Day in Complement 2025

McMaster University | Health Sciences Continuing Professional Development

THE CANADIAN HEMATOLOGY SOCIETY
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Complement pathologies – when regulation fails

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JOHNS HOPKINS MEDICINE

CONFLICTS OF INTEREST

- **Relationships with for-profit and not-for-profit interests:**
  - **Financial Payments/Honoraria:** Takeda, Alexion, Novartis, Star Pharma, Sanofi
  - **Advisory Board:** Sobi, Takeda, Sanofi, Alexion, Novartis
  - **Grants, Research or Clinical Trials:** Sanofi, Sobi, Takeda, Novartis
  - **Other: (including employment)**
    - **Royalties:** UpToDate.com
    - **Membership on Board of Directors:** Hemostasis and Thrombosis Research Society, US TMA Consortium

LEARNING OBJECTIVES

At the end of this presentation learners will be able to:

1. **Understand why and how complement fails**
2. **Describe the consequences of complement regulation**
3. **Understand the role of complement in blood disorders**

Outline

How does complement regulation fail?

What are the consequences of complement dysregulation?

Complement dysregulation in hematologic disorders

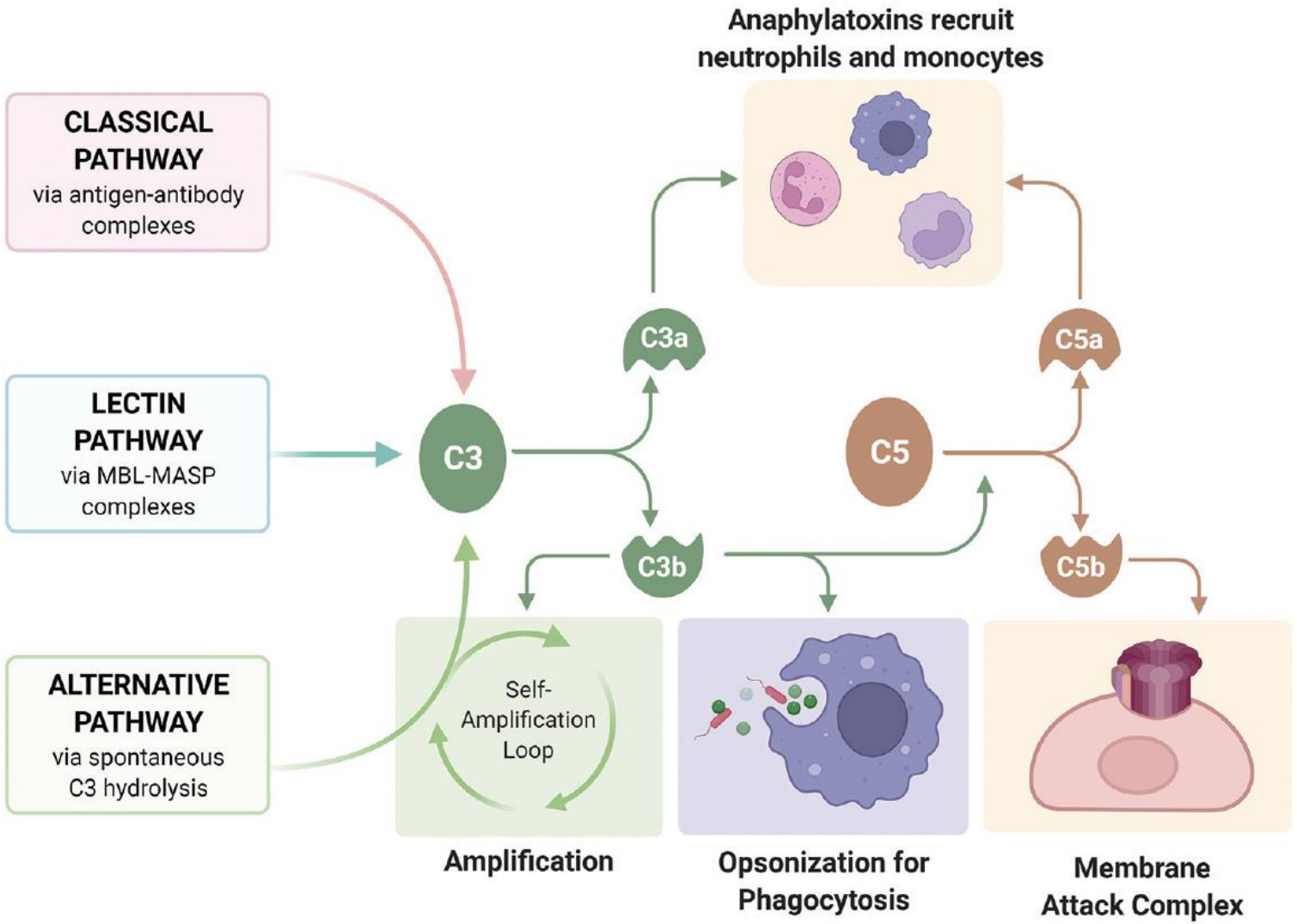
What you already know

- Complement is a part of the innate immune system

- Three major functions
  - Identify and ‘tag’ foreign materials or damaged self materials
  - Eliminate these targets (phagocytosis, direct lysis by MAC)
  - Promote inflammatory and immune responses

- Tightly regulated system

What you already know



Outline

How does complement regulation fail?

What are the consequences of complement dysregulation?

Complement dysregulation in hematologic disorders

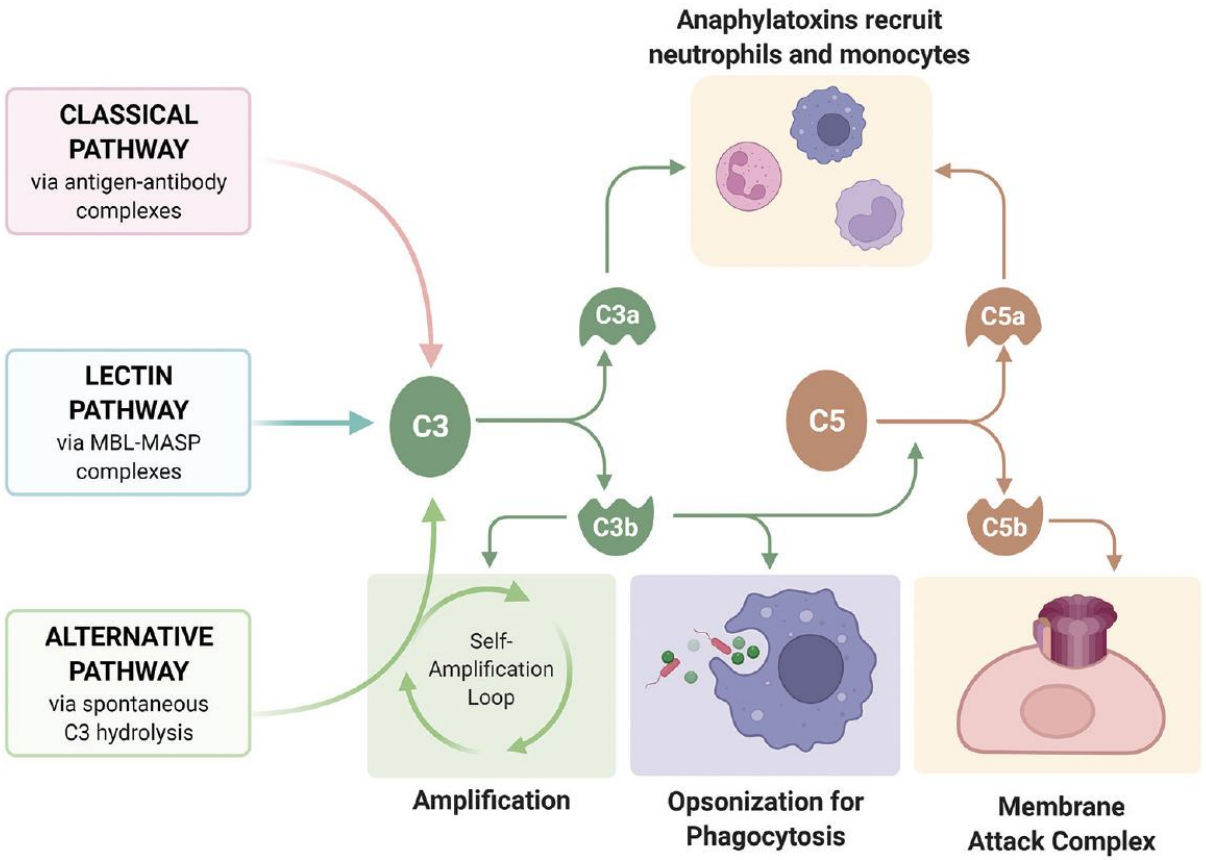
How does complement regulation fail ?

Too much stimulation

Ag – Ab complexes (↑antibodies)

Infection

Inflammation
Free heme
Coagulation / endothelial injury



Failure of (down)regulation

Mutations in complement regulation genes (aHUS, macular degeneration)

Acquired loss of regulators (PNH)

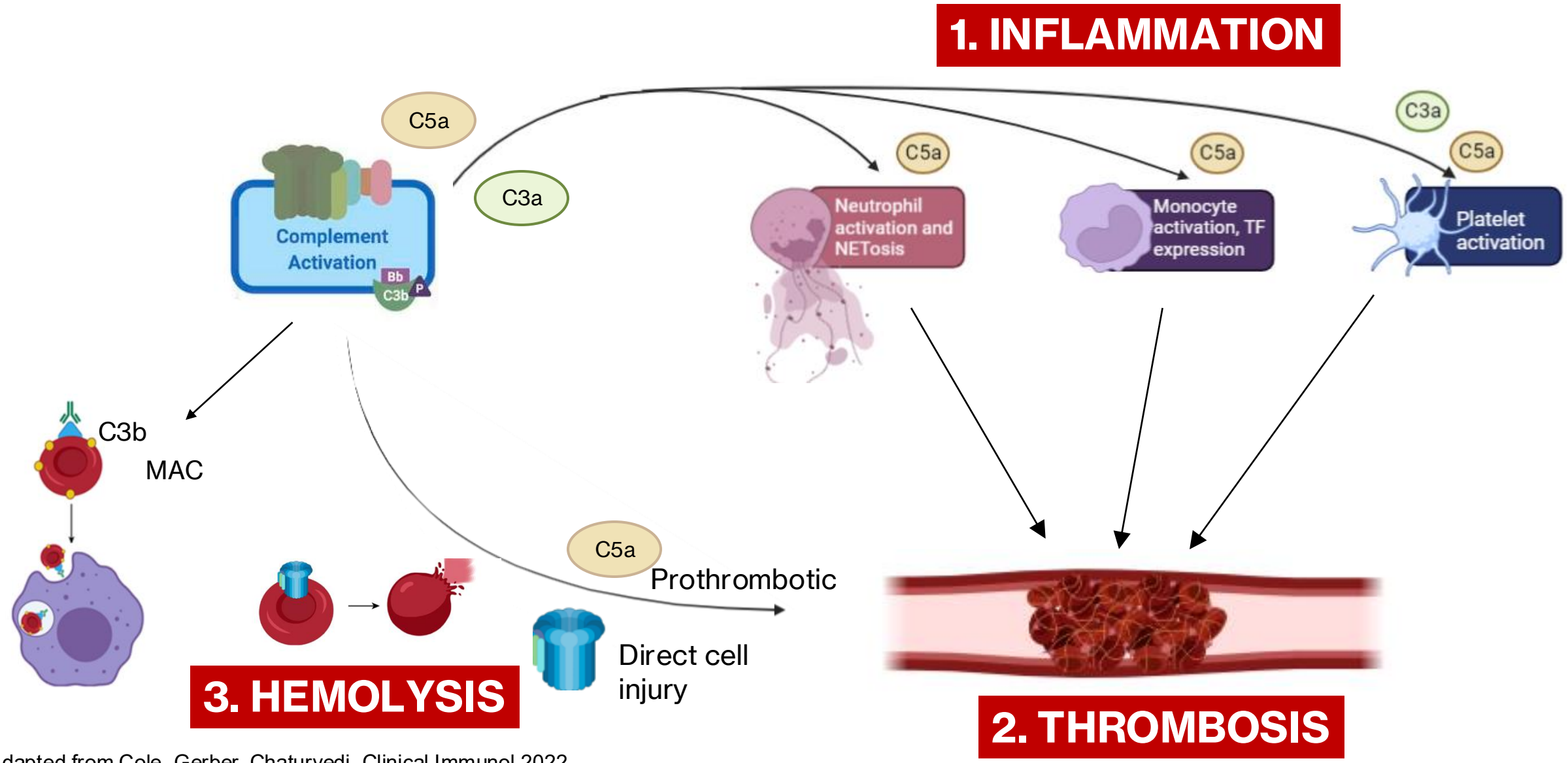
Outline

How does complement regulation fail?

Consequences of complement dysregulation?

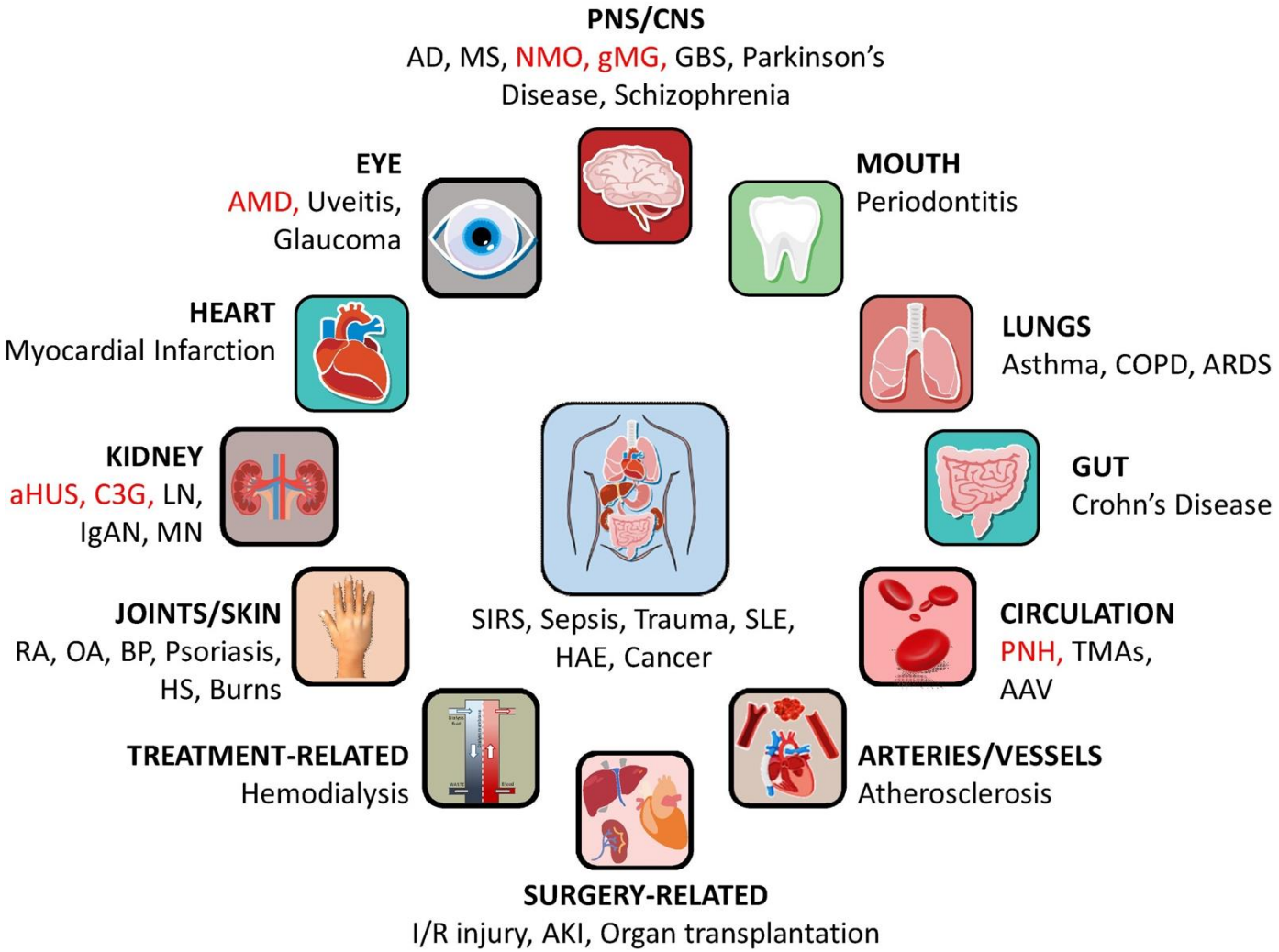
Complement dysregulation in hematologic disorders

Effects of complement (over)-activation



Adapted from Cole, Gerber, Chaturvedi. Clinical Immunol 2022

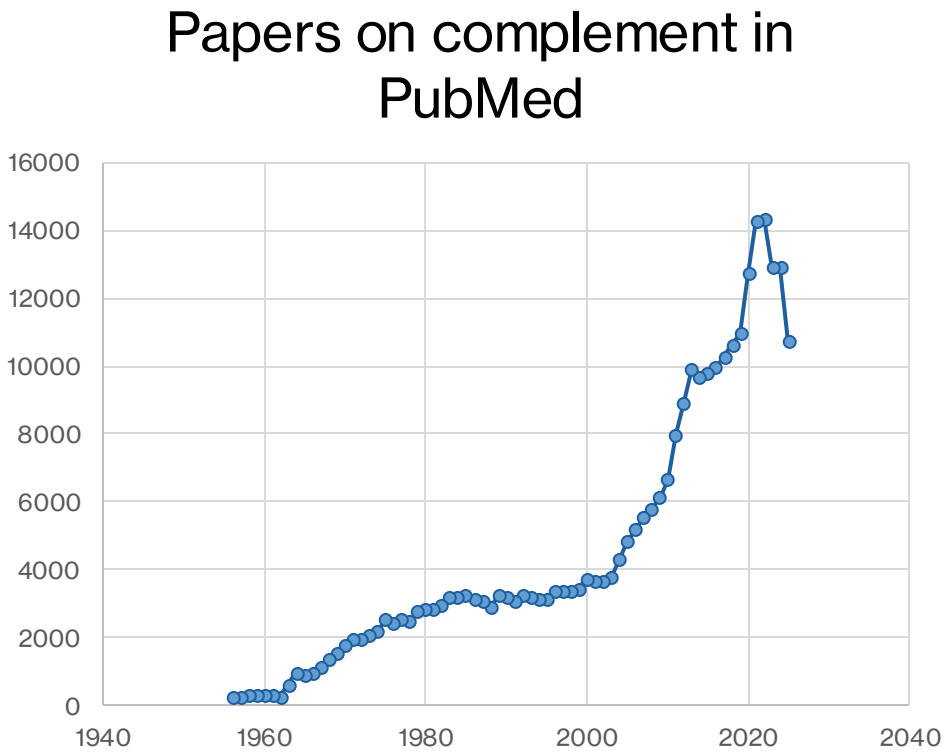
Complement contributes to pathogenesis of several disorders (inflammation is key)



ITP
Antiphospholipid syndrome
COVID-19
Vascular disease (atherosclerosis)
Sickle cell disease

Zelek et al. Mol immunology 2019

Why do we care?



We have drugs.

Outline

How does complement regulation fail?

Consequences of complement dysregulation?

Complement dysregulation in hematologic disorders

Complement disorders in hematology

Genetic

Immune

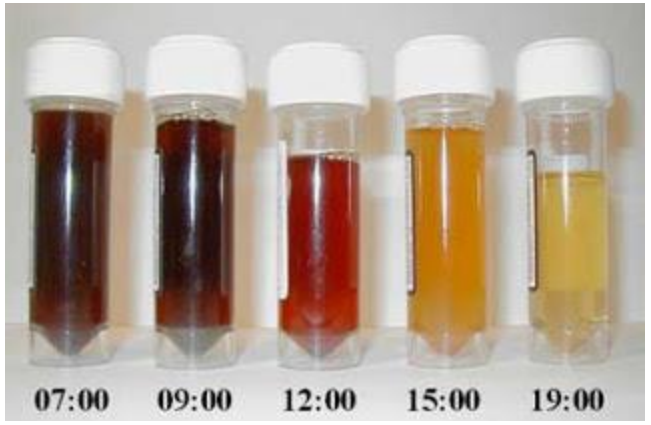
Disorder	Mechanism of complement activation
Paroxysmal nocturnal hemoglobinuria	Acquired, clonal loss of complement regulators
Atypical HUS or complement mediated TMA (CM-TMA)	Genetic loss of complement regulation
Cold Agglutinin disease	Immune complexes
Antiphospholipid syndrome	Immune complexes
Immune thrombocytopenia	Immune complexes
Sickle cell disease	Free heme, thromboinflammation

Environmental factors

Paroxysmal nocturnal hemoglobinuria (PNH)

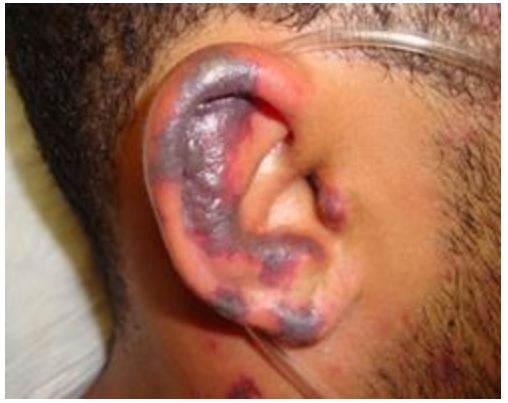
- Acquired clonal stem cell disorder
- Somatic *PIGA* mutation – loss of GPI anchor – cells don't express surface complement regulators (CD55 and CD59)
- Thrombosis rate 29- 44%: leading cause of death

HEMOLYSIS



Medscape

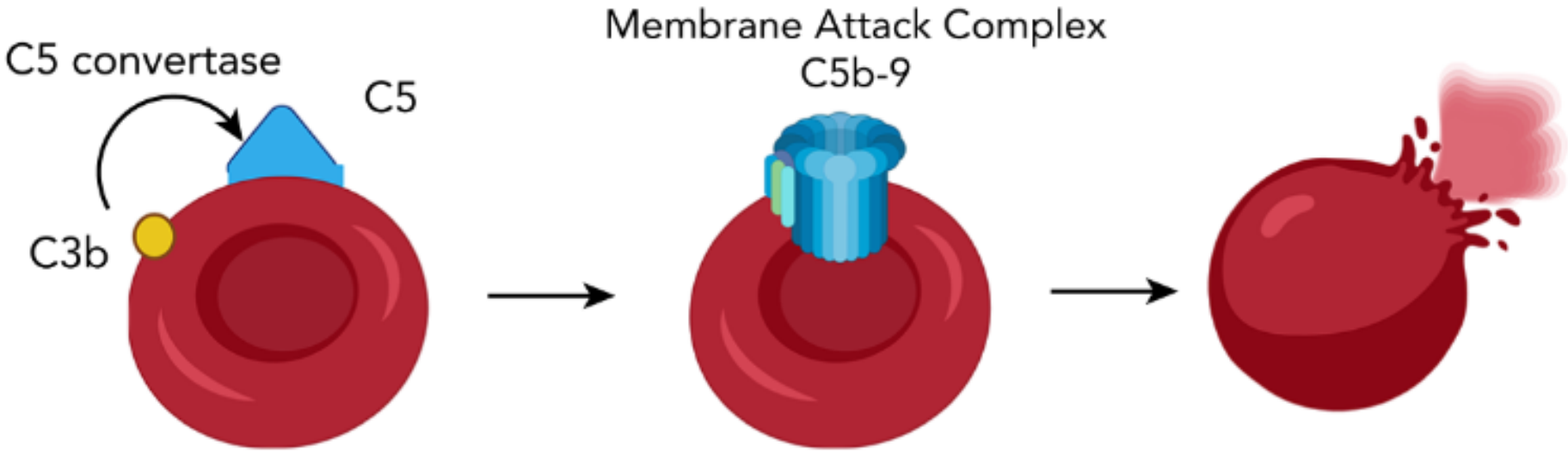
THROMBOSIS



Courtesy R. Brodsy

PNH –mechanisms of hemolysis

- PIGA mutation : Loss of CD55 and CD59 on cell surface
- RBC are susceptible to complement mediated hemolysis



Brodsky RA. Blood 2021

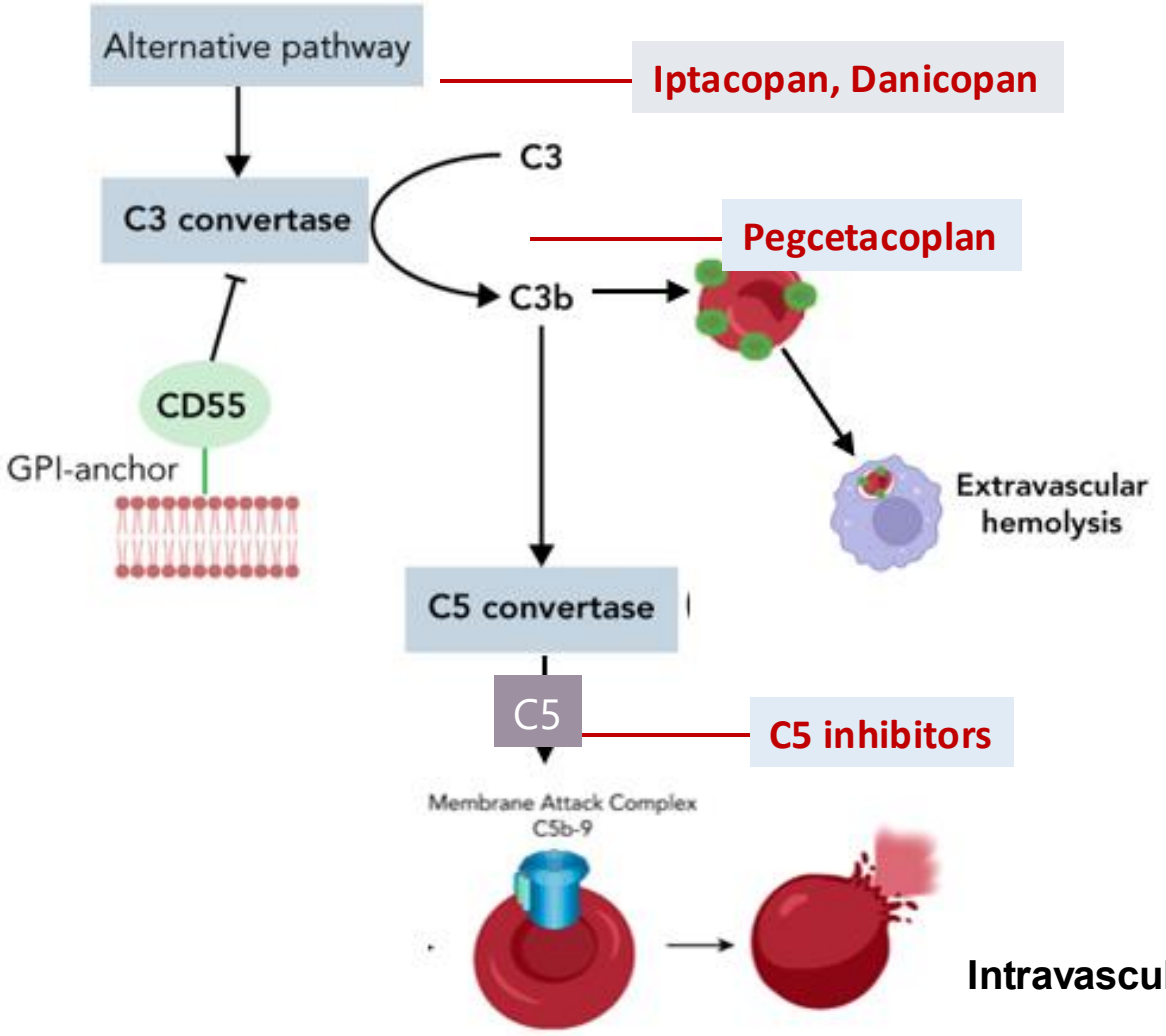
C5 Inhibitors: Eculizumab and Ravulizumab

- Reduce (>90%) or eliminate (~70-75%) need for red cell transfusions
- Reduce risk of thrombosis by >90%
- Improved quality of life
- Mortality comparable to age-matched controls

Study	Pilot	TRIUMPH	SHEPHERD	Extension
N	9	23	51	103
TE rate before ecu*	8.83	12.74	15.46	10.61
TE rate after ecu*	0	0	0	0.62
*Thromboembolism rate per 100 patient years				

QoL = quality of life; RBC, red blood cell.
Hillmen P, et al. *Br J Haematol*. 2013; Hillmen et al. Blood 2007 ; Brodsky RA. *Blood*. 2021;137(10):1304-1309.

Proximal inhibitors target both intravascular and extravascular hemolysis



C3 fragments on RBC act as opsonins -→ breakthrough hemolysis on C5 inhibitors

Complement-mediated TMA - a genetic disease

Gene	Protein affected	Frequency
CFH	Factor H	20-30%
CFHR1/3	Factor H R1/R3	6%
CFI	Factor I	4-10%
CFB	Factor B	1-2%
MCP	Membrane cofactor protein	10-15%
C3	Complement C3	5-10%
THBD	Thrombomodulin	5%

- Mostly genes of the alternative pathway

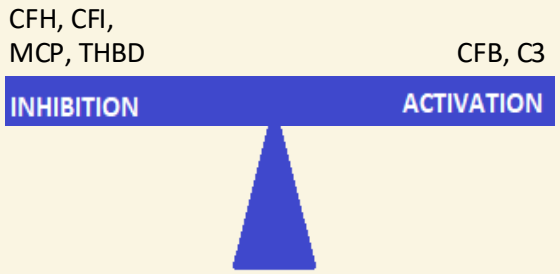
Complement mutations are not necessary or sufficient for CM-TMA)

- 30-50% do not have an identifiable mutation
- Penetrance is only 20%

Noris M, Remuzzi G. N Engl J Med. 2009 Oct 22;361(17):1676-87.

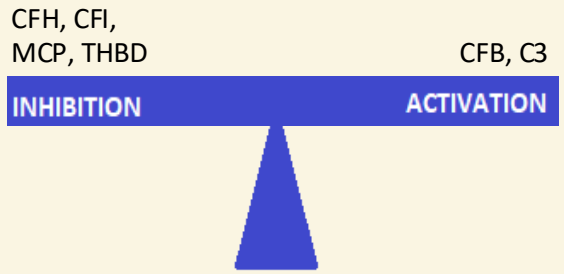
CM-TMA Pathogenesis

NORMAL

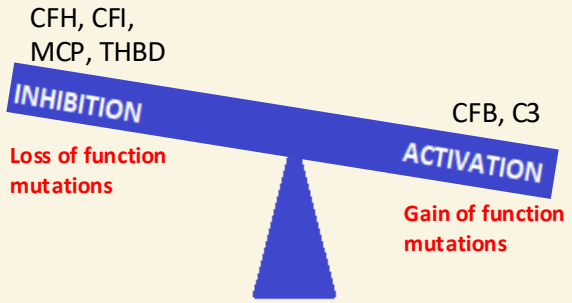


CM-TMA Pathogenesis

NORMAL



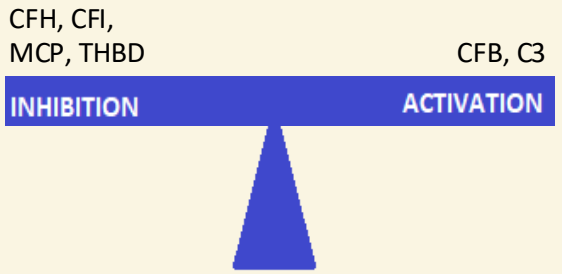
AT RISK FOR aHUS



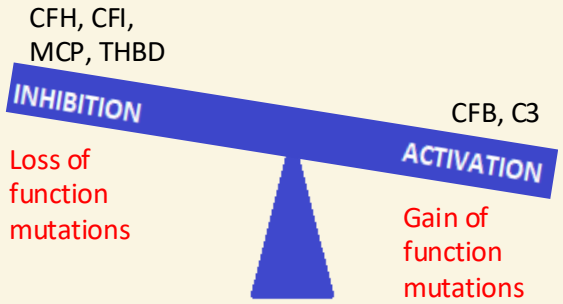
CM-TMA Pathogenesis

Trigger
Inflammation
Surgery
Pregnancy
Autoimmunity

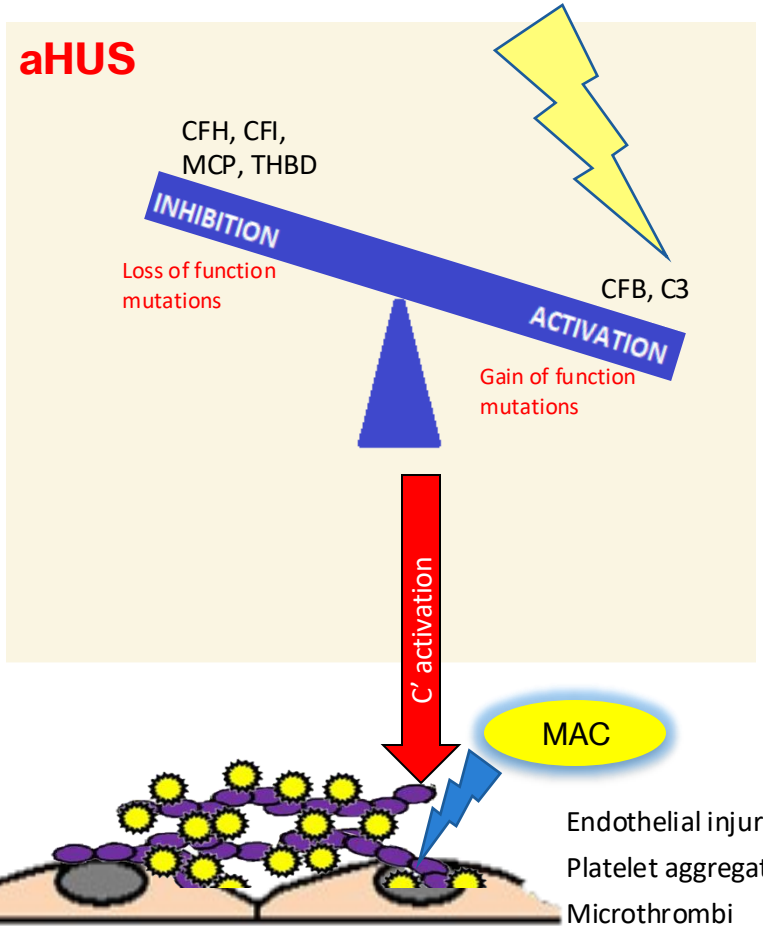
NORMAL



AT RISK FOR aHUS

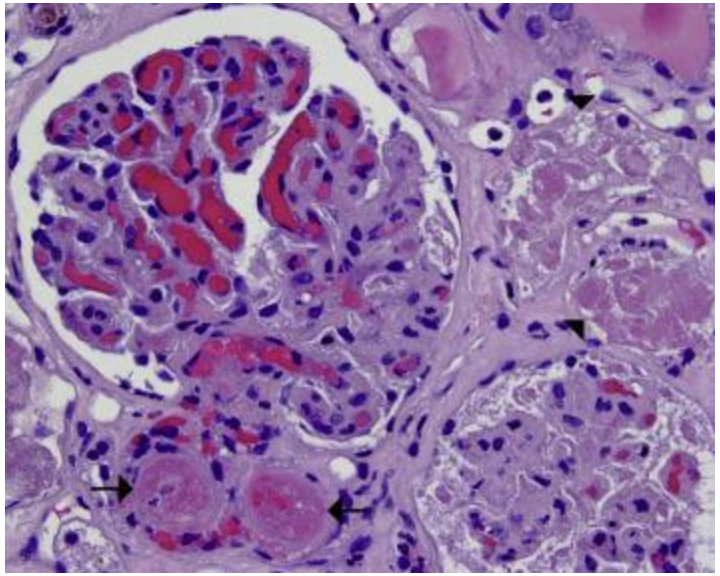


aHUS



CM-TMA is a two-hit disease
Mutations are risk factors, trigger needed

Atypical HUS – pleomorphic manifestations



RENAL
AKI
50-75% need acute dialysis

Pulm
Dyspnea
Pulmonary edema
Alveolar h'ge

GI
Diarrhea,
Colitis
GI bleeding
Transaminitis
Pancreatitis

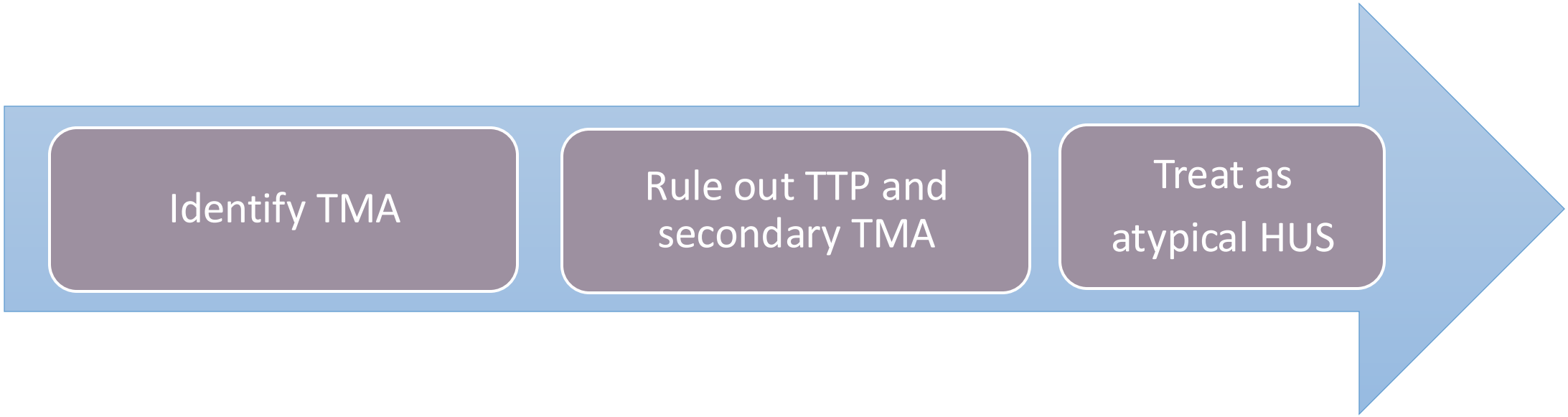
CV
Malignant HTN
MI
Peripheral ischemia
Cardiomyopathy

CNS
Stroke
Seizures
Vision problems
Confusion
Headache

Heme
MAHA
Schistocytes
VTE

Noris M, et al. Clin J Am Soc Nephrol. 2010;5(10):1844-59

aHUS is (mostly) a diagnosis of exclusion



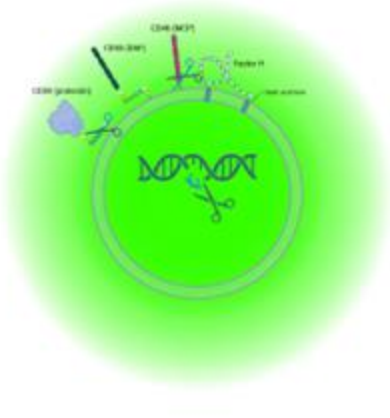
Most types of complement testing cannot establish aHUS diagnosis

- Serology for complement proteins (e.g. C3, C5, soluble C5b-9, factor H and I) have low sensitivity and specificity for aHUS
- Genetics – negative in 50%; testing helps to inform recurrence risk and counsel relatives

Fakhouri et al. Blood 2023

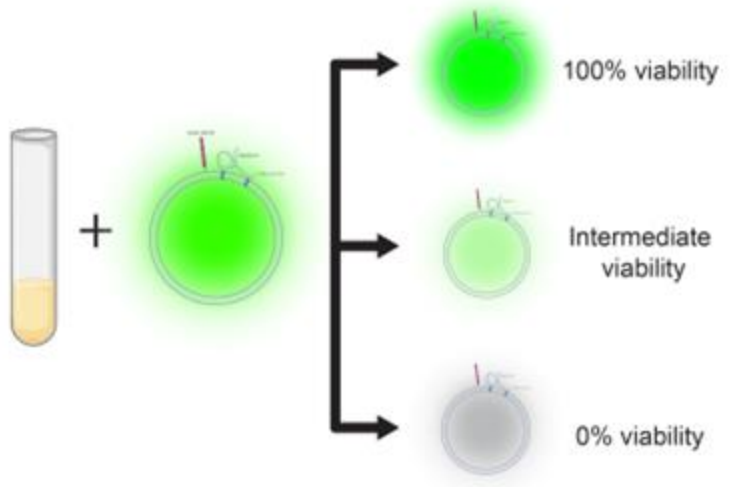
Modified Ham 2.0 – aHUS can be a diagnosis of inclusion

Principle: Cell line lacking complement regulators (e.g. CD55, CD59) is susceptible to complement mediated killing.



. Genetic engineering of autonomously bioluminescent cell line.

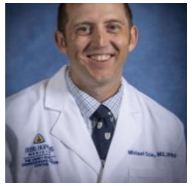
PIGA knock out
CD46 knock out
Double knock out



. Incubate complement biosensors with serum of healthy controls or CM-HUS samples and measure luminescence continuously. Exact metabolic/viability effect dependent upon both the surface as well as the serum.

Available for clinical testing 24 hour turn around time in the US

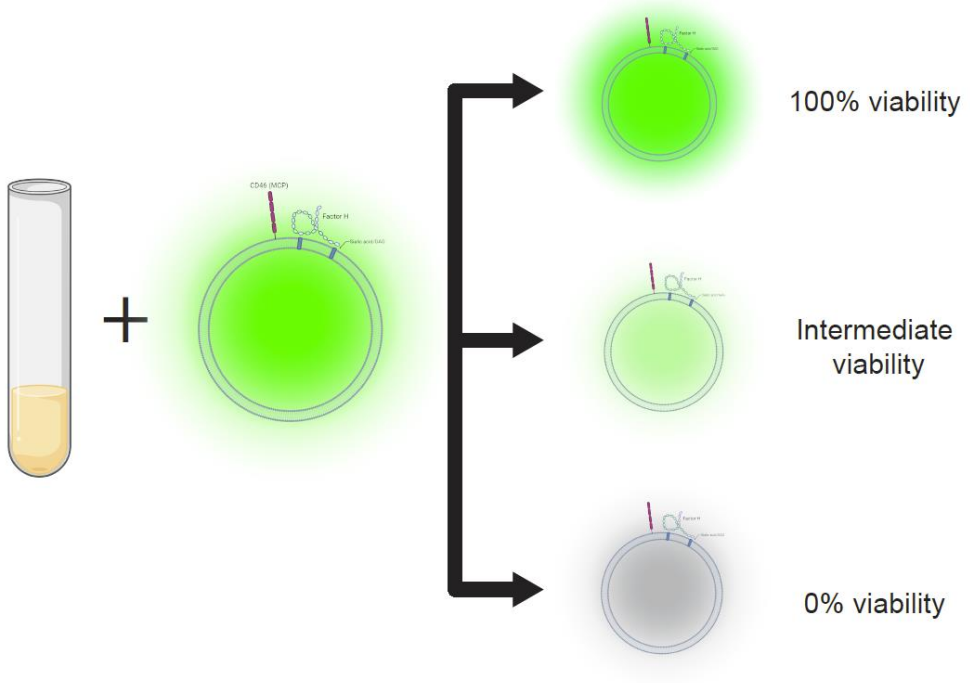
Mham.machaondiagnostics.com



Michael Cole

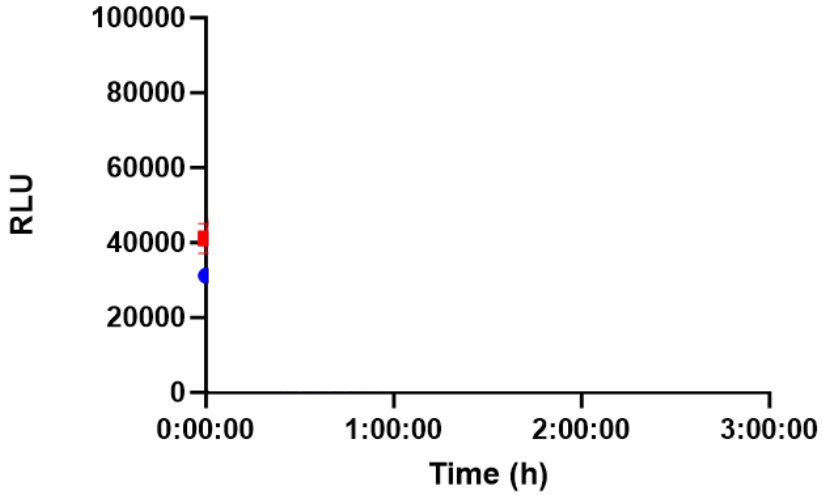
Cole MA et al. Blood 2024

Design of complement biosensors: mHam 2.0



3. Incubate complement biosensors with serum of healthy controls or CM-HUS samples and measure luminescence continuously. Exact metabolic/viability effect dependent upon both the surface as well as the serum.

Representative output



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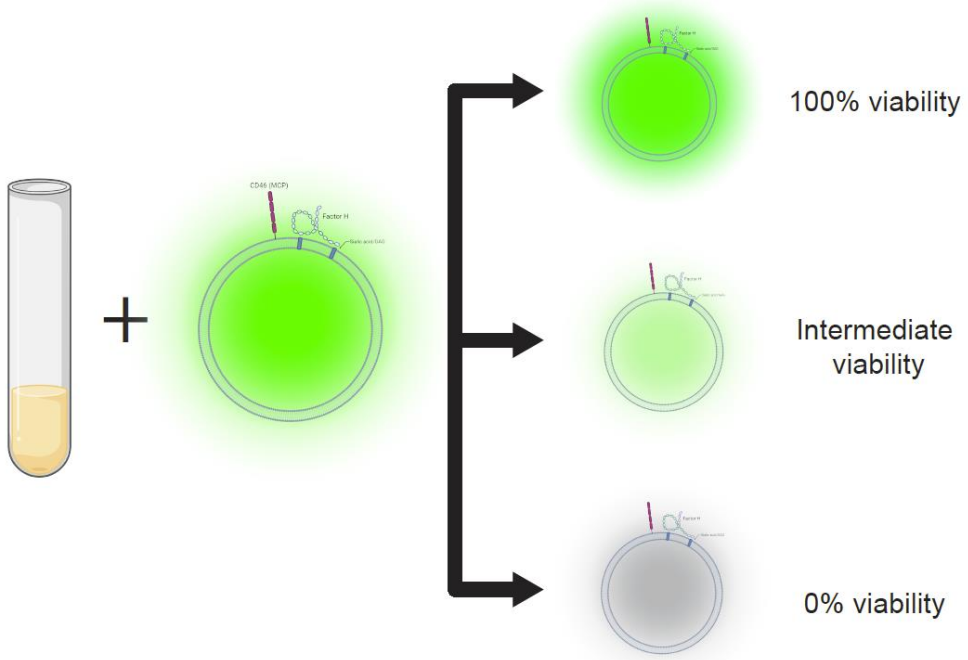

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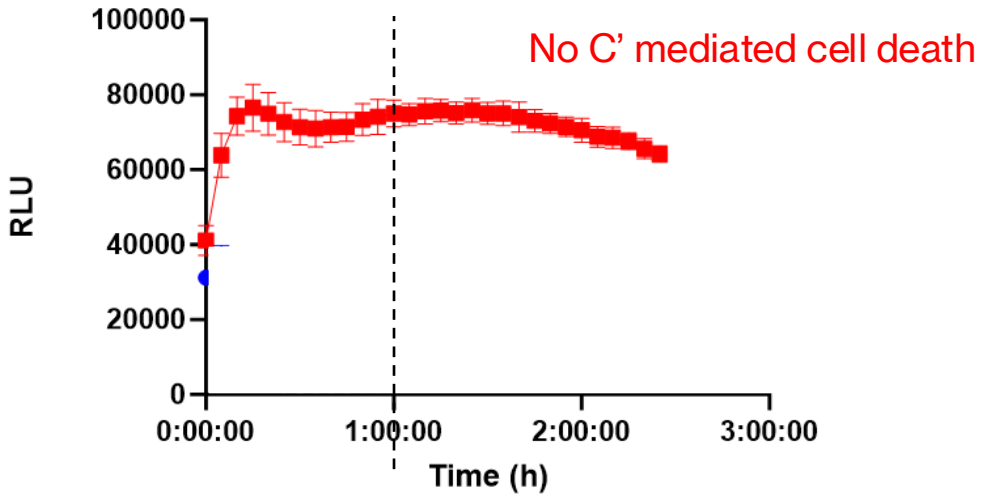
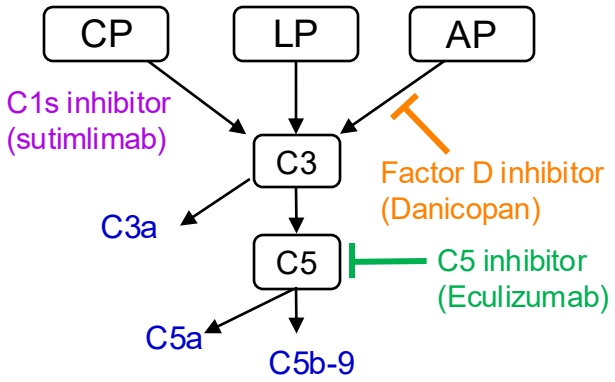
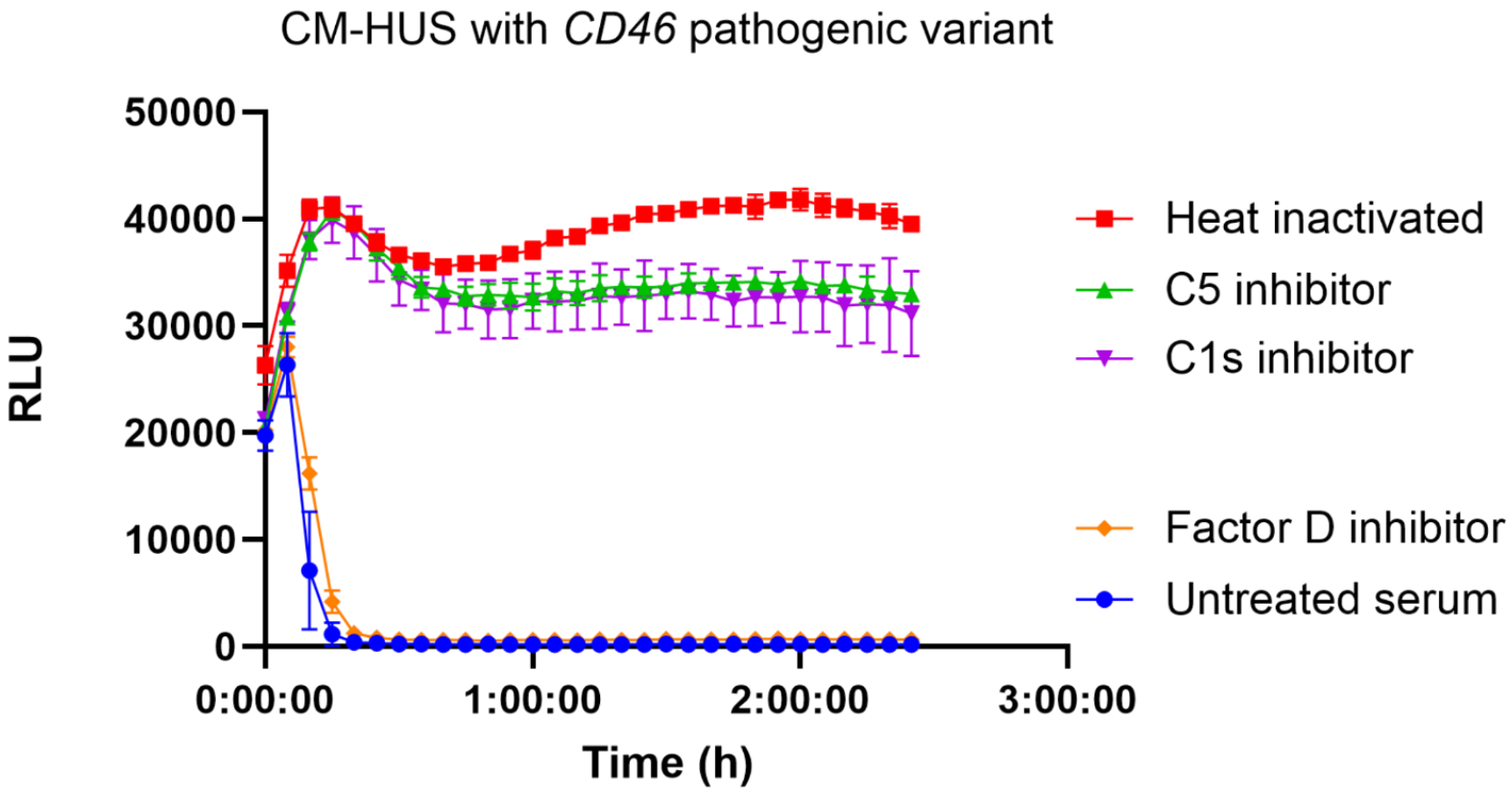


CM-TMA is a ~~alternative~~ classical pathway disease

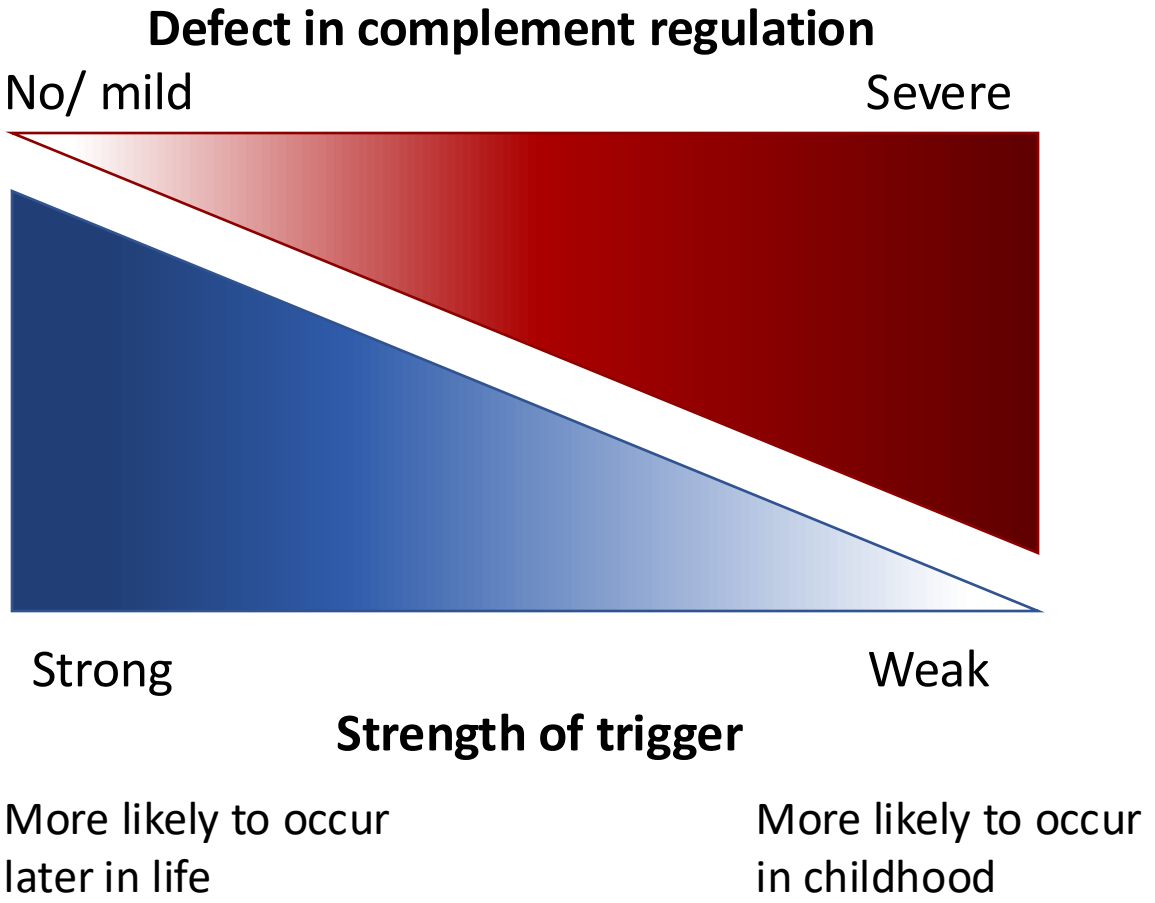




Cole MA et al. Blood 2024

What explains aHUS without mutations?

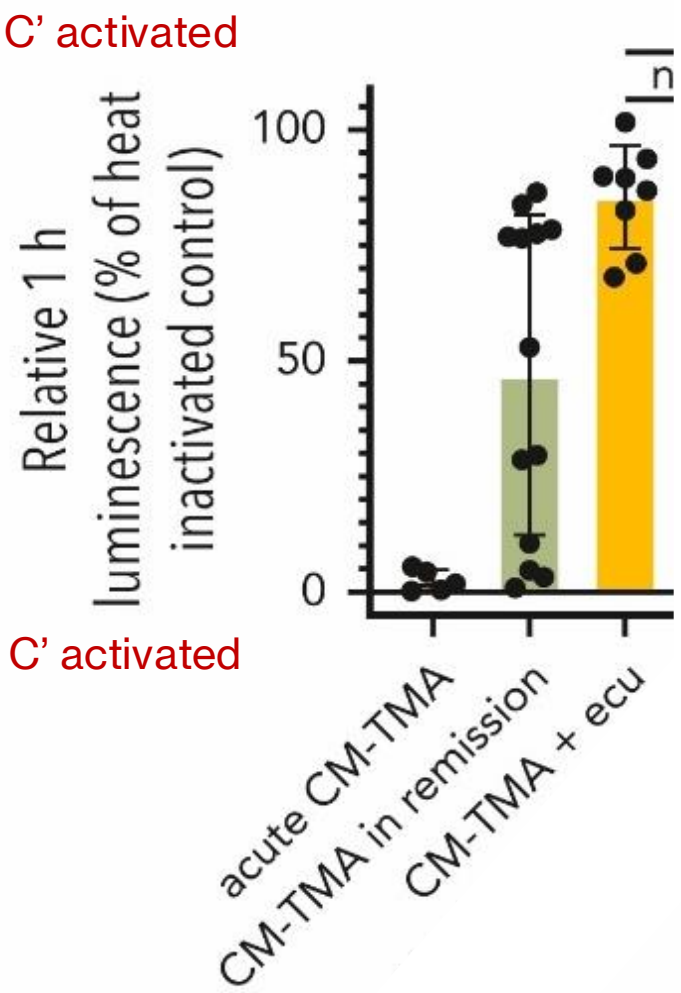
- Mutations are aHUS ‘predisposing’ rather than ‘causing’ (need trigger)
  - Some mutations are more severe than others (think CFH, C3, CFB)
- Strong enough trigger, don’t need mutation



Adapted from Ardissino et al. Kidney Int Rep 2021, Bresin et al. JASN 2013

What explains aHUS without mutations?

Less C' activated



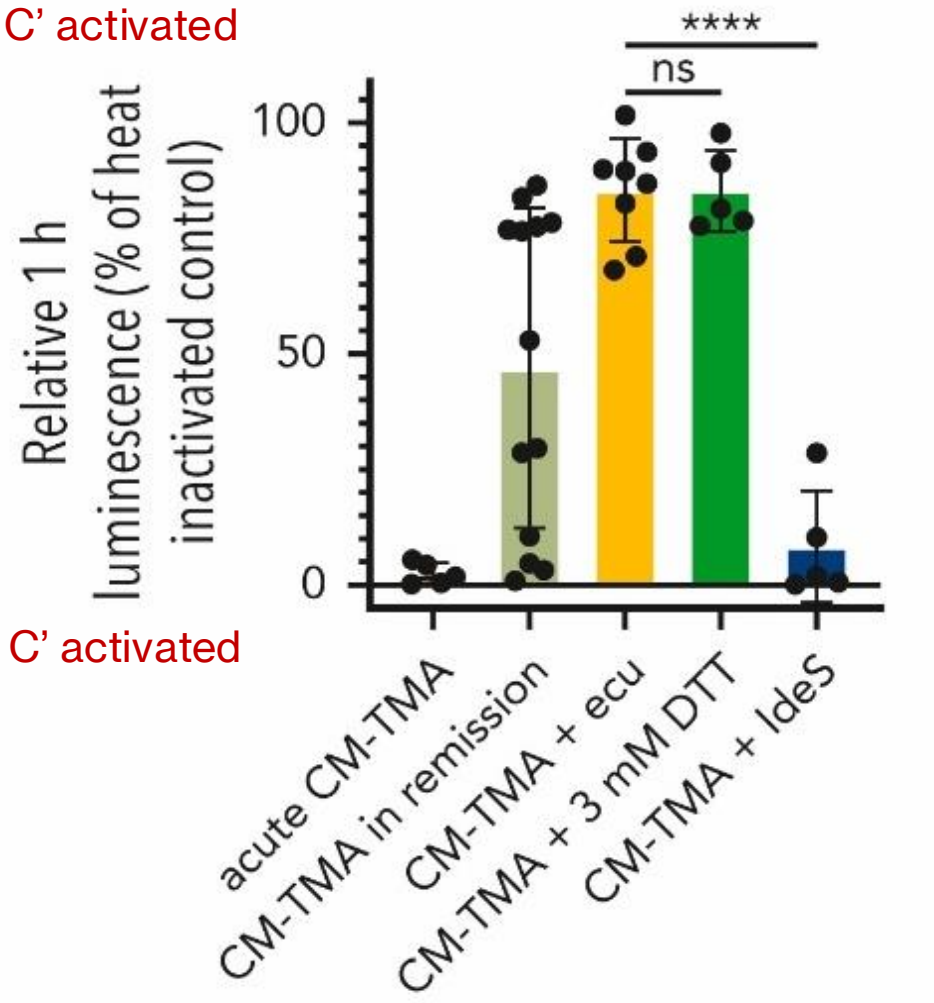
More C' activated

- Classical pathway – antibody triggered, IgG or IgM ???
- Depleted IgG (using IdeS) or IgM (DTT)

Cole MA et al. Blood 2024

What explains aHUS without mutations?

Less C' activated



More C' activated

- Classical pathway – antibody triggered, IgG or IgM ???
- Depleted IgG (using IdeS) or IgM (DTT)
- Depleting IgM blocks complement activation
- Depleting IgG does not block complement activation
- IgM activates complement in aHUS

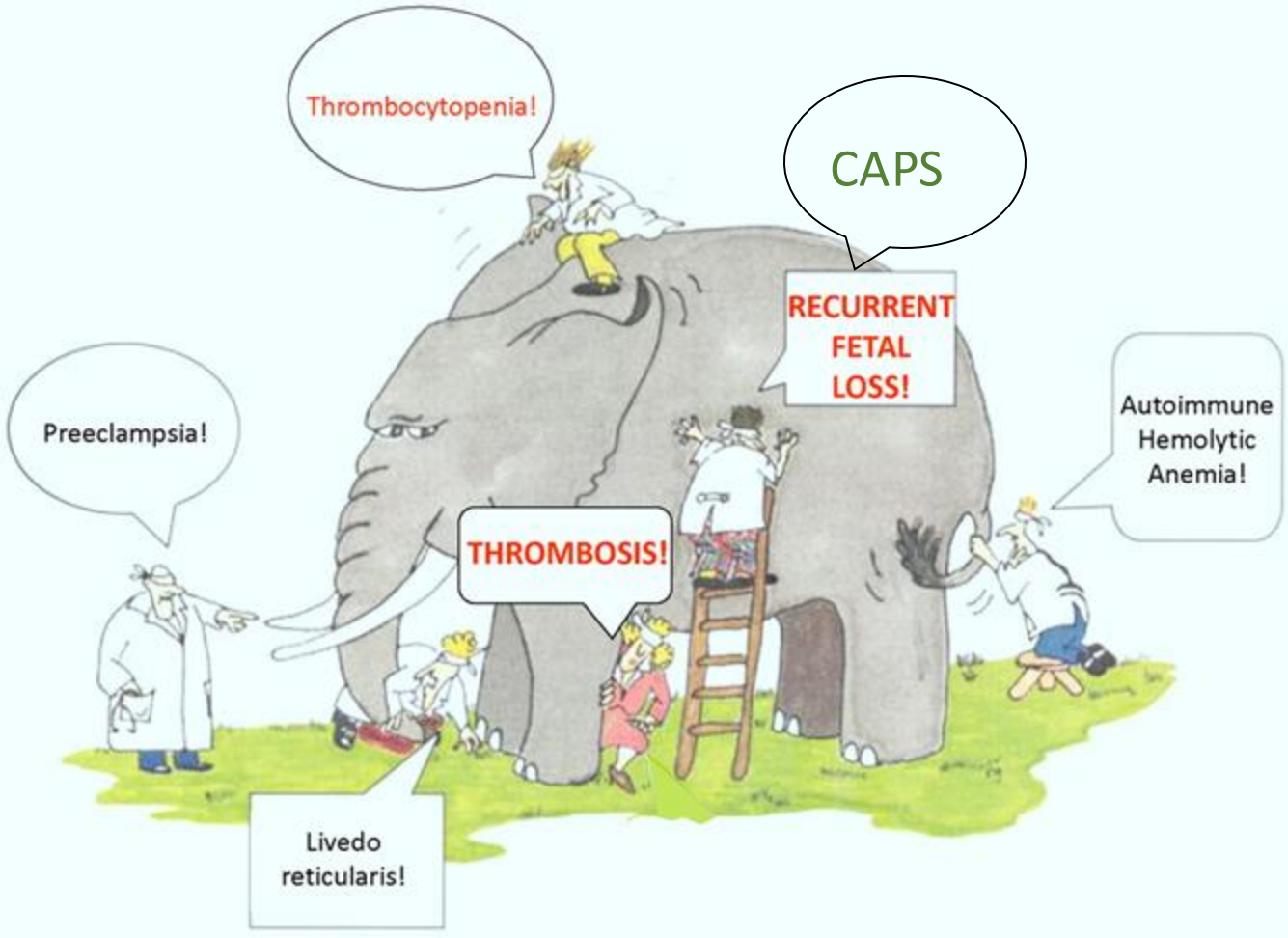
Cole MA et al. Blood 2024

Treatment options for aHUS

Historical	Plasma exchange – Older reports suggested benefit in aHUS. No clinical trials and does not appear to benefit long term.
Current standard of care	**Eculizumab and Ravulizumab** - Terminal complement blocking drugs (anti-C5) - Very effective:Risk of end stage renal disease at 1-2 years reduced to 6-15% (from 50%)
Future	New complement inhibitors are being developed Crovalimab (NCT04958265) – C5 (terminal parthway) Iptacopan (NCT04889430) – factor B (alternative pathway) Others....

Antiphospholipid syndrome (APS)

Systemic **autoimmune** disorder characterized by arterial or venous **thrombosis and/or pregnancy morbidity** accompanied by persistently **positive antiphospholipid antibody tests**



McCrae KR. Blood 2010

Long-term anticoagulation with standard intensity warfarin is the standard of care for thrombotic APS

- Some retrospective studies suggest high thrombosis even on anticoagulation
  - Not seen in randomized trials in APS
  - From specialized centers, selection bias (10-60%)

There is a small and clinically challenging proportion of anticoagulation refractory patients (? prevalence)

Crowther et al. NEJM 2003, Finazzi et al. J Thromb Haemost 2005

Garcia et al. Blood 2013, Rosove et al. Ann Int Med 1992, Ruiz Irastorza et al. Arch Int Med 2002

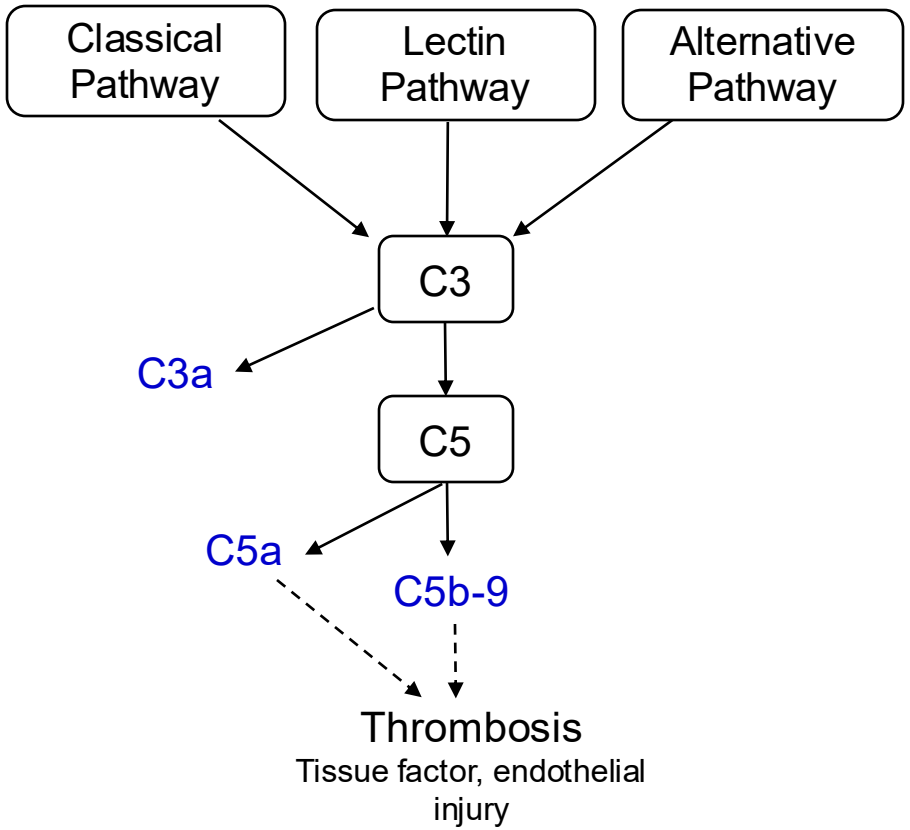
Refractory and catastrophic APS

- **Anticoagulant refractory APS**
  - Small but clinically meaningful proportion of patients have recurrent thrombosis despite anticoagulation
  - Microvascular forms of APS

- **Catastrophic APS**
  - Rapidly developing widespread thrombosis with multiorgan failure
  - Often ‘triggered’ by surgery, infection, pregnancy/delivery, etc.
  - Rare (<1 % of APS) but carries up to 30-50% mortality

Cervera, et al Arth Rheum 2002, Asherson RA et al. Medicine (Baltimore) 2001 , Asherson et al. Lupus 2003, Garcia et al. Blood 2013, Rosove et al. Ann Int Med 1992, Ruiz Irastorza et al. Arch Int Med 2002

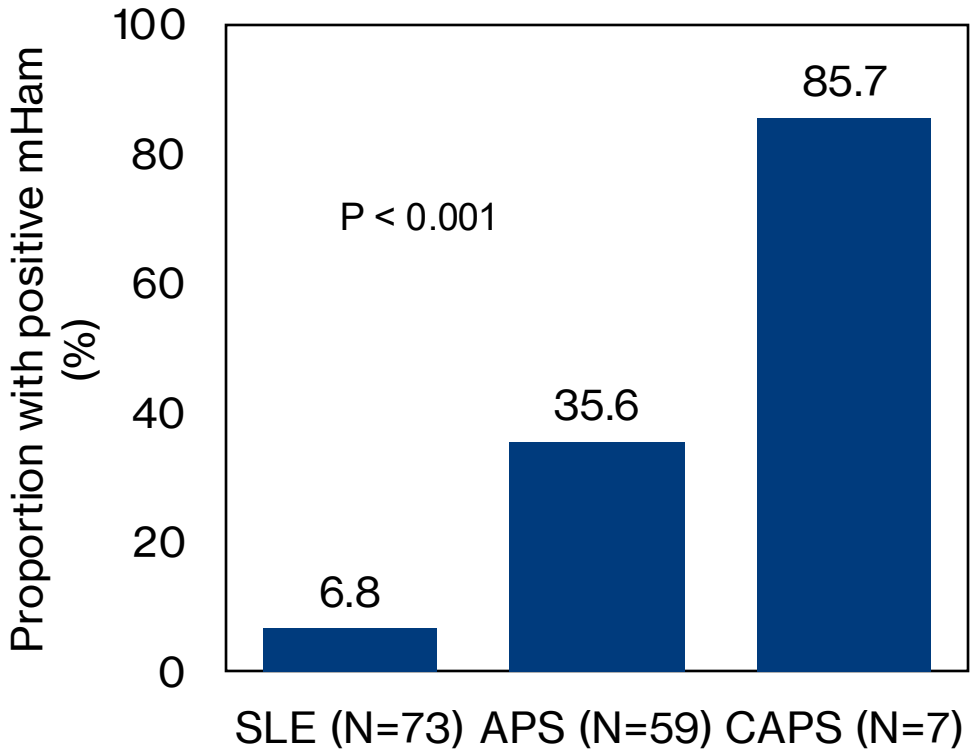
Complement in APS and CAPS



- Complement is critical for aPL-induced thrombosis in mice
- Evidence of complement activation in APS sera
- ~90% of CAPS exhibits complement activation in a functional assay (mHam)
- 50% of CAPS patients have mutations in complement regulation genes
- Anecdotal reports of eculizumab (anti-C5) efficacy in refractory APS and CAPS)

Fischetti et al. Blood 2005, Devreese et al. Thromb Haemost 2010, Oku et al. Ann Rheum Dis 2009, Chaturvedi et al. Front Immunol 2019, Chaturvedi et al. Blood 2020

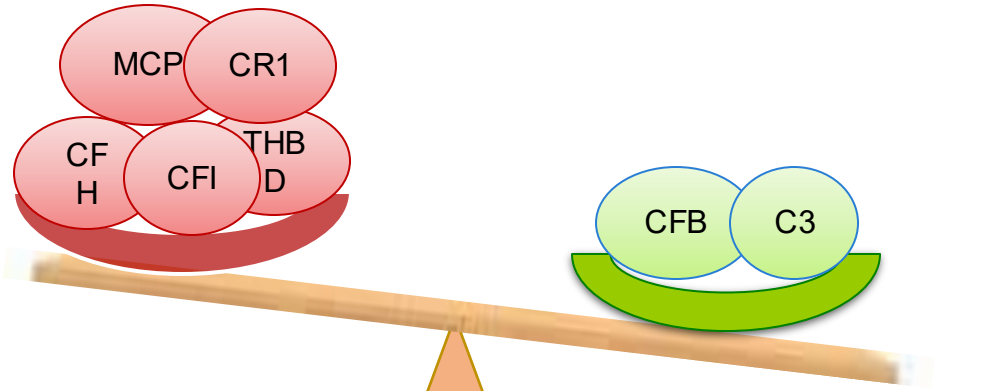
Complement activation in thrombotic APS and CAPS



Complement mutations in CAPS		
Diagnosis	N=171	Rare (MAF < 0.005) germline variants
aHUS	17/33	51.5%
Normal	10/43	23.3%
CAPS	9/19	47.3%
SLE	6/21	28.6%
APS	12/55	21.8%

Chaturvedi et al. Blood 2020

'Multi-hit' model for CAPS



Mutations in complement regulatory genes

+

aPL activate complement

TRIGGER (infection, surgery, pregnancy, etc.)

Thrombosis

APS

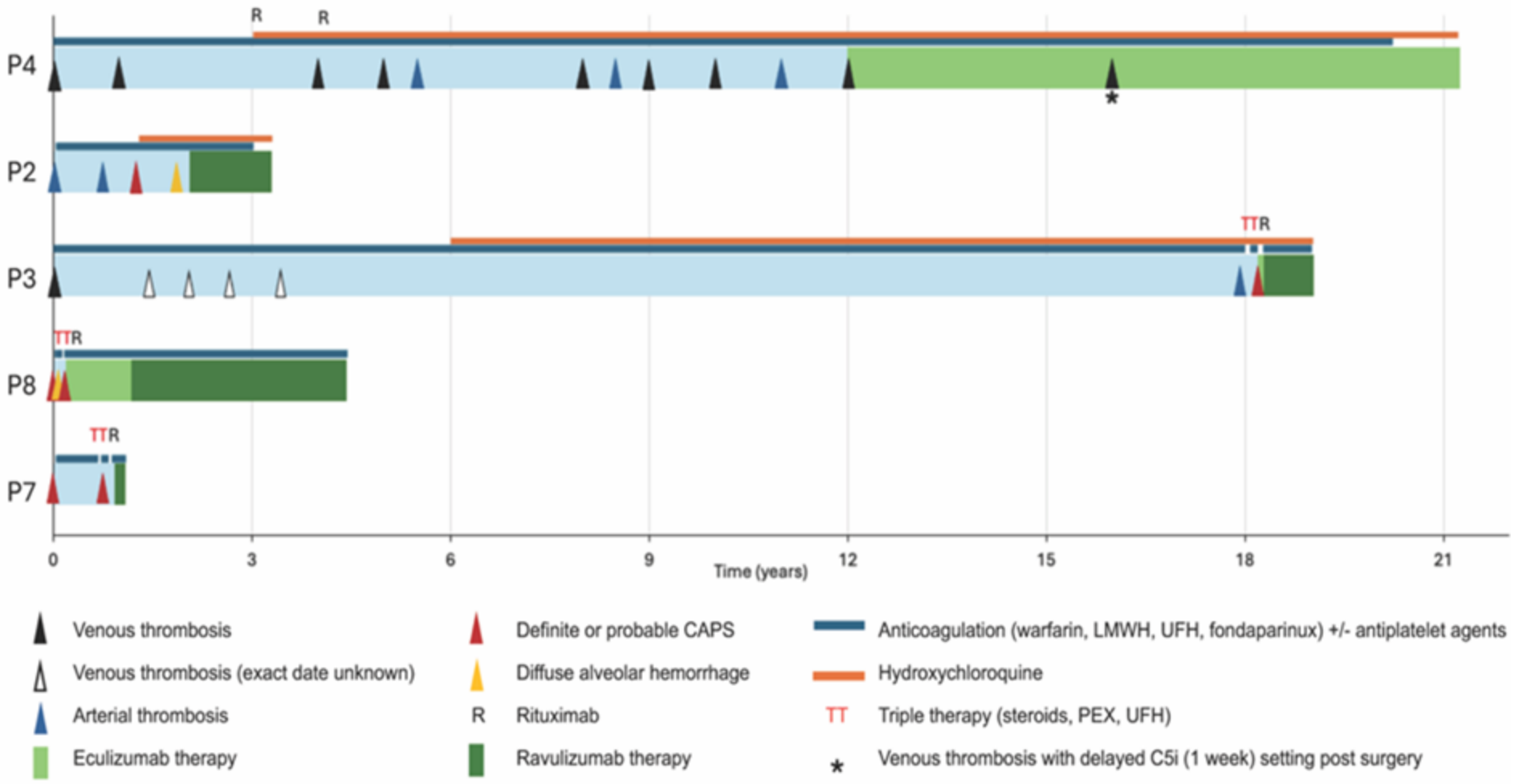
aPL activate complement

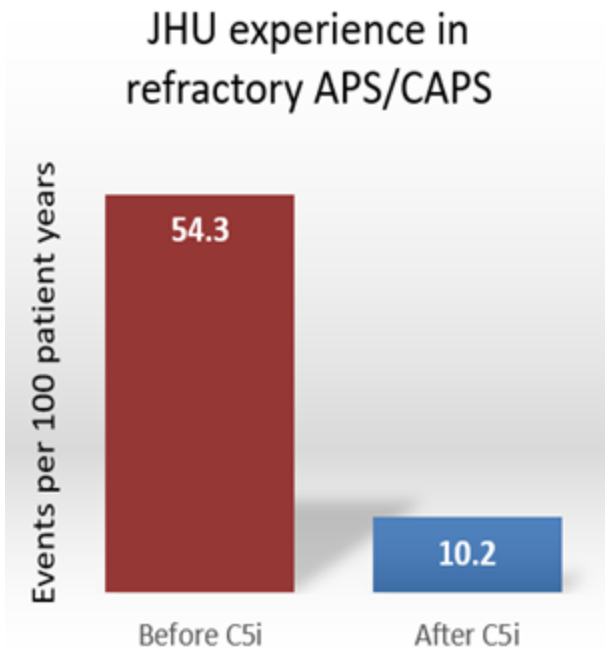
Disseminated thrombosis
Multiorgan failure

CAPS

Chaturvedi et al. Blood 2020

Johns Hopkins experience: C5 inhibition reduces thrombosis in CAPS and refractory APS

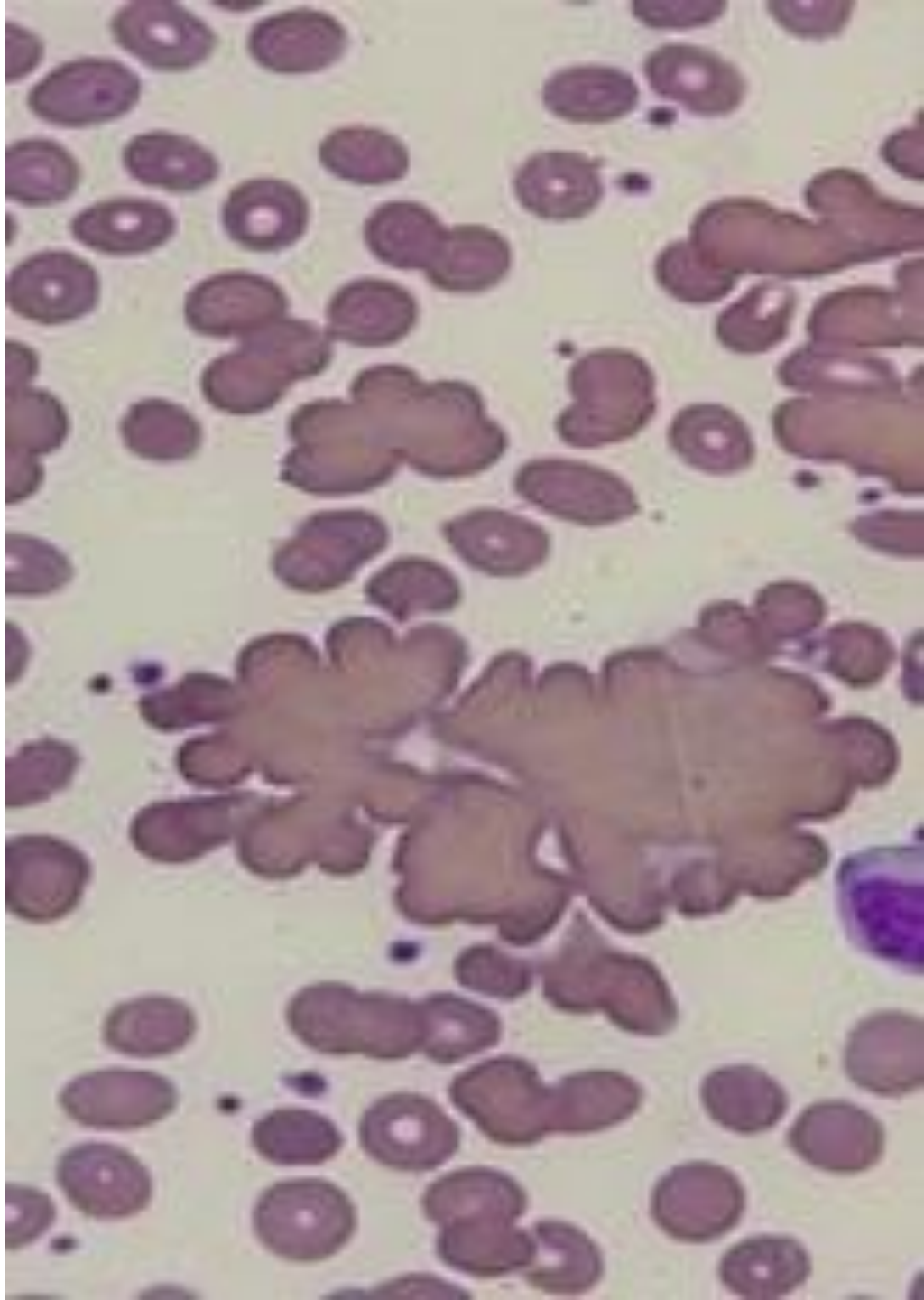




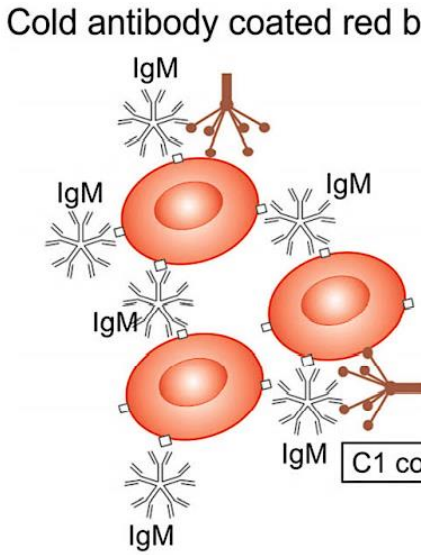
Ranjan N. Arthritis Rheum 2025

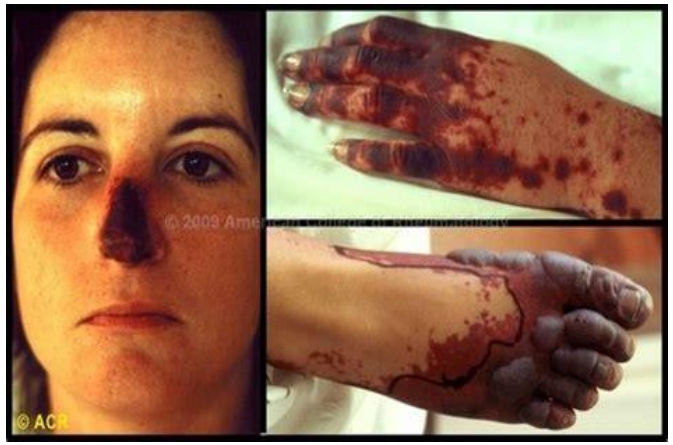
Cold agglutinin disease

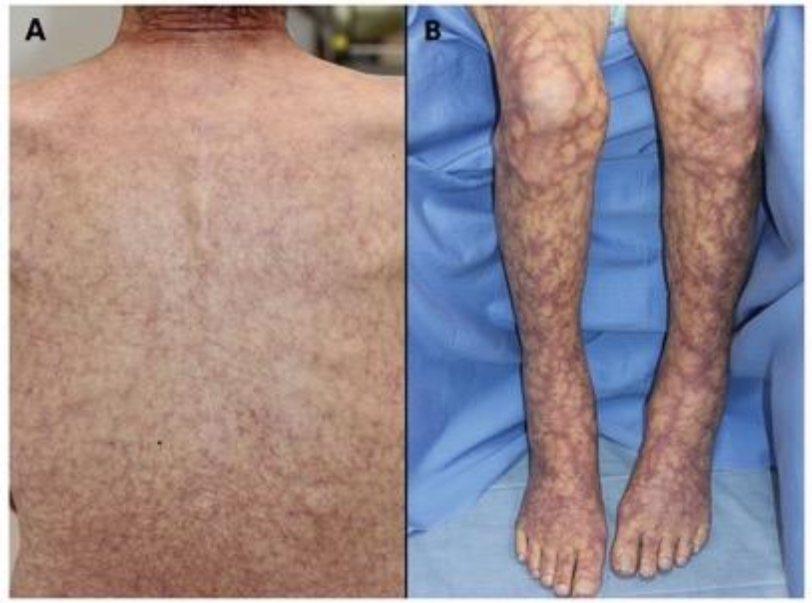
- IgM antibodies against red cells that are reactive at cold temperature.
- Most patients have an underlying B cell lymphoproliferative disorder
- Features
  - Agglutination
  - Circulatory symptoms
  - Hemolytic anemia
  - Thrombosis (26.8%, 62% increased rate)



Aggluination causes circulatory symptoms

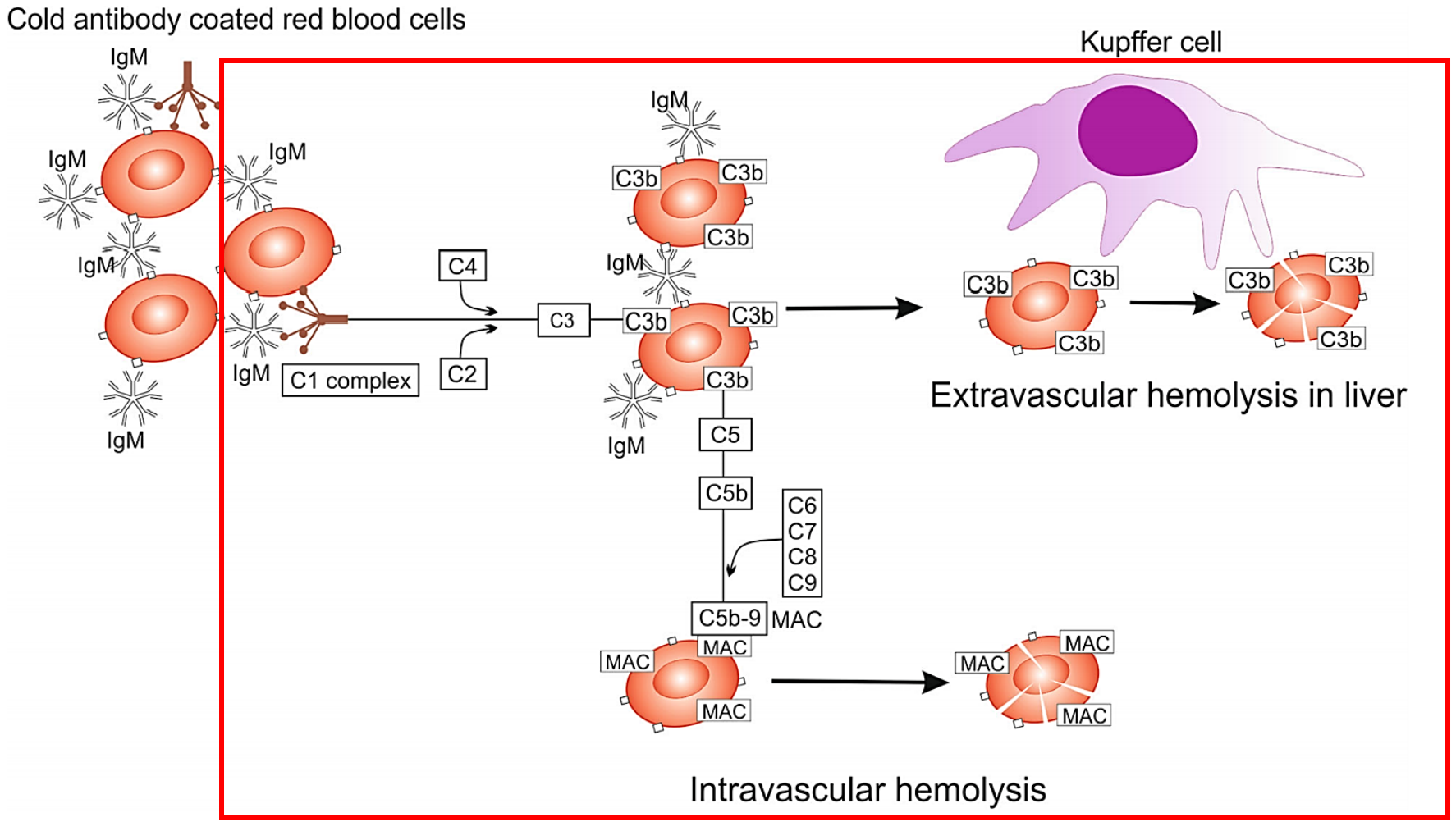






Berentsen, 2018. Shiiya & Ota, 2017.

Complement causes hemolysis in CAD



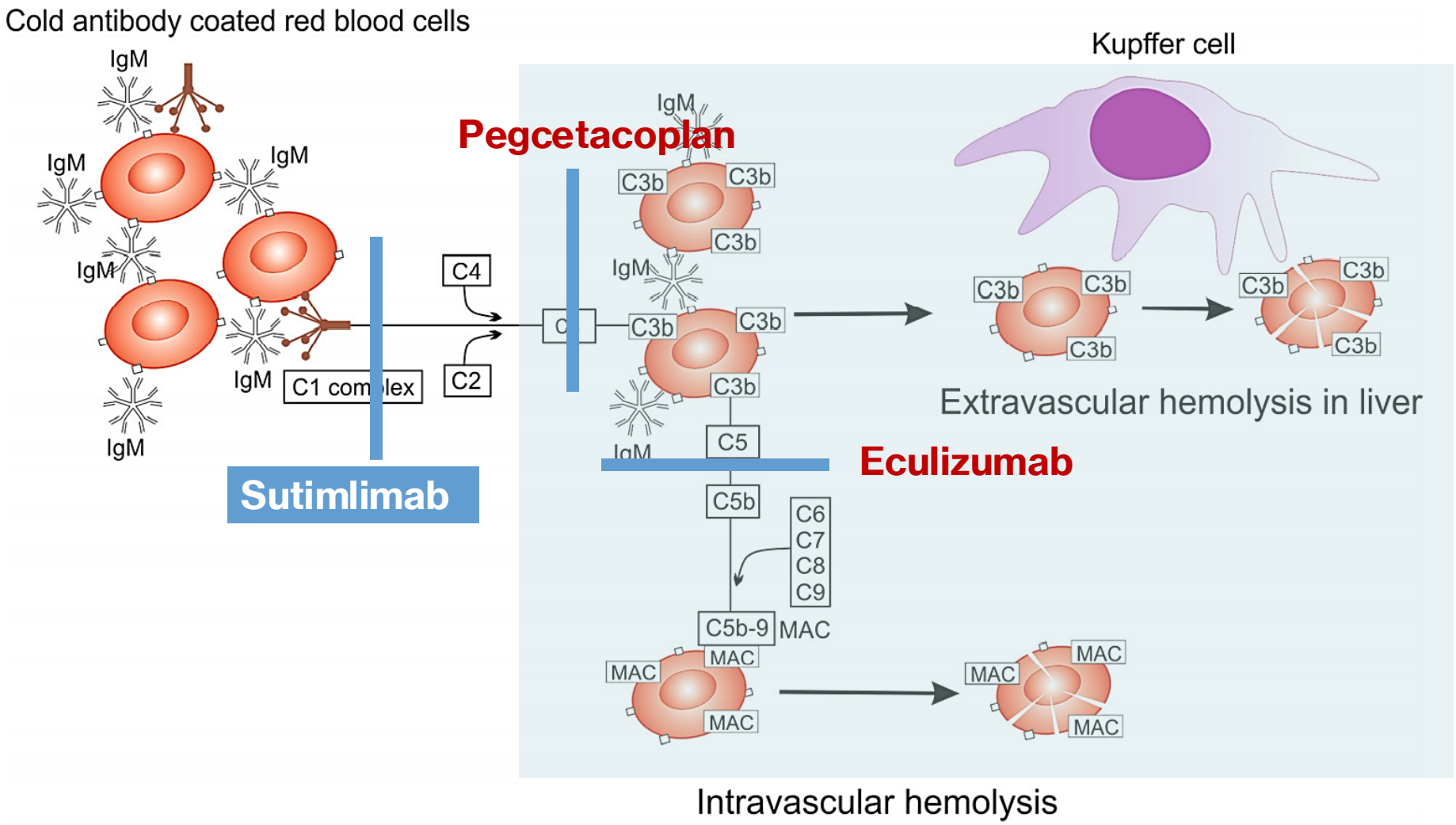
Michalak et al, 2020.

Unmet medical need in CAD

- High frequency of persisting anemia despite B cell directed therapy
  - Rituximab monotherapy – overall responserate , ORR 50%
  - Rituximab + bendamustine – 78% ORR (53% complete)
- Need for rapid-acting therapy for acute and severe exacerbations, or in relation to acute illness/surgery

Berentsen, 2020; Gertz, 2007; Berentsen et al, 2007; Petz, 2008; Röth & Dührsen, 2010; Berentsen et al, 2015; Wouters & Zeerleder, 2015.

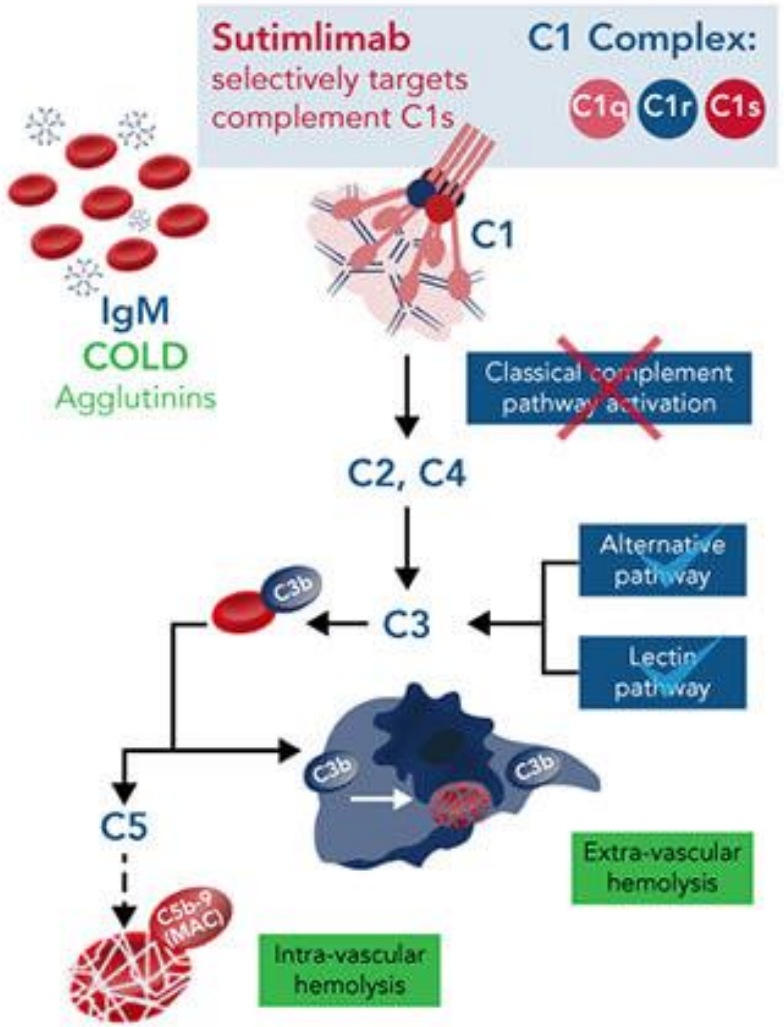
Complement directed therapy in CAD



Michalak et al, 2020.

Sutimlimab in patients with cold agglutinin disease (CAD):

Randomized placebo-controlled phase 3 cadenza trial (NCT03347422)

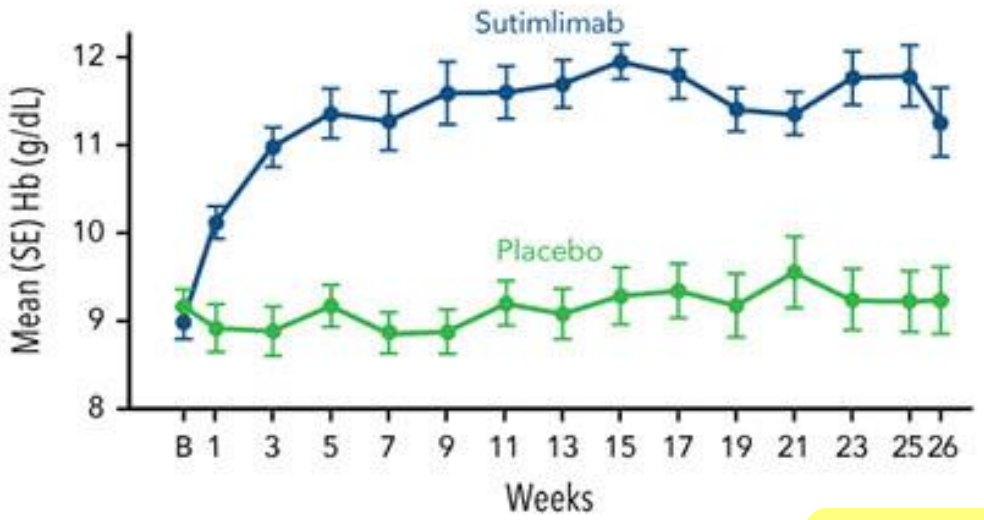


Patient with **CAD**

(No recent history of RBC transfusion)

	26-week Treatment period	Met composite Primary endpoint
Sutimlimab	N=22	73% (n=16)
Placebo	N=20	15% (n=3)

OR: 15.9, 95% CI 2.9–88.0; p<0.001



Early and sustained
Effects of sutimlimab on:

- ✓ Anemia
- ✓ Hemolysis
- ✓ Fatigue

No meaningful changes observed with placebo

More this afternoon

CI, confidence interval; Hb, hemoglobin; IgM, immunoglobulin M; MAC, membrane attack complex; OR, odds ratio; RBC, red blood cells; SE, standard error

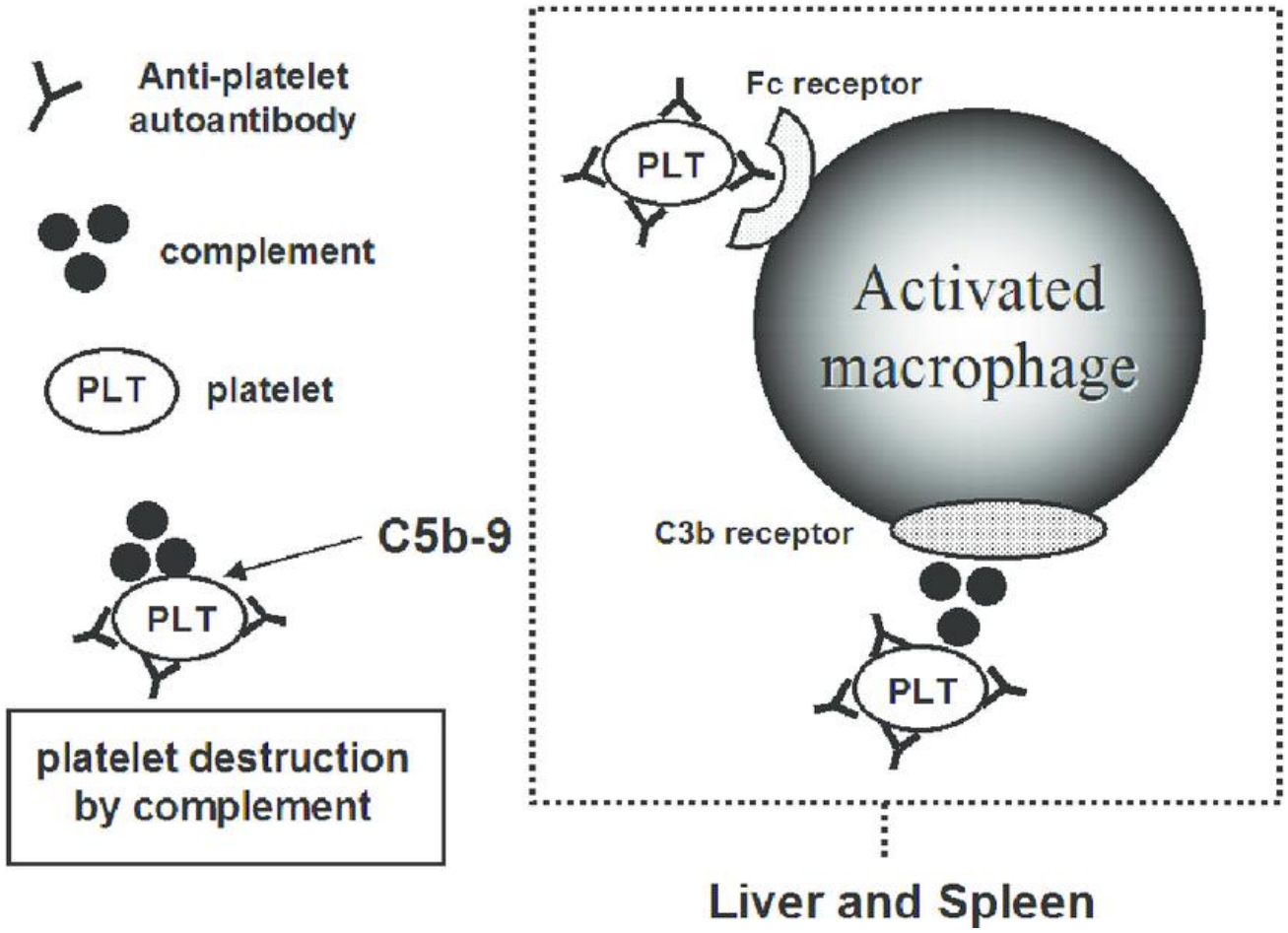
Alexander Röth et al. *Blood*

Sutimlimab treatment was effective and generally well tolerated. Results from CADENZA demonstrate that sutimlimab has the potential to be an important advancement in the treatment of hemolysis in CAD.

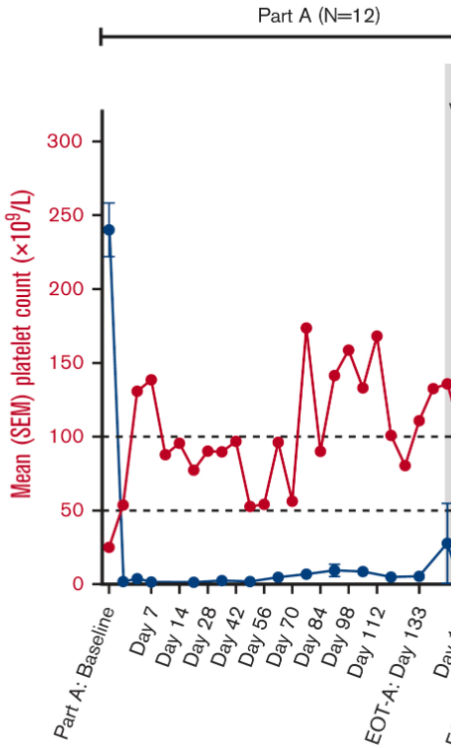
Emerging role of complement

- Immune thrombocytopenia
- Sickle cell disease

Complement in ITP



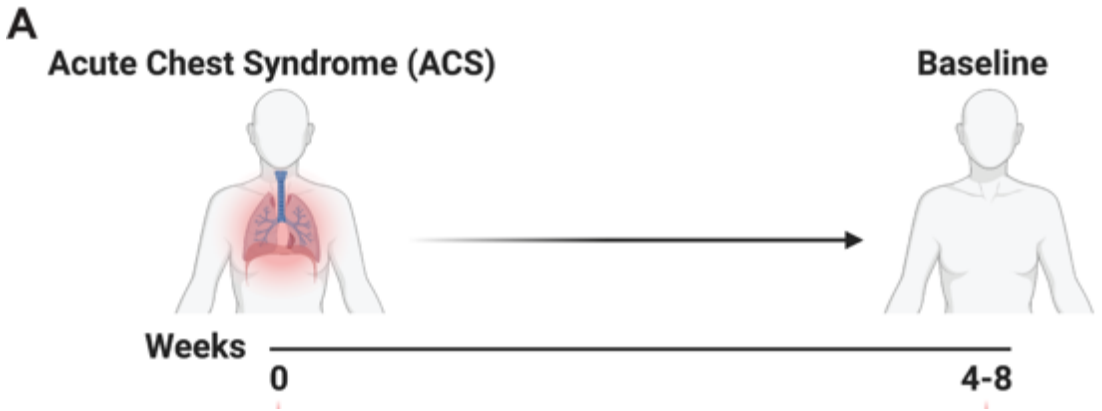
Response to sutimlimab (C1s inhibitor)

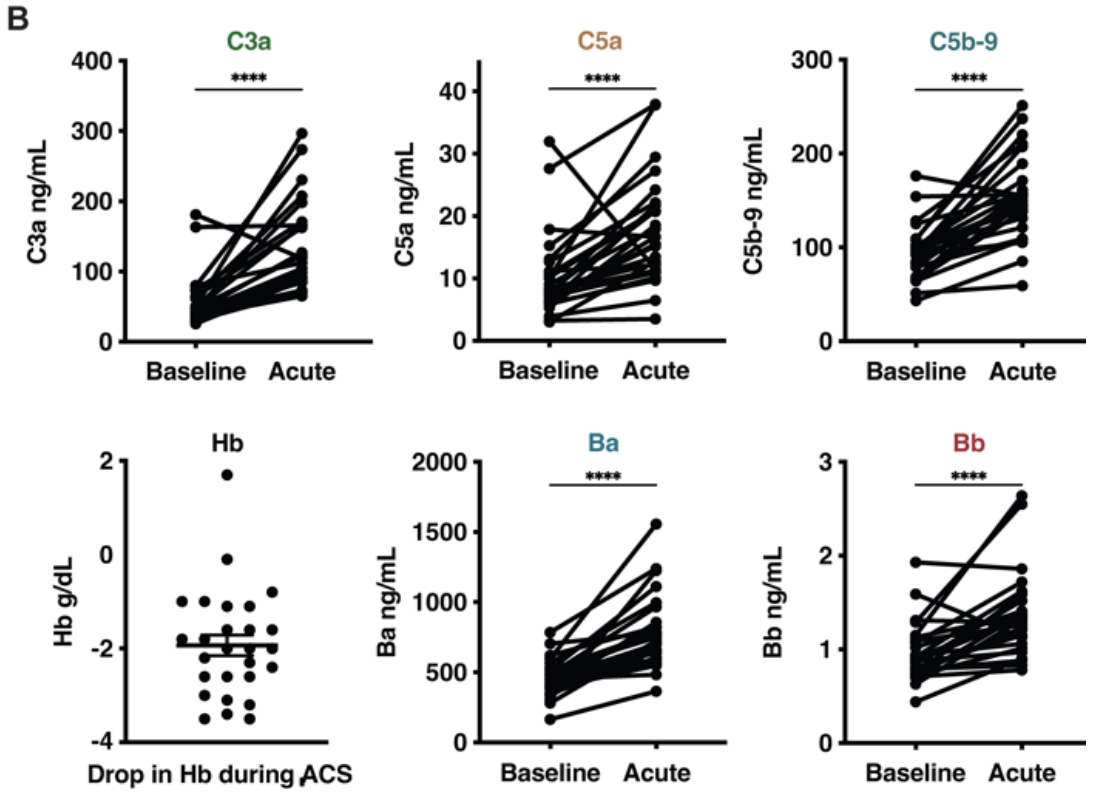


More this afternoon

Shosaku et al. Blood Dis 2016, Castellu et al. Clin Exp Immunol 2020, Broome et al. Blood Adv 2025

Sickle cell disease: complement levels rise in acute ‘crisis’





How does hemolysis drive complement activation in ACS?

More this afternoon

Chonat, Science Transl Med 2025

Free heme activates complement in sickle cell

JCI insight

Intravascular hemolysis activates complement via cell-free heme and heme-loaded microvesicles

Nicolas S. Merle, … , Olivier P. Blanc-Brude, Lubka T. Roumenina

Heme Interferes With Complement Factor I-Dependent Regulation by Enhancing Alternative Pathway Activation

Alexandra Gerogianni[1,2], Jordan D. Dimitrov[3], Alessandra Zarantonello[3], Victoria Poillerat[3], Satheesh Chonat[4,5], Kerstin Sandholm[2], Karin E. McAdam[6], Kristina N. Ekdahl[1,2,7], Tom E. Mollnes[6,8,9], Camilla Mohlin[1,2], Lubka T. Roumenina[3] and Per H. Nilsson[1,2,6]*

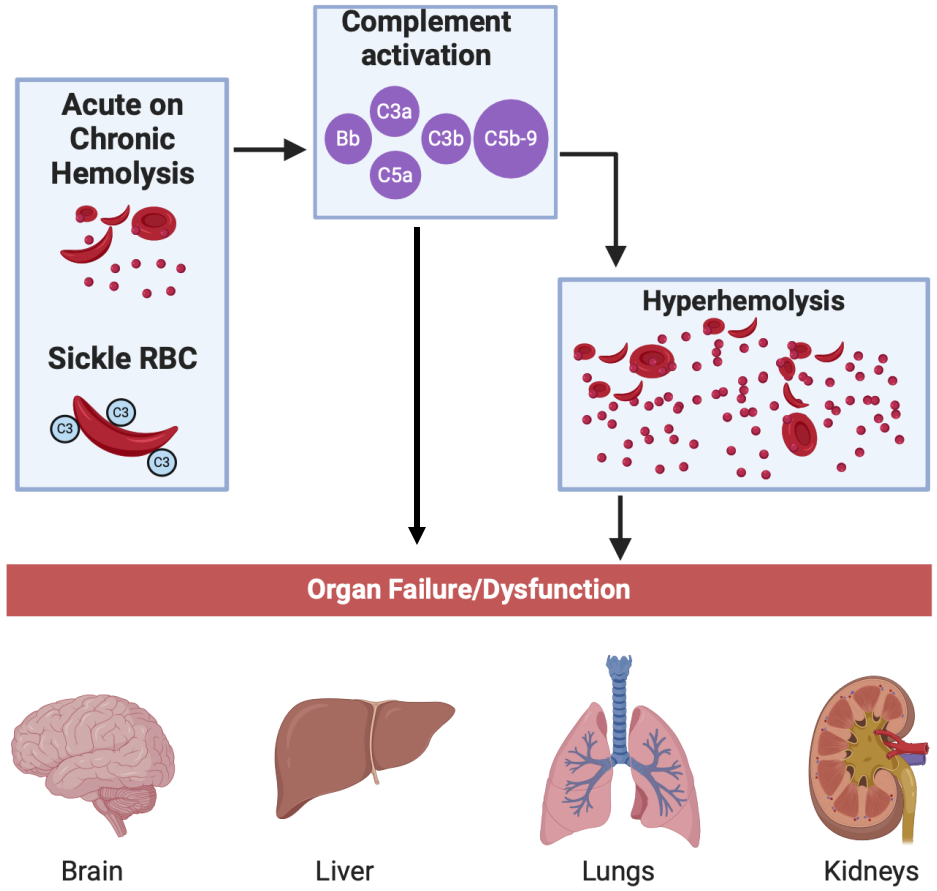
Contribution of alternative complement pathway to delayed hemolytic transfusion reaction in sickle cell disease

by Satheesh Chonat, Maa-Ohui Quarmyne, Caroline M. Bennett, Christina L. Dean, Clinton H. Joiner, Ross M. Fasano, and Sean R. Stowell

Complement activation by heme as a secondary hit for atypical hemolytic uremic syndrome

Marie Frimat,[1-5] Fanny Tabarin,[1-4] Jordan D. Dimitrov,[1-3] Caroline Poitou,[2,4] Lise Halbwachs-Mecarelli,[1-4] Veronique Fremeaux-Bacchi,[1,6] and Lubka T. Roumenina[1-3]

Multiorgan failure is common in rapidly progressive acute chest syndrome and hyper-hemolysis syndrome



	Hyperhemolysis pediatric (26, Dave)	RP-ACS adult (N=16)
Multiorgan failure	44%	93.8%
Severe AKI	11%	68.8%
Thrombocytopenia	NR	81.3%
Resp failure	40%	100%

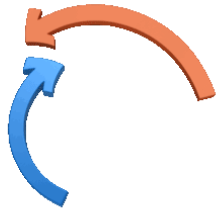
Looks like a TMA?

Dave et al, ASPHO 2025, Chaturvedi Am J Hematol 2016

A Model for Complement-Mediated TMA in SCD

Susceptible state

Low level of hemolysis
Ineffective scavenging
Sickle RBC
Plasma factors/Procoagulant
Complement Regulators



Second hit (triggers)

Hemolytic transfusion reactions
Vasoocclusive Crisis
Acute chest syndrome
Drugs
Infection
Chronic inflammation, Others

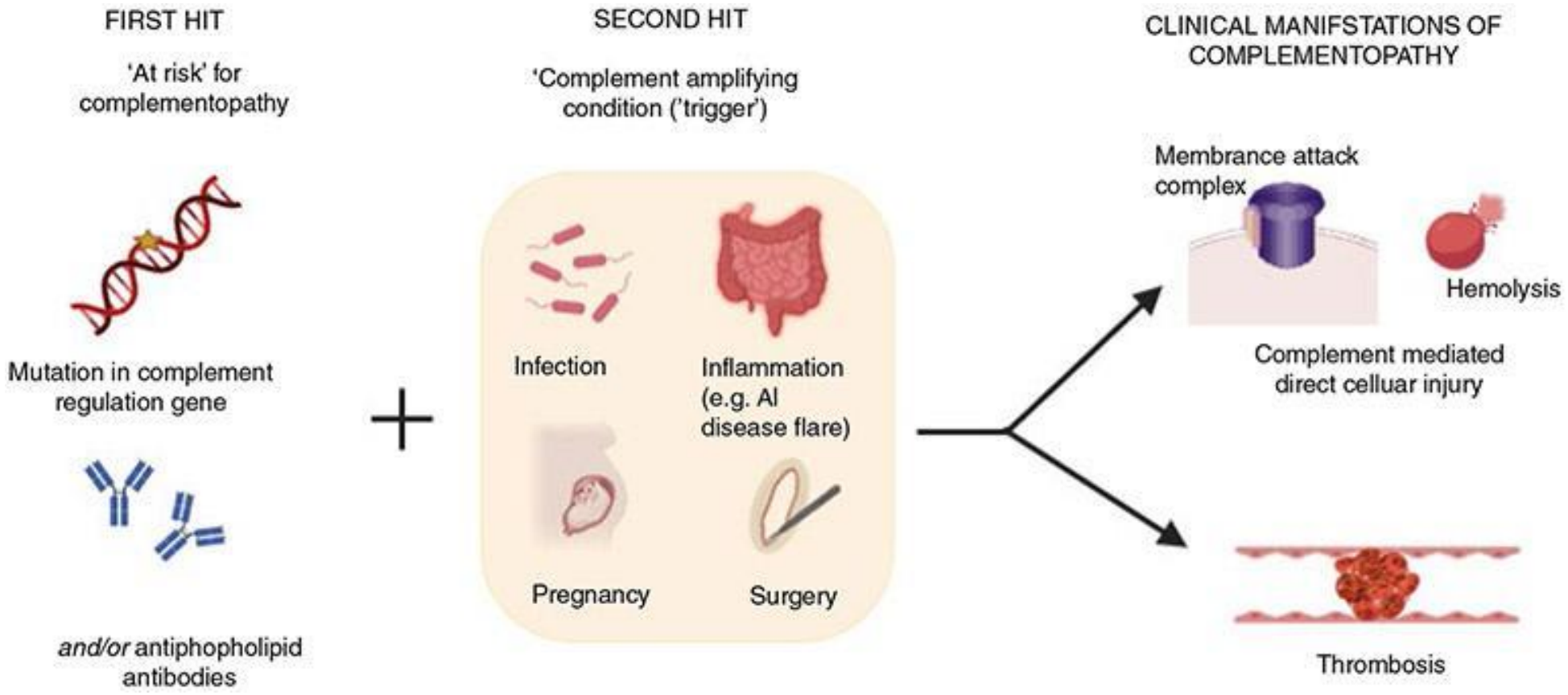
Complement activation
Inadequate regulation
Ineffective clearance

Hyperhemolysis
Multi organ failure
Organ damage

More this afternoon

Chonat et al. *Haematologica* 2020
Chonat et al. *Curr Opin Hematol* 2020

Take home - cardinal features of complement disorders



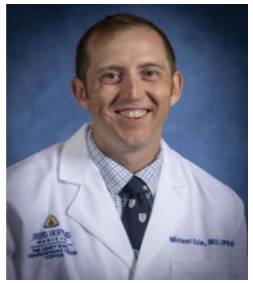
Adapted from Chaturvedi, McCrae, Brodsky. JTH 2021

Take home points

- Complement dysregulation can be genetic or acquired
  - Interplay between predisposition for dysregulation and environment (triggers) is common
- Complement dysregulation causes thromboinflammation
- Common manifestations: thrombosis, hemolysis, inflammation, cell injury
- Clear targetable driver in: PNH, TMA, CAD, APS
- Expanding role in : Sickle cell, transfusion reactions, ITP

Acknowledgements


Rob Brodsky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