Role of complement in other forms of pediatric TMA

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ESPN Research Conference
(Complement)

Florence, March 13, 2026

The Doctor (1891) Sir Luke Fildes

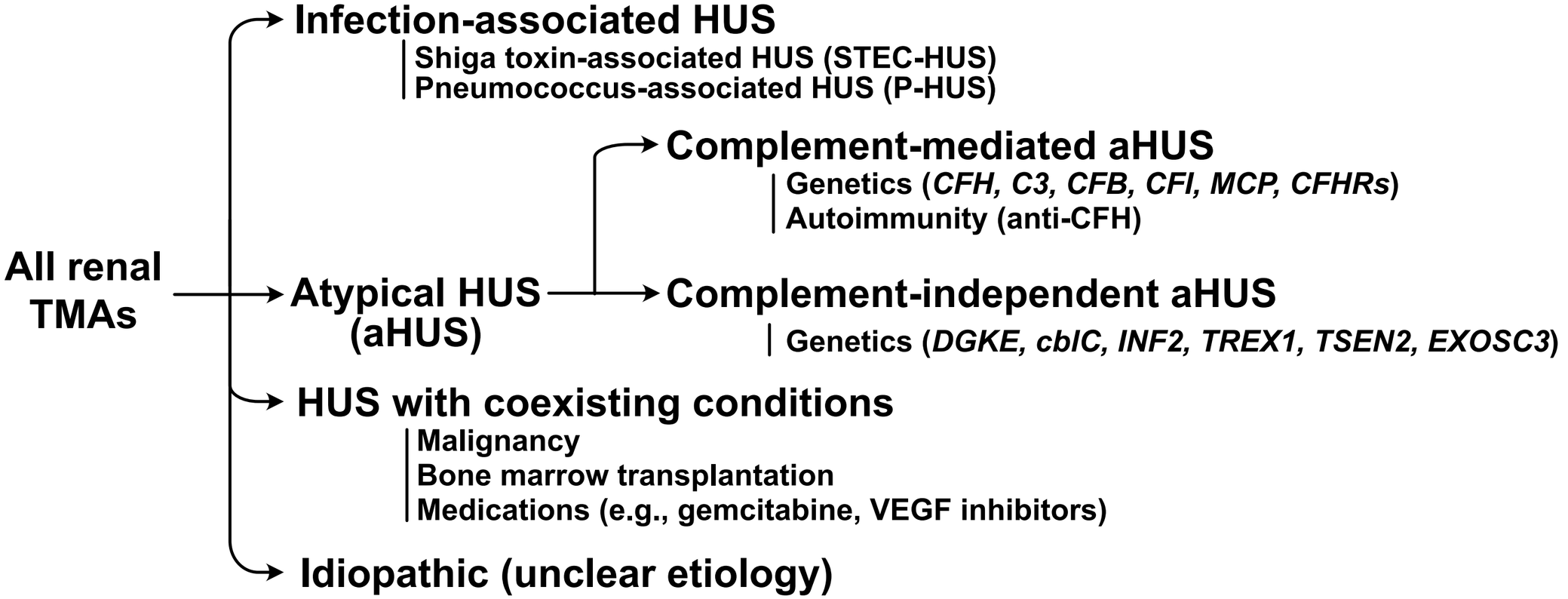
Disclosures

- Speaker and consulting services, Alnylam
- Consulting services: Novo Nordisk, Arbor Biotechnologies

Overview

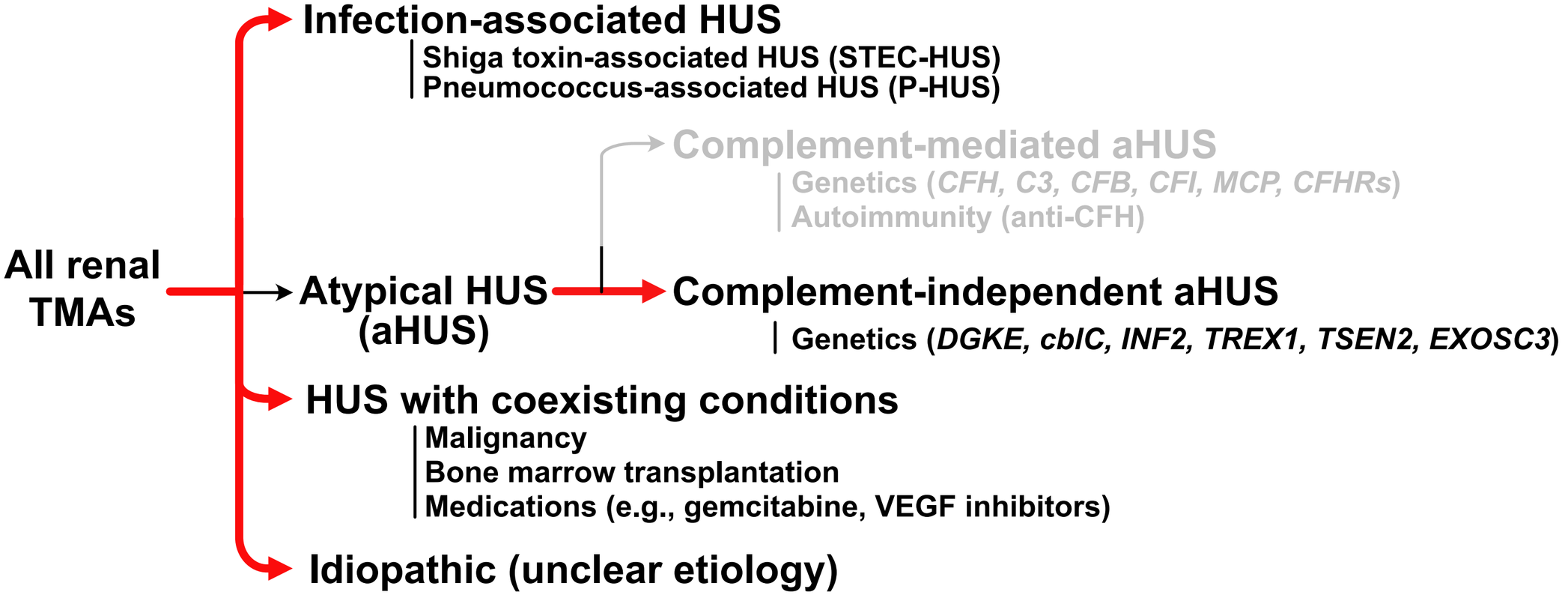
- Mendelian, complement-independent kidney TMAs
- Non-Mendelian, complement-mediated kidney TMA

Framework to classify the known forms of kidney TMA



Modified from Lemaire et al. (2021) *CJASN*

Framework to classify the known forms of kidney TMA



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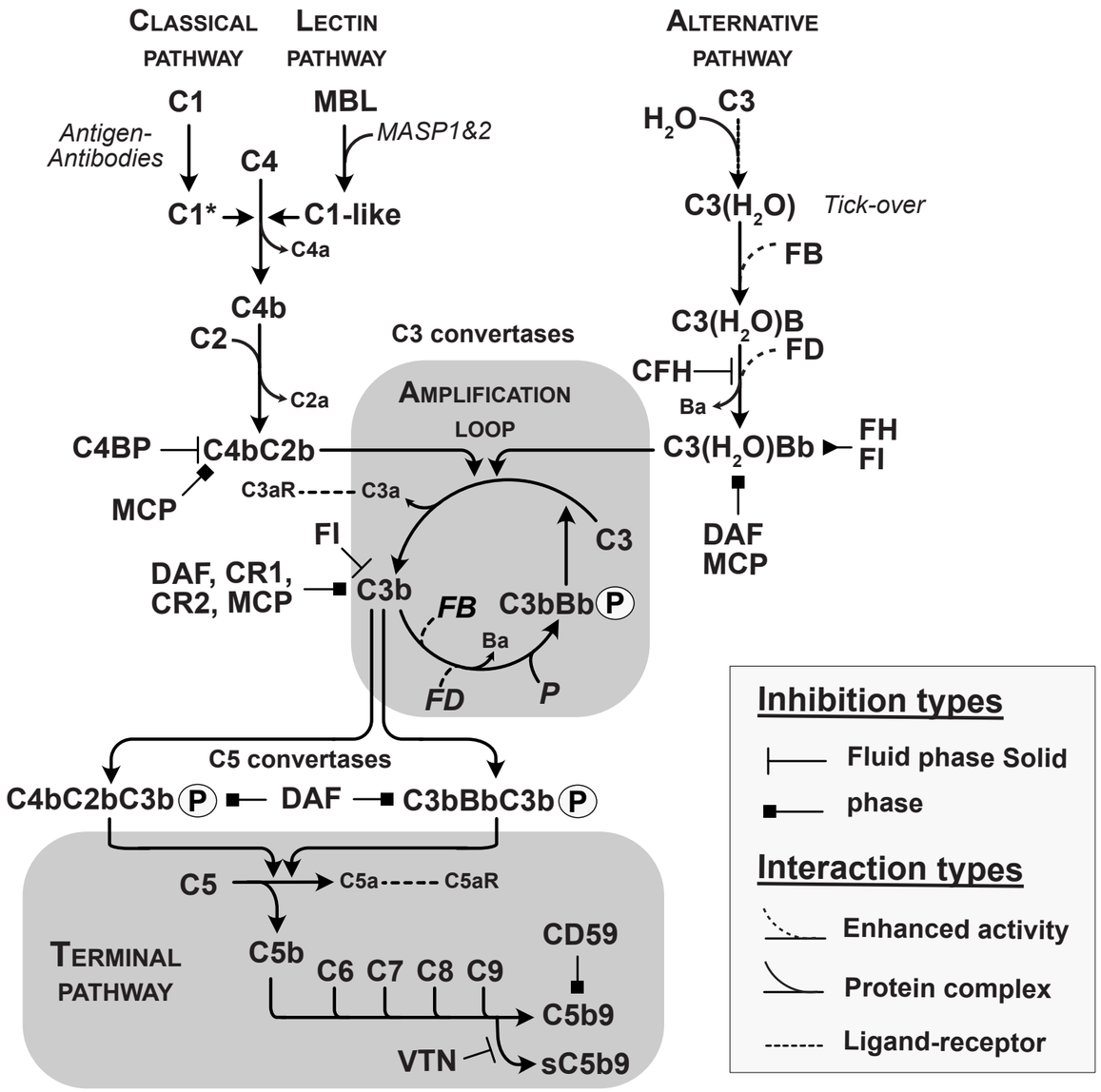


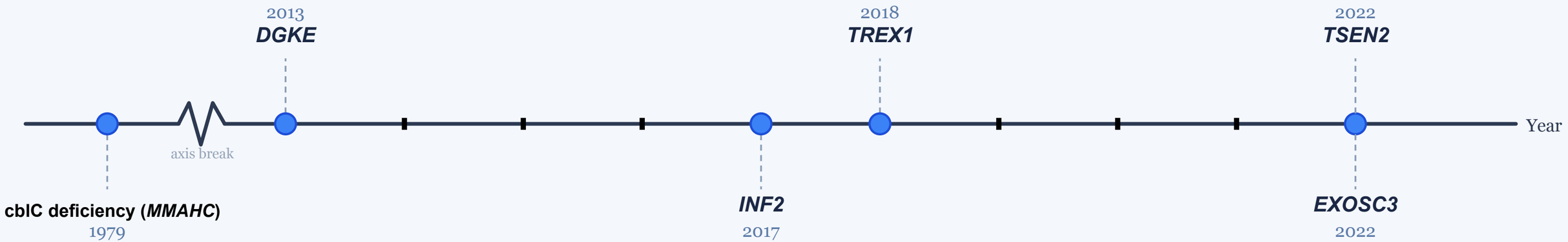
Modified from Lemaire et al. (2021) *CJASN*

Key problem when prescribing anti-complement Rx
You must decide early, and reassess later

- In the first few days, most severe kidney TMAs look the same
  - Diagnostic triad for TMA is present
  - No reliable, available and rapid test to determine if complement is central
- The likely diagnosis and pathophysioogy is revealed only after you prescribe because
  - the clinical response to complement blockade is rapid, or
  - of genetics/autoantibody/functional assay results (usually resulted weeks later)
- That uncertainty is shared by everyone, including the "experts"

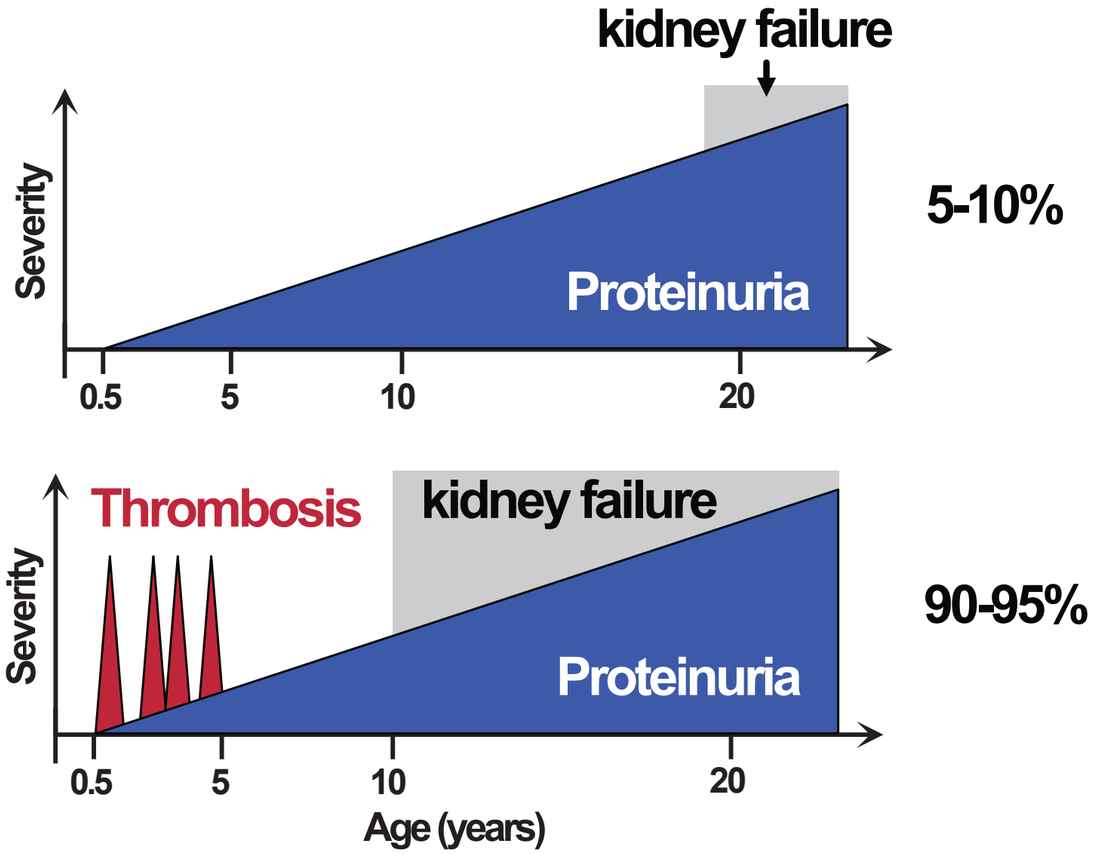
A renal fellow and a kidney doctor in 2026 [modified from Sir Luke Fildes 1891]

Non-Complement–Mediated kidney TMA



DGKE nephropathy[a]

- Age of onset < 1 yr
- Recurrent TMA, triggered by infection
- Also HTN, proteinuria, microhematuria
- End-stage renal disease before adulthood
- No TMA recurrence after kidney transplant
- No extra-renal phenotype
- No complement activation
- **Note: Two disease forms**

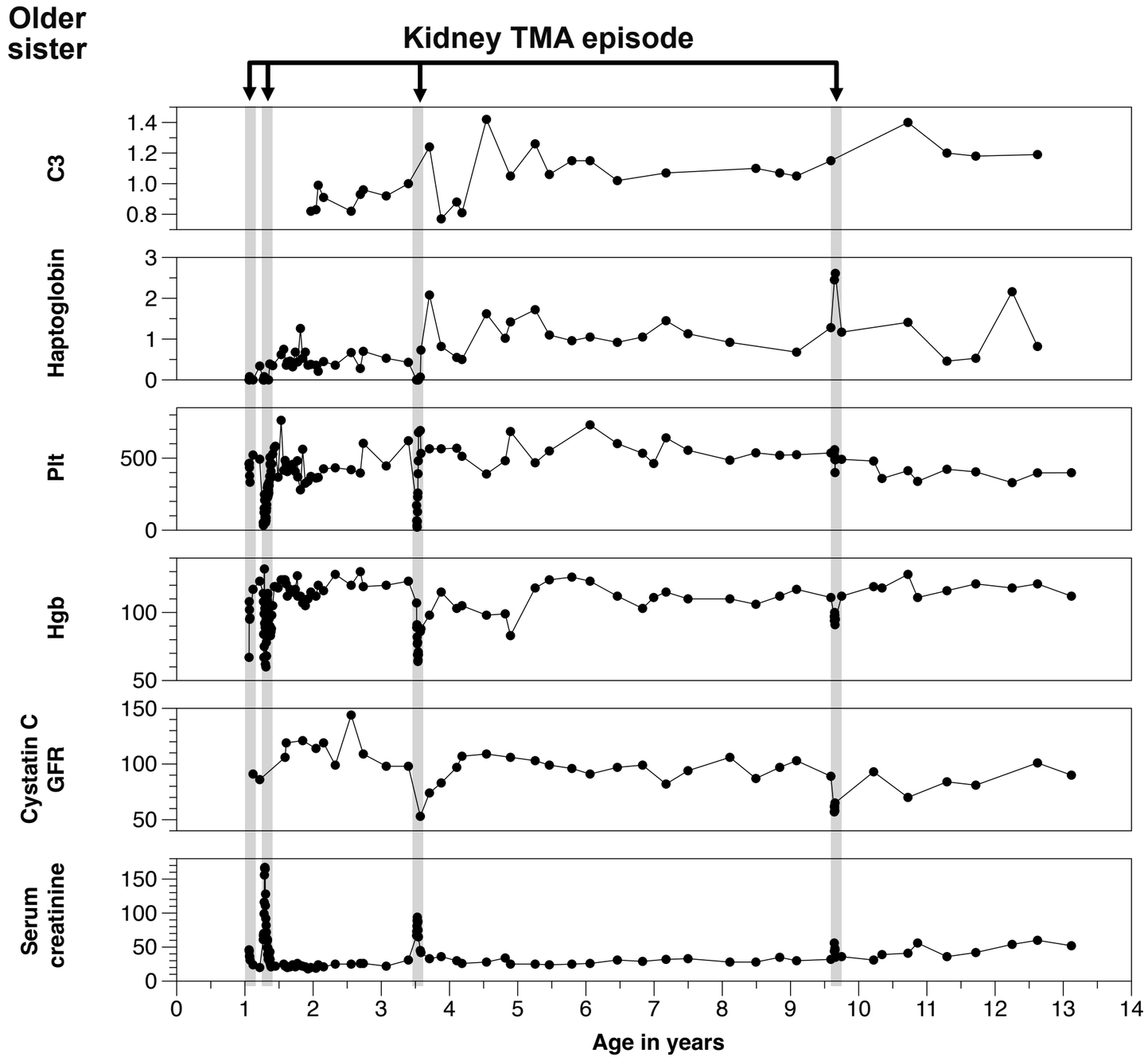


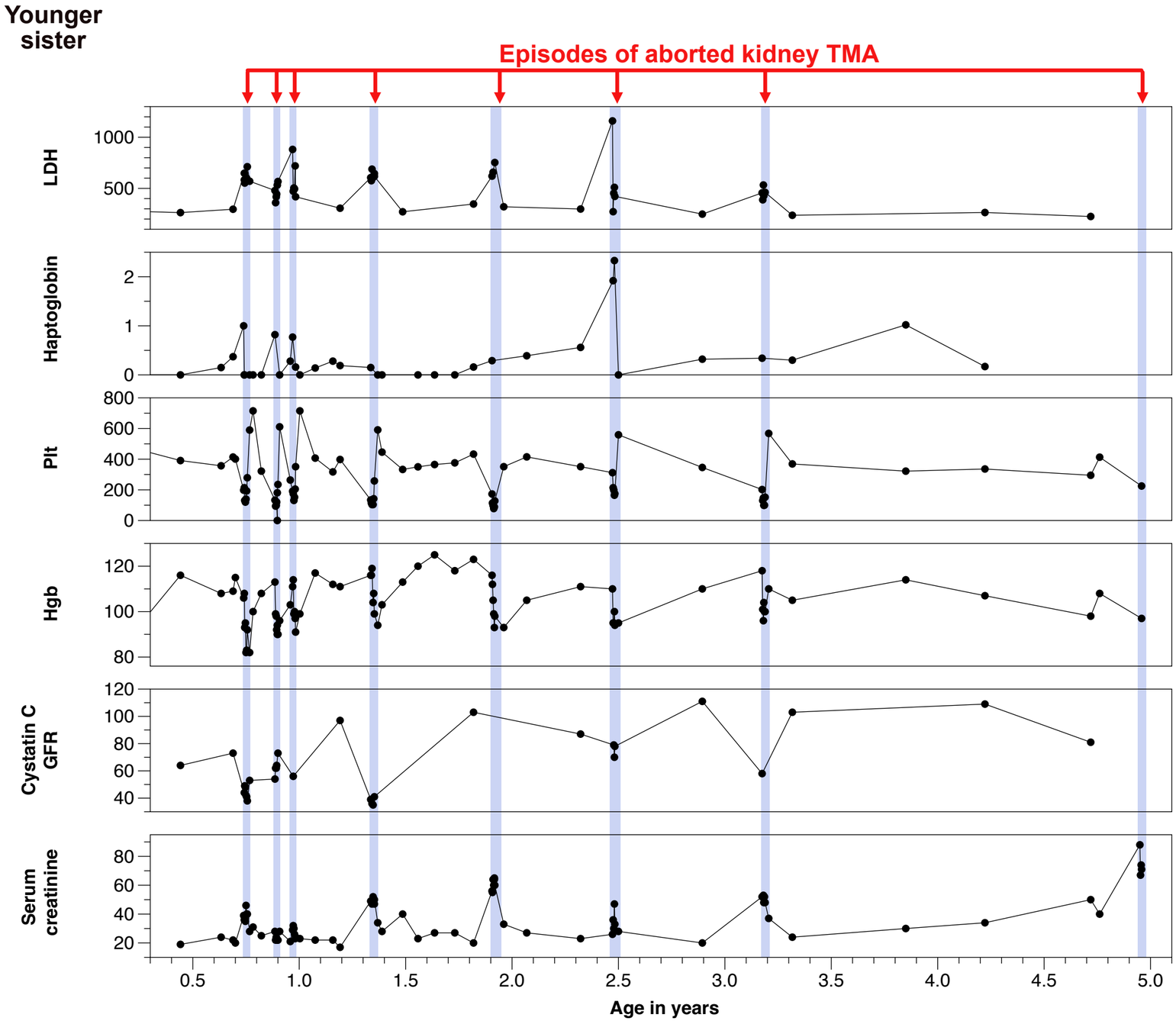
Similarly pathogenic DGKE genotypes in both groups

[a] Lemaire et al. (2013) *Nat Genet*

Intriguing cases

- Female Dx *DGKE* nephropathy, homozygous c.A494G;p.D165G
  - long PICU admission ~1 y of age
- Consanguineous union
- New pregnancy, prenatal testing shows same genotype
- *Observations:chistorical DGKE nephropathy cases thought to respond to plasma-baed therapies*
- Implement protocol
  - Whenever infection -> test urine for protein
  - If +ve, seen in ED for TMA labs
  - If TMA labs +ve, plasma infusion until resolution
  - If no improvement, trial PEX


Older sister
Kidney TMA episode
C3
1.4
1.2
1.0
0.8
Haptoglobin
3
2
1
0
Plt
500
0
Hgb
100
50
Cystatin C GFR
150
100
50
Serum creatinine
150
100
50
0
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Age in years


Younger sister
Episodes of aborted kidney TMA
LDH
1000
500
Haptoglobin
2
1
0
Plt
800
600
400
200
0
Hgb
120
100
80
Cystatin C GFR
120
100
80
60
40
Serum creatinine
80
60
40
20
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
Age in years

Conclusions

- patient only had many mild AKI, always triggered by infections
- rapid resolution with only plasma infusions in ~3 days in all cases
- long-term impact?
- ongoing work:
  - mechanism? Which plasma factor is replace or dampened?
  - publish case (now that she is >5)
  - n-of-1 RCT

Negative complement genetics, yet complement is central to pathophysiology?

1) Autoimmune kidney complement-mediated TMA
 - Anti-CFH autoantibodies

2) Risk variants/polygenic burden & incomplete penetrance
 - Understanding the complotype

3) Secodnary forms
 - Post-trasnplant TMA
 - Durg-induced TMA
 - Other autoimmune/inflammatory forms

Anti-CFH autoantibodies[1]

Functional effect
- Inhibits FH surface regulation → ↑ surface C3b deposition and endothelial injury

"Compartment" bias
- Cell surface-phase dysregulation

Genetic risk/predisposition
- Strong association with homozygous *CFHR3–CFHR1* deletion (Δ*CFHR3-CFHR1*)
- usually with a complete *CFHR1* deficiency
- other *CFH/CFHR* locus structural variants

Treatment
- Plasma exchange or anti-complement therapies
- Immmunosuppresion (pred, cyclo, or ritux)

Presumed mechanism of autoimmunity
- *CFHR1* shares high sequence similarity with *CFH*
- especially in regions where anti-CFH bind
- absent CFHR1 ➡ weaker immune tolerance to shared epitopes

Notes about other potential forms
- A few recent reports of patients with kidney TMAs found to have anti-CFB and C3nef[2]
- but the vast majority of cases with high titers are diagnosed with C3G

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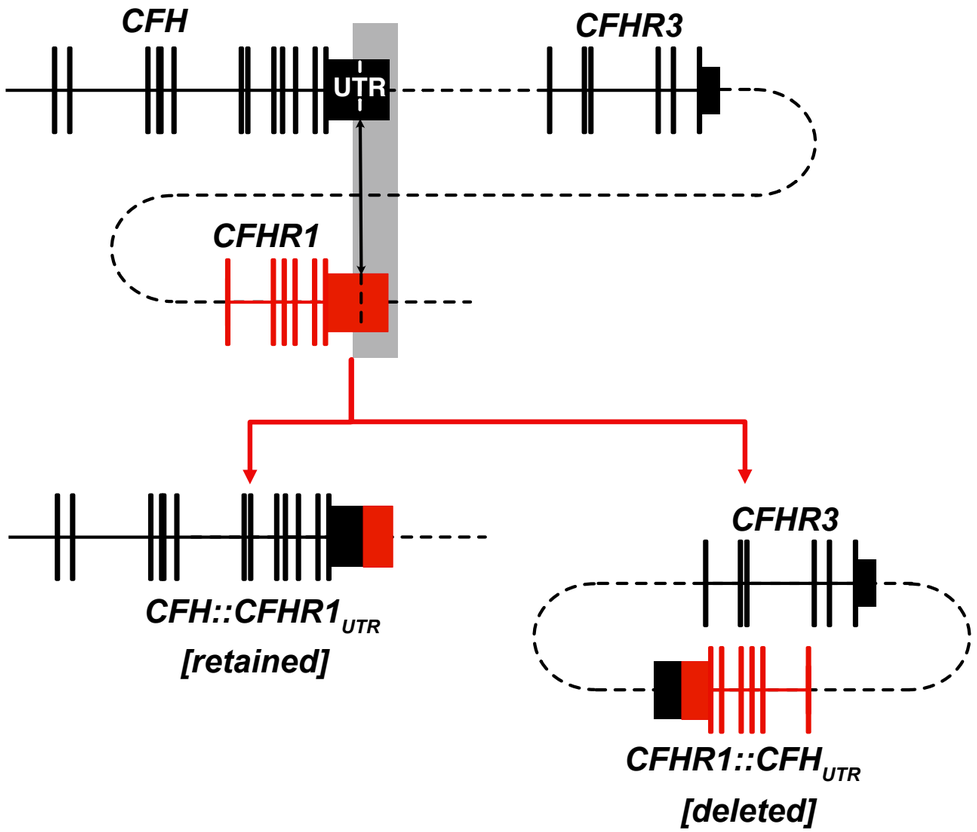
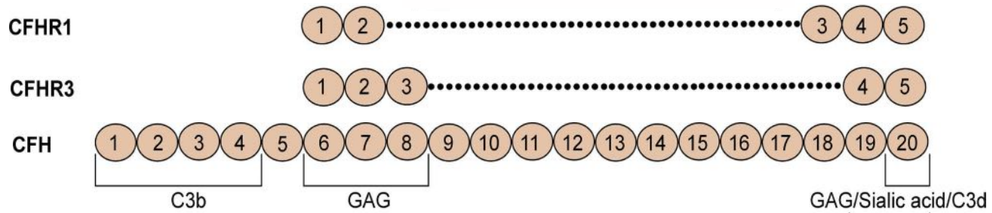
[1] Khandelwal & Bagga (2024) *Pediatr Nephrol*

[2] Khandelwal et al. (2024) *Pediatr Nephrol*; Thorsen et al. (205) *Front Immunol*

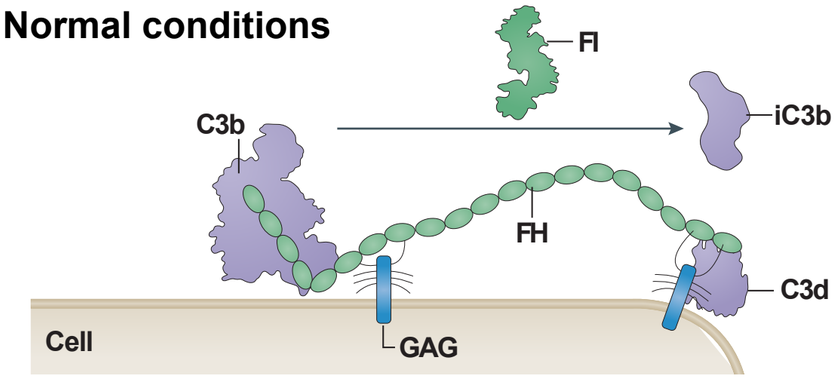
Hybrid FH:FHR1 proteins via *CFHR3-CFHR1* deletion



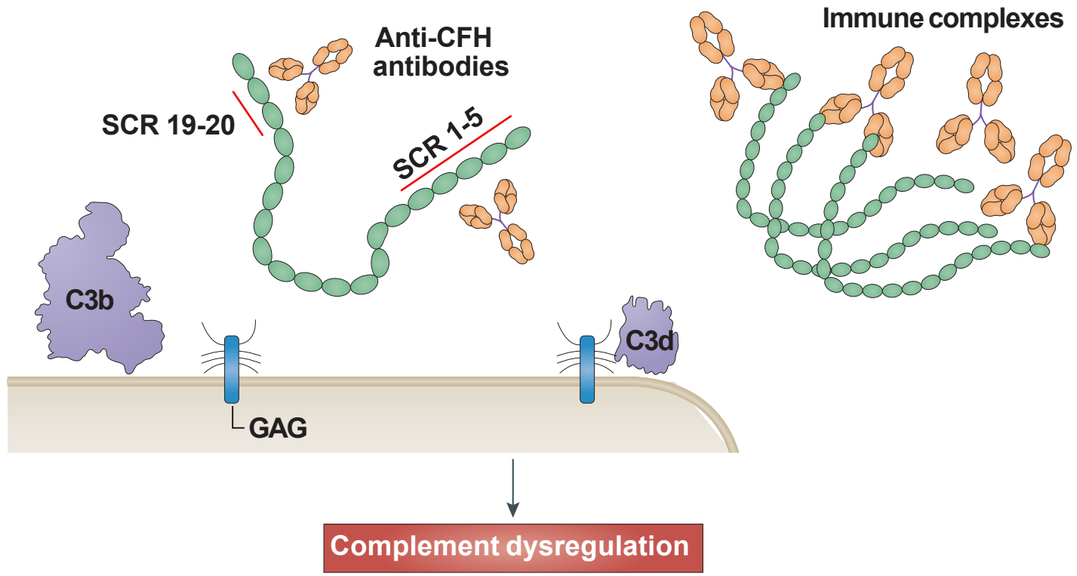


Modified from Hannan et al. (2016) Mapping the Complement Factor H-Related Protein 1 (CFHR1):C3b/C3d Interactions. *PLoS One*

Normal conditions



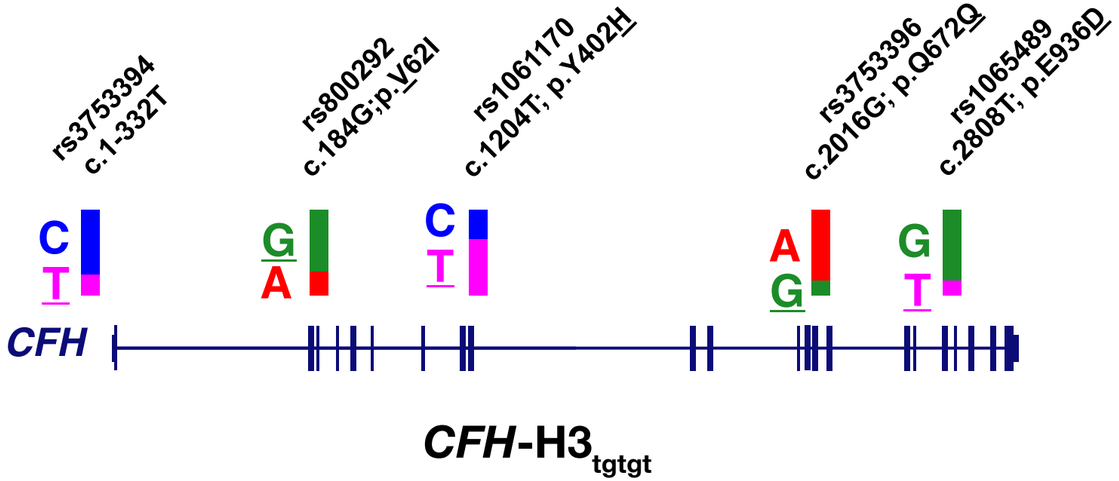
anti-CFH-associated TMA

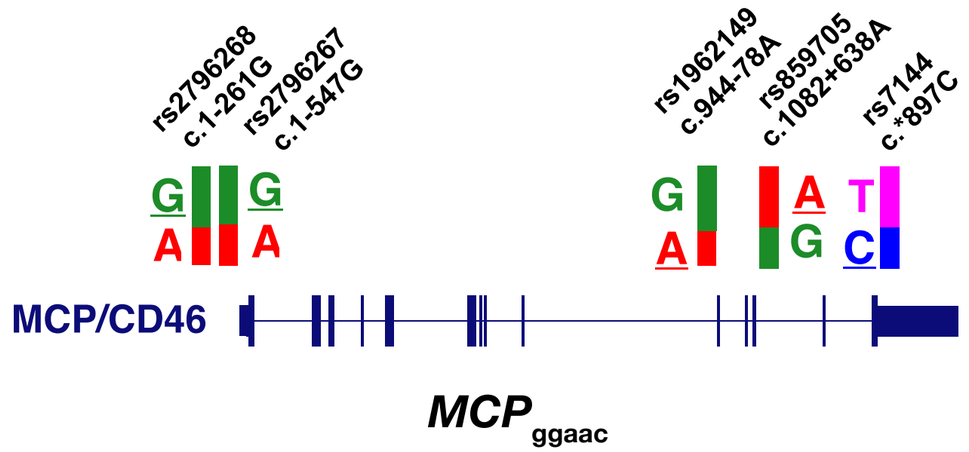


Modified from Durey et al. (2016) Anti-complement-factor H-associated glomerulopathies. *Nat Rev Nephrol.*

Sets of modulatory common variants

- Combinations of common risk alleles produce quantifiable, yet hard-to-predict, ⬆ in complement activity
- Help explain variable penetrance in Mendelian form: rare variant+common risk alelle(s)+trigger
- 2 common haplotypes ⬆ aHUS risk, especially with other variants: *CFH*-H3$_{tgtgt}$ & *MCP*$_{ggaac}$ (other haplotypes are protective)
- functional polymorphisms ⬆⬇ complement activity: *CFB* R32Q, *CFH* V62I, *C3* R102G



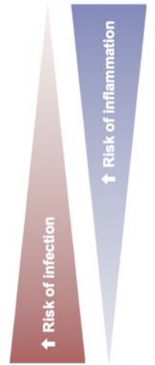


Use in the clinic?

- Only reported by dedicated complement genetic labs
- If available, useful to interpret variable penetrance in patients with a pathogenic complement genotype
- Another potential near-term utility: select kidney recipients[3] and donors[4]
  - *with* protective haplotypes
  - *without* risk haplotypes

Probability of individuals of having risk and protective complement genotypes in various genetic ancestry groups (gnomAD v4; accessed 01/24)

Genetic Ancestry Groups	Number of subjects	Probability of triple homozygous genotype		Overall impact of genotype on risk of increased...	
		risk genotypes	protective genotypes	inflammation	infections
Ashkenazi Jewish	14795	1/53	1/8455	High	Low
European (non-Finnish)	589345	1/50	1/3923	High	Low
Middle Eastern	3027	1/72	1/7075	High	Low
European (Finnish)	31986	1/84	1/4916	High	Low
Admixed American	29995	1/354	1/1366	Medium	Medium
South Asian	45519	1/169	1/651	Medium	Medium
Amish	456	1/1243	1/1741	Low	Medium
East- Asian	22397	Absent	1/1075	Low	Medium
African/African American	37435	1/11442	1/93	Low	High



very common **somewhat rare**

Risk alleles:	*C3* (p.R102G)	*CFB* (p.R32Q)	*CFH* (p.V62I)	**2 major | 1 minor**
Protective alleles:	*C3* (p.R102G)	*CFB* (p.R32Q)	*CFH* (p.V62I)	**1 major | 2 minor**

[3] Mező (2020) *Transplant Direct* [data from non-TMA patients]

[4] Poppelaars (2023) *medRxiv* [data from non-TMA patients]

Post-transplant TMA

- Transplantation-associated TMA after hematopoietic stem cell Tx
- No good evidence to stop CNIs
- Growing evidence that anti-C therapy works
- Recent single arm study showed benefit for ECU in pediatrics
- Unpublished report showed the saem with Raviluzimab
- RCT ongoing in adult patients (NCT04543591)

Table 4. Studies comparing different diagnostic criteria for TA-TMA in the same cohort

Study definition	Adult TA-TMA incidence		Pediatric TA-TMA incidence	
Empiric clinical diagnosis	Li 2009, Retrospective	70/2145 (3%)	Schoettler 2020, Retrospective	8/307 (3%)
C-TMA (modified Cho)		192/2145 (9%)		62/307 (20%)
New consensus (modified Jodele 4/7)		Not reported		110/307 (36%)
Empiric clinical diagnosis	Vasu 2024, Prospective	10/101 (10%)	Li 2023, Prospective	4/32 (13%)
C-TMA (modified Cho)		Not reported		5/32 (16%)
New consensus (modified Jodele 4/7)		47/101 (47%)		12/32 (38%)

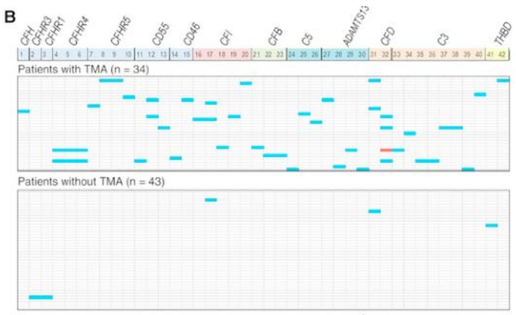
Number of patients diagnosed with TA-TMA among total number of patients undergoing hematopoietic cell transplantation. The median follow-up duration varies by study from 100 days to 180 days.

Li & Sartain (2024) *Hematology Am Soc Hematol Educ Program*

BLOOD, 25 FEBRUARY 2016 • VOLUME 127, NUMBER 8

The genetic fingerprint of susceptibility for transplant-associated thrombotic microangiopathy

Sonata Jodele,[1] Kejian Zhang,[2] Fanggeng Zou,[2] Benjamin Laskin,[3] Christopher E. Dandoy,[1] Kasiani C. Myers,[1] Adam Lane,[1] Jaroslav Meller,[4,5] Mario Medvedovic,[5] Jenny Chen,[5] and Stella M. Davies[1]



CLINICAL TRIALS AND OBSERVATIONS

blood® 21 MARCH 2024 | VOLUME 143, NUMBER 12

A prospective multi-institutional study of eculizumab to treat high-risk stem cell transplantation–associated TMA

Sonata Jodele,[1,2] Christopher E. Dandoy,[1,2] Paibel Aguayo-Hiraldo,[3,4] Adam Lane,[1,2] Ashley Teusink-Cross,[5] Anthony Sabulski,[1,2] Kana Mizuno,[2,6] Benjamin L. Laskin,[7] Jason Freedman,[8] and Stella M. Davies[1,2]

Early therapy with the C5 blocker eculizumab signicantly improved outcomes in patient with high-risk TA-TMA and attenuated organ dysfunction.
N=23, no genetics...

Major form of drug-induced TMA

Drugs	Medication class (target)	Typical DITMA "pattern"	Evidence for response to complement blockade
Calcineurin inhibitors (CNIs) (tacrolimus, cyclosporine)	Immunosuppressants (calcineurin inhibition)	Often **post-transplant TMA**, sometimes renal-limited; can also "unmask" C-TMA biology in a susceptible host	**Weak** mostly case reports/series with selected severe/refractory responders; no robust comparative data
Gemcitabine	Antimetabolite chemotherapy (nucleoside analogue)	Often delayed/cumulative exposure; systemic or renal TMA	**Moderate** recurring case-report/case-series signal for benefit in severe/refractory cases; some rechallenge experiences reported
Carfilzomib	Proteasome inhibitor (myeloma therapy)	Often severe AKI; may be triggered/ worsened by intercurrent illness	**Weak / inconsistent** early case reports suggested benefit larger cohort, no clear improvement with eculizumab/PEX
Bevacizumab	Monoclonal antibody against VEGF-A (anti-angiogenic)	Often **renal-limited TMA** with HTN/ proteinuria; may improve after stopping drug	**Weak** mainly case reports/small series of use in persistent/severe cases

Best candidate for drug-induced, complement-mediated TMA

Gemcitabine

(GITMA = gemcitabine-induced TMA)

Mechanism is unclear

Table 2. Published experience of eculizumab treatment for GITMA

Study	Year	No. of patients	Treatments failed before eculizumab	Eculizumab doses	Outcome after eculizumab: Renal	Outcome after eculizumab: Hematologic
Al Ustwani *et al.*[9]	2013	4	Drug cessation Drug cessation Drug cessation PLEX	8 6 6 5	Improved[a] Improved Improved Improved	Improved Improved Improved Improved
Starck *et al.*[7]	2013	1	Glucocorticoids, PLEX, RTX	4	Improved	Improved
Rogier *et al.*[S2]	2016	1	PLEX	7	Improved	Improved
Turner *et al.*[S7]	2017	2	Drug cessation Drug cessation	NR NR	Improved Improved	Improved Improved
Facchini *et al.*[8]	2017	1	RTX, PLEX, IVIG	7	Improved	Improved
Rubio *et al.*[S3]	2017	1	PLEX	7	Improved	Improved
Gosain *et al.*[S5]	2017	1	PLEX	NR	Improved	Improved
Krishnappa *et al.*[S6]	2018	1	PLEX	18[b]	Improved	Improved
Martin *et al.*[S1]	2019	1	Glucocorticoids, PLEX	10[b]	Improved	Improved
Daviet *et al.*[6]	2019	5	PLEX (n = 4) Drug cessation (n = 1)	NR	Improved Not improved Not improved Not improved Not improved	Improved Improved Improved Improved Not improved
Burns *et al.*[S4]	2020	1	Drug cessation	1	Improved	Improved
Efe *et al.* [present study]	2021	1	Drug cessation	6	Improved	Improved

GITMA, gemcitabine-induced thrombotic microangiopathy; IVIG, intravenous immunoglobulin; NR, not reported; PLEX, plasma exchange; RTX, rituximab.
[a]Improved is defined as the study reporting an improvement in renal function and resolution of hemolysis and thrombocytopenia, respectively.
[b]Not explicitly reported; number of doses was estimated based on reported schedule of eculizumab.

Efe et al. (2021) ***Kidney Int Rep.***

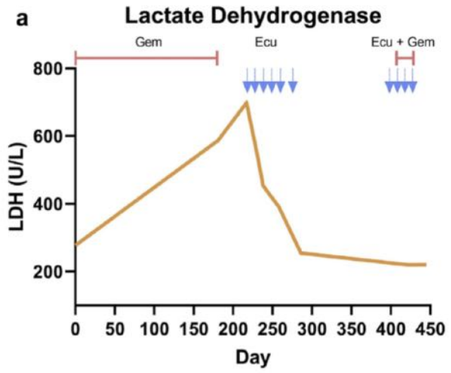
Table 1. Previous Studies Reporting Gemcitabine Rechallenge After GITMA

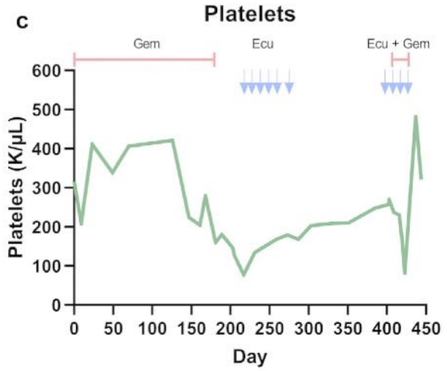
Study	Country	No. of Patients	Age	Cumulative Dose of Gemcitabine Rechallenge	Outcomes
Walter et al[11] (2002)	Switzerland	1	45	2,000 mg/m^2	Recurrent GITMA with AKI, hematuria, slight increases of LDH, and a decrease of the platelet counts. Dexamethasone was given along with the first dose of gemcitabine rechallenge.
Glezerman et al[12] (2009)	USA	1	50	NR	Recurrent GITMA after 3 doses of gemcitabine resumption with increase in LDH, worsening thrombocytopenia and undetectable haptoglobin.
Daviet et al[14] (2019)	France	1	NR	NR	Recurrent GITMA after gemcitabine rechallenge and spontaneously went into remission upon gemcitabine withdrawal.
Sharma et al[16] (2023)	USA	1	78	NR	No evidence of recurrent GITMA with concomitant eculizumab and gemcitabine after 3 months.
Current study (2025)	USA	1	72	3,200 mg/m^2	No evidence of recurrent GITMA with concomitant eculizumab and gemcitabine after 4 months.

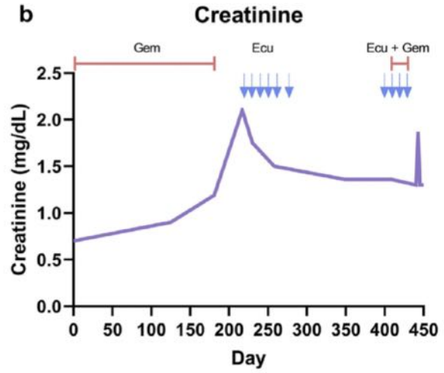
Abbreviations: AKI, acute kidney injury; GITMA, gemcitabine-induced thrombotic microangiopathy; LDH, lactate dehydrogenase; NR, not reported.

Chewcharat et al. (2025) ***Am J Kidney Dis.***

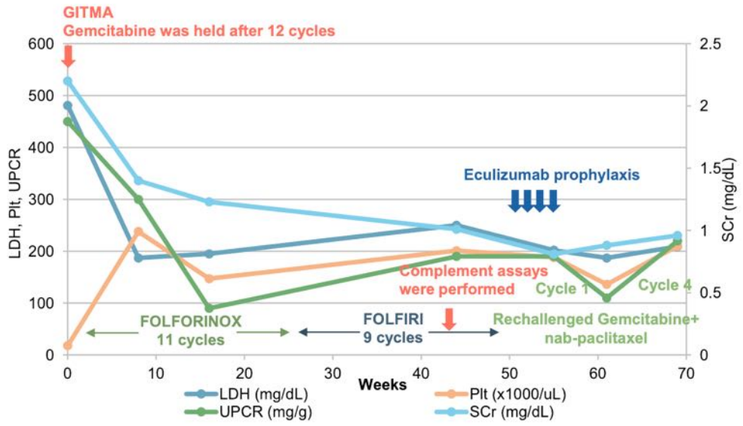
Two cases of GITMA treated with ECU and ?GITMA recurrence prevented by ECU prophylaxis







Efe et al. (2021) *Kidney Int Rep.*



Chewcharat et al. (2025) *Am J Kidney Dis.*

Only 1 pediatric case reported!

Journal of Medical Case Reports (2017) 11:209

Role of eculizumab in a pediatric refractory gemcitabine-induced thrombotic microangiopathy: a case report

Ludovica Facchini[1], Maurizio Lucchesi[1], Alessia Stival[1], Rosa Maria Roperto[2], Francesca Melosi[3], Marco Materassi[2], Silvia Farina[1], Veronica Tintori[4], Maurizio de Martino[5] and Iacopo Sardi[1*]

- **Patient:** 3-year-old White boy with **medulloblastoma**
- **Prior treatment: High-dose chemo** + **craniospinal irradiation**
- **Maintenance regimen: Gemcitabine + oxaliplatin**
- **Complication: Systemic TMA**
- **Initial therapy: Rituximab → no clinical improvement**
- **Subsequent therapy: Eculizumab** given in **repeated cycles**
- **Response:** After **7 infusions**, **gradual improvement** leading to **complete remission** of presumed **GITMA**

Other forms of autoimmune/inflammatory conditions vs complement-mediated TMA

. BMC Nephrology (2020) 21:245

A systematic review of the role of eculizumab in systemic lupus erythematosus-associated thrombotic microangiopathy

Rachael D. Wright[1*], Fariba Bannerman[2], Michael W. Beresford[1,3] and Louise Oni[1,4]

n=30
93% "favorable outcome"

Conclusions: Scientific evidence supports the involvement of complement in the pathogenesis of LN however the role of complement inhibition in clinical practice is limited to those with TMA features. This systematic review showed that in cases of LN complicated with TMA, eculizumab seems to be a very efficacious therapy. Further evidence is required to determine whether patients with refractory LN may benefit from adjunctive complement inhibition.

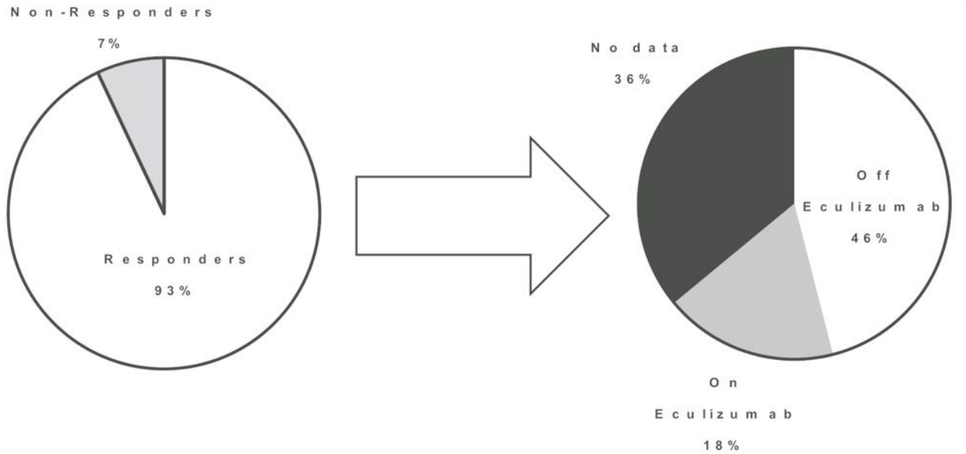


Fig. 2 Patient response to Eculizumab therapy. 93% of patients to whom eculizumab was administered responded favourably. Of these 46% were withdrawn from treatment, 18% remained on treatment at follow up and 36% had no data available

Autoimmunity Reviews 21 (2022) 103055

Eculizumab use in catastrophic antiphospholipid syndrome (CAPS): Descriptive analysis from the "CAPS Registry"

Brenda López-Benjume[a,1], Ignasi Rodríguez-Pintó[b,1], Mary Carmen Amigo[c], Doruk Erkan[d], Yehuda Shoenfeld[e,f], Ricard Cervera[a,*], Gerard Espinosa[a], on behalf the CAPS Registry Project Group/European Forum on Antiphospholipid Antibodies[2]

Registry = 584 patients,
n=39 prescribed eculizumab
75% recovere

Conclusion: According to the real-world experience provided by the "CAPS Registry", eculizumab can be considered in some patients with CAPS refractory to previous therapies, especially if they present with features of complement-mediated thrombotic microangiopathy.

Seminars in Arthritis and Rheumatism 63 (2023) 152256

Studying the Role of C5-Inhibition Therapy in Scleroderma Renal Crisis-Induced Thrombotic Microangiopathy – A Review of Literature

Larabe Farrukh[a,*], Virginia D. Steen[b], Lee Shapiro[c], Swati Mehta[d]

n=17
83% improvement

Conclusion: These findings should prompt testing on a larger cohort of SRC-TMA patients. This would help us determine whether aggressive treatment combining ACE-I and Eculizumab can target the various underlying endothelial, inflammatory, and immunologic mechanisms involved in SRC-TMA, and improve patient outcomes.

Conclusions

- Dont forget that many forms of of kidney TMA appear to be independent of C
  - a low C3 does not mean it is complement-mediated!
- Could plasma-based therapy be useful for DGKE nephropathy
- For many forms of non-Mendelian kidney TMA, C plays a key role
  - Important to leverage knowledge about risk polymorphism/ haplotype data in these forms

Thank you!

Any questions?

Rules to get access to anti-complement therapies

Locale	Label-level eligibility (who qualifies)
United States (FDA)	- Complement-mediated kidney TMA - Not indicated for STEC-HUS - Ravulizumab: if ≥1 month old - Management by expert centers
European Union (EMA)	- complement-mediated kidney TMA - Exclude key mimics (TTP/ADAMTS13 and STEC-HUS) - Ravulizumab (aHUS): a) Body weight ≥10 kg, and either: b) Treatment-naïve, or c) switch from eculizumab - Management by expert centers
England (NHS / NICE)	- TMA confirmation + exclusion of alternatives - Eculizumab for aHUS -Ravulizumab for aHUS: - ≥10 kg, and either: - Complement-inhibitor naïve, or - Responded to ≥3 months eculizumab - Management by expert centers - Renewal based on response is common
Canada (CDA)	- Complement-mediated kidney TMA - Not indicated for STEC-HUS or TTP - Ravulizumab for aHUS (varies by province) - Renewal based on objective response