(3):475-486. **4.** Fremeaux-Bacchi V, et al. *Clin J Am Soc Nephrol.* 2013;8(4):554-562. **5.** Maga TK, et al. *Hum Mutat.* 2010;31(6):E1445-E1460.

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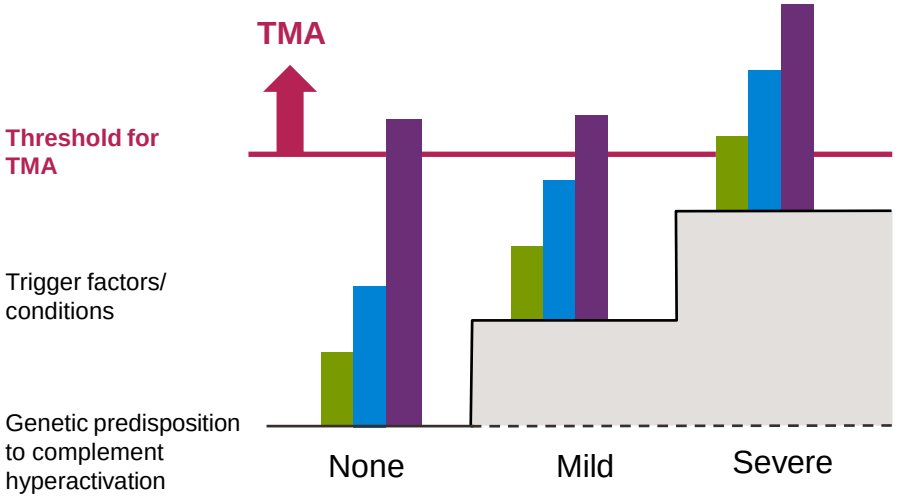
THE MULTIPLE HIT HYPOTHESIS OF TMA[1,2]



Mild triggering condition

Moderate triggering condition

Severe triggering condition

TMA manifestations can be unpredictable, with a highly variable clinical presentation and course across the patient population[3]

TMA, thrombotic microangiopathy.

1. Riedl M, et al. *Semin Thromb Hemost.* 2014;40(4):444-464. **2.** Tsai HM. *Transfus Med Rev.* 2014;28(4):187-197. **3.** Schaefer F, et al. *Kidney Int.* 2018;94(2):408-418.

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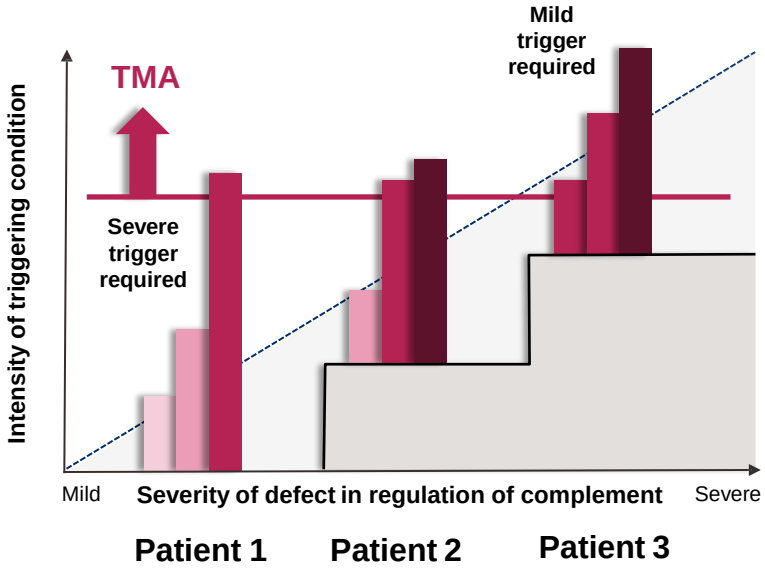
INDIVIDUAL PATIENT RISK FACTORS AND SEVERITY OF THE TRIGGERING CONDITION FURTHER CONTRIBUTE TO THE SPECTRUM OF TMA[1-4]



Potential Patient Outcomes Based on Genetic Burden and Severity of Etiologic Trigger

- No clinically evident TMA
- No systemic TMA; some endothelial dysfunction
- Transient, self-limiting TMA
- Self-perpetuating, progressive TMA (aHUS)

MM/US/DISEAS
E/0729

The initial triggering condition should be adequately managed. If TMA does not resolve, then consider that aHUS has been unmasked and is now the primary cause of TMA[5]

This is a representative schematic of how a concomitant condition may contribute to disease pathophysiology.

aHUS, atypical hemolytic uremic syndrome; **TMA,** thrombotic microangiopathy.

1. Riedl M, et al. *Semin Thromb Hemost.* 2014;40(4):444-464. **2.** Tsai HM. *Transfus Med Rev.* 2014;28(4):187-197. **3.** Schaefer F, et al. Kidney *Int.* 2018;94(2):408-418.
4. Hanna RM, et al. *Curr Opin Nephrol Hypertens.* 2019;28(3):278-287. **5.** Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14(11 suppl 11):2-15.

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aHUS COMPLICATIONS AND PROGNOSIS

aHUS, atypical hemolytic uremic syndrome.

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RENAL AND EXTRARENAL COMPLICATIONS IN PATIENTS WITH aHUS[1,a]

Central nervous system: Up to 49% (76/156) of patients experience neurologic symptoms, including[1,2]

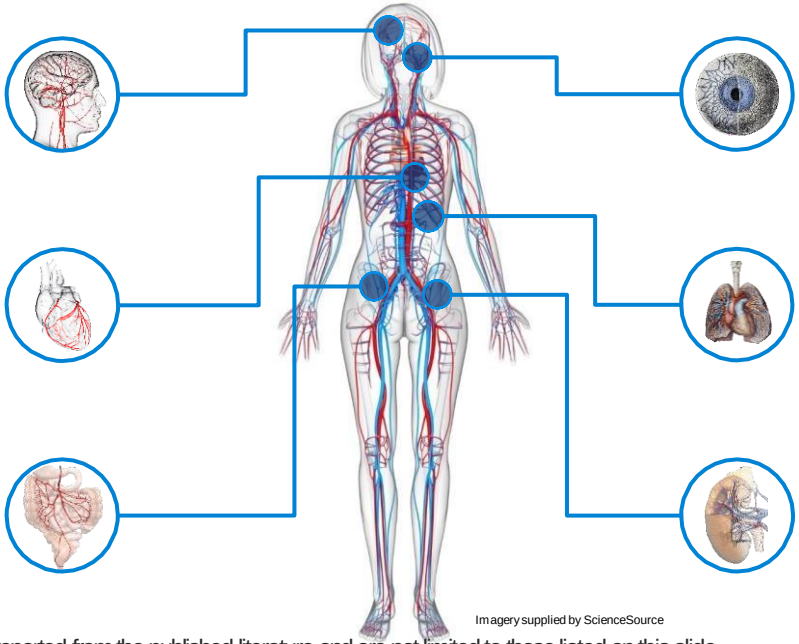
- Confusion[3]
- Stroke[3]
- Seizures[1,2]
- Encephalopathy[2,3]

CV: Up to 44% (69/156) of patients experience CV symptoms, including[1]

- MI[2,3]
- Hypertension[1]
- Arterial thrombosis[3]
- Vascular stenosis[2]
- Cardiomyopathy[1,2]

GI: Up to 51% (80/156) of patients experience GI symptoms, including[1]

- Diarrhea[1,3]
- Nausea/vomiting[3]
- Abdominal pain[1,3]
- Gastroenteritis[4]
- Pancreatitis[3]
- Colitis[3]



Imagery supplied by ScienceSource

Visual: Case reports of patients with visual impairments[5]

- Pain and blurred vision[5]
- Retinal vessel occlusion[6]
- Ocular hemorrhage[5,6]

Pulmonary: Up to 46% (31/67) of patients experience pulmonary symptoms, including[7]

- Dyspnea[8]
- Pulmonary hemorrhage[9]
- Pulmonary edema[8]

Renal: More than 50% of patients progress to ESRD[1,10]

- Elevated serum creatinine level[1,11]
- Decreased eGFR[11]
- Proteinuria[12]

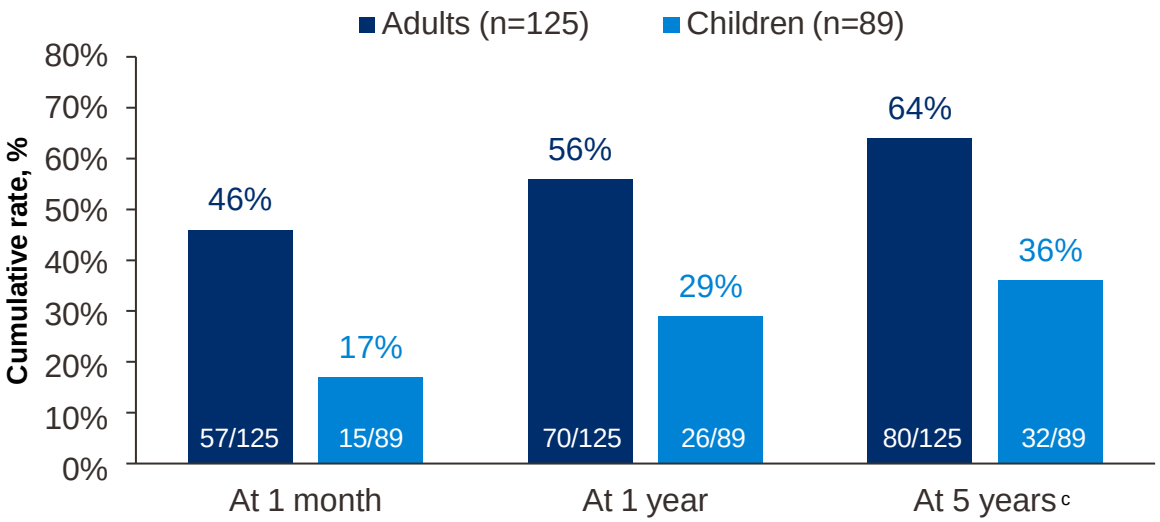
[a]The organ-specific symptoms associated with aHUS are reported from the published literature and are not limited to those listed on this slide.

aHUS, atypical hemolytic uremic syndrome; **CV,** cardiovascular; **eGFR,** estimated glomerular filtration rate; **ESRD,** end-stage renal disease; **GI,** gastrointestinal; **MI**, myocardial infarction.

1. Jamme M, et al. *PLoS One*. 2017;12(5):e0177894. doi:10.1371/journal.pone.0177894 **2.** Hofer J, et al. *Front Pediatr*. 2014;2:97. doi: 10.3389/fped.2014.00097 **3.** Campistol JM, et al. *Nefrologia*. 2015;35(5):421-447. **4.** Goodship TH, et al. *Kidney Int*. 2017;91(3):539-551. **5.** Larakeb A, et al. *Pediatr Nephrol*. 2007;22(11):1967-1970. **6.** Zheng X, et al. *J Pediatr Ophthalmol Strabismus*. 2014;51:e62-e65. **7.** Muus P, et al. Abstract published for: 18th Congress of the European Hematology Association; June 13-16, 2013; Stockholm, Sweden. **8.** Sallée M. *Nephrol Dial Transplant*. 2010;25(6):2028-2032. **9.** Sellier-Leclerc AL, et al. *J Am Soc Nephrol*. 2007;18(8):2392-2400. **10.** Frémeaux-Bacchi V, et al. Supplementary appendix. *Clin J Am Soc Nephrol*. 2013;8(4):554-562. Accessed October 12, 2021. https://cjasn.asnjournals.org/content/clinjasn/suppl/2013/01/09/CJN.04760512.DCSupplemental/CJN04760512SupplementaryData.pdf **11.** Legendre CM, et al. *N Engl J Med*. 2013;368(23):2169-2181. **12.** Krishnappa V, et al. *Ther Apher Dial*. 2018;22(2):178-188.

ESRD-FREE SURVIVAL PROBABILITY IN ADULT AND PEDIATRIC PATIENTS WITH aHUS[a]

Cumulative Rate of ESRD or Death According to Time After aHUS Onset in Adult and Pediatric Patients From a French Study (N=214)[b]



Graph adapted from Fremeaux-Bacchi V, et al. *Clin J Am Soc Nephrol.* 2013;8(4):554-562.

After 1 year of disease onset, 56% (70/125) of adult patients and 29% (26/89) of pediatric patients with aHUS experienced ESRD or death

[a]This study was conducted between 2000 and 2008. [b]*P*<0.001. [c]The 5-year data are a Kaplan-Meier estimate.
aHUS, atypical hemolytic uremic syndrome; **ESRD,** end-stage renal disease.
Fremeaux-Bacchi V, et al. *Clin J Am Soc Nephrol.* 2013;8(4):554-562.

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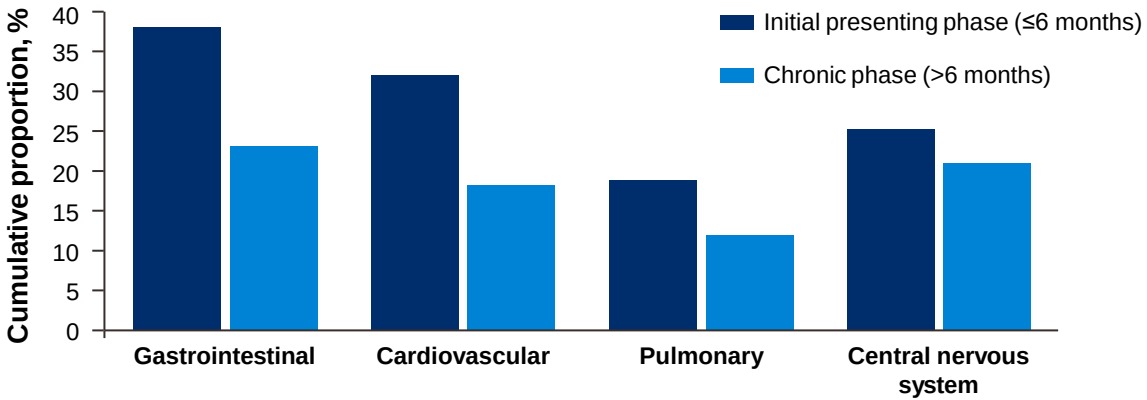
EXTRARENAL COMPLICATIONS IN ADULT AND PEDIATRIC PATIENTS WITH aHUS MANAGED WITH HISTORICAL CARE[1-4]

Extrarenal Manifestations in Adult and Pediatric Patients With aHUS Managed With Historical Care (N=851)[1,a,b]



Adapted from Schaefer F, et al. *Kidney Int*. 2018;94(2):408-418.

aHUS affects all organ systems, leading to not only renal complications but also CV, GI, visual, pulmonary, and central nervous system complications[1-4]

[a]From a study of 851 adult and pediatric patients enrolled in the Global aHUS Registry on historical supportive care, with a data cutoff of November 30, 2015.[1]

[b]Patients were managed with TPE/PI, kidney transplant, and/or dialysis.[1]

aHUS, atypical hemolytic uremic syndrome; **CV,** cardiovascular; **GI,** gastrointestinal; **TPE/PI,** therapeutic plasma exchange/plasma infusion.

1. Schaefer F, et al. *Kidney Int.* 2018;94(2):408-418. **2.** Jamme M, et al. *PLoS One.* 2017;12(5):e0177894. doi:10.1371/journal.pone.0177894
3. Zheng X, et al. *J Pediatr Ophthalmol Strabismus.* 2014;51:e62-e65. **4.** Sallée M. *Nephrol Dial Transplant.* 2010;25(6):2028-2032.

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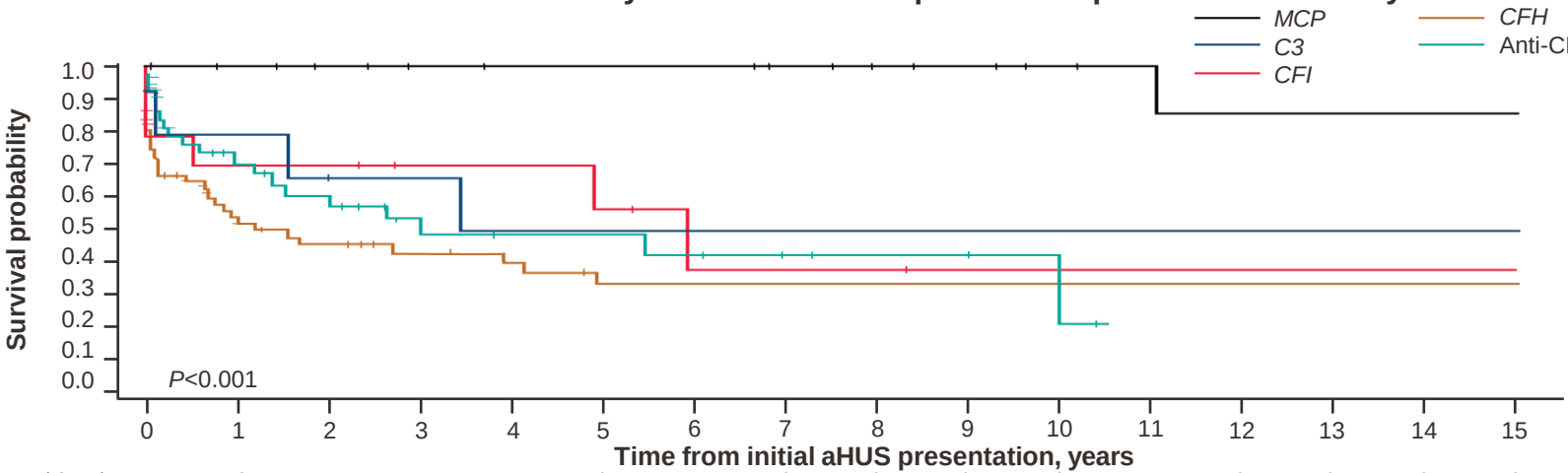
ESRD-FREE SURVIVAL IN PATIENTS WITH KNOWN MUTATIONS ASSOCIATED WITH aHUS[1-3]

ESRD-Free Survival by Identification of Specific Complement Abnormality[1,a]



Anti-CFH ab	Events	13	4	1	1	0	1	0	0	0	0	1	0	0	0	0
	At risk	60	22	17	11	8	8	7	4	3	3	2	0	0	0	0
C3	Events	2	1	0	1	0	0	0	0	0	0	0	0	0	0	0
	At risk	13	6	4	4	3	3	2	2	2	2	2	2	2	3	1
CFH	Events	31	3	1	1	2	0	0	0	0	0	0	0	0	0	0
	At risk	74	26	16	16	13	9	7	7	5	5	5	4	2	2	1
CFI	Events	4	0	0	0	1	0	0	0	0	0	0	0	0	0	0
	At risk	14	8	5	5	5	4	2	2	2	1	1	1	1	2	1
MCP	Events	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	At risk	29	22	16	17	16	16	16	14	12	8	8	7	5	5	4

Identification of a specific mutation in a patient with aHUS may inform prognosis[1,2]

[a]From a study of 851 adult and pediatric patients enrolled in the Global aHUS Registry on historical supportive care, with a data cutoff of November 30, 2015.[3]

aHUS, atypical hemolytic uremic syndrome; **C3,** complement component 3; **CFH,** complement factor H; **CFI,** complement factor I; **ESRD,** end-stage renal disease; **MCP,** membrane cofactor protein.

1. Schaefer F, et al. Supplementary appendix. *Kidney Int.* 2018;94(2):408-418. Accessed October 12, 2021. https://www.kidney-international.org/article/S0085-2538(18)30243-6/fulltext#articleInformation
2. Fremeaux-Bacchi V, et al. *Clin J Am Soc Nephrol.* 2013;8(4):554-562. **3.** Schaefer F, et al. *Kidney Int.* 2018;94(2):408-418.

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Impact of MDT Approach on Patients Outcomes

Spain Experience

A retrospective study of 28 patients evaluating the impact of a MDT in TMA management[1,a]

Diagnosis Rate

5x higher diagnosis

18 pts in 8 years vs. 10 pts in 8 months

Response time

11x Faster Response

Time to response after MDT
0 days vs. 11 days

Length of Hospitalization

2x shorter Hospitalization

Average 16 days vs. 33 days before MDT

Chronic Renal Replacement Therapy

0%

0% required renal replacement vs. 39 % before MDT

[no notes on this page]

ICU, intensive care unit; TMA, thrombotic microangiopathy. Chronic replacement therapy is a method of slower, continuous dialysis to allow solute and fluid homeostasis. [a]From a retrospective study of 28 patients diagnosed with TMA at a tertiary referral centre in Spain either between January 2008 and April 2016 (pre-MDT) and between May 2016 and December 2016 (post-MDT).

1. Uriol Rivera MG *et al. PLoS One* 2018;13:e0206558. 2. Tandukar S, Palevsky PM. Continuous Renal Replacement Therapy: Who, When, Why, and How. Chest. 2019 Mar;155(3):626-638.

Risk factor considerations for long-term patient management with aHUS

Genetic abnormalities

- Ongoing risk of ESRD, death, extrarenal manifestations, subsequent TMA, and graft loss after kidney transplant varies among genotypes[1,2]

Ongoing renal dysfunction

- Most patients with aHUS are at ongoing risk of death or permanent renal impairment, even following recovery from acute kidney injury[1,3,4]

Age at first manifestation

- Mortality rate is higher among patients with aHUS diagnosed as children, whereas renal involvement is higher in adults[1,a]

Clinical history of TMA

- A clinical history of TMA demonstrates the ongoing susceptibility to complement-mediated TMA experienced by all patients with aHUS3–5

Extrarenal TMA complications

- Patients with aHUS are at ongoing risk of extrarenal complications that may progress despite no overt thrombocytopenia or hemolysis2,6

History of renal transplant

- Ongoing risk of subsequent TMA and graft loss is high for patients with aHUS following renal transplant2,3,7

[no notes on this page]

aHUS, atypical hemolytic uremic syndrome; ESRD, end-stage renal disease; TMA, thrombotic microangiopathy.
[a]Mortality in 89 pediatric patients with aHUS vs in 125 adult patients with aHUS was 7.8% vs 1.6% (P<0.02). Progression to ESRD after the first aHUS manifestation in adult patients with aHUS vs in pediatric patients with aHUS was 46% vs 17% (P<0.001). Median follow-up of 57 (range, 1-353) months for adults and of 45 (range, 1-493) months for pediatric patients (pre-Soliris era).[1]

1. Fremeaux-Bacchi V *et al. Clin J Am Soc Nephrol* 2013;8:554–62. **2.** Noris M *et al. Clin J Am Soc Nephrol* 2010;5:1844–59. **3.** Campistol JM *et al. Nefrologia* 2015;35:421–47. **4.** Loirat C *et al. Pediatr Nephrol* 2016;31:15–39. **5.** Noris M *et al. Nat Rev Nephrol* 2012;8:622–33. **6.** Macia M *et al. Clin Kidney J* 2017;10:310–19. **7.** Le Quintrec M *et al. Am J Transplant* 2013;13:663–75.

RATIONALE FOR A LONG-ACTING THERAPY FOR COMPLEMENT-MEDIATED TMAs[1,2,3,4,5]

Eculizumab for atypical-HUS[2]

- longer-term eculizumab therapy maintained inhibition of complement activity, TMA, and improvements in hematologic parameters and renal function[2]
- the favorable safety profile of eculizumab is compatible with its longer-term use[2]

Ravulizumab for atypical-HUS[1,4]

- Built on the foundation of eculizumab
- A long-acting C5 inhibitor
- Weight-based dosing, 4- or 8-week intervals
- It has the same mechanism of action as eculizumab,

but with a 4-fold longer duration of action, which substantially reduces the frequency of maintenance doses.

Mean Half-Life Comparison

Eculizumab[3,5]	Ravulizumab[1]
• *Patients with atypical-HUS* • *Adults: Elimination t1/2 of 12.1 days* • *Children: Elimination t1/2 of 14.5 days*	*Patients with atypical-HUS* *In adults: Mean (%CV) terminal elimination t1/2 of 51.8 days*

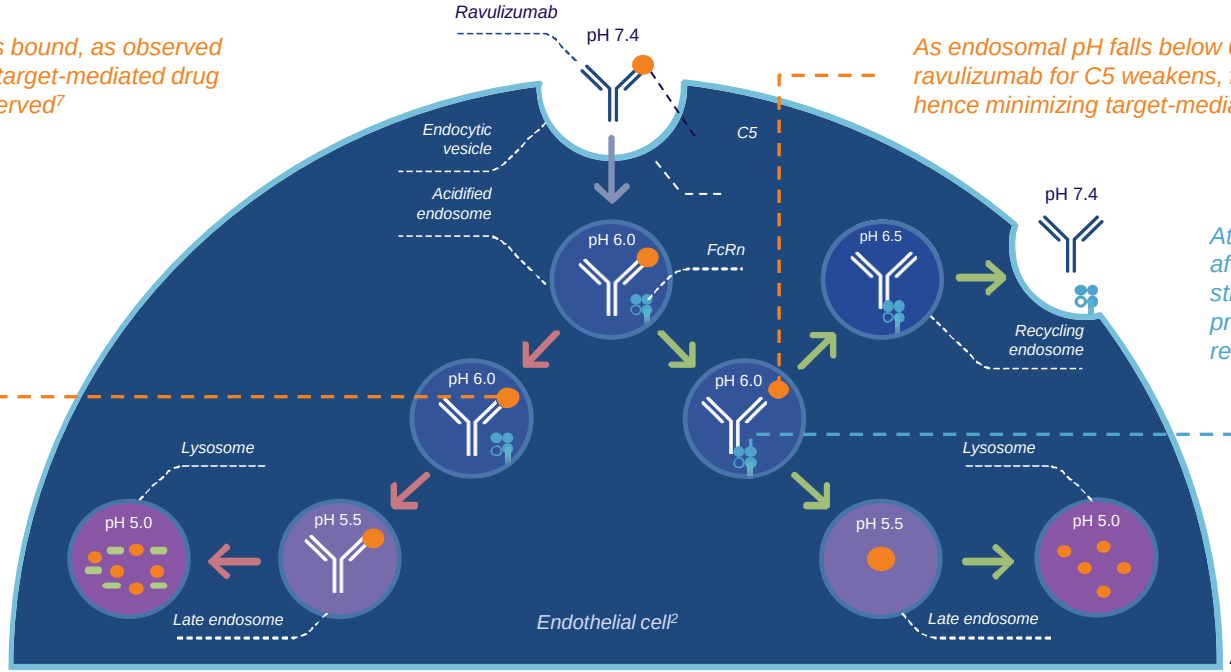
a Sustained throughout the entire 26-week treatment period in the majority (93%) of adult and pediatric patients with atypicalHUS. CV, coefficient of variation; IV, intravenous; PNH, paroxysmal nocturnal hemoglobinuria; t1/2, half-life ,TMAs Thrombotic microangiopathy

A graphical representation of the mechanism of ravulizumab half-life prolongation[6]

When C5 remains bound, as observed with eculizumab, target-mediated drug disposition is observed[7]

As endosomal pH falls below 6.0, the affinity of ravulizumab for C5 weakens, favoring their dissociation, hence minimizing target-mediated drug disposition

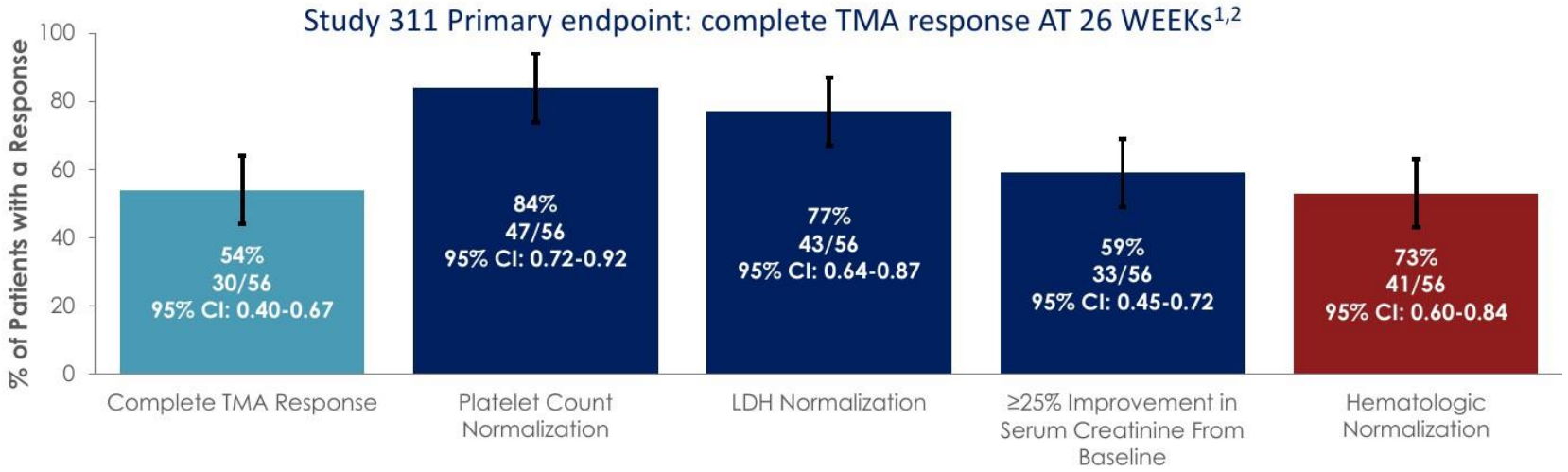
At lower endosomal pH, the affinity of ravulizumab for FcRn strengthens, hence increasing the probability of free ravulizumab recycling back to circulation



Adapted from Yang 2017

FcRn, neonatal Fc receptor; MOA, mechanism of action. WARNING, regarding serious and life-threatening me

Treatment outcomes with Ravulizumab in patients with aHUS



More than half of patients (54%) achieved complete TMA response, with the majority (84%) demonstrating platelet count normalization

2. Egyptian drug authority. Ultomiris 300mg/3ml leaflet approval date 4/12/2023.
3. Egyptian drug authority. Ultomiris 1100/11ml leaflet approval date 4/12/2023.

The criteria for complete TMA response are met when all criteria are concurrently met, and each criterion was met for at least 28 days.
95% confidence intervals (CIs) are represented by the lines at the top of each bar. **LDH**, lactate dehydrogenase; **TMA**, thrombotic microangiopathy

1. Data on file. Alexion Pharmaceuticals, Inc.; 2019. **2.** ULTOMIRIS® (ravulizumab-cwvz) [prescribing information]. Alexion Pharmaceuticals, Inc., Boston, MA; 2022.

Treatment outcomes with Ravulizumab in patients with aHUS

29 patients were on dialysis at study entry

CKD Stage at Baseline Total Patients (%) (N=47*)		Patients at CKD Stage at Day 183 (%)					
		1	2	3A	3B	4	5
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	3 (6.4)	2 (4.3)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3A	1 (2.1)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3B	2 (4.3)	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	7 (14.9)	1 (2.1)	0 (0.0)	0 (0.0)	3 (6.4)	1 (2.1)	2 (4.3)
5	34 (72.3)	6 (12.8)	6 (2.8)	3 (6.4)	3 (6.4)	5 (10.6)	11 (23.4)

Improved Neutral Worsened

- **68% of patients achieved CKD stage improvement (1 or more stage) from baseline**
- **17/29 patients were able to discontinue dialysis by the end of the available follow-up**

- Patients with CKD Stage 5 cannot worsen and may not be able to improve
- 6/27 patients who were off dialysis at baseline were on dialysis at last available follow up

[no notes on this page]

https://www.researchgate.net/figure/Study-design-and-endpoint-observations-by-actual-randomisation-sequence-Primary-care_fig2_344669039

*CKD shift analyzed in a subset of patients (N=47) Chronic kidney disease (CKD) stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stage 5 is considered the worst category, whereas stage 1 is considered the best. Data on file. Alexion Pharmaceuticals, Inc; 2019.

Safety of Ravulizumab in aHUS patients

Most common AEs (≥20%) were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension, and pyrexia

	Overall (N=58)	
	n (%)	Events
Any adverse event (AE)	58 (100.0)	818
Treatment related	20 (34.5)	58
Not treatment related	58 (100.0)	760
Any serious adverse event (SAE)	30 (51.7)	71
Fatal TEAEs	3 (5.2)	3
Study discontinuation due to		
TEAEs	3 (5.2)	3
TESAEs	3 (5.2)	3
Drug discontinuation due to		
TEAEs	3 (5.2)	3
TESAEs	3 (5.2)	3
AEs during study drug infusion		
TEAEs	4 (6.9)	6
TESAEs	0 (0)	0
Meningococcal infections	0 (0.0)	0

[no notes on this page]

Adverse Events (AEs) Across Studies:

- The most frequent adverse reactions reported in ≥20% of adults and pediatric patients treated with ravulizumab-cwvz were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension and pyrexia

Serious Adverse Events (SAEs):

- Serious adverse reactions were reported in 42 (57%) adults and pediatric patients with aHUS receiving ravulizumab-cvwz. The most frequent serious adverse reactions reported in more than 2 patients (2.7%) treated with ravulizumab-cvwz were hypertension, pneumonia and abdominal pain
- 1 patient with treatment-emergent positive result for ADAs was observed, with no neutralizing antibodies and no apparent effect on PK/PD
- 4 deaths determined by study investigators to be unrelated to study drug

ADAs, antidrug antibodies; **PK/PD,** pharmacokinetics/pharmacodynamics; **TEAE,** treatment-emergent AE.

1. Data on file. Alexion Pharmaceuticals, Inc.; 2019. **2.** ULTOMIRIS® (ravulizumab-cwvz) [prescribing information]. Alexion Pharmaceuticals, Inc., Boston, MA; 2022.


Thank you