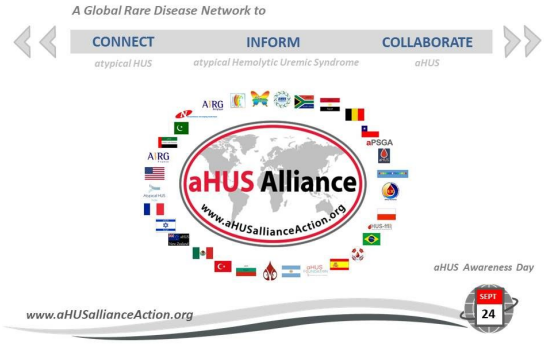
Atypical HUS: Key Facts & Research

Atypical Hemolytic Uremic Syndrome - a Rare Disease

2019 - SEPT - 2020



aHUS Research: What's New?

Since the September release of the 2018 aHUS Alliance Fact Sheets to mark aHUS Awareness Day (24 Sept), research for the rare disease atypical HUS has expanded in both scope and depth. While a variety of new aHUS research is noted below, we encourage you to conduct a more detailed exploration of the wide range of research available:

Newly Expanded for Sept 2019: aHUS Alliance website

aHUS Publications Page*: aHUS Research & Studies (by Topic)*

https://www.ahusallianceaction.org/research-publications/

Looking for a Single Page of aHUS Facts to Print & Share?

Atypical HUS: In Brief *(2019-Sept-2010 Edition)*

NCBI-NIH PubMed Central (*as of Sept 2019)*:

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

1496 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 Global Patients' Research Agenda

The aHUS Alliance, an umbrella group of aHUS advocates and patient groups in over 30 nations, launched its aHUS Global Patients' Research Agenda on Rare Disease Day 2019.

An international project developed over 4 years, the aHUS Global Patients' Research Agenda lists 15 central questions grouped into 5 main categories: Causes and Precautions, Diagnosis, Treatment, Impact: Clinical/Psychological, and Impact: Socio-Economic.

Article (Info & Resources): http://bit.ly/aHUSpatientResearchAgenda ***Print & Share*** (pdf): http://bit.ly/2lA17e8

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aHUS Clinicians & Investigators – A Global Networking Hub
aHUS Advocacy & Patient Organizations – Connecting global aHUS advocates & efforts in 30+ Nations

aHUS Alliance: Publications (Authors/Participants)

Raina et al. Optimal management of atypical hemolytic uremic disease: challenges and solutions. Intl Journal of Nephrology and Renovascular Disease, Vol. 12, Sept 2019

Goodship et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int. 2017 Mar;91(3):539-551.

Harris et al. Increasing access to integrated ESKD care as part of universal health coverage. Kidney Int. 2019 Apr;95(4S).

Raina et al. Atypical Hemolytic-Uremic Syndrome: An Update on Pathophysiology, Diagnosis, and Treatment. Ther Apher Dial. 2019 Feb;23(1):4-21.

Woodward et al. An innovative and collaborative partnership between patients with rare disease and industry-supported registries: the Global aHUS Registry. Orphanet J Rare Dis. 2016 Nov 21;11(1):154.

A Global Rare Disease Network to

CONNECT *atypical HUS* **INFORM** *atypical Hemolytic Uremic Syndrome* **COLLABORATE** *aHUS*

The Year at a Glance: Highlights in aHUS Research Topics

Critical Care *MORE*: NCBI-NIH PubMed Central

Chan et al. Seizure as the Presenting Symptom for Atypical Hemolytic Uremic Syndrome. J Emerg Med. 2019 Apr;56(4):441-443.

Chen et al. Hypertensive Crisis and Refractory Hypertension Caused by Atypical Hemolytic Uremic Syndrome and Effect of Eculizumab. Acta Cardiol Sin. 2018 Sep; 34(5): 446–449.

Iba et al. Sepsis-associated disseminated intravascular coagulation and its differential diagnoses. J Intensive Care. 2019; 7: 32.

Rivera et al. Impact of a multidisciplinary team for the management of thrombotic microangiopathy. PLoS One. 2018; 13(11): e0206558.

Vincent et al. Thrombocytopenia in the ICU: disseminated intravascular coagulation and thrombotic microangiopathies—what intensivists need to know. Crit Care. 2018; 22: 158.

Diagnosis *MORE*: NCBI-NIH PubMed Central

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Le Clench et al. Atypical and secondary hemolytic uremic syndromes have a distinct presentation and no common genetic risk factors. Kidney Int. 2019 Jun;95(6):1443-1452.

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Mohammed et al. Atypical Hemolytic Uremic Syndrome: A Case Report. Cureus. 2019 May; 11(5): e4634.

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Tao et al. A rare case of Alport syndrome, atypical hemolytic uremic syndrome and Pauci-immune crescentic glomerulonephritis. BMC Nephrol. 2018; 19: 355.

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Weiss et al. Renal failure, respiratory distress, and an atypical purpuric rash in a full-term infant with omphalocele and hypospadias: Answers. Pediatr Nephrol. 2019 Jun 24.

Multi-Organ Involvement (Extra-Renal) *MORE*: NCBI-NIH PubMed Central

Bris et al Ulcerative Colitis and Atypical Hemolytic-Uremic Syndrome: An Unusual But Potentially Life-threatening Complication Inflamm Bowel Dis. 2019 Mar 14;25(4):e27-e28.

Chaturvedi et al. Chronic Kidney Disease, Hypertension and Cardiovascular Sequelae during Long Term Follow up of Adults with Atypical Hemolytic Uremic Syndrome. Blood Nov 2018, 132 (Suppl 1) 3754.

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Formeck et al. Extra-renal manifestations of atypical hemolytic uremic syndrome. Pediatr Nephrol. 2019 Aug;34(8):1337-1348.

Giordano et al. A pediatric neurologic assessment score may drive the eculizumab-based treatment of Escherichia coli-related hemolytic uremic syndrome with neurological involvement. Pediatr Nephrol. 2019 Mar;34(3):517-527.

Kichloo et al Atypical Hemolytic Uremic Syndrome Presenting as Acute Heart Failure-A Rare Presentation: Diagnosis Supported by Skin Biopsy J Investig Med High Impact Case Rep. 2019 Jan-Dec

Schoettler et al. Severe, persistent neurotoxicity after transplant-associated thrombotic microangiopathy in a pediatric patient despite treatment with eculizumab. Pediatr Transplant. 2019 May; 23(3): e13381.

Shin et al Comorbidity of inflammatory bowel disease with atypical hemolytic uremic syndrome in pediatric patients Clin Nephrol Case Stud. 2019; 7: 35–40.

Tavasoli et al. Chronic Neurological Complications in Hemolytic Uremic Syndrome in Children. Iran J Kidney Dis. 2019 Jan;13(1):32-35.

Togarsimalemath et al. Gastrointestinal pathogens in anti-FH antibody positive and negative Hemolytic Uremic Syndrome. Pediatr Res. 2018 Jul;84(1):118-124.

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

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Arumugam et al. Does severe ADAMTS13 deficiency in thrombotic microangiopathy rule out complement-mediated atypical hemolytic uremic syndrome. Saudi J Kidney Dis Transpl. 2019 May-Jun;30(3)

Ashida et al. Clinical features in a series of 258 Japanese pediatric patients with thrombotic microangiopathy. Clin Exp Nephrol. 2018 Aug;22(4):924-930.

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

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Çelakil et al. CFH and CFB mutations in Shiga toxin-associated haemolytic uraemic syndrome in a 6-year-old boy. Paediatr Int Child Health. 2019 Jun 27:1-3.

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Khandelwal 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.

Schönauer et al. Deleterious Impact of a Novel CFH Splice Site Variant in Atypical Hemolytic Uremic Syndrome. Front Genet. 2019; 10: 465.

Transplants *(See Global Registry box)* *MORE*: NCBI-NIH PubMed Central

Abbas et al. Complement-mediated renal diseases after kidney transplantation - current diagnostic and therapeutic options in de novo and recurrent diseases. World J Transplant. 2018 Oct 22; 8(6): 203–219.

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Raina et al. Effect of Immunosuppressive Therapy on the Occurrence of Atypical Hemolytic Uremic Syndrome in Renal Transplant Recipients Ann Transplant. 2018; 23: 631–638.

Siedlecki et al. Eculizumab Use for Kidney Transplantation in Patients With a Diagnosis of Atypical Hemolytic Uremic Syndrome. Kidney Int Rep. 2019 Mar; 4(3): 434–446.

Suarez et al. Outcomes of Kidney Transplant Patients with Atypical Hemolytic Uremic Syndrome Treated with Eculizumab: A Systematic Review and Meta-Analysis. J Clin Med. 2019 Jul; 8(7): 919.

Szymczak et al Combined Liver-Kidney Transplantation in Children: Single-Center Experiences and Long-Term Results. Transplant Proc. 2018 Sep;50(7):2140-2144.

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

Aigner et al. An updated classification of thrombotic microangiopathies and treatment of complement gene variant-mediated thrombotic microangiopathy. Clin Kidney J. 2019 Jun; 12(3): 333–337.

Arumugam et al. Does severe ADAMTS13 deficiency in thrombotic microangiopathy rule out complement-mediated atypical hemolytic uremic syndrome. Saudi J Kidney Dis Transpl. 2019 May-Jun;30(3)

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Dvorak et al. Transplant-Associated Thrombotic Microangiopathy in Pediatric Hematopoietic Cell Transplant Recipients: A Practical Approach to Diagnosis and Management. Front Pediatr. 2019 Apr 9;7:133.

Pregnancy *(See Global Registry box)* *MORE*: NCBI-NIH PubMed Central

Kalambay et al. Atypical Hemolytic Uremic Syndrome Presenting as Pre-eclampsia in a 24-year-old Woman with Chronic Kidney Disease: Pathogenesis and Genetics. Cureus. 2018 Sep; 10(9): e3358.

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Mancini et al. HELLP syndrome and hemolytic uremic syndrome during pregnancy: two disease entities, same causation. Case report and literature review. G Ital Nefrol. 2019 Apr;36(2). pii: 2019-vol2.

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Rondeau et al Pregnancy Outcomes in Patients Enrolled in the Global aHUS Registry
Nephrology Dialysis Transplantation, Volume 34, Issue Supplement 1, June 2019

Complement *MORE*: NCBI-NIH PubMed Central

Bjerre et al. Clinical and Complement Long-Term Follow-Up of a Pediatric Patient with C3 Mutation-Related Atypical Hemolytic Uremic Syndrome. Case Rep Nephrol. 2018; 2018: 3810249.

Haapasalo et al. Regulation of the Complement System by Pentraxins. Front Immunol. 2019; 10: 1750

Michels et al. The role of properdin in complement-mediated renal diseases: a new player in complement-inhibiting therapy? Pediatr Nephrol. 2019; 34(8): 1349–1367.

Noris et al. Terminal complement effectors in atypical hemolytic uremic syndrome: C5a, C5b-9, or a bit of both? Kidney Int. 2019 Jul;96(1):13-15.

Park et al. Complement-mediated thrombotic microangiopathy associated with lupus nephritis. Blood Adv. 2018 Aug 28; 2(16): 2090–2094.

Sissy et al. Clinical and Genetic Spectrum of a Large Cohort With Total and Sub-total Complement Deficiencies. Front Immunol. 2019; 10: 1936.

Sridharan et al. Diagnostic Utility of Complement Serology for Atypical Hemolytic Uremic Syndrome. Mayo Clin Proc. 2018 Oct;93(10):1351-1362.

Consensus/Guidelines *MORE*: NCBI-NIH PubMed Central

Bagga et al. Hemolytic uremic syndrome in a developing country: Consensus guidelines
Pediatric Nephrology August 2019, Volume 34, Issue 8, pp 1465–1482.

Fox et al. Consensus opinion on diagnosis and management of thrombotic microangiopathy in Australia and New Zealand. Nephrology (Carlton). 2018 Jun;23(6):507-517

Summary/Reviews *MORE*: NCBI-NIH PubMed Central

Berger BE. Atypical hemolytic uremic syndrome: a syndrome in need of clarity. Clin Kidney J. 2019 Jun; 12(3): 338–347.

Menne et al. Outcomes in patients with atypical hemolytic uremic syndrome treated with eculizumab in a long-term observational study. BMC Nephrol. 2019; 20: 125.

Yoshida et al. Pathogenesis of Atypical Hemolytic Uremic Syndrome. J Atheroscler Thromb. 2019 Feb 1; 26(2): 99–110.

aHUS: Varied Topics

Ariceta, G. Optimal duration of treatment with eculizumab in atypical hemolytic uremic syndrome (aHUS)—a question to be addressed in a scientific way. Pediatr Nephrol. 2019 May;34(5):943-949.

Demeulenaere et al. Thrombomodulin and Endothelial Dysfunction: A Disease-Modifier Shared between Malignant Hypertension and Atypical Hemolytic Uremic Syndrome. Nephron 2018;140:63–73

Kimman et al. Validity of the Patient Experiences and Satisfaction with Medications (PESaM) Questionnaire. Patient (2019) 12: 149

Sharkey et al. Anti-Factor H Antibody Reactivity in Young Adults Vaccinated with a Meningococcal Serogroup B Vaccine Containing Factor H Binding Protein. mSphere. 2019 Jul-Aug; 4(4): e00393-19.

Drug Discovery/ Research *(See* aHUS Alliance *2018 aHUS Therapeutic Drug Pipeline)*

Gavriilaki et al Complement in Thrombotic Microangiopathies: Unraveling Ariadne's Thread Into the Labyrinth of Complement Therapeutics Front Immunol. 2019; 10: 337

Mastellos et al Clinical promise of next- generation complement therapeutics Nat Rev Drug Discov. 2019 Jul 19.

Wijnsma et al. Pharmacology, Pharmacokinetics and Pharmacodynamics of Eculizumab, and Possibilities for an Individualized Approach to Eculizumab. Clin Pharmacokinet. 2019; 58(7): 859–874.

Global aHUS Registry *MORE*: NCBI-NIH PubMed Central

Rondeau et al Pregnancy Outcomes in Patients Enrolled in the Global aHUS Registry
Nephrology Dialysis Transplantation, Volume 34, Issue Supplement 1, June 2019

Rondeau et al. Eculizumab Safety: 5-Year Experience From the Global Atypical Hemolytic Uremic Syndrome Registry. Kidney Int Reports, 2 August 2019.

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Kidney Int: August 2018 Volume 94, Issue 2, Pages 408–418

Siedlecki et al. Eculizumab Use for Kidney Transplantation in Patients With a Diagnosis of Atypical Hemolytic Uremic Syndrome. Kidney Int Rep. 2019 Mar; 4(3): 434–446.

Atypical HUS: Key Facts & Research

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 percent of children affected and 40 percent 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]
- Death rates amongst aHUS patients are as high as 25 percent, and progression to end-stage kidney disease occurs in more than 50 percent 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 per cent 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.[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]
- 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

aHUS Global Patients' Research Agenda http://bit.ly/aHUSpatientResearchAgenda *Know aHUS, Know Us* https://bit.ly/2xBinlU

aHUS Awareness Day is 24 September

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

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]
- Dialysis cannot completely compensate for the loss of kidney function, and can lead to deadly infections and shortened life expectancy [17]

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 2019 on ClinicalTrials.gov: 26 Studies for 'atypical HUS' https://bit.ly/2QIz1Zl and 339 Studies listed under 'thrombotic microangiopathy' or TMAs http://bit.ly/2m3C7fL

Access to Treatment

- As of Sept 2019, 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]. Proposal: ***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)
- aHUS Drug Access 'Patient Perspective' section in ***Optimal management of atypical hemolytic uremic disease***: challenges and solutions. Int J Nephrol Renovasc Dis. Vol. 12, Sept 2019 http://bit.ly/2lYD7Sd

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

SOURCES: See our CITATIONS section later in this document

Atypical HUS: In Brief **Click HERE for a 2019 'Print & Share' page of aHUS Facts**

A Deeper Dive into Information & Topics relevant to Atypical HUS

Diseases/Disorders: Potential for Cross-Over to aHUS Research

AAV	(ANCA)-associated vasculitis Note: ANCA – anti-neutrophil cytoplasmic Abs
AMD	Age-related Macular Degeneration
AMR	Antibody mediated rejection
CAD	Cold Agglutinin Disease
CAD	Coronary Artery Disease
CMV	Cytomegalovirus
C3G	C3 glomerulopathy, Subtypes: Dense deposit disease (DDD) and C3 glomerulonephritis (C3GN)
CMND	Complement-Mediated Neurodegeneration
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular Disease
DDD	Dense Deposit Disease (see also C3G)
DFG	Delayed Graft Function
DM	Dermatomyositis
GBS	Guillain Barre Syndrome
GvHD	Acute Graft v Host Disease
HAE	Hereditary Angioedema
HSCT	Hematopoietic Stem Cell Transplant
IBMIR	Instant Blood-mediated Inflammation Reaction
IgAN	Immunoglobulin A Nephropathy (form of glomerulonephritis) Note: IgA – Immunoglobulin A
IRI	Ischemia-reperfusion Injury
MG	Myasthenia Gravis
MMN	Multifocal Motor Neuropathy
MPGN	Membranoproliferative glomerulonephritis
NMOSD	Relapsing Neuromyelitis Optica Spectrum Disorder

PNH	Paroxysmal Nocturnal Hemoglobinuria
RA	Rheumatoid arthritis
SLE	Systemic Lupus Erythematosus
STEC	HUS – Shiga toxin-releasing Escherichia coli-Hemolytic Uremic Syndrome
TMA	Thrombotic microangiopathy (often plural)
TTP	Thrombotic Thrombocytopenic Purpura

Note: Research done for other complement-mediated diseases, or those with similar underlying mechanisms, may provide knowledge to advance aHUS research and therapeutic drug discovery. Listed are some diseases for which future investigations may provide cross-over information for aHUS researchers.

aHUS Alliance Article (2018) regarding aHUS Therapeutic Drugs & *Drug Discovery and Market Factors within the Atypical HUS Arena*

http://bit.ly/2IWaWmS

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

(Table created Sept 2017, updated 2019) [26,27]

Therapeutic Drug Discovery

aHUS and other Complement Mediated Diseases

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		

*Clinical Trials, Stages of Development: http://www.nlm.nih.gov/services/ctphases.html
Check for updated information on Clinical Trials at www.ClinicalTrials.gov

aHUS Patient Perspective: In Depth Look at Drug Access Issues, a section within

Raina et al. *Optimal management of atypical hemolytic uremic disease: challenges and solutions*. Int J Nephrol Renovasc Dis. Vol. 12, Sept 2019. http://bit.ly/2lYD7Sd

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%

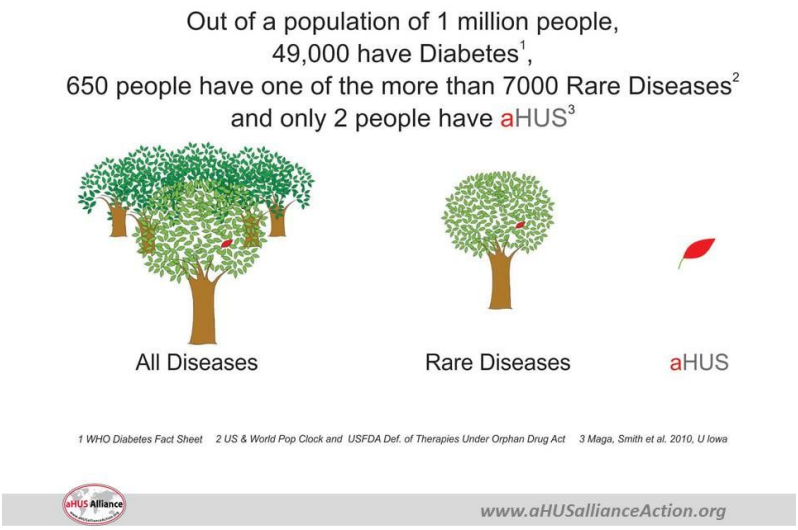
- aHUS Research - Participation 50% of Respondents have already done so, and 36% more would like participate but don't know how to engage.

- 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

Resources – More about aHUS

Press Kit: aHUS Alliance - *Click HERE to view*

*In ENGLISH: Disease OVERVIEW with definitions & research links

NCBI GeneReviews©, affiliated with the National Institutes of Health (NIH)
http://www.ncbi.nlm.nih.gov/books/NBK1367/

*In ENGLISH: OVERVIEW with detailed Info & Tables on aHUS triggers, genetics, extra-renal involvement (aHUS affecting other organs), and other topics

Kavanagh D, Goodship T H, and Richards A. Atypical Hemolytic Uremic Syndrome. Semin Nephrol 2013 Nov; 33(6): 508–530. doi: 10.1016/j.semnephrol.2013.08.003 http://ow.ly/QjUD303Tqlp

*In ENGLISH: Pediatric Focus

An international consensus approach to the management of atypical hemolytic uremic syndrome in children, Abstract: http://www.ncbi.nlm.nih.gov/pubmed/25859752

*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)

*aHUS Clinical & Diagnostic Checklist, Courtesy of www.RareRenal.org (UK): http://ow.ly/BuOR303SaLv

*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.

Rare Disease Day

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. Learn More about
aHUS Awareness Day 2019 - aHUS Alliance

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