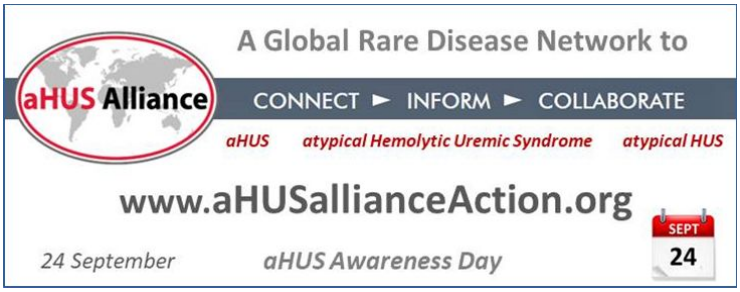
Atypical HUS: Key Facts & Research

Atypical Hemolytic Uremic Syndrome - a Rare Disease

2018 - 2019 EDITION



aHUS Research: What's New?

Since the release of the last aHUS Alliance fact sheets to mark aHUS Awareness Day (24 September), research has expanded in both scope and depth. While some new aHUS research is noted below, we encourage you to conduct a more detailed exploration of the wide range of research available:

NCBI-NIH PubMed Central (as of Sept 2018):

814 items (search term "***atypical HUS***", 5 yr filter for publication date)

1313 items (search term "***atypical hemolytic uremic syndrome***", 5 yr filter for publication date)

NIH NCBI GeneReview: ***Genetic Atypical Hemolytic-Uremic Syndrome*** **http://ow.ly/CmhB30euQTi**

Note: Many important findings regarding the knowledge base of this rare disease is grouped under the following terms and abbreviations: complement mediated disease, thrombotic microangiopathy, hemolytic uremic syndromes, complement dysregulation diseases, TMA, aHUS, SHUa, CM-TMA, and STEC-HUS, and more.

aHUS Alliance article on this topic: ***How to: Research Tips for aHUS Families***

CONNECT ► INFORM ► COLLABORATE

aHUS Clinicians & Investigators – A Global Networking Hub
aHUS Advocacy & Patient Organizations – Connecting Nations & aHUS Advocates

Resources at* aHUSallianceAction.org *Include:

- Know aHUS: Know Us - Living with the Rare Disease atypical HUS
- Clinical Tracker - A trifold about symptoms & issues, to foster meaningful physician/patient dialogue
- 2018 aHUS Therapeutic Drug Pipeline - Drug Discovery & Market Factors within the aHUS arena
- aHUS & TMA Study Centers - Article exploring the topic of Centres of aHUS Excellence (Whistle Stop Tour)
- Thrombotic Microangiopathy Symposium: Through the Lens of aHUS - Med Ed Event & Videos
- An innovative and collaborative partnership between patients with rare disease and industry-supported registries: the Global aHUS Registry (Woodward, L et al 2016)

Recent Research Includes these topics and titles, click heading link for additional research articles.

Critical Care

- Azoulay E et al. *Expert Statements on the Standard of Care in Critically Ill Adult Patients With Atypical Hemolytic Uremic Syndrome*. CHEST Journal, Vol 152, Issue 2 , 424 – 434. Aug 2017
- Rafat J et al. Early Differentiation of Shiga Toxin-Associated Hemolytic Uremic Syndrome in Critically Ill Adults With Thrombotic Microangiopathy Syndromes. Crit Care Med. 2018 Sep;46(9):e904-e911
- Vincent JL et al. Thrombocytopenia in the ICU: disseminated intravascular coagulation and thrombotic microangiopathies—what intensivists need to know. Crit Care. 2018; 22: 158. 13 June 2018

aHUS - Diagnosis ***MORE: NCBI-NIH*** PubMed Central

- Claes KJ et al. Belgian consensus statement on the diagnosis and management of patients with atypical hemolytic uremic syndrome. Acta Clin Belg. 2018 Feb;73(1):80-89. doi: 10.1080/17843286.2017.1345185.
- Jokiranta S et al. Differential diagnosis of thrombotic microangiopathy in nephrology. BMC Nephrol. 2017 Oct 28;18(1):324.
- Sridharan M et al. Atypical hemolytic uremic syndrome: Review of clinical presentation, diagnosis and management. J Immunol Methods. 2018 Oct;461:15-22.
- Sverdlin D, Peters-Watral B Atypical Hemolytic Uremic Syndrome: Achieving Positive Patient Outcomes With Early Diagnosis and Appropriate Management Clin J Oncol Nurs. 2017 Aug 1;21(4):481-487
- *aHUS Alliance article: Is it aHUS, TTP, or another TMA?*

aHUS as Thrombotic Microangiopathy (TMA): ***MORE: NCBI-NIH*** PubMed Central

- Åkesson A et al. At the Cross Section of Thrombotic Microangiopathy and Atypical Hemolytic Uremic Syndrome: A Narrative Review of Differential Diagnostics and a Problematization of Nomenclature. Ther Apher Dial. 2017 Aug;21(4):304-319
- Bommer M The Differential Diagnosis and Treatment of Thrombotic Microangiopathies. Dtsch Arztebl Int. 2018 May 11;115(19):327-334
- Tsai HM. Atypical Hemolytic Uremic Syndrome: Beyond Hemolysis and Uremia. Am J Med. 2018 Aug 23. pii: S0002-9343(18)30795-2.
- *aHUS Alliance article*: *TMA Symposium: through the Lens of aHUS*

Complement ***MORE: NCBI-NIH*** PubMed Central

- Wong E and Kavanagh D**.** Diseases of complement dysregulation—an overview. Semin Immunopathol. 2018; 40(1): 49–64. 2018 Jan
- Fakhouri F, Loirat C Anticomplement Treatment in Atypical and Typical Hemolytic Uremic Syndrome. Semin Hematol. 2018 Jul;55(3):150-158
- Noris M, Remuzzi G. Genetics of Immune-Mediated Glomerular Diseases: Focus on Complement. Semin Nephrol. 2017 Sep;37(5):447-463
- Reusz G. Atypical hemolytic uremic syndrome caused by primary complement defects. Orv Hetil. 2018 Jun;159(23):929-936
- Hossain MA et al. Atypical hemolytic uremic syndrome: Laboratory characteristics, complement-amplifying conditions, renal biopsy, and genetic mutations. Saudi J Kidney Dis Transpl. 2018 Mar-Apr;29(2):276-283
- Ardissino G et al. Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome: an update. Pediatr Nephrol. 2018 Mar;33(3):457-461
- *aHUS Alliance article: Complement-Mediated TMA as aHUS*

Genetics / Mutations ***MORE: NCBI-NIH*** PubMed Central

- Brocklebank, Vicky et al. Factor H autoantibody is associated with atypical hemolytic uremic syndrome in children in the United Kingdom and Ireland. Kidney Int. 2017 Nov; 92(5): 1261–1271
- Shaefer F et al. Clinical and genetic predictors of atypical hemolytic uremic syndrome phenotype and outcome. Kidney Int. 2018 Aug;94(2):408-418
- Krishnappa V et al. Atypical Hemolytic Uremic Syndrome: A Meta-Analysis of Case Reports Confirms the Prevalence of Genetic Mutations and the Shift of Treatment Regimens. Ther Apher Dial, 22: 178-188.
- Knoop M et al. Human genetics in atypical hemolytic uremic syndrome-its role in diagnosis and treatment]. Internist (Berl). 2018 Jul 11
- Khandelwal P et al. Mutations in membrane cofactor protein (CD46) gene in Indian children with hemolytic uremic syndrome. Clin Kidney J. 2018 Apr;11(2):198-203.
- Almalki AH et al. Atypical hemolytic-uremic syndrome due to complement factor I mutation. World J Nephrol. 2017 Nov 6;6(6):243-250
- Osborne AJ et al. Statistical Validation of Rare Complement Variants Provides Insights into the Molecular Basis of Atypical Hemolytic Uremic Syndrome and C3 Glomerulopathy. J Immunol. 2018 Apr 1;200(7):2464-2478
- Almalki AH et al. Atypical hemolytic-uremic syndrome due to complement factor I mutation. World J Nephrol. 2017 Nov 6;6(6):243-250.
- Fujisawa M et al. Clinical characteristics and genetic backgrounds of Japanese patients with atypical hemolytic uremic syndrome. Clin Exp Nephrol. 2018 Oct;22(5):1088-1099.

Multi Organ Involvement ***MORE: NCBI-NIH*** PubMed Central

- Formeck C, Swiatecka-Urban A. Extra-renal manifestations of atypical hemolytic uremic syndrome. Pediatr Nephrol. 2018 Aug 14.
- Noronha N et al. Complement factor B mutation-associated aHUS and myocardial infarction. BMJ Case Rep. 2017 Jul 14;2017
- Togarsimalemath SK et al. Gastrointestinal pathogens in anti-FH antibody positive and negative Hemolytic Uremic Syndrome. Pediatr Res. 2018 Jul;84(1):118-124.
- Viada Bris JF et al. Ulcerative Colitis and Atypical Hemolytic-Uremic Syndrome: An Unusual But Potentially Life-threating Life Complication. Inflamm Bowel Dis. 2018 Jun 20.
- aHUS Alliance article: *aHUS Patient Care – the Need for Multidisciplinary Collaboration*

Drug Discovery ***MORE: NCBI-NIH*** PubMed Central

- Harris C et al. Developments in anti-complement therapy; from disease to clinical trial. Molecular Immunology. Volume 102, October 2018, Pgs 89-119.
- Ricklin, D et al. The renaissance of complement therapeutics**.** Nat Rev Nephrol. 2018 Jan; 14(1): 26–47.
- ClinicalTrials.gov: Atypical HUS and Thrombotic Microangiopathies

- *aHUS Alliance article: 2018 Drug R&D and aHUS Market Factors*

aHUS & Treatment Options ***MORE: NCBI-NIH*** PubMed Central

- Keenswijk W, Walle JV Atypical Hemolytic Uremic Syndrome in Low Resource Settings: Which Options Do We Have? Ther Apher Dial. 2018 Apr;22(2):206-20
- Merrill SA et al. Eculizumab cessation in atypical hemolytic uremic syndrome. Blood. 2017 Jul 20;130(3):368-372.
- Moake JL A new therapeutic strategy for atypical HUS. Blood. 2017 Jul 20;130(3):243-244.
- Olson SR et al. When to Stop Eculizumab in Complement-Mediated Thrombotic Microangiopathies. Am J Nephrol. 2018;48(2):96-107.
- Patterson JM et al. Case Series of 3 Patients Diagnosed With Atypical Hemolytic Uremic Syndrome Successfully Treated With Steroids, Plasmapheresis, and Rituximab. Can J Kidney Health Dis. 2017 Dec 31;5:2054358117747262.
- Rodriguez E et al. Should eculizumab be discontinued in patients with atypical hemolytic uremic syndrome? Clin Kidney J. 2017 Jun;10(3):320-322
- Teoh CW et al. Clinical Relapses of Atypical HUS on Eculizumab: Clinical Gap for Monitoring and Individualised Therapy. Case Rep Nephrol. 2018 Feb 6;2018:2781789
- Volokhina E Eculizumab Dosing Regimen in Atypical HUS: Possibilities for Individualized Treatment. Clin Pharmacol Ther. 2017 Oct;102(4):671-678.
- *aHUS Alliance Article: So African Pediatric Nephrology: Global Panel Proposed for aHUS Drug Access*

aHUS – Reviews ***MORE: NCBI-NIH*** PubMed Central

- Dixon BP, Gruppo RA. Atypical Hemolytic Uremic Syndrome. Pediatr Clin North Am. 2018 Jun;65(3):509-525.
- Kherder-Elfekih R et al. Atypical hemolytic uremic syndrome: A monocentric adult Tunisian study and review of literature. Saudi J Kidney Dis Transpl. 2018 Mar-Apr;29(2):297-302
- Zhang K et al. Atypical Hemolytic Uremic Syndrome: A Brief Review. Hematol Rep. 2017 Jun

aHUS & Pregnancy ***MORE: NCBI-NIH*** PubMed Central

- Bruel A et al. Hemolytic Uremic Syndrome in Pregnancy and Postpartum. Clin J Am Soc Nephrol. 2017 Aug 7;12(8):1237-1247
- Gaggl M et al. Maternal and Fetal Outcomes of Pregnancies in Women with Atypical Hemolytic Uremic Syndrome. J Am Soc Nephrol. 2018 Mar;29(3):1020-1029.
- Gupta M et al. Thrombotic microangiopathies of pregnancy: Differential diagnosis. Pregnancy Hypertens. 2018 Apr;12:29-34.
- Grand'Maison S, Lapinsky S. Insights into pregnancy associated and atypical hemolytic uremic syndrome. Obstet Med. 2018 Sep;11(3):137-140.
- Huerta A et al. A retrospective study of pregnancy-associated atypical hemolytic uremic syndrome. Kidney Int. 2018 Feb;93(2):450-459
- *aHUS Alliance Article: Atypical HUS & Pregnancy: Questions, Concerns, Research*

Transplantation ***MORE: NCBI-NIH*** PubMed Central

- Duineveld C et al. Living Donor Kidney Transplantation in Atypical Hemolytic Uremic Syndrome: A Case Series. Am J Kidney Dis. 2017 Dec;70(6):770-777
- Kim S et al. Kidney Transplantation in Patients with Atypical Hemolytic Uremic Syndrome due to Complement Factor H Deficiency: Impact of Liver Transplantation. J Korean Med Sci. 2018 Jan 1;33(1):e4.
- Legendre CM et al. Outcomes of patients with atypical haemolytic uraemic syndrome with native and transplanted kidneys treated with eculizumab: a pooled post hoc analysis. Transpl Int. 2017 Dec;30(12):1275-1283
- Legendre C et al. The role of complement inhibition in kidney transplantation. Br Med Bull. 2017 Dec 1;124(1):5-17.
- Noris M, Ruggenenti P, Remuzzi G. Kidney Transplantation in Patients With Atypical Hemolytic Uremic Syndrome: A Therapeutic Dilemma (or Not)? Am J Kidney Dis. 2017 Dec;70(6):754-757.
- Raina R et al. Effect of Immunosuppressive Therapy on the Occurrence of Atypical Hemolytic Uremic Syndrome in Renal Transplant Recipients. Ann Transplant. 2018 Sep 7;23:631-638

Atypical HUS FACTS *(citations below)*

About aHUS

- Atypical Hemolytic Uremic Syndrome (aHUS) is a very rare, chronic and life-threatening genetic condition
- aHUS can occur at any age, with roughly 60 per cent of children affected and 40 per cent adults [2]
- aHUS is caused by chronic, uncontrolled activation of the complement system, a part of the body's natural immune system [1]
- As a result, the immune system attacks the body's unhealthy and healthy cells, which can cause abnormal blood clotting and blood vessel damage [2, 3]
- The presence of blood clots causes damage to organs, leading to heart attack, stroke, kidney failure and death [2]
- Within a year of diagnosis, over half of patients will need dialysis, will have irreversible kidney damage, or will not survive [2]
- The majority of patients progress to end-stage kidney failure within three years of diagnosis [2,5]
- Death rates amongst aHUS patients are as high as 25 per cent, and progression to end-stage kidney disease occurs in more than 50 per cent of patients [2, 5]
- Kidneys are often transplanted in aHUS patients with permanent kidney failure, however, the disease recurs in 60 per cent of patients, and more than 90 percent of patients experience failure of transplanted kidney [2]

Diagnosis

- Atypical HUS encompasses a group of diseases that share in the clinical features of a microangiopathic hemolytic anemia associated with thrombocytopenia and renal failure. In practice there is little agreement on what defines or limits classifying someone as an aHUS patient, given the nonspecific nature of the term aHUS. aHUS clumps together a group of diseases with very different underlying pathologies. [25]
- The causes of aHUS are not fully understood, but in 70 per cent of cases it is associated with an underlying genetic or acquired abnormality of the complement system [10]
- Doctors and their healthcare team must look at many factors when making a diagnosis – including clinical symptoms, lab findings, and results from more specialized tests such as gene analysis [11]
- During initial onset of aHUS, or during recurring episodes, tell-tale signs can be detected from lab findings relating to [9]
    - platelet levels
    - hemoglobin and haptoglobin levels
    - creatinine levels
    - BUN (blood urea nitrogen) levels

Symptoms

- aHUS disease can be characterized by three key features:[12]
    - thrombocytopenia (low platelet count in the blood)
    - anemia (low red blood cell/platelet count in the blood)
    - kidney symptoms (starting as acute kidney failure but can progress to end-stage kidney disease)
- There are a number of symptoms secondary to kidney failure, which include [10]
    - nausea and vomiting
    - confusion
    - shortness of breath (dyspnea)
    - fatigue
- aHUS can impact multiple organs and body systems. Central nerve system involvement is the most frequent extra-renal organ manifestation of aHUS (10–48%)[29] , but issues due to TMA may occur in the heart, lungs, GI tract, skin, eyes as well.
- In aHUS, patients present with symptoms of diarrhea, fatigue, irritability, and lethargy to a point where hospitalization is needed [12]
- The majority of patients have genetic abnormalities that impair cell surface control of complement [18]

Treatment

Plasma Therapy & Dialysis

- The prognosis for patients with aHUS is very poor,[13] with existing supportive therapies unproven and unreliable

- The management of aHUS has relied on plasma infusion and plasma exchange therapies with variable results[14]
- To date, there have been no well-controlled trials that show plasma exchange or plasma infusion to be safe or effective in aHUS [15]

- In studies where the majority of patients with aHUS were treated with plasma therapy, patient outcomes were reported as being poor[16]
- Despite plasma exchange or plasma infusion, 65 percent of all aHUS patients die, require dialysis, or have permanent renal damage within the first year after diagnosis [6]
- Dialysis cannot completely compensate for the loss of kidney function, and can lead to deadly infections and shortened life expectancy [17]
- Complications related to plasma exchange have been reported to occur in up to 55 percent of plasma exchange sessions in children and in 15 percent of sessions in adults [16]

Treatment- Therapeutics

- Eculizumab has shown greater efficacy than plasma therapy in the prevention and treatment of aHUS[16, 19]
- Switching from plasma therapy to eculizumab has been shown to improve renal function even in patients with long-lasting and stable chronic kidney disease [16]
- KDIGO Controversies Conference on aHUS and C3G: See *Treatment Strategies*, *Section V*. Goodship et al, Dec 2016. Kid. Intl. http://ow.ly/DCjf30euh7n
- aHUS Alliance – aHUS Therapeutic Drugs, R & D, with tables. *May 2018* https://bit.ly/2xpfg0T
- Clinical Trials – As of Sept 2018 on ClinicalTrials.gov: 24 Studies for 'atypical HUS' https://bit.ly/2QIz1Zl and 308 Studies listed under 'thrombotic microangiopathy' or TMA https://bit.ly/2QIz1Zl

Access to Treatment

- As of Sept 2018 aHUS patients in many nations still do not have access to eculizumab, and coverage within some of those countries is further restricted: dependent on the aHUS patient's location within their nation or their individual health status [26]. In 2018: ***Global Panel for aHUS Drug Access*** https://bit.ly/2MKPIQQ
- Inequality in Treatment Options among Nations - Access to eculizumab for treatment of aHUS patients worldwide plummets from 77% to only 37% for poll respondents in nations outside of the US & EU. [28] (White Paper at http://ow.ly/Dbzb303ZqhU, with 2016 aHUS Poll Results: http://ow.ly/1DA7303FoJx)

Note: The aHUS Alliance wishes to extend thanks to aHUS Canada for their efforts in providing core facts here. For Citations & More Info, see the Full Version of this Document: **aHUS Key Facts & Information**

NIH NCBI GeneReview: *Genetic Atypical Hemolytic-Uremic Syndrome* http://ow.ly/CmhB30euQTi

Note: The aHUS Alliance wishes to extend thanks to aHUS Canada for their efforts in providing core facts contained in this document.

Diseases/Disorders with Potential for Cross-Over Impact Regarding Atypical HUS Research

Table 2: aHUS Alliance 2018

AAV:	ANCA-associated vasculitis (ANCA: anti-neutrophil cytoplasmic Abs)	**HAE:**	Hereditary Angioedema
AIHA:	Autoimmune hemolytic anemia (Subtype: warm, or WAIHA)	**HCT-TMA:**	HCT-TMA: Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy
AMD:	Age-related Macular Degeneration	**HSCT:**	Hematopoietic Stem Cell Transplant
AMR:	Antibody-mediated rejection	**IBMIR:**	Instant Blood-mediated Inflammation Reaction
CAD:	Cold Agglutinin Disease	**IgAN:**	Immunoglobulin A Nephropathy (form of glomerulonephritis)
CAD:	Coronary Artery Disease	**IRI:**	Ischemia-Reperfusion Injury
CMV:	Cytomegalovirus	**LN:**	Lupus nephritis
C3G:	C3 glomerulopathy Subtypes: Dense deposit disease (DDD) and C3 glomerulonephritis (C3GN)	**MAHA:**	Microangiopathic Hemolytic Anemia
CMND:	Complement-Mediated Neurodegeneration	**MG:**	Myasthenia Gravis (gMG: generalized MG)
COPD:	Chronic Obstructive Pulmonary Disease	**MMN:**	Multifocal Motor Neuropathy
CVD:	Cardiovascular Disease	**MPGN:**	Membranoproliferative glomerulonephritis
DDD:	Dense Deposit Disease (see also C3G)	**NMOSD:**	Relapsing Neuromyelitis Optica Spectrum Disorder

DFG:	Delayed Graft Function	**PNH:**	Paroxysmal Nocturnal Hemoglobinuria
DITMA:	Drug-Induced TMA	**RA:**	Rheumatoid Arthritis
DM:	Dermatomyositis	**SLE:**	Systemic Lupus Erythematosus
GA:	Geographic Atrophy (see AMD)	**STEC-HUS:**	Shiga toxin–releasing Escherichia coli - Hemolytic Uremic Syndrome
GBS:	Guillain–Barré Syndrome	**TMA:**	Thrombotic microangiopathy (often plural)
GvHD:	Acute Graft v Host Disease	**TTP :**	Thrombotic Thrombocytopenic Purpura

Note: Research done for other rare or complement-mediated diseases, or those with similar underlying mechanisms, may provide some degree of cross-over knowledge with potential to advance atypical HUS research and therapeutic drug discovery. Table 2, created by the aHUS Alliance May.

***Click to download* the PDF of Diseases/Disorders with related research.**

Atypical HUS Therapeutic Drug Pipeline in 2018:

Drug Discovery & Market Factors within the aHUS Arena

Advancing aHUS Treatment - Pipeline of R & D for new Therapeutics

(Table from the aHUS Alliance overview - May 2018) [26,27]

Therapeutic Drug Discovery: aHUS and other Complement Mediated Diseases

Atypical HUS: 2018 Therapeutic Drug Discovery aHUS Alliance – Pharma Overview

Table 1

COMPANY	DRUG/Molecule	TARGET/Mechanism	FOCUS, Other
Alexion	ALXN 1210	longer-acting C5 inhibitor	aHUS
			PNH
	ALXN1210 SC	C5	Extended dose intervals
	ALXN1007	C5a	GvHD
			APS
	ALXN1102, ALXN1103 (TT30)	C3	PNH
	Soliris®/ eculizumab	C5	aHUS
			PNH
			More
Achillion	ACH-4471	Factor D	Focus: C3G, PNH, other info (XR)
	ACH-4471XR	Factor D	Extended Release, Tablet
	ACH-5228, ACH-5548	Factor D	Next-Gen Oral: Complement Diseases
ADIENNE Pharma & Biotech	MUBODINA®	C5	Focus: Typical HUS
	BEGEDINA®	CD26	GvHD

	Ergidina	C5	IRI
Akari Therapeutics	Coversin®	C5	PNH
			aHUS, GBS, MG
			Clinical Trial: PNH
	Coversin® Long Acting	C5 and LTB4	Other
	Coversin® Dual Acting	C5 and LTB4	Other
Alnylam	Cemdisiran(ALN-CC5)	C5	aHUS
			PNH
Amgen	ABP 959	C5 (Biosimilar to eculizumab)	aHUS
			PNH
			ANZCTR Trial
Amyndas Pharmaceuticals	AMY-101 C3	C3 (compstatin Cp40)	PNH
			C3G, Others
	AMY-201	C3	Other: mini-FH
	AMY-301	C3	AMD
Annexon	ANX005	C1q	Autoimmune
			IVIg
			Complement Mediated Disease
Apellis	Compstatin®/APL-2	C3	PNH: Paddock
			PNH: Pharaoh

			Glomerulopathies
			Other APL-2 Trials
Argenx	ARGX-113/ Efgartigimod	FcRn	MG, IgG-mediated autoimmune diseases
- collaboration with Broteio	ARGX-117	Novel target	complement-mediated indications
		NHance™	
Attune	ATN-249	Kallikrein inhibitor	HAE
	Unnamed	oral Sm Molecules	PNH
			complement mediated diseases
Bioverativ	BIVV009(formerly TNT009)	C1s	CAD
- a Sanofi company	BIVV020(formerly TNT020)	mAb to activated C1s	CAD
ChemoCentryx	Avacopan	oral C5aR inhibitor	AAV
	(formerly CCX168)		C3G
			aHUS
			Other
Chugai	RG6107	C5, SC	Complement mediated diseases
- a ROCHE company	- aka SKY59		
	- aka RO7112689		
Genentech	SKY59	C5, SC	Complement mediated diseases

- a ROCHE company	- aka RO7112689		
	- aka RG6107		
	Rituxan®/rituximab	CD20	RA, NHL, CLL, GPA and MPA
	MPGN, IgAN, Other		
	lampalizumab (RG7417)	CT Terminated Jan 2018	AMD, GA
Genentech	TNX-558	C5a	Inflammatory Disease, others
- Tanox (a Genentech subsidiary)			
Genmab	Ofatumumab	CD20	chronic lymphocytic leukemia
- also see Novartis (listed below)			
Genzyme	Thymoglobulin®, new indication		Kidney transplant rejection
- also see Sanofi (listed below)	Genzyme/Sanofi Research Pipeline		Fabry, MS, Gaucher Type 3, others
GlaxoSmithKline (GSK)	Benlysta® (belimumab)		SLE
	3196165		RA
	2831781	GM-CSF	OA, Autoimmune Disease
	Daprodustat	PHI	Anemia with Chronic Renal Disease
Greenovation	Moss-FH	Factor H, C3	C3G, aHUS and PNH,
			aHUS Alliance Interview
InflaRx	IFX-1 / IFX-2	C5a	Complement inhibition: Sepsis

			Hidradenitis suppurativa
			AAV, autoimmune/ inflammatory
Inflazyme	Mirococept®/APT070	C3 convertase inhibitor	IRI, DGF
ISU Abxis	ISU305	Biosimilar, C5 inhibitor	PNH
LFB Group	hCFH	Factor H	aHUS
		Anti-cd303	SLE, autoimmune diseases
Novo Nordisk / G2 Therapies	Neutrazumab	C5aR	SLE, RA, other
Novartis	LFG316	C5	PNH
- also see Sandoz (listed below)			Transplant Assoc Microangiopathy
	KRP203	S1PR	GvHD, SCLE
	CFZ533	CD40	Renal Transplant
			MG
Novartis	Ofatumumab	CD20	chronic lymphocytic leukemia
- also see Genmab (listed above)			
NovelMed	unnamed	C3b and C5b-9	PNH, aHUS, Others
	Bikaciomab	Factor B	AMD
	NM9405	Properdin	PNH

Noxxon Pharma	NOX-D15	C5a	Complement Diseases
Omeros	OMS721 (IV and SC)	MASP-2, Lectin pathway	aHUS
			HCT-TMA
			IgAN
			Others
	OMS906	MASP-3, Alternative pathway	PNH, aHUS, AMD Others
Opthotech	Zimura (ARC1905)	C5	AMD, GA
Ra Pharma	RA101495	C5	PNH
	RA101495SC	C5	PNH, aHUS and LN
	RA101495 XR	C5	not specified
	Unnamed	Factor D, SC	C3GN and DDD, AMD
	Unnamed	C5, oral	PNH, gMG, and LN
	Unnamed	C1s	CAD, SLE, GBS, others
Regenesance/Complement Pharma	Regenemab	C6	PNH, Myasthenia Gravis, Others
Resverlogix	apabetalone / RVX-208	BET, Sm molecule	CVD, DM, CKD, Other
ROCHE	SKY59	C5, SC	Complement mediated diseases
- also see Chugai	RO7112689		
- also see Genentech	RG6107		
	Rituxan®/rituximab	CD20	RA, NHL, CLL, GPA and MPA

			MPGN, IgAN, Other
	lampalizumab (RG7417)	CT Terminated Jan 2018	AMD, GA
Sandoz	see Novartis/Sandoz above	biopharmaceuticals	Biosimilar Pipeline
- a Novartis division			
Sobi	SOBI005	C5	PNH, aHUS
(Swedish Orphan Biovitrum AB)	SOBI003	Enzyme Replacement Therapy	MPS IIIA (CNS)
Sanofi	Various affiliations	Sanofi and Alnylam RNAi	Sanofi R & D
	`	Sanofi Aquires Bioverativ	Sanofi/Bioverativ Pipeline
		Sanofi / Genzyme	Sanofi/Genzyme Pipeline
True North (Bioverativ/Sanofi)	TNT009	C1s	Complement Mediated Disorders, CAD
Various Pharma	Cinryze	C1-INH	Therapy Target: HAE
	Berinert		
	Ruconest		
	Others		

Note: Created by the aHUS Alliance as a snapshot of aHUS drug discovery information available to the general public in early 2018, this chart contains basic information and therefore should not be considered a comprehensive review of companies, or investigational drugs. Inclusion in this table is not an indicator of endorsement for companies, research teams or products, so any mention or omissions should not be considered relevant for investment or other purposes.

***Click to download** the PDF of 2018 aHUS Drug Discovery table.*

aHUS Alliance RESOURCE List

2016 aHUS Global Poll: aHUS Patient Voice [28]

An international poll of aHUS patients and pediatric caregivers was launched on 29 February 2016 (world Rare Disease Day) and was completed 15 April 2016. The poll was offered in 6 languages and contained 45 questions to include patient profiles as well as diagnosis and treatment experiences. Additional information and insights were sought regarding aHUS challenges, patient engagement views, clinical trials, and orphan drug development issues.

233 respondents from 23 countries provided data for the 2016 aHUS Global Poll, with results reported within these assets, graphs and commentary:

- 2016 aHUS Global Poll OVERVIEW: http://ow.ly/gSj8303GcdH
- 2016 aHUS Global Poll, RESULTS & Graphs: http://ow.ly/1DA7303FoJx
- RareConnect 2016 aHUS Poll Webinar (commentary by Dr. C Licht): http://ow.ly/ACiN303GajE

2014 aHUS Poll: *In Collaboration with RareConnect, previous aHUS poll Results & Webinar with commentary by Dr. T Goodship:* http://ow.ly/hRau303OZG2

aHUS Insights – Select Info from the 2016 Global Poll [28]**– *(View Complete Data at Links above)***

Poll respondent Profile - 48% of responses were from caregivers of pediatric aHUS patients, with the remaining 52% of data representing adult patients. 66% of people completing the 2016 aHUS global poll were female, 34% were male.

- Response rate by Nation – Of the 23 countries participating in the 2016 poll, respondents living in these three countries had the highest participation rates with the other 20 nations created less than 10% of survey responses. (The poll was available in 6 languages:EN, ES, FR, RUS, IT and JPN)
  USA - 43% UK - 18% Canada - 11%
- Genetic Testing – 84% have or are awaiting Genetic Test Results
- aHUS Info Sources - When seeking Information, most:
- Check aHUS Patient Organizations– 37% Rely on their Doctor – 17% Utilize Search Engines – 26%

- Dialysis - 46% of poll respondents stated the most significant dialysis issue was it interferes with normal routines. Other dialysis issues:
  - Impact on Other ORGANS 29%
  - Negative affect on QUALITY at Work/School 28%
  - Issues with ANXIETY or DEPRESSION 27%

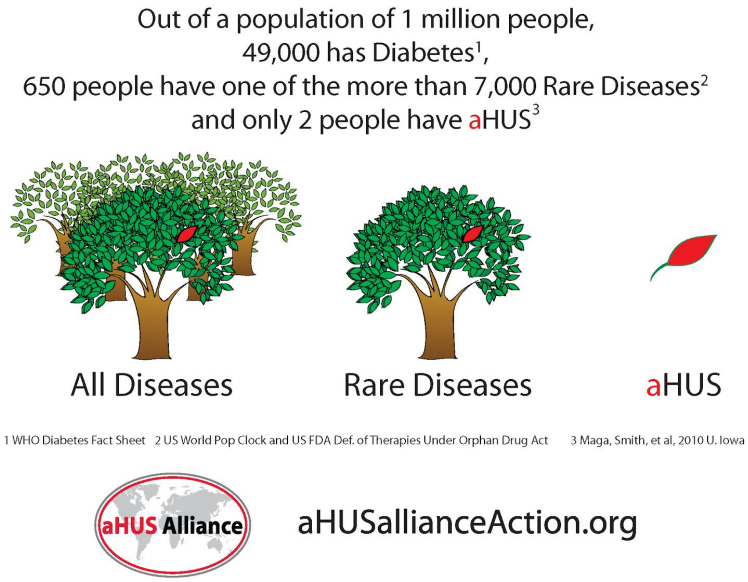
- aHUS Research - Participation 50% of Respondents have already done so, and 36% more would like participate but don't know how to engage.

- Inequality in Treatment Options among Nations - Access to eculizumab for treatment of aHUS patients worldwide plummets from 77% to only 37% for poll respondents in nations outside of the US & EU. (White Paper at http://ow.ly/Dbzb303ZqhU)

- COST Impact - 7 out of 10 state their specialist or medical team mention COST of aHUS treatment in discussing patient care options. 16% state cost concerns affect their treatment options or medical care.

- COST Treatment Access - 24% of respondents state aHUS medical care or treatment is limited by their National or Heath Ministry policies. 29% note that cost of medical care and treatment concern them and their family.

- Advancements in aHUS treatment or drug therapies- Factors or key considerations for use:
  - Cost of new drugs would likely affect our usage - 33%
  - Recommendation of our medical team - 28%
  - Type of drug delivery/Ease & Convenience of New Treatment - 24%



2016 aHUS Global Poll, RESULTS & Graphs: http://ow.ly/1DA7303FoJx

DIRECTORY of aHUS Patient Organizations: http://ow.ly/TlLw303QQGn

Access to aHUS Treatment: 2016 aHUS Global Poll White Paper – click here to view
aHUS and Dialysis Insights: 2016 aHUS Global Poll White Paper – click here to view

Press Kit: aHUS Alliance - click here to view

Resources – More about aHUS

*Know aHUS: Know US - Living with Atypical HUS (in EN, FR, ES)

*aHUS Organizations around the World - Direct links to websites & social media for Nations with aHUS Advocacy

*aHUS Alliance Network: Clinicians & Investigators

*In ENGLISH: Disease OVERVIEW with definitions & research links

Atypical HUS NCBI GeneReviews©, affiliated with the National Institutes of Health (NIH)

*In ENGLISH and Multiple Languages: KDIGO GLOBAL CONSENSUS

An international consensus approach to the diagnosis and management of patients with complement-mediated kidney disease, such as aHUS. *Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference* (Goodship, THJ et al, 2017)

*Atypical HUS Clinical Channel - YouTube: http://ow.ly/mSyT303ZDch Atypical HUS Patient Voice - YouTube

Rare Diseases – Fast Facts

- There are approximately 7,000 diseases and conditions designated as a rare disease, each affecting fewer than 200,000 Americans. In Europe, a disease is considered rare if it affects fewer than 1 in 2,000 people.
- Rare diseases as a group affect an estimated 25 to 30 million Americans, 1 out of 10 people. Eighty percent of rare diseases are genetic in origin, and it is estimated that about half of all rare diseases affect children.

EURORDIS: Founders of Global Rare Disease Day: Info & Resources www.eurordis.org
NORD: Rare Disease Day Info & Resources, specific to the USA www.rarediseases.org
RareConnect : Disease-Specific Webpages, sponsored by NORD and EURORDIS www.rareconnect.org

These organizations provide information, services, resources, and support to the rare disease community. Their Rare Disease Day resources include press kits, social media tools, Rare Disease Day graphics and more.

World Rare Disease Day, recognized annually on the last day of February, encourages patients and their families, medical professionals, researchers, government officials, and companies developing treatments for rare diseases to join together to focus attention on rare diseases as a public health issue.

aHUS Awareness Day is marked annually on 24 September

Created by the aHUS Alliance in 2015, and marked in various nations around the world, aHUS Awareness Day provides an opportunity for individuals and organizations around the world to join together in support of people living with aHUS. An opportunity to provide aHUS insights, information and outreach, we encourage participation of all stakeholders who seek to provide advancement for patients globally.

Follow aHUS Awareness Day on Twitter

@aHUS24Sept

CITATIONS

[1] Genetics Home Reference. Atypical hemolytic-uremic syndrome.
[2] Noris M, Caprioli J,Bresin E, et al. Relative Role of Genetic Complement Abnormalities in Sporadic and Familial aHUS and Their Impact on Clinical Phenotype. Clin J Am Soc Nephrol. 2010;5:1844-1859.
[3] Benz K and Amann K. Thrombotic microangiopathy: new insights. Curr Opin Nephrol Hypertens. 2010;19(3):242-247.
[4] Tsai HM. The molecular biology of thrombotic microangiopathy. Kidney Int 2006 Jul;70(1):16-23.
[5] Noris M and Remuzzi G. Review Article: Atypical Hemolytic–Uremic Syndrome. N Engl J Med [1212]2009;361:1676-87.
[6] Caprioli J, Noris M, Brioschi S, et al. Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. Blood. 2006;108:1267-1279.

[7] Kavanagh D and Goodship T. Atypical Hemolytic Uremic Syndrome, Genetic Basis, and Clinical Manifestations. Acquired Hematopoietic Disorders: Complement-Mediated Blood Disorders. 2011:15-20.
[8] Frémeaux-Bacchi, V. Treatment of atypical uraemic syndrome in the era of eculizumab. Clin Kidney J. 2012;5:4–6.
[9] Bresin E, Daina E, Noris M, et al. Outcome of renal transplantation in patients with non–Shiga toxin-associated hemolytic uremic syndrome: prognostic significance of genetic background. Clin J Am Soc Nephrol. 2006;1:88-99.
[10] aHUS Action. Atypical Haemolytic Uremic Syndrome (aHUS). Available here.
[11] Burke L, et al. The Atypical HUS Foundation (USA). A Parent's Perspective - aHUS Bootcamp. April 23, 2013. Available here.
[12] Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011 Sep 8; 6:60.
[13] Tschumi S, Gugger M, Bucher B, Riedl M, Simonetti G. Eculizumab in atypical hemolytic uremic syndrome: long-term clinical course and histological findings. Pediatric Nephrology. November 2011;26(11):2085-2088.
[14] Mache C, Acham-Roschitz B, Frémeaux-Bacchi V, et al. Complement Inhibitor Eculizumab in Atypical Hemolytic Uremic Syndrome. Clin J Am Soc Nephrol. 2009; 4:1312–1316.
[15] Loirat C, Garnier A, Sellier-Leclerc AL, Kwon T. Plasmatherapy in atypical hemolytic uremic syndrome. Semin Thromb Hemost 2010:36(6):673-681.
[16] Zuber J, Fakhouri F, Roumenina LT, Loirat C, Frémeaux-Bacchi V on behalf of the French Study Group for aHUS/C3G. Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. Nat Rev Nephrol 2012:8:643-657.
[17] Dialysis – Side Effects. National Health Service. NHS Choices. Available here.
[18] Nester CM, Barbour T, Rodriquez de Cordoba S, Dragon-Durey MA, Fremeaux-Bacchi V, Goodship THJ, Kavanagh D, Noris M, Pickering M, Sanchez-Corral P, Skerka C, Zipfel P, Smith RJH. Atypical aHUS: state of the art. Mole Immunol 2015 Apr 3 [Epub ahead of print]; 67(1):31-42, 2015. Available here.
[19] Fakhouri F, Frémeaux-Bacchi V, Loirat C. Atypical hemolytic uremic syndrome: From the rediscovery of complement to targeted therapy. European Journal of Internal Medicine 2013:24:492-495.
[20] Legendre C, Babu S, Furman R, et al. Safety and Efficacy of Eculizumab in aHUS Patients Resistant to Plasma Therapy: Interim Analysis from a Phase 2 Trial. Abstract presented at the 43rd annual meeting of the American Society of Nephrology, Denver, CO, USA, 16–21 November 2010.
[21] Muus P, Legendre C, Douglas K et al. Safety and Efficacy of Eculizumab in aHUS Patients Resistant to Plasma Therapy: Interim Analysis of a Phase 2 Trial. Abstract presented at the 43rd annual mtg. of the American Society of Nephrology, Denver, CO, USA, 16-21 November 2010.
[22] Legendre C.M., Licht, Muus P et al. Terminal Complement Inhibitor Eculizumab in Atypical hemolytic-Uremic Syndrome. N Engl J Med 2013;368:2169-81.
[23] Kim J, Waller S and Reid C. Clinical Report: Eculizumab in atypical haemolytic-uraemic syndrome allows cessation of plasma exchange and dialysis. Clin Kidney J. 2012,0:-3.
[24] Kim Maga, TK, Nishimura CJ, Weaver, AE, Frees KL, Smith RJ. Mutations in alternative pathway complement proteins in American patients with atypical hemolytic uremic syndrome. Available here.
[25] Nester CM, Smith RJH. Factors influencing treatment of atypical hemolytic uremic syndrome. Clin J Am Soc Nephrol 2014 Aug 18 [Epub ahead of print]; 9(9):1516-8, 2014.
[26] 28 June 2015, aHUS Alliance mtg. of international aHUS patient organizations. London.
[27] Risitano, Antonio. The Future of Complement Treatment. At the European Society for Blood and Marrow Transplantation, Sept 29-Oct.1, 2014. Slide 4. Naples. Available here.
[28] 2016 aHUS Global Poll. Conducted by the aHUS Alliance, 45 questions were offered in a poll for aHUS adult patients and pediatric caregivers, made available in 6 languages. (N=233, from 23 countries) Poll Overview. Poll Questions & Results. Poll Webinar, courtesy of RareConnect with commentary by Dr. C. Licht:
[29] Hofer J et al. Extra-Renal Manifestations of Complement-Mediated Thrombotic Microangiopathies. Front Pediatr. 2014; 2: 97.

@aHUSallianceAct
@aHUS24Sept

@aHUSalliance

Atypical HUS CLINICAL CHANNEL
Atypical HUS PATIENT VOICES

E: info@aHUSalliance Action.org

www.aHUSallianceAction.org