Re-Thinking aHUS in 2017
Diagnosis: Modified Hamm Test for atypical Hemolytic Uremic Syndrome (Gavriilaki, E et al 2015)
Multi-Disciplinary Care Teams: Thrombotic Microangiopathy: A Multidisciplinary Team Approach (Gordon et al, 2017)
Atypical HUS is a type of TMA: Clinical evaluation of thrombotic microangiopathy: identification of patients with suspected atypical hemolytic uremic syndrome (Yu-Min Shen, 2016)

aHUS Alliance

An innovative and collaborative partnership between patients with rare disease and industry-supported registries: the Global aHUS Registry (Woodward, L et al 2016)
aHUS Clinicians & Investigators – A Global Networking Hub
aHUS Advocacy & Patient Organizations – Connecting global aHUS advocates and efforts

Recent Research – aHUS & Thrombotic Microangiopathy
Atypical HUS (A Year in Research)
A look at aHUS research in over the last 12 months (2017), NCBI: US Library of Medicine
Thrombotic Microangiopathy, TMA (A Year in Research)
A look at TMA research in over the last 12 months (2017), NCBI: US Library of Medicine

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
- aHUS is caused by chronic, uncontrolled activation of the complement system, a part of the body’s natural immune system
• 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 per cent of patients experience failure of transplanted kidney. \(^2\)

**Diagnosis**
• Atypical HUS encompasses a group of diseases that share 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 nervous system involvement is the most frequent extra-renal organ manifestation of aHUS (10–48%)\(^9\), 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 per cent 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 per cent of plasma exchange sessions in children and in 15 per cent of sessions in adults\(^ {16}\)

Treatment - Therapeutics

- Eculizumab has shown greater efficacy than plasma therapy in the prevention and treatment of aHUS\(^ {16,19}\)
- In June 2013, an international study in the New England Journal of Medicine showed aHUS patients treated with eculizumab were able to discontinue plasma infusion/exchange and dialysis therapies, and saw improved kidney function, reduced blood vessel damage and decreased risk of blood clots\(^ {22}\)
- Clinical Trials – Currently recruiting as of Sept 2017 on www.ClinicalTrials.gov (atypical HUS): ALXN1210 and OMS721, with more aHUS clinical trials expected soon. [Click HERE](http://ow.ly/DCj30euhZn) for clinical trial updates.

Access to Treatment

- As of Sept 2017 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.\(^ {26,28}\)
- In September 2013, National Health Service (NHS) England recommended that eculizumab be funded for aHUS patients, following a positive reimbursement recommendation from the Clinical Priorities Advisory Group (CPAG). The final draft guidance recommending eculizumab for funding for treating aHUS was issued by the National Institute for Health and Care Excellence (NICE) in November of 2014.

Note: The aHUS Alliance wishes to extend thanks to aHUS Canada for their efforts in providing core facts contained in this document.
### Diseases/Disorders: Potential for Cross-Over to aHUS Research

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
</table>
| 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 “Barr Syndrome |
| GvHD    | Acute Graft v Host Disease |
| HAE     | Hereditary Angioedema |
| HSCT    | Hematopoietic Stem Cell Transplant |
| IBI MIR | 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.

**FMI please visit** [http://www.ahusallianceaction.org/ahus-therapeutic-drugs-research-development/](http://www.ahusallianceaction.org/ahus-therapeutic-drugs-research-development/)

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**Advancing aHUS Treatment - Pipeline of R & D for new Therapeutics**  
*(Table created Sept 2017)*  

**Therapeutic Drug Discovery**  
aHUS and other Complement Mediated Diseases

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>DRUG/Molecule</th>
<th>TARGET/Mechanism</th>
<th>Other INFO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexion</td>
<td>ALXN1210</td>
<td>longer-acting C5 inhibitor</td>
<td>aHUS and PNH</td>
</tr>
<tr>
<td></td>
<td>ALXN1007</td>
<td>C5a</td>
<td>Focus: GvHD</td>
</tr>
<tr>
<td></td>
<td>ALXN1102 (TT30)</td>
<td>C3</td>
<td>Focus: PNH</td>
</tr>
<tr>
<td>Soliris®/eculizumab</td>
<td>C5</td>
<td></td>
<td>aHUS, PNH, More</td>
</tr>
<tr>
<td>Achillion</td>
<td>ACH-4471</td>
<td>Factor D</td>
<td>Focus: PNH Complement Mediated Diseases</td>
</tr>
<tr>
<td>ADIENNE Pharma &amp; Biotech</td>
<td>MUBODINA®</td>
<td>C5</td>
<td>Focus: Typical HUS</td>
</tr>
<tr>
<td>Akari Therapeutics</td>
<td>Coversin®</td>
<td>C5</td>
<td>PNH Trial, Initial Data (PNH)</td>
</tr>
<tr>
<td>Alnylam</td>
<td>ALN-CC5</td>
<td>RNAi, C5</td>
<td>Focus: PNH, and Others</td>
</tr>
<tr>
<td>Amgen</td>
<td>ABP 959</td>
<td>Biosimilar to eculizumab, C5</td>
<td>ANZCTR Trial</td>
</tr>
<tr>
<td>Amyndas Pharmaceuticals</td>
<td>AMY-101</td>
<td>C3, Cp40</td>
<td>Focus: C3G, PNH, Others</td>
</tr>
<tr>
<td></td>
<td>AMY-201</td>
<td>C3</td>
<td>Other: mini-FH</td>
</tr>
<tr>
<td>Company</td>
<td>Product(s)</td>
<td>Target(s)</td>
<td>Focus/Indications</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------------------------------------------</td>
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<td>----------------------------------------------------------------------------------</td>
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<tr>
<td>Annexon</td>
<td>ANX005</td>
<td>C1q</td>
<td>Alternative pathway, Auto-immune, Clinical Trial</td>
</tr>
<tr>
<td>Apellis</td>
<td>Compstatin®/APL-2</td>
<td>C3</td>
<td>Clinical Trials: PNH, AMD, Other</td>
</tr>
<tr>
<td>ChemoCentryx</td>
<td>CCX168  Avacopan</td>
<td>C5αR</td>
<td>AAV, other</td>
</tr>
<tr>
<td>Genentech</td>
<td>Lampalizumab</td>
<td>Factor D  (FCFD4514S, RG7417)</td>
<td>Clinical Trial: Eyes</td>
</tr>
<tr>
<td>Rituxan/Rituximab</td>
<td>CD20</td>
<td></td>
<td>Focus: MPGN, IgAN, Other also RA</td>
</tr>
<tr>
<td>Greenovation</td>
<td>Moss-FH</td>
<td>Factor H, C3</td>
<td>Complement Disorders, Plant-based</td>
</tr>
<tr>
<td>InflaRx</td>
<td>IFX-1/ IFX-2</td>
<td>C5α</td>
<td>Clinical Trials: AAV, other</td>
</tr>
<tr>
<td>Infazyme</td>
<td>Mirococept®/APT070</td>
<td>C3 convertase inhibitor</td>
<td>Focus: IBMIR, IRI</td>
</tr>
<tr>
<td>LFB Group</td>
<td>hCFH</td>
<td>Factor H</td>
<td>Focus: Factor H, DDD</td>
</tr>
<tr>
<td>Novartis (Sandoz)</td>
<td>LFG316</td>
<td>C5</td>
<td>Clinical Trials: PNH, also Transplant</td>
</tr>
<tr>
<td>KRP203</td>
<td>S1PR</td>
<td></td>
<td>Clinical Trials</td>
</tr>
<tr>
<td>CFZ533</td>
<td>CD40</td>
<td></td>
<td>Clinical Trials</td>
</tr>
<tr>
<td>NovelMed</td>
<td>NM9401</td>
<td>Properdin</td>
<td>Pharma Focus: PNH, Hemodialysis, Others</td>
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<tr>
<td>Omeros</td>
<td>OMS721</td>
<td>MASP-2, Lectin pathway</td>
<td>Clinical Trials: aHUS, TMA, and IgAN &amp; Others</td>
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<tr>
<td>OMS906</td>
<td>MASP-3, Alternative pathway</td>
<td></td>
<td>Early Focus: PNH, aHUS, Others</td>
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<tr>
<td>Opthotech</td>
<td>Zimura (ARC1905)</td>
<td>C5</td>
<td>Clinical Trial: AMD</td>
</tr>
<tr>
<td>Ra Pharma</td>
<td>RA101495</td>
<td>C5, oral small molecules</td>
<td>Focus: PNH, LN, MG, Others</td>
</tr>
<tr>
<td>Resverlogix</td>
<td>RVX-208/apabetalone (RVX-000222)</td>
<td>BET</td>
<td>ESRD w/ Hemodialysis, CAD, BETonMACE for CVD</td>
</tr>
<tr>
<td>Sobi</td>
<td>SOBI005</td>
<td>C5</td>
<td>Focus: PNH, aHUS</td>
</tr>
<tr>
<td>True North, Acquired by</td>
<td>BIVV009, formerly TNT009</td>
<td>C1s, Classical Pathway</td>
<td>Clinical Trial: Complement Mediated Disorders, Autoimmune Hemolytic Anemia, CAD</td>
</tr>
<tr>
<td>Various Pharma</td>
<td>Cinryze, Berinert, Ruconest, Others</td>
<td>C1-INH</td>
<td>Clinical Trials</td>
</tr>
</tbody>
</table>
2016 aHUS Global Poll: aHUS Patient Voice

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/g5j8303GcdH](http://ow.ly/g5j8303GcdH)
- 2016 aHUS Global Poll, RESULTS & Graphs: [http://ow.ly/1DA7303FoJx](http://ow.ly/1DA7303FoJx)

2014 aHUS Poll: In Collaboration with RareConnect, previous aHUS poll Results & Webinar with commentary by Dr. T Goodship: [http://ow.ly/hRau303OZh2](http://ow.ly/hRau303OZh2)

aHUS Insights – Select Info from the 2016 Global Poll – [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 Health 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%

![Out of a population of 1 million people, 49,000 have Diabetes1, 650 people have one of the more than 7000 Rare Diseases2 and only 2 people have aHUS3](image)

2016 aHUS Global Poll, RESULTS & Graphs:  http://ow.ly/IDA7303FoJx

DIRECTORY of aHUS Patient Organizations:  http://ow.ly/TLw303QQGn

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

*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


*In ENGLISH: Pediatric Focus


*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.
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 2017 - aHUS Alliance

CITATIONS

12 Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011 Sep 8; 6:60.
26. 28 June 2015, aHUS Alliance mtg. of international aHUS patient organizations. London.
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: http://ow.ly/g5j8303GcdH Poll Questions & Results: http://ow.ly/1DA7303Fx Poll Webinar, courtesy of RareConnect with commentary by Dr. C. Licht: http://ow.ly/ACiN303GaiE