Day in Complement 2025 Conference Proceedings

Canadian Institute for the Transfer of Knowledge

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On September 20th, 2025, a diverse range of health care providers gathered at the David Braley Health Sciences Centre of McMaster University in Hamilton, Ontario, to hear knowledge leaders speak on research, diagnosis, and management of the complement cascade.

Learning objectives included:

- Describe the structure, function, and regulatory mechanisms of the complement cascade in health and disease.
- Analyze the clinical manifestations and diagnostic implications of complement dysregulation in diseases such as paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.
- Evaluate current and emerging complement-targeted therapies for their clinical applicability and efficacy.
- Discuss multidisciplinary and patient-centred approaches to managing complement-mediated disorders.
- Reflect on the future directions in complement research and the translation of novel findings into clinical practice.

Speakers

Shruti Chaturvedi, MBBS, MS

Benjamin Chin-Yee, MD, PhD, FRCPC

Mark Crowther, MD, MSc, LLM, FRCPC, FRSC

Michael Eygenraam, patient advocate

Christoph Licht, MD, FRCPC, FASN

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The complement cascade: Fundamentals and emerging therapeutics

The complement system comprises a collection of proteins that are integral to the immune system, serving to augment the body's defenses against pathogens. It functions by initiating a cascade of reactions that ultimately result in the eradication of invaders through various mechanisms, including opsonization, lysis, and inflammation.

Congenital and acquired deficiencies in the complement system may result in disorders characterized by a variety of clinical manifestations. An understanding of complement pathogenesis has facilitated the development of effective targeted therapies.

Awareness and early recognition are essential, particularly in the context of ultra-rare diseases, as timely intervention may be lifesaving.

Complement 101: Introduction to that *other* cascade

Christopher Patriquin, MD, MSc, FRCPC

Dr. Patriquin offered a primer to the complement cascade, reviewing key components of component activation and regulation and the basics of therapeutic complement inhibition.

The history of understanding complement began in the late 1800s, with Buchner proposing the existence of antibacterial proteins in blood serum which he called "alexines". Evolutionary biology and genetic research have shown that complement is a primitive and prehistoric form of immunity dating back over a billion years. Complement is not limited to antimicrobial protection but also serves protean homeostatic functions.

> *"Many immunologists hold that complement is baffling or irrelevant or, most conveniently, both… but a recent meeting emphasized that complement is interesting and that it may be important…"*
>
> *~ Hobart, 1984 (Trends in Immunology)*

Complement system pathway and defects

Complementopathy contributes variably to many hematologic diseases. Key complement-mediated diseases include atypical hemolytic uremic syndrome (aHUS), and paroxysmal nocturnal hemoglobinuria (PNH). Increasing the awareness of complement-related conditions and offering testing to at-risk patients can decrease time to diagnosis and improve morbidity and mortality. While certain assays are available to determine complement deficiencies and biomarkers, access remains limited in Canada.

Understanding whether complement is playing a central role in or as companion to pathology is critical to determining therapeutic targets. Registry data is essential to provide clarity and long-term outcomes in this area, particularly given the rarity of many of these conditions.

Therapeutic manipulation of complement is possible, generally safe, and effective in the treatment of complement-mediated disease. C5 inhibition was the first target, with eculizumab, ravulizumab, and crovalimab offering hope to patients with PNH and aHUS. Complement inhibitors targeting other molecules, such as C3, Factor B, and Factor D, have been more recently approve for various conditions, and trials are ongoing across a wide array of diseases.

Is the complement system druggable?

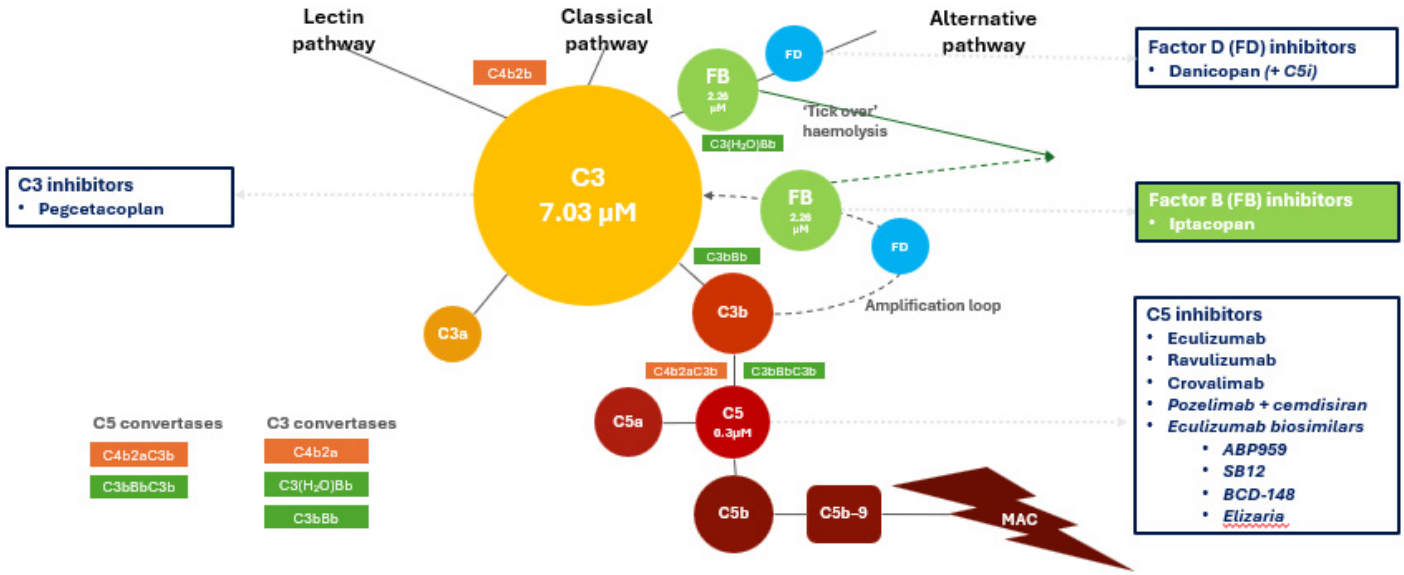


Image modified from: Kulasekararaj AG & Lazana I (2023) Am J Hematol

Complement pathologies: When regulation *fails*

Shruti Chaturvedi, MBBS, MS

Dr. Chaturvedi's research at Johns Hopkins focuses on the role of complement in thrombotic disorders. Her presentation touched on why and how complement fails, the consequences of complement regulation, and the role of complement in blood disorders.

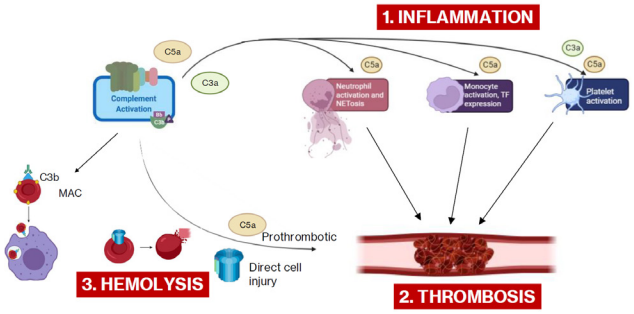
Complement is a tightly regulated part of the innate immune system with significant functions in homeostasis and essentially any biological function, particularly:

1. Identifying and 'tagging' foreign or damaged-self materials.
2. Eliminating these targets via phagocytosis or direct lysis by the membrane attack complex.
3. Promoting inflammatory and immune responses.

Complement dysregulation occurs when there is too much stimulation, including increased antibody and antigen complexes through the classical pathway, infection through the lectin pathway, and the alternative pathway, which is constitutively active, can be further amplified through inflammation, increased availability of free heme, or coagulation/endothelial injury.

Alternatively, there can be a failure of down regulation, through mutations in complement regulation genes, as in aHUS or macular degeneration, or an acquired loss of regulators, as in PNH.

Opportunity - C' is involved in broad disease processes



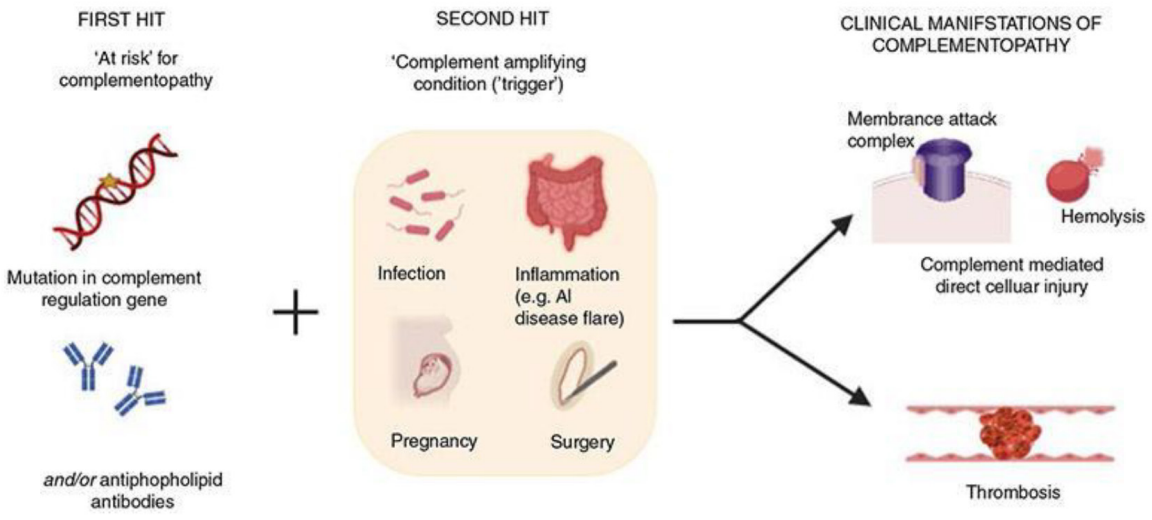
Adapted from Cole, Gerber, Chaturvedi. Clinical Immunol 2022

Complement disorders usually have a "two hit" pathogenesis – a person is at risk due to mutations in complement regulation genes, and/or polymorphism; followed by a trigger that amplifies complement, such as inflammation, infection, pregnancy, or surgery.

Complement pathology commonly manifests as thrombosis, hemolysis, inflammation, or cell injury. Currently, there are clear targetable drivers in PNH, complement-mediated thrombotic microangiopathy, cold agglutinin disease, and antiphospholipid syndrome, with an expanding role in more complex and heterogenous such as sickle cell anemia, transfusion reactions, antiphospholpiid syndrome, and immune thrombocytopenia.

Phenotyping patients better to understand which subgroup may benefit from complement inhibition is an unmet need for acute vs. long-term complement inhibition.

Cardinal features of complement disorders



Adapted from Chaturvedi, McCrae, Brodsky. JTH 2021

Diseases with complement-mediated pathogenesis

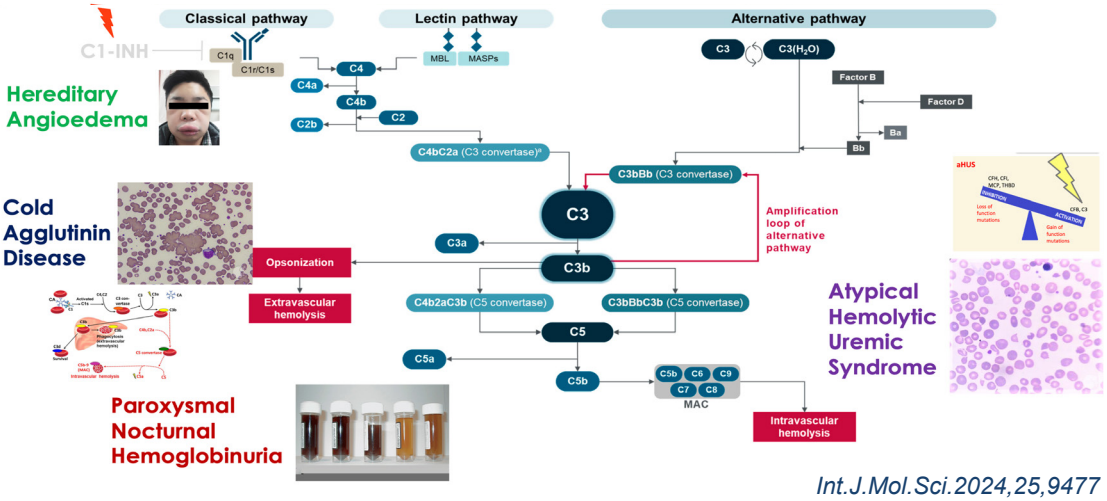
Benjamin Chin-Yee, MD, PhD, FRCPC

Dr. Chin-Yee, a hematologist at London Health Sciences Centre studying complement-related diseases, added to the overview of the complement system. Complement is a complex, ancient, evolutionary innovation; a proto-immune system that enabled hosts to defend themselves against pathogens.

The classical pathway bridges the innate and adaptive immune systems, which is triggered by antibodies. The lectin pathway is amplified by carbohydrates. Both the classical and lectin pathways lead to the formation of C3 convertase. The alternative pathway, along with C3, factor B and factor D, lead to the alternative C3 convertase. C3 plays the role of "quarterback" in the complement cascade, leading to cleaving of C3 and a range of downstream effects.

Like many aspects of the immune system, complement needs to be kept in a fine balance; when dysregulated can lead to pathophysiology, including PNH, cold agglutinin disease, aHUS, and hereditary angioedema.

Complement in Human Diseases



Int.J.Mol.Sci.2024,25,9477

An overview of complement-mediated diseases

Benjamin Chin-Yee, MD, PhD, FRCPC

Atypical hemolytic uremic syndrome (aHUS)/ complement-mediated thrombotic microangiopathy (CM-TMA)

aHUS is a very rare disease with a historically poor prognosis. It can occur at any age, with a slightly more frequent onset during childhood. aHUS is characterized by hypertension, thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury.

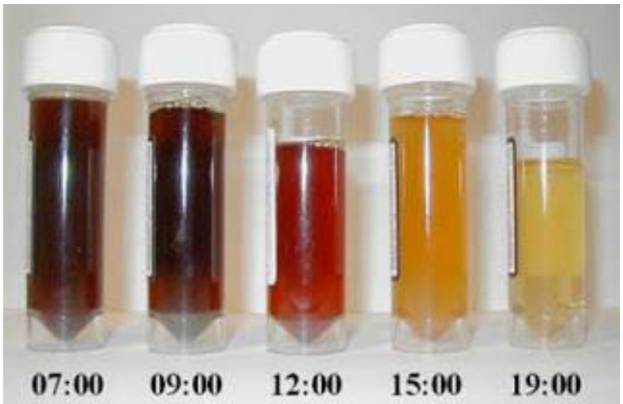
It is associated with genetic mutations that are involved in regulation of the alternative pathways, such as *CFH, CFHR1/3*, and *CFI*. While present in about 50% of patients, complement mutations are not necessary or sufficient to diagnose aHUS, as 30-50% of patients do not have one of these mutations. Carriers of these genes only have about a 20% lifetime chance of disease. Pathogenesis occurs in those who are at risk for aHUS, and then a complement activating condition occurs, such as inflammation, surgery, pregnancy, or autoimmunity.

aHUS is a diagnosis of exclusion, distinguished from thrombotic thrombocytopenic purpura (TTP), and secondary HUS to malignancy, drugs, and infection. aHUS panel testing is available at London Health Sciences Centre and the Hospital for Sick Children to help identify genetic mutations which can help to inform recurrence risk and counsel relatives. Acute aHUS is treated using C5 inhibitors, with considerations for long-term therapy.

Antiphospholipid syndrome (APS):

A systemic autoimmune disorder characterized by arterial or venous thrombosis and/or pregnancy morbidity accompanied by persistently positive antiphospholipid antibody tests. Long-term anticoagulation with standard intensity warfarin is the standard of care for thrombotic APS. Some patients experience refractory or catastrophic APS, associated with complement activation. Refractory APS experience recurrent thrombosis despite anticoagulation.

Hemolysis



Medscape

Catastrophic APS (CAPS) is rapidly developing widespread thrombosis with multiorgan failure, often 'triggered' by surgery, infection, pregnancy or delivery. While it is rare, it has a 30-50% mortality rate. Mechanistic parallels are found with CAPS and aHUS, with the addition of complement receptor 1 (CR1), which allows for immune complex degradation and may have a particular role in CAPS. Anecdotal evidence has found that C5 inhibition reduces thrombosis in CAPS and refractory APS, potentially leading to discontinuation of anticoagulation.

Cold agglutinin disease (CAD):

CAD is a primary, clonal B-cell lymphoproliferative disorder of bone marrow that leads to chronic hemolysis mediated by complement activation. Characterized by acrocyanosis, a painless, bluish discolouration, clinical features include autoantibodies binding to red blood cells at sub-core body temperatures, most pronounced at acral/peripheral sites and exacerbated by cold exposure. On warming, IgM dissociates from C1 complex, but remains bound to C3b and degrades to C3d, leading to downstream effects, such as circulatory symptoms, agglutination, hemolytic anemia, and increased risk of thrombosis.

Kohlert S, et al., J Otolaryngol Head Neck Surg. 2019;48(1):52

Supportive measures can often manage symptoms through cold avoidance and supplementation with folic acid, and B-cell directed therapy can be effective. There is a need for rapid-acting therapy for acute and severe exacerbations, or in relation to acute illness/surgery. Sutimlimab is an emerging therapy, and eculizumab has been studied with acute intravascular hemolysis.

Hereditary angioedema (HAE):

LucyHAE - Own work, CC BY-SA 3.0

Primarily a bradykinin disorder caused by a *mutation in the gene SERPING1* encoding the C1 inhibitor, HAE is a more prevalent disease that has onset in youths, often exacerbated at puberty. Type 1 is most common (~85%) with reduced levels of C1-INH; type 2 has dysfunctional C1-INH, and a rare type has normal C1-INH. HAE attacks are caused by excess bradykinin in the contact system as result of the absence of C1 inhibition, binding to endothelial B2 receptors and causing increased vascular permeability and swelling. Presentation includes recurrent angioedema of the skin and submucosal tissues without urticaria or pruritus, often precipitated by stress, that can lead to life-threatening laryngeal edema and airway obstruction. Acute and prophylactic HAE therapy is C1-inhibitor replacement therapy, as well as bradykinin B2 receptor antagonists and plasma kallikrein inhibitors.

Paroxysmal nocturnal hemoglobinuria (PNH):

A rare disease that often presents with dark, tea coloured urine. Prior to the advent of complement inhibitors, the 5-year mortality rate was 35%, primarily due to thrombosis, often in unusual sites, such as the ears, tonsils, abdomen, or gonadal veins. However, people with PNH on complement therapy now have survival rates that match controls.

PNH is an acquired clonal stem cell disorder caused by a somatic mutation in the PIGA *gene* resulting in a clone that lack GPI-anchored hematopoietic stem cell clone that lack GPI-anchored complement regulatory proteins (CD55 and CD59) essential to protecting red blood cells from complement. Without this protection, GPI-deficient PNH red blood cells are destroyed by the complement system. Free hemoglobin is released and scavenges nitrous oxide. Common clinical features include chest pain, dyspnea, abdominal pain, renal failure, and smooth muscle dystonia.

A number of therapies target different aspects of the complement system to mitigate hemolysis, shifting PNH from a life-threatening disease to a chronic disease that can be controlled. C5 inhibitors significantly reduce the risk of thrombosis in PNH. Patients on C5 inhibitors and experiencing anemia and breakthrough hemolysis can add on more proximal complement inhibitors that target both intravascular and extravascular hemolysis.

A patient perspective on complement-mediated diseases

Michael Eygenraam, patient advocate, Principal, aHUS Canada

Patient stories help to ground practitioners in the why of research and therapies. Married, with two young children, Michael first began experiencing serious symptoms in 2002 and was misdiagnosed with TTP, as little was known about aHUS at the time. Allergic reactions followed plasma exchange, a kidney biopsy led to significant, painful internal bleeding, hospitalization, and transient ischemic attack; then nocturnal home dialysis conducted five nights a week. His wife, Margriet, in an act of courage and love, donated one of her kidneys to Michael in 2006, which failed after initial improvement. In 2007, he was no longer able to work. They educated and advocated for themselves, encouraging collaboration between multidisciplinary teams.

In 2010, after hearing about his case from colleagues, Michael was contacted by Dr. Christoph Licht. Further genetic testing revealed Michael's aHUS diagnosis driven by a C3 mutation. However, public funding was not available for the expensive emerging medication he needed, eculizumab. After ten years without community or support, they became board members of the newly formed patient group, aHUS Canada, to support patients and advocate for access to the drug. In 2021, Michael received a second kidney transplant, a vastly different experience to his first one. While recovery was difficult and he experienced complications, Michael was treated as a partner, and the team's collaborative approach made all the difference, both medically and emotionally.

Michael's journey has been a story of resilience in the face of uncertainty, the power of patient voices in driving system change, and the profound impact of communications and collaboration.

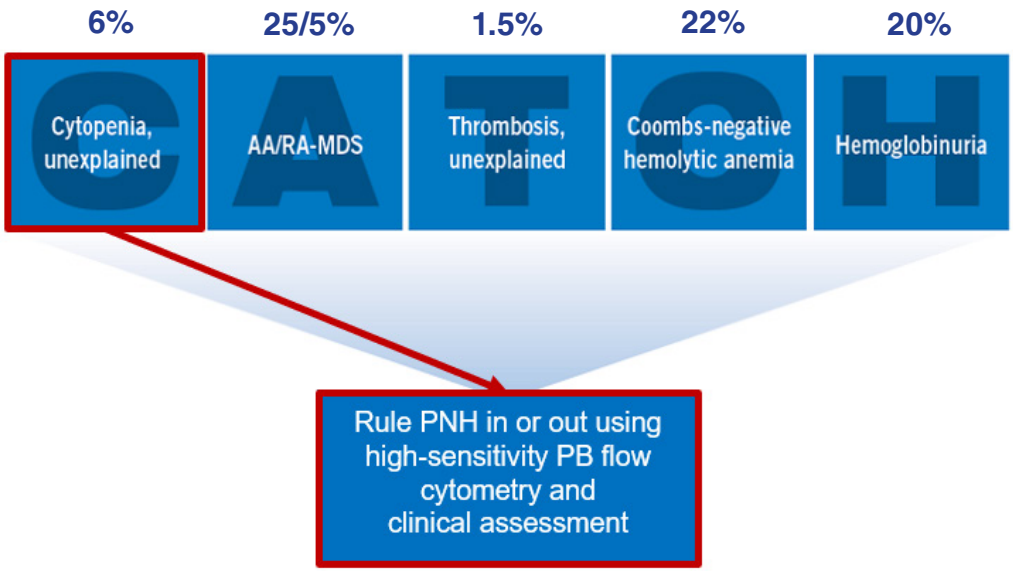
> *"Canadians with rare diseases deserve the same chance at life and health as anyone else."*
>
> *~ Michael Eygenraam*

Optimizing PNH management: *new* treatments, *new* discussions, *new* decisions

Christopher Patriquin, MD, MSc, FRCPC

PNH is a rare, progressive, life-threatening disease where uncontrolled complement activation leads to the hemolysis of red blood cells, and increases thrombosis risk from damage and activation of involved platelets and leukocytes. Chronic complement-mediated hemolysis causes thrombosis (responsible for 40-50% of deaths), end-organ damage, and impaired quality of life. Patients are usually seen by multiple clinicians before diagnosis.

PNH is a chronic condition requiring long-term treatment and monitoring. The early identification of PNH cells has important prognostic and therapeutic implications, therefore it is important that clinicians maintain a high index of suspicion and low threshold for testing. The CATCH criteria note higher-risk patient populations where patients should be screened for PNH using high-sensitivity flow cytometry and comprehensive clinical assessment, offering guidance to identify those who may benefit from treatment.

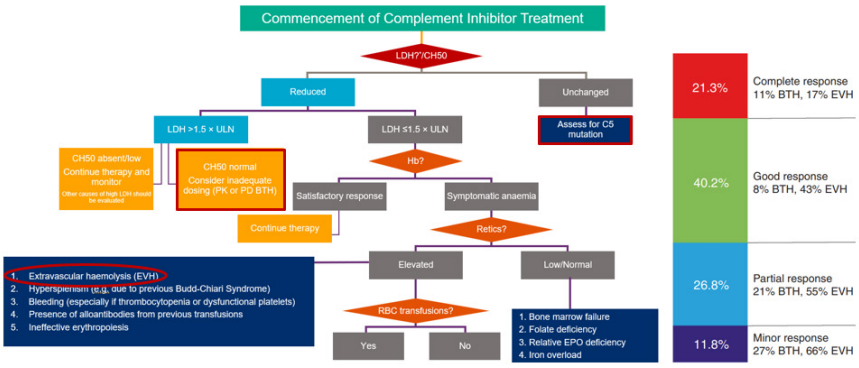


Movalia M et al. (2011) ASH 2011 Abstract #1033
Patriquin CJ et al. (2019) Eur J Hematol

Treatment with complement inhibitors (e.g. eculizumab, ravulizumab) can lead to near normalization of survival of patients with PNH, preventing thrombosis risk and progressive end-organ damage, such as kidney failure and pulmonary hypertension. Survival data for more recently approved inhibitors (e.g. pegcetacoplan, iptacopan, danicopan, crovalimab) are not yet available. Early intervention is paramount, and patients should undergo prophylaxis following treatment initiation with meningococcal vaccination (ACWY + MenB), after which anti-meningococcal antibiotics are required for >14 days. Additional encapsulated bacterial vaccinations may also be considered.

Evaluating a PNH Patient on C5 Inhibition

An algorithm was proposed by Kulasekararaj et al in 2021 to evaluate PNH patients on C5 inhibitors.



Kulasekararaj AG et al. (2021) Am J Hemato
Debureaux PE et al. (2021) BMTI

An algorithm was proposed by Kulasekararaj et al in 2021 to evaluate PNH patients on C5 inhibitors.

If a patient on C5 inhibition is not showing improvement in lactate dehydrogenase (LDH), they should be assessed for C5 polymorphism.
If LDH is not reduced to 1.5x the upper limit of normal or increased after reduction, CH50 should be assessed to ensure adequate blockade (e.g., breakthrough hemolysis).

Breakthrough hemolysis can occur in patients on any complement inhibitor, and can bring with it a return of the risks associated with intravascular hemolysis and untreated PNH. Patients should be counselled to recognize the symptoms and signs, which include a return of dark urine, dysphagia, suddent onset shortness of breath, or overwhelming fatigue, among others. A higher/more frequent dose, or different therapy may be needed.

Targeting complement in aHUS: *Latest data*

Christoph Licht, MD, FRCPC, FASN

aHUS is an ultra-rare, life-threatening, complex, unpredictable disease of uncontrolled complement activation that manifests as complement-mediated TMA, which can lead to progressive, severe organ damage/failure. The disease has a poor prognosis with supportive care, which has changed with the use of complement inhibitors.

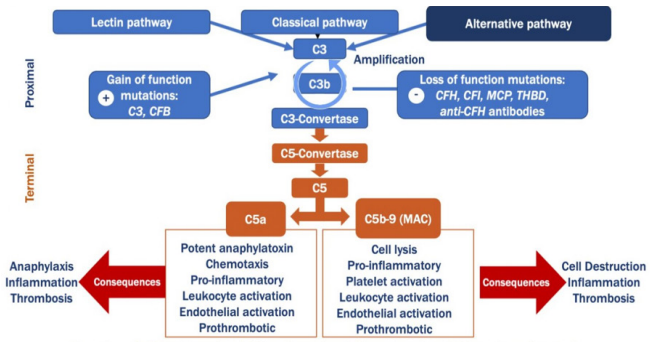
Complement-related genetic mutations, such as complement factor H and thrombomodulin, are associated with aHUS, as well as other non-complement genetic mutations, but a diagnosis is made clinically based on exclusion and does not require the presence of mutations.

Current approved complement inhibitor agents include eculizumab and ravulizumab. Eculizumab showed efficacy in both acute and chronic aHUS.

Ravulizumab is a long-acting C5 inhibitor engineered from eculizumab to achieve immediate, complete, and sustained terminal complement C5 inhibition.

In the ravulizumab-aHUS-312 trial in C5i-naïve pediatric patients, complete, immediate terminal complement inhibition was observed in the initial evaluation period and sustained throughout the 2-year extension. Most patients had mild side effects, no deaths were reported, and serious adverse events were minimal.

In aHUS, Complement Dysregulation Leads to Chronic, Uncontrolled Complement Activation[1-6]



C3, complement 3; CFB, complement factor B; CFH, complement factor H; CFI, complement factor I; 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.

In a real-world effectiveness trial (aHUS IMPACT) of ravulizumab, adults with aHUS who switched to ravulizumab within 3 months of eculizumab treatment were found to result in further hematologic and renal improvement as demonstrated by both an early response and continued improvement through 1 year after ravulizumab initiation.h

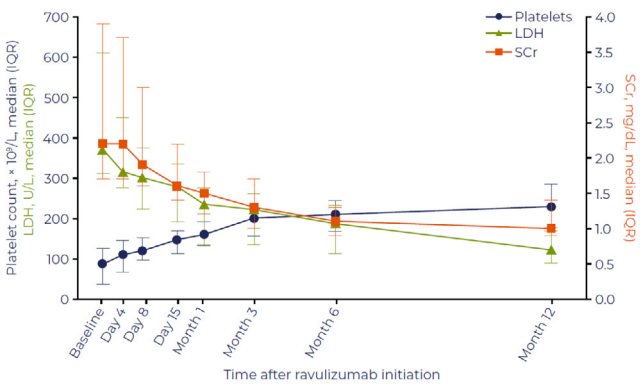
In another real-world effectiveness trial among C5i-naïve patients, results from a physician panel-based chart review supported the immediate and sustained benefits of treatment initiation with ravulizumab based on the early response to treatment and continued improvement.

Even though eculizumab is a very effective drug for management of aHUS, based on this data, Dr. Licht considered that ravulizumab's treatment benefit seems to be stronger, with a superior sustained benefit. There may be a therapeutic window, and those with more moderate response to eculizumab may benefit with ravulizumab therapy,

Emerging complement inhibitor agents in clinical trials investigating aHUS include iptacopan (factor B), pegcetacoplan (C3), crovalimab (C5), avacopan (C5aR1), and narsoplimab (MASP2).

Real-World Effectiveness Of Ravulizumab Among C5I-NAÏVE Patients with aHUS: A Physician Panel-Based Chart Review Study (aHUS Impact)

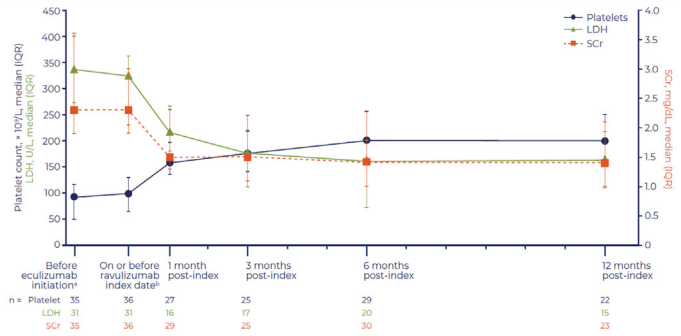
Figure 2. Platelet count, LDH level and SCr level from baseline to month 12 after ravulizumab initiation



Hanna et al. 2024. Presented at ASN November 2024.

Results: RWE of aHUS Patients Who Switched To Ravulizumab Within 3 Months of Eculizumab Treatment (aHUS Impact)

Figure 3. Platelet count, LDH level and SCr level from before eculizumab initiation to Month 12 after switch to ravulizumab from eculizumab



[a]Laboratory values were collected on the date of eculizumab initiation or at the point closest to eculizumab initiation within the previous 6 months.
[b]Laboratory values were collected on the index date or at the point closest to the index date within the previous 6 months. All laboratory values collected on or before ravulizumab index date were collected after eculizumab initiation.

Chaturvedi et al. 2024. Presented at ASH December 2024.

Insights into current and future therapies for complement disorders *(other than PNH and aHUS)*

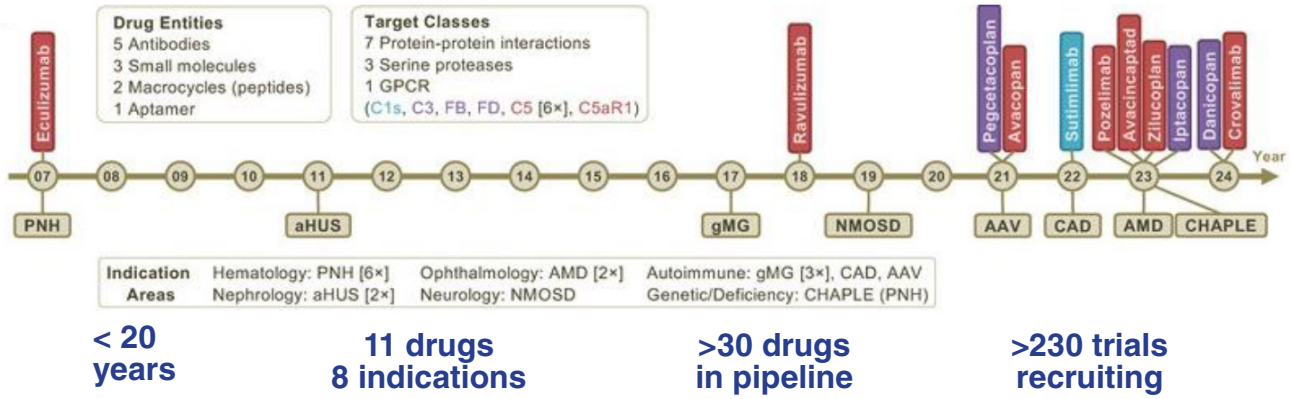
Shruti Chaturvedi, MBBS, MS

In Dr. Chaturvedi's breakout session, she focused on the opportunities and challenges of developing complement inhibitors and the emerging role of complement blockade in more complex blood disorders. Since 2007, at least 11 complement inhibitors have been approved in the United States across eight indications. Beginning with C5 inhibition, there are now inhibitors targeting almost every path in the complement pathways. Medication cost and access continue to be a challenge given the high cost and lack of coverage.

Opportunities exist in:

- Precision targeting: Proximal inhibitors may allow tailored intervention
- New modalities: siRNA against C3, antisense, small molecules, and gene therapy approaches
- Oral agents: Improved convenience and adherence
- Combination strategies: Dual inhibition (e.g., C5 + Factor B, or C5 + siRNA) may overcome residual disease activity

Complement therapeutic - a sucess story



< 20 years | **11 drugs 8 indications** | **>30 drugs in pipeline** | **>230 trials recruiting**

Successfully deploying complement inhibition requires understanding the mechanism of activation. The challenges lay in that complement has a variable role in pathogenesis. In conditions where complement is the primary driver in pathogenesis, such as PNH and aHUS, complement inhibition is highly effective. However, in more complex pathophysiology, complement may be the secondary driver of pathogenesis, for example, free heme in sickle cell anemia and antibodies in APS are causing complement activation.

Further, the multifactorial pathogenesis and variable role of complement across patients [e.g., antiphospholipid syndrome (APS), immune thrombocytopenic purpura (ITP)], and the smaller role of complement (e.g., warm autoimmune hemolytic anemia) in cell destruction but is not likely to be the primary driver, makes it more difficult to understand which patients will benefit from complement inhibition.

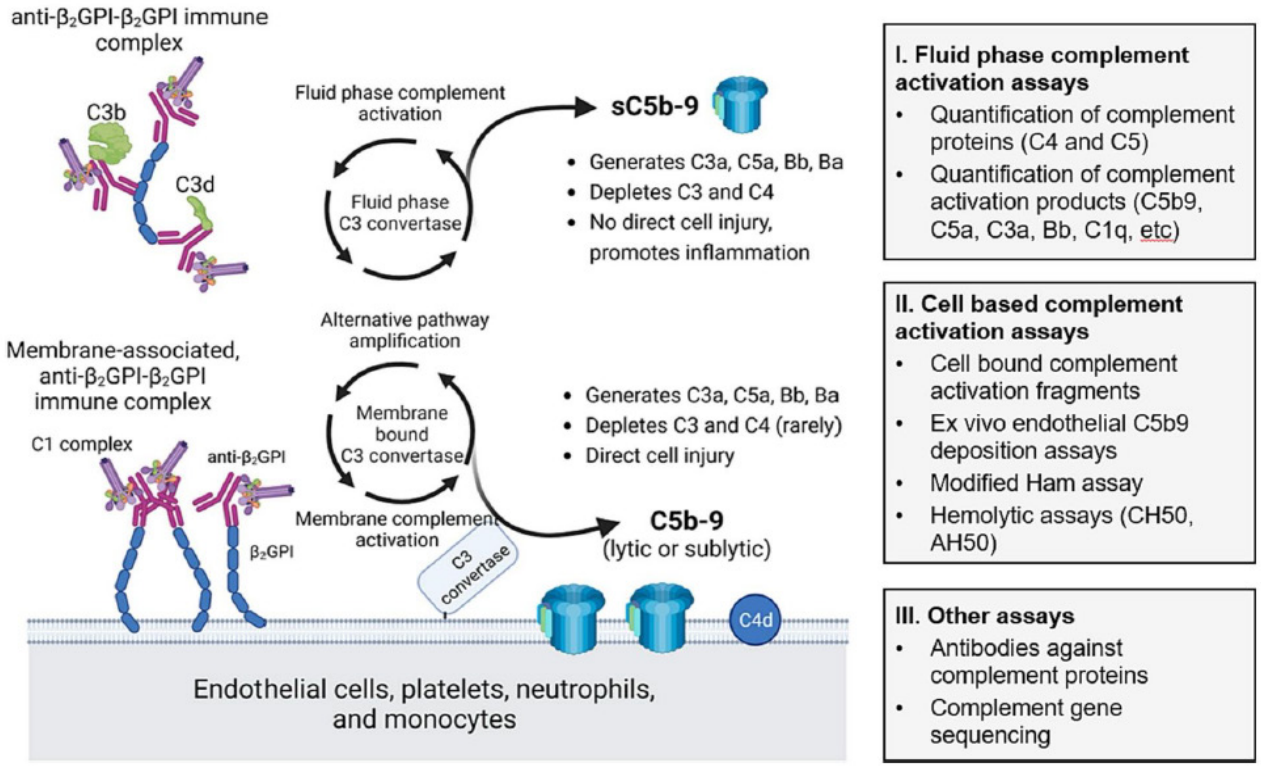
When selecting a proximal inhibitor, it is necessary to understand which pathways are involved in pathogenesis, as activation through more than one pathway may lead to predictable treatment failure. Advantages of proximal inhibition include possible preservation of some complement function.

Deciding between focusing on complement inhibition or another target can be challenging in disorders where complement is not the primary driver, such as antibodies in APS. In sickle cell disease, complement levels rise in acute ‘crisis’, however, free heme activates complement – a “chicken or the egg” situation.

Further, determining who will respond to which therapy can be difficult to predict due to patient heterogeneity, as disease mechanisms differ across individuals and limited biomarkers exist to monitor complement activity or predict treatment response in real time. Currently available biomarker approaches include measuring serum levels of complement activation by products, testing for anti-complement factor H antibodies, sequencing complement genes, and evaluating the hemolytic activity of complement (CH50 testing used to monitor anti-C5 therapy or detect complement deficiencies). More 'functional' cell based assays such as the modified Ham test have been developed but are not widely available in practice.

Challenges with use of biomarkers in assessing complex complement disorders, such as sickle cell disease (SCD), APS, and TMA, find that complement does damage to cell surfaces, and circulating fluid phase (serum) markers do not reflect complement activity at the cell surface. Unfortunately, cell-based assays, such as the modified Ham 2.0, are not widely available.

Circulating immune complexes



Bu et al. AJKD 2015, Cole, Gerber, Chaturvedi. Clin Immunol 2023

Emerging complement disorders in hematology include CAD, immune thrombocytopenia, SCD,and antiphospholipid syndrome/CAPS.

In CAD, there is a high frequency of persisting anemia despite B-cell directed therapy, a need for rapid-acting therapy for acute and severe exacerbations, or in relation to acute illness/surgery in which complement inhibition may play a role. Eculizumab, sutimlimab, and pegcetacoplan have been studied in this space.

The DECADE phase 2 trial for eculizumab in CAD found the overall median LDH decreased, and hemoglobin levels increased, with eight patients becoming transfusion independent and no effects on circulatory symptoms. This indication was not developed further as C5 was not the optimal target, although participant selection with a larger proportion of extravascular hemolysis may have played a part.

The CASCADE trial for pegcetacoplan considered that it could block the C3 B-mediated hemolysis as well as C5 and found significant improvement in hemoglobin levels with normalization of hemolysis markers. The safety profile was similar with that of PNH. While results were promising, further development was deprioritized. The PLAUDIT open-label phase 2 study assessed pegcetacoplan in both CAD and warm autoimmune hemolytic anemia (wAIHA). Results found a lesser LDH response in wAIHA, highlighting the fact that complement activation is not the primary driver.

Sutimlimab is approved in the US for CAD based on two phase 3 studies: CARDINAL, in patients with a recent history of transfusion, and CADENZA, in those without transfusion. Changes in complement biomarkers correlated with improvement of hemoglobin, hemolysis, fatigue, and bilirubin response measures, associated with increase in C4 levels. Safety profiles found minimal treatment-related adverse events, with no clinical evidence of meningococcal infections, SLE, or autoimmune disease. Sutimlimab can be used as a bridge to B-cell directed therapy, although B-cell directed monotherapy is recommended in patients with primarily circulatory symptoms. Sutimlimab can also be used as a long-term strategy in those who do not respond to B-cell directed therapy.

Anecdotal reports of eculizumab have found efficacy in **refractory APS and CAPS**. A retrospective cohort of 11 triple positive patients with CAPS refractory to anticoagulation, steroids, and plasma exchange found a clinical response in 45% (n=5). This study found that eculizumab can be considered in patients with a lower platelet count and a TMA like picture, compared to nonresponders, who were more likely to be on dialysis prior.

A clinical trial of sutimlimab in **ITP** found rapid and sustained improvement in platelet counts, with a response rate of 33%.

A model for complement-mediated TMA in SCD found potential roles for complement inhibition. Complement levels rise in acute crisis, such as acute chest syndrome and vasoocclusive pain, with free heme adding further activation. Dense sickle red blood cells are more prone to hemolysis and complement activation, leading to more surface damage. Two studies using crovalimab in SCD are underway, the phase 1b CROSSWALK-a trial for management of vasoocclusive episode and the phase IIa CROSSWALK-c for prevention of vasoocclusive episode.

The *future* of complement-targeted therapies

Panel: Dr. Chris Patriquin, Dr. Shruti Chaturvedi, Dr. Christoph Licht
Moderator: Dr. Mark Crowther

What are the most promising areas of complement biology that might come to drug development in the next 5-10 years?

The current landscape of complement therapy for PNH and aHUS is safe, efficient, and precise. It has nearly normalized survival for PNH. However, complement is constantly circulating and is involved in all biological functions and whole spectrum of conditions.

- More in-depth understanding of the complement cascade will lead to development of an increasing diversity of therapeutic targets, both in chronic and acute scenarios, balancing complement activation and inactivation.
- Improved understanding of the underlying mechanisms can further explain treatment response, breakthrough symptoms, therapeutic windows, and the impact of longer disease duration.
- Development of immunotyping can help to individualize therapy.
- Added competition through development of additional agents and biosimilars could provide impetus to reduce the costs of therapy, which are quite high and offer challenges to access and equity.

What are your thoughts about the use of biomarkers to better understand therapeutic decision making and dose?

- A very complex system is needed to emulate what is happening in the body; there will not be clear biomarker panels for every disease; a suite of assays should include serum markers, fluid or functional tests, and genetic testing that includes complement phenotypes.
- A collaborative approach to researching the complement system is needed, including "normal" responses in a variety of phenotypes.
- Ideal biomarkers should be able to predict the disease and be negative in those without the disease.
- A unified platform is desired: many biomarkers have been tested, it is difficult to understand which test is needed, is available, where to send them, and how they are paid for.
- Assays need to be readily available and covered.
- Assays should be validated to each disease to assist in make diagnostic, prognostic, treatment, and monitoring decisions, although clinical judgement is still needed ("don't use a test that might mislead you").
- Don't underestimate the utility of non-complement-related markers that inform the affected environment in which complement is activated, such as endothelial damage markers.
- Added competition through development of additional agents and biosimilars could provide impetus to reduce the costs of therapy, which are quite high and offer challenges to access and equity.

Given the rapid expansion of complement inhibitors, what do you see as the greatest unmet need (not including cost)?

- Clinical trial outcomes that demonstrate change in the natural history of the disease or clinically important improvement in patient outcomes.
- Clinical trials and agents in areas that do not have an approved therapy, such as TTP.
- While a lot of progress has been made in understanding complement in terms of "categories" (on/off, activated/not activated), complement still needs to be considered a continuous system.

How do we improve access to complement therapies?

- Orphan drugs are very expensive; there are ethical challenges as >80% of the world does not have access to these expensive therapeutics.
- Asking pharma to reduce costs is not practical as the investment to investigate medications is very expensive. A new contract is required between pharma and society to share the upfront cost and risk of drug development, as this will not change in the current free market scenario. However, different regions pay variable costs for the same drug, so price negotiation is a tactic that should be examined.
- A more transparent, realistic, full-circle cost assessment of therapeutics is needed, for example, the cost of the drug vs. years of dialysis in aHUS.
- We need a societal reckoning to reassess clinical utility, what is valued, and how healthcare dollars are spent, with an example provided of cancer medications that only extend a person's life by a few weeks.
- A well-organized Canadian clinical trial platform needs to be developed.
  - The current landscape makes it difficult to build the preapproval process and recruit patients for trials that can be used to support filings through Health Canada and health technology assessment bodies.
  - Some therapies are not available in Canada because the trials have been unable to run here.
  - We are no longer able to rely on National Institute of Health studies in the US as new rules specify that trial participants must live within the United States, which led to cancellation of several pediatric oncology studies in Canada.

If we reconvene in 10 years, what do you expect to be the biggest breakthrough?

- Better access for medications, with global coverage – getting the right drug to the right patient and getting them paid for.
- More modulation towards homeostasis leading to improvement in conditions that simply require inhibition.
- Bedside testing of biomarkers to allow for rapid assessment and intervention.
- Other avenues are necessary: the inability to access the drugs is used as an excuse to "not think about the disease, not advocate for access to the drugs, and give up before we even start."