IPNA

IPNA teaching course
"Microangiopathic Hemolytic Anemia"

El Cairo, December 6th, 2023

Predictors of good and bad prognosis in atypical hemolytic uremic syndrome

Prof. Gema Ariceta
Pediatric Nephrology
Hospital Vall d' Hebron
Universitat Autonoma Barcelona

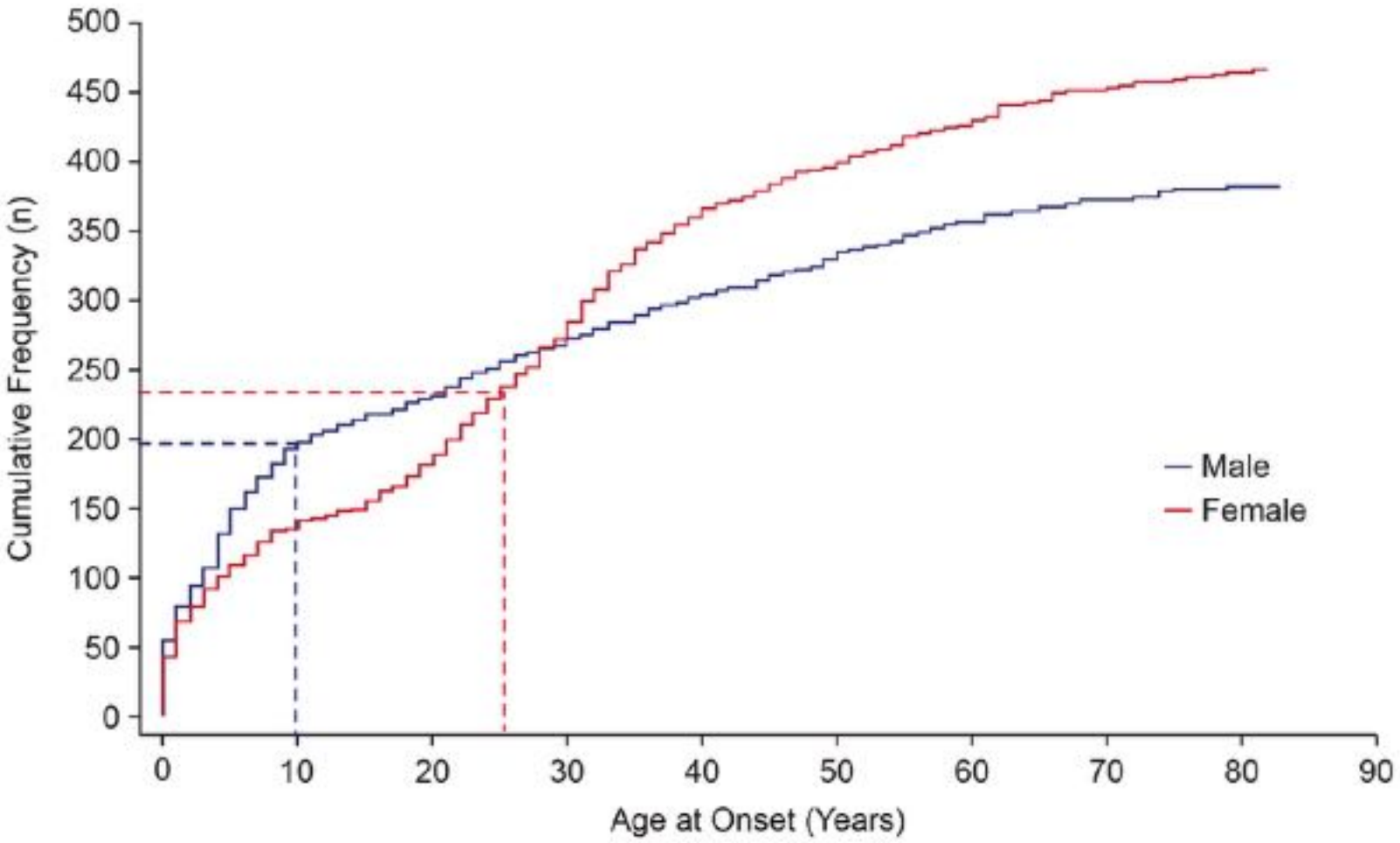
Disclosures

- Educational lectures sponsored by Alexion (Astra Zeneca Rare Diseases)
- Advisor (Alexion. (Astra Zeneca Rare Diseases)
- Member of the Scientific board if the Global aHUS Registry (Alexion)

Outline

- age: children vs. adults
- family history
- genetic risk: complement gene variant
- antiFH antibodies
- native kidneys vs. kidney transplantation
- trigger
- pregnancy
- complement blockade and discontinuation

Age at diagnosis of aHUS



Schaefer et al, Kidney Int, 2018

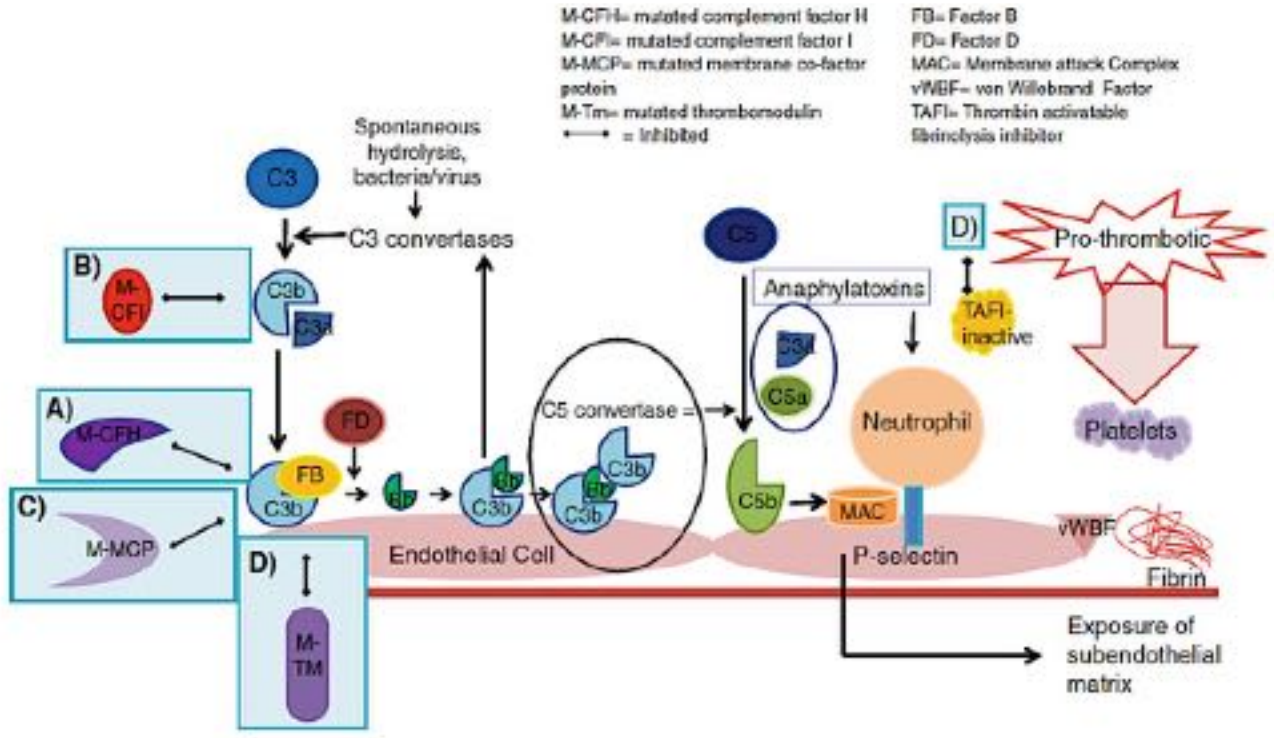
Patient characteristics at the onset of aHUS

Table 1. Patients' characteristics at onset

Characteristic	Children	Adults	*P* Value
Patients (*n*)	89	125	
Female/male (*n*/*n*)	42/47	93/32	<0.001
Mean age at onset (yr)	1.5 (0 to <15)	31 (15–85)	
Familial HUS history, *n* (%)	24 (26.9)	18 (14.4)	0.02
Triggering events, *n* (%)	42 (47)	41 (33)	0.03
Diarrhea	35 (39)	19 (15)	<0.001
Respiratory infections	7 (8)	1 (1)	0.03
Pregnancy		18/93 females (19.3)	
Neurologic involvement, *n* (%)	14 (16)[a]	10 (8)	0.08
Mean serum creatinine (μmol/L)	257 (28–990) (*n*=82)	640 (111–2408) (*n*=113)	<0.001
Dialysis required, *n* (%)	48/81 (59)	93/115 (81)	<0.001
Platelets count, *n* (%)			
$> 150 \times 10^9$/L	12/81 (15)	15/93 (16)	0.78
$100–150 \times 10^9$/L	9/81 (11)	22/93 (24)	0.02
$50–99 \times 10^9$/L	26/81 (32)	31/93 (33)	0.84
$< 50 \times 10^9$/L	34/81 (42)	25/93 (27)	0.05
Mean hemoglobin (g/dl)	6.8 (3–12) (*n*=84)	7.2 (5–11.8) (*n*=93)	0.004
Hemoglobin > 10 g/dl, *n* (%)	5/84 (6)	10/93 (11)	0.16
Complete triad, *n* (%)[b]	60/81 (74)	77/93 (83)	0.11

Fremeaux-Bacchi V. cJASN, 2013

Complement dysregulation leads to the development of aHUS



Keir L, Coward RJ. *Ped Nephrol.* 2011;26:523-533.

Gene	% of cases
CFH + *CFH/CFHR* hydrid genes	25-30
CFI	4-10
C3	2-10
THBM	3-4
MCP	10-15
CFH Ab	5-10
No mutations	~ 40

Mele C, Remuzzi G, Noris M. Semin Immunopathol, 2014; Fakhouri F, Loirat C, Semin Hematol, 2018

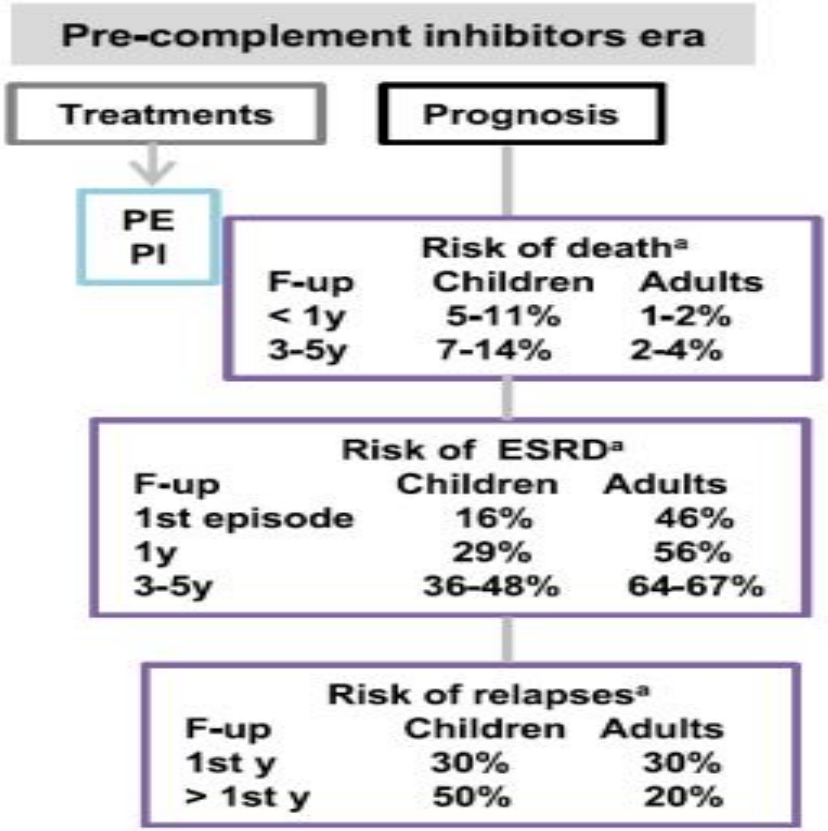
Noris et al, Clin J Am Soc Nephrol. 2010;

Genetic Complement Abnormalities in Sporadic and Familial aHUS, their Impact on Clinical Phenotype and outcome with plasma (The Italian experience)

Alteration in	ESRF or Death (3 years)	Response to Plasma (outcome of episode = CR or PR/total of treated episodes)	Good Kidney Transplantation Outcome (at 1 year)
CFH	49 (77%)	57 (63%)	5 (29%)
CFI	6 (60%)	2 (25%)	2 (33%)
C3	8 (67%)	8 (57%)	4 (57%)
THBD	7 (54%)	7 (88%)	0
MCP	1 (6%)	28 (97%)	3 (100%)
CFH Ab	5 (63%)	9 (75%)	0
Non mut	60 (50%)	71 (69%)	12 (41%)
Sporadic	83 (49%)[a]	139 (69%)	19 (46%)
Familial	53 (74%)	43 (68%)	7 (30%)
Children	70 (48%)[b]	131 (78%)[c]	8 (33%)
Adults	63 (67%)	51 (53%)	18 (45%)

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

aHUS outcome before eculizumab
The French experience



Fakhouri F, Loirat C. Semin Hematol. 2018

aHUS treatment with plasma (before eculizumab)

Plasmaexchange / plasma infusion in aHUS:

- uncertain benefit
- hematological remission
- impaired kidney function persists

- In 71 children treated with plasma:

Hematologic remission: 11.5 days (11% active on day + 33)
Dialysis: 17% on day + 33

High rate of side effects:

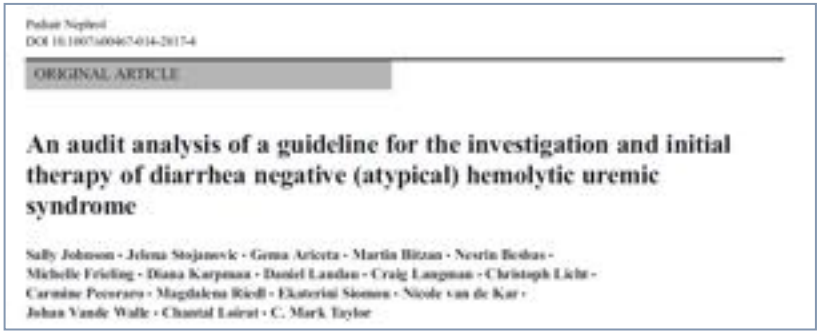
Hypertension (23%)

Central vein obstruction (20%)

Clotting (18%)

Catheter-related infections (16%)

Thrombosis (12%)


Pediatr Nephrol
DOI 10.1007/s00467-014-2817-4

ORIGINAL ARTICLE

An audit analysis of a guideline for the investigation and initial therapy of diarrhea negative (atypical) hemolytic uremic syndrome

Sally Johnson · Jelena Stojanovic · Gema Ariceta · Martin Bitzan · Nesrin Besbas · Michelle Frieling · Diana Karpman · Daniel Landau · Craig Langman · Christoph Licht · Carmine Pecoraro · Magdalena Riedl · Ekaterini Siomou · Nicole van de Kar · Johan Vande Walle · Chantal Loirat · C. Mark Taylor

Rizvi et al. Transfusion, 2000. McMinn et al. Transfusion, 2003. Howard et al. Transfusion, 2006. Johnson et al, Pediatr Nephrol, 2014

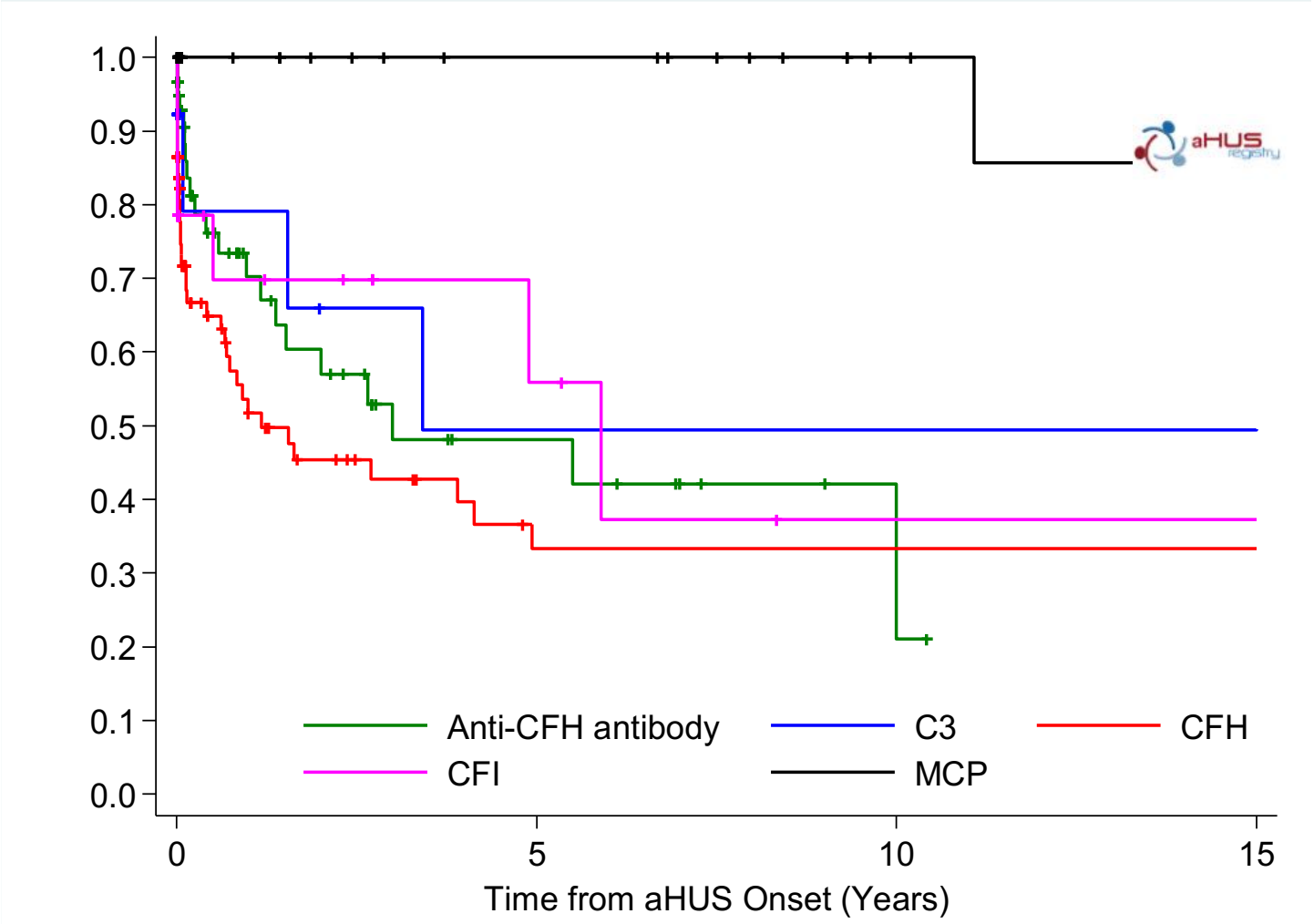
Plasma Support is Life-disrupting, Associated With Fatal Complications and Requires Proximity to Experienced Centers

Plasma exchange; Oklahoma HUS/TTP Registry (n=249)[4]

Complication	No. (%)	Comments
Death due to catheter complications	7 (3%)	Bacterial sepsis from catheter ; hemorrhage from catheter insertion
Nonfatal cardiac arrest	2 (1%)	Right ventricle perforation by catheter insertion guide wire with cardiac tamponade ; plasma allergic reaction
Catheter insertion complications	5 (2%)	Pulmonary and retroperitoneal hemorrhage requiring transfusion; pneumothorax requiring chest tube
Systemic infection	29 (12%)	Documented bacteremia or fungemia ; suspected bacteremia treated with systemic antibiotics
Catheter obstruction	17 (7%)	Requiring catheter removal and insertion of a new catheter
Hypotension	7 (3%)	Requiring vasopressor treatment
Venous thrombosis	5 (2%)	Requiring anticoagulant treatment

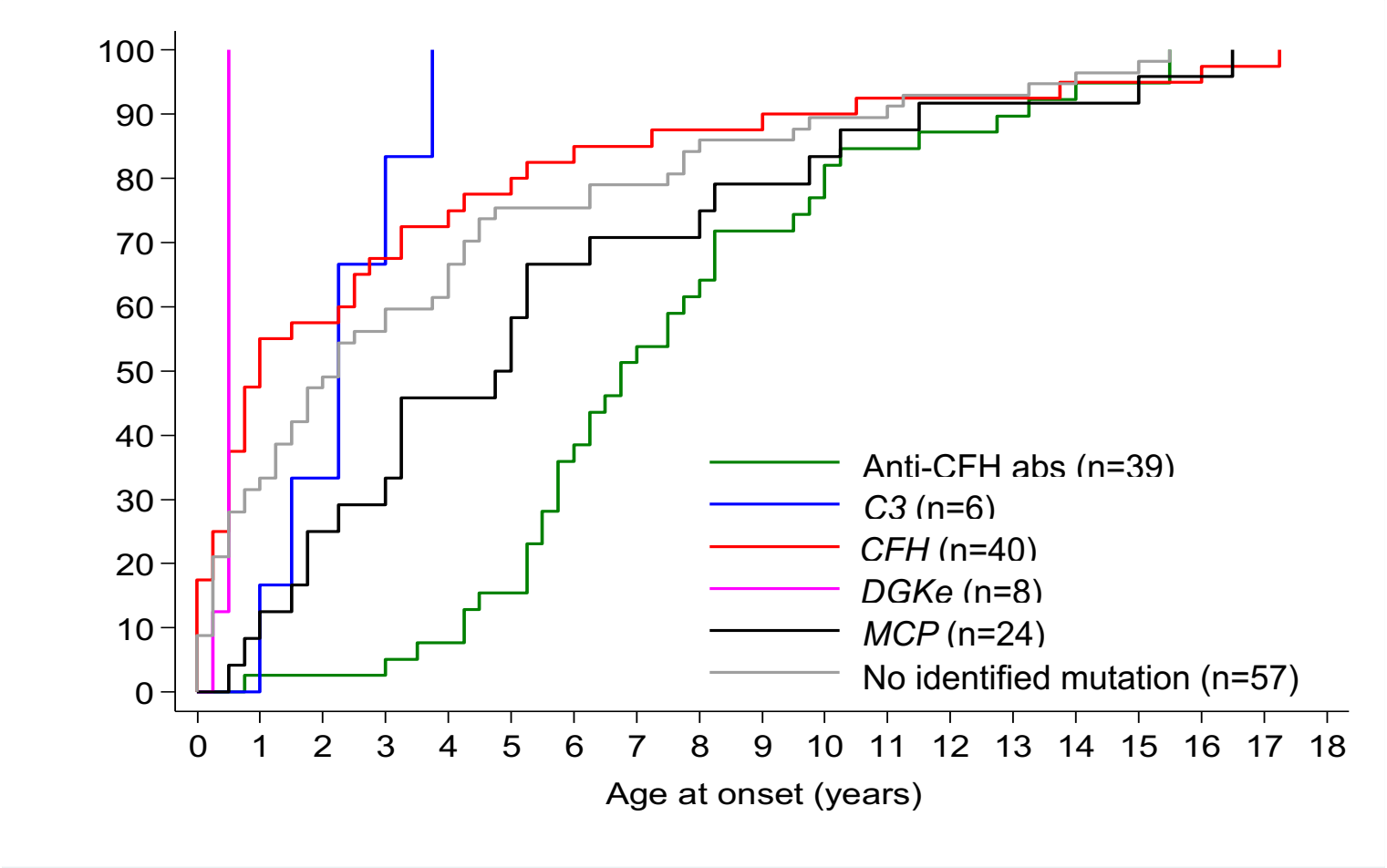
1. Rizvi et al. *Transfusion*. Vol 40. August 2000. 2. McMinn et al. *Transfusion*. Vol 43. Mar 2003. 3. Howard et al. *Transfusion*. Vol 46. Jan 2006. 4. George et al. *Blood*. 2010;116(20):4060-69.

Kidney survival in aHUS based on complement gene mutation



Schaefer et al, Kidney Int, 2018

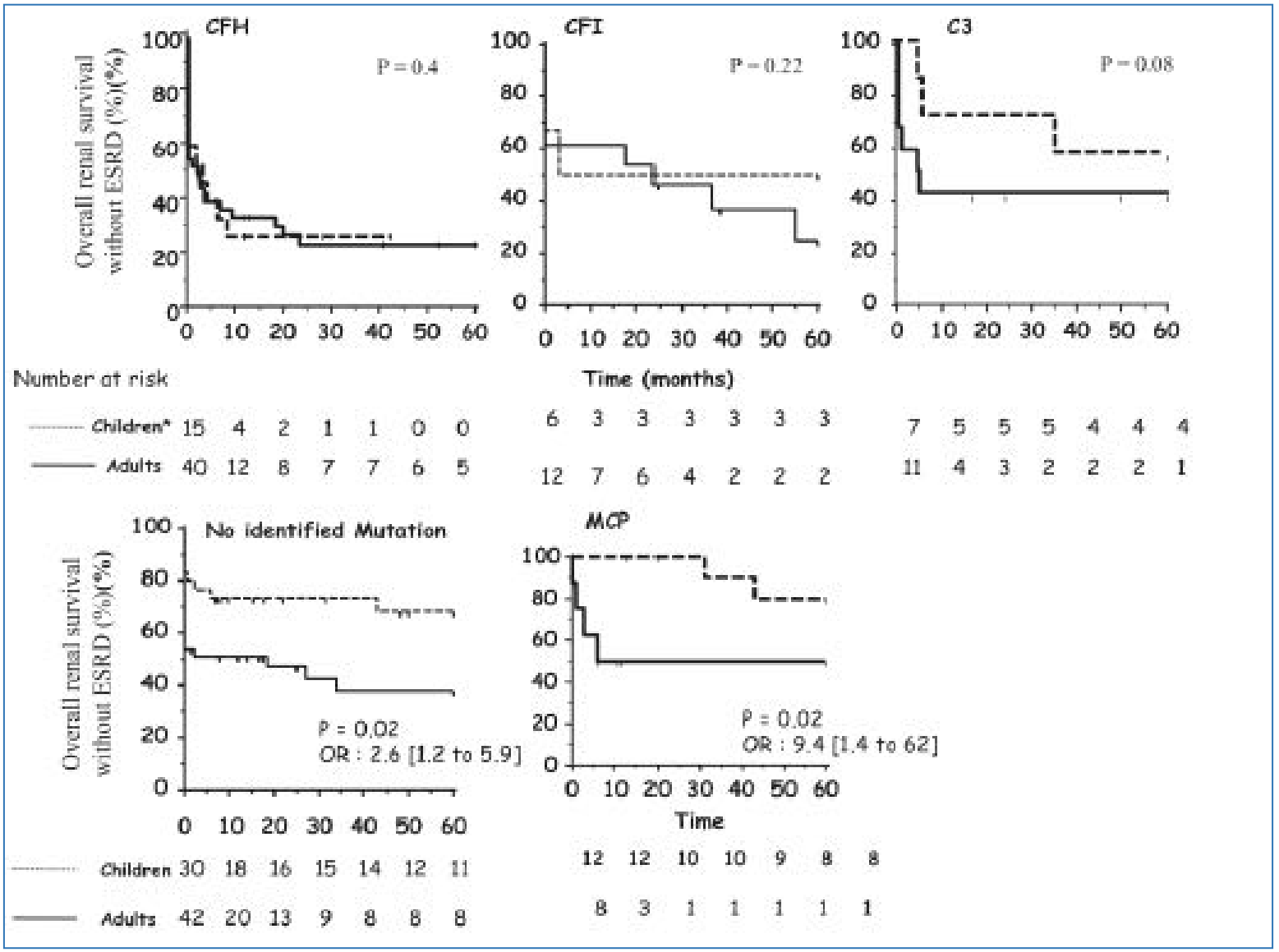
Age of Onset by Abnormality
Paediatric Patients Only



Note: Only patients with single mutations were included. Patients with ≥1 identified mutations were excluded.
abs, antibodies; *CFH*, complement factor H; *DGKe,* diacyl glycerol kinase epsilon; *MCP,* membrane cofactor protein.

Schaefer et al, Kidney Int, 2018

aHUS outcome in children vs adults by C' gene mutations



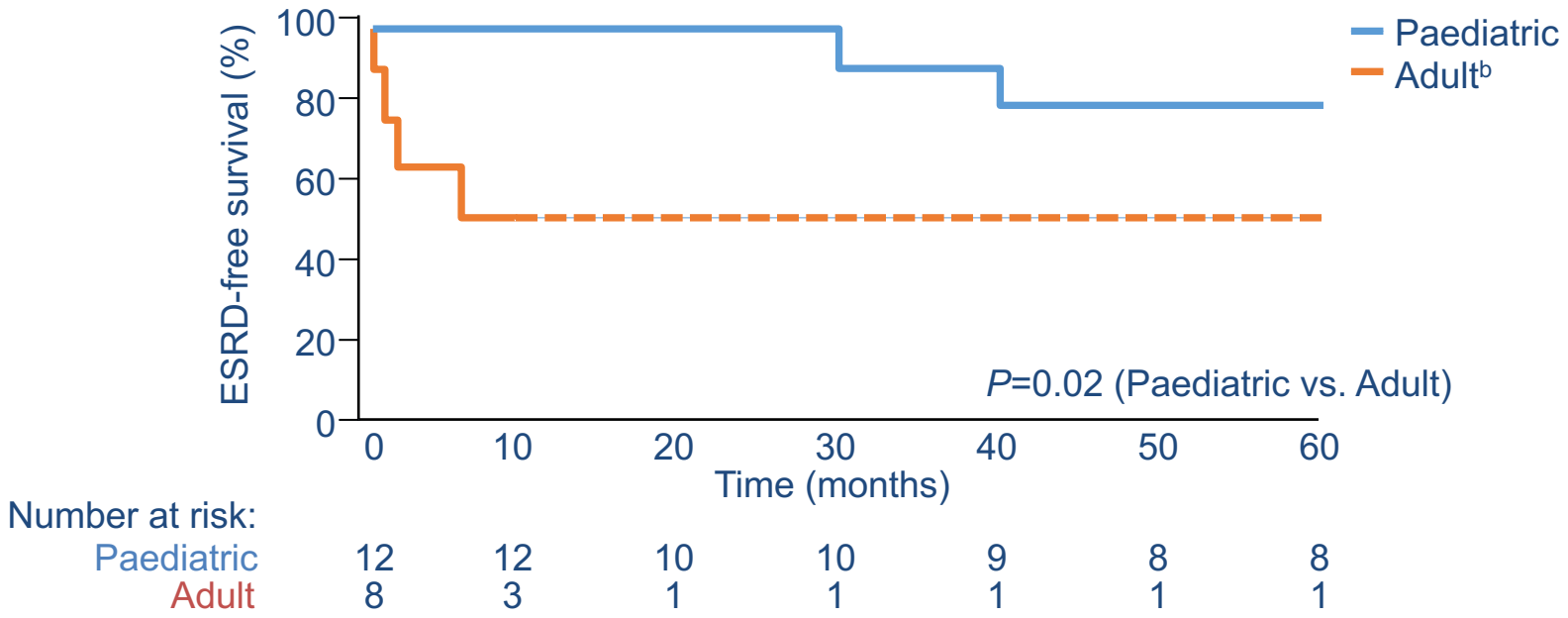
Frémeaux-Bacchi et al. CJASN, 2013

Risk of ESRD or Death Varies for Patients with *MCP* Mutations Depending on Age and the Presence of Other Complement Mutations[1,2]

- While paediatric patients with isolated *MCP* mutations experience the highest risk of subsequent TMA manifestations, their long-term outcomes are less severe[1,3] Adult patients with isolated *MCP* mutations experience poor outcomes similar to those with other mutations[1]

- 22.6% of Patients With MCP Mutations Show Mutations in Other Complement Genes & worse outcome

Estimated rate of ESRD or death is significantly different between paediatric and adult patients with aHUS and an isolated *MCP* mutation[1,a]



[a] Pre-eculizumab era.; [b] Line becomes dotted where the number of patients at risk falls below 5.

1. Frémeaux-Bacchi V, et al. *Clin J Am Soc Nephrol*. 2013;8:554-562. 2. Bresin E, et al. *J Am Soc Nephrol*. 2013;24:475-486. 3. Campistol JM, et al. *Nefrologia*. 2015;35:421-427.

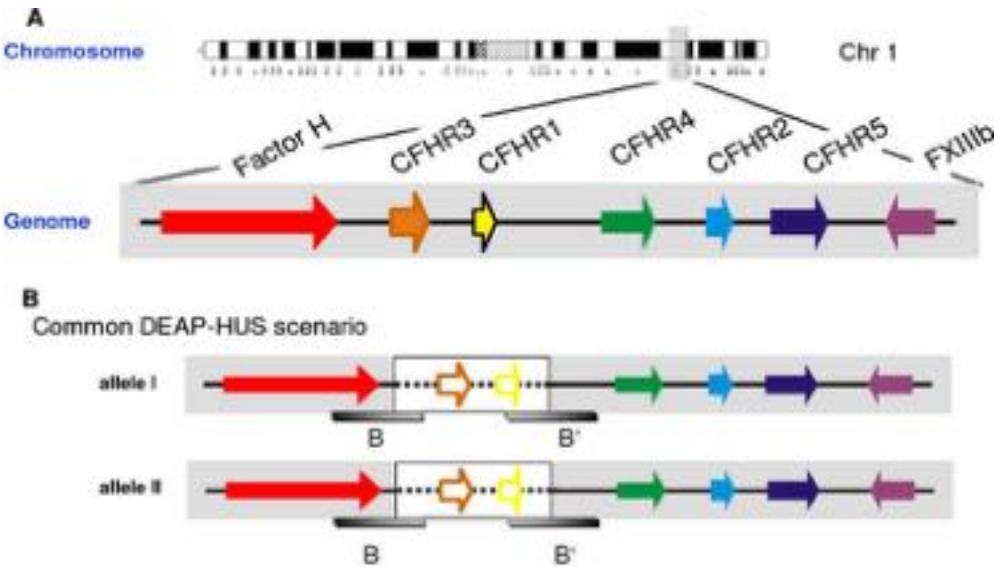
Phenotype-genotype relationship in aHUS

gene	frequency	age of onset	outcome
FH	15-30%	infants (<1 year)	ESKD common 1st episode 70-80% dialysis in 5-10 y 80-90% recurrence after KTx
MCP / CD46	10-15%	children (m 4 years)	ESKD uncommon 1st episode 20-30 dyalisis in 5-10 y rarely recurrence after KTx
FI	5-10%	infants (<1 year)	ESKD common 1st episode 70-80% dialysis in 5-10 y 80-90% recurrence after KTx
FB	1-2%	infants	Few data 70-80% dialysis in 5-10 y 100%recurrence after KTx (3 cases)
C3	5-10%	Variable	Few data 50-60% dialysis in 5-10 y 50% recurrence after KTx
antiFH Ab	6-11%	3-17 years	Early plasmaexchange and IS lead to remission. KTx successful with low Ab

Sánchez-Corral P, Melgosa M. BJH, 2010; 150: 529-542

CFHR proteins deficiency and FH auto-Ab

- 10% aHUS cases
- "juvenile" HUS (3-17 y. age)
- + FH autoantibodies
- aHUS risk is linked to the titer of anti-FH ab

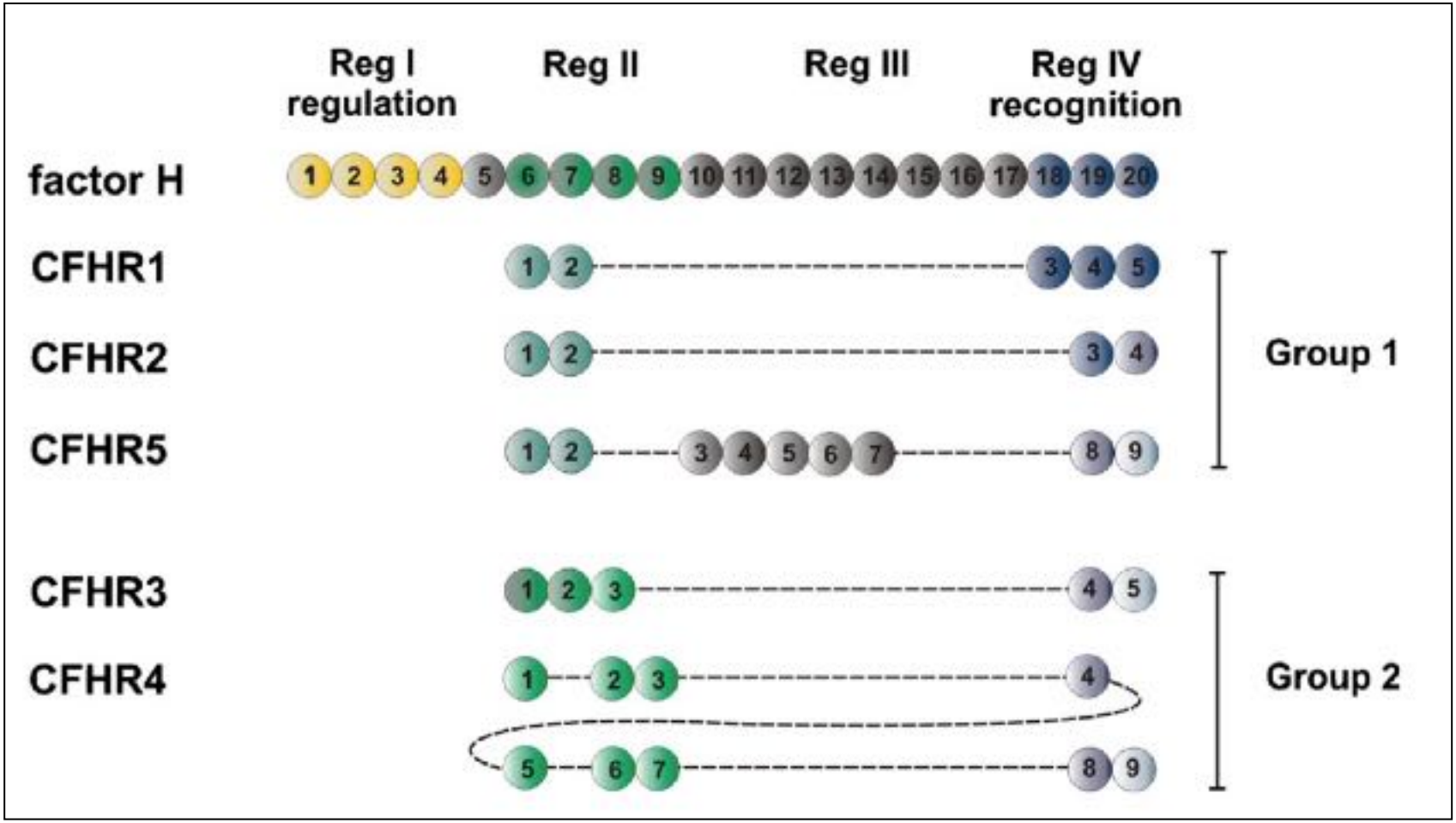


- Chromosome 1q32 (84kb deletion) involving CFHR1 and CFHR3 genes (encodes proteins that represent C3 convertase C3bBb components or regulators)
- Non- standardized treatment:
  1. plasma exchange + immunosuppressors (corticosteroids, MMF, RTX)
  2. C5 blockade
- Its is unclear how FH autoAb develop, how long are they expressed before HUS onset, and how long FH autoAb persist

Skerka C et al. Thromb Haemost 2009; Dragon-Durey MA, et al. JASN, 2010; Lee et al. Pediatr Int. 2015 , Brocklebank et al. Kidney Int, 2017

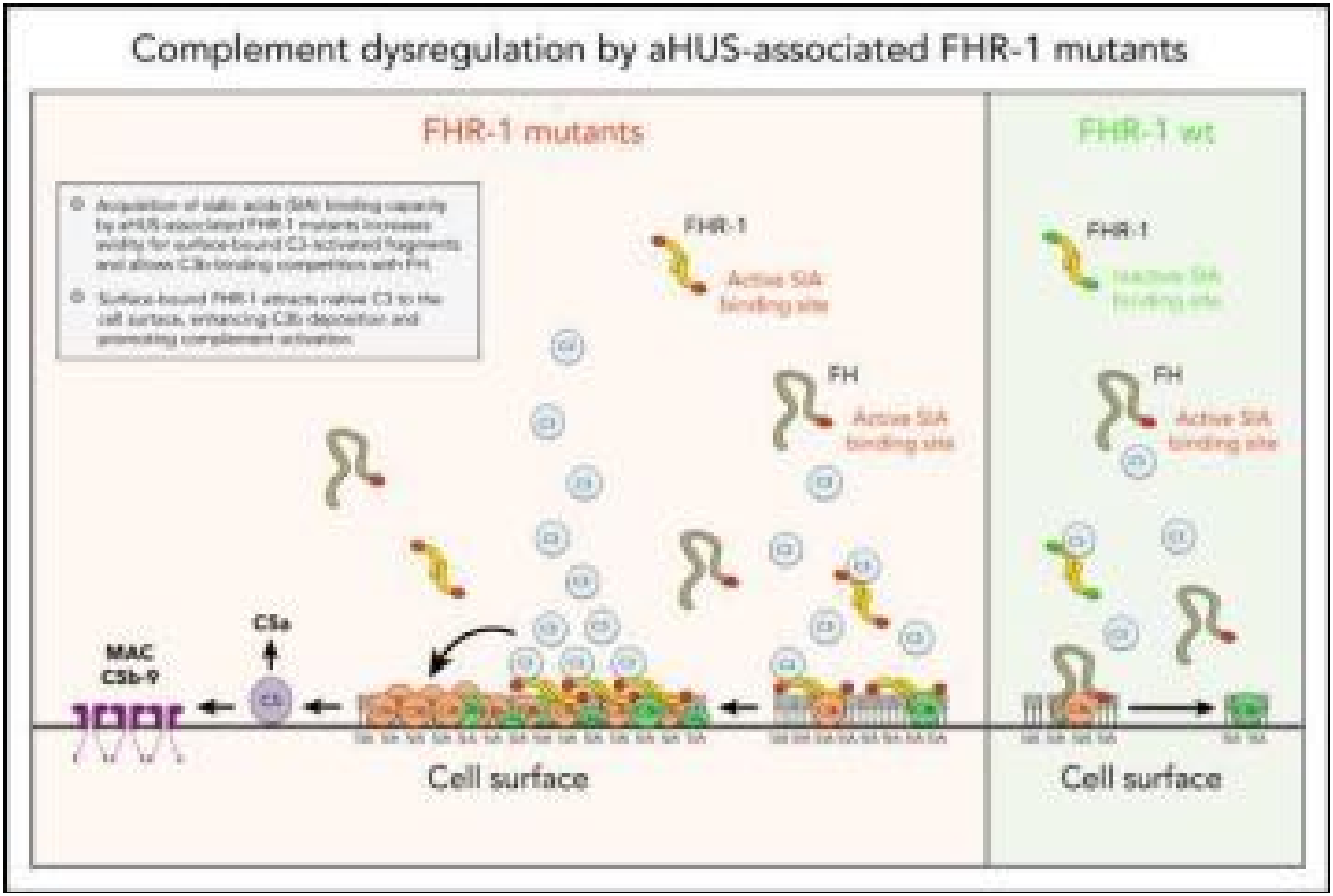
FH related proteins family (CFHRs

FHR-1 lacks the complement-regulatory domains of FH but presents a highly conserved FH-like C-terminal surface-recognition domain



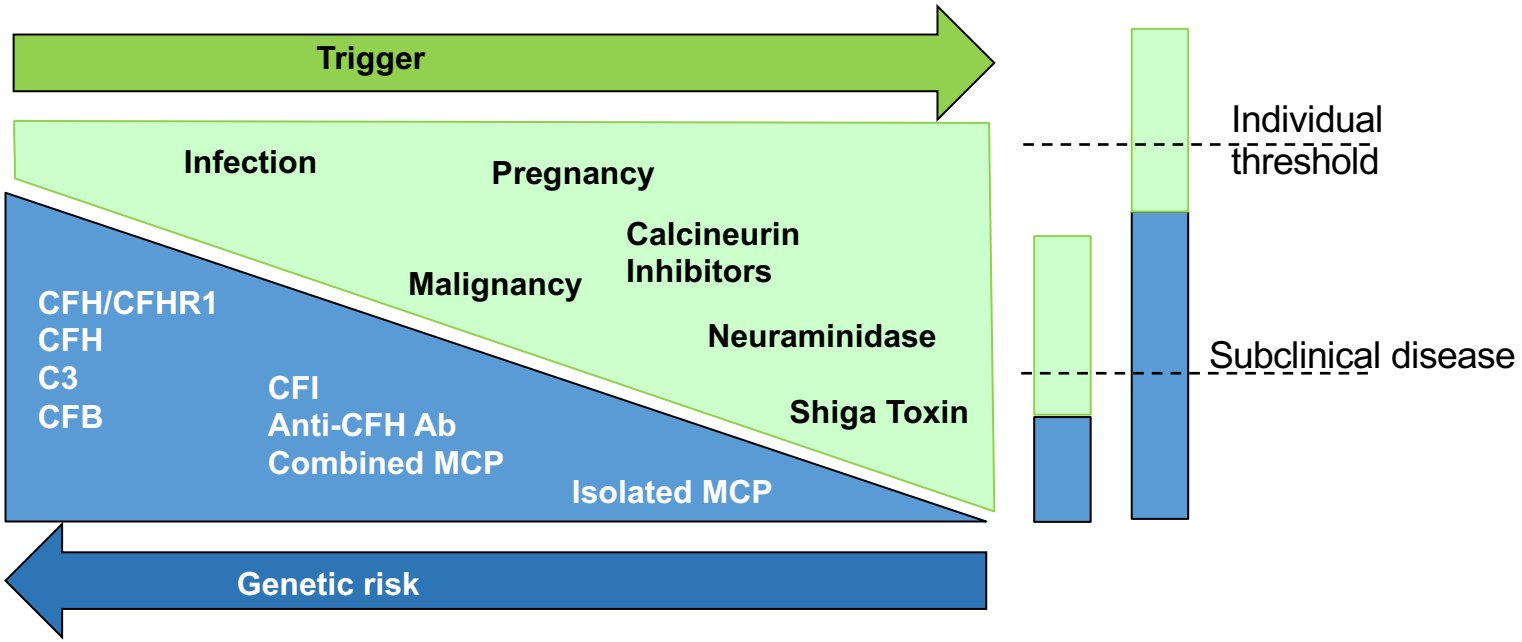
Trends in Immunology June 2015, Vol. 36, No. 6

CFH, antiFH ab and C3b regulation



Sánchez-Corral P, et al . Front. Immunol. 2018; 9:1607
Martin Merinero H, Blood 2021.

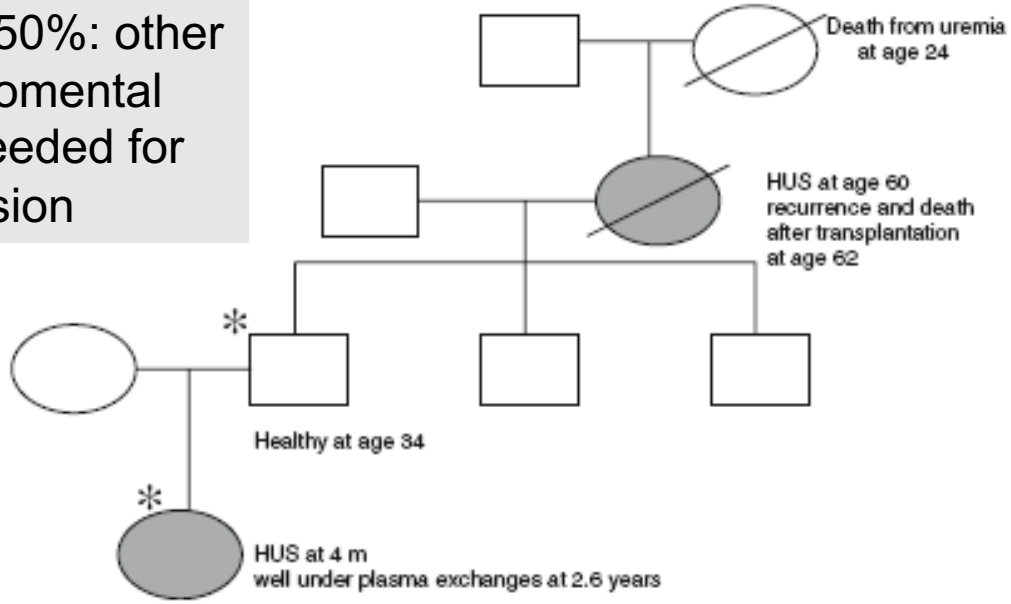
Risk factors and triggers for aHUS: two hit hypothesis



Adapted from Riedl M et al, Semin Thromb and Hemostasis 2014

Intrafamilial phenotype variability in a family with heterozygous CFH mutation

In mutation carriers, aHUS penetrance is ≈50%: other genetic or enviromental modifiers are needed for disease expression



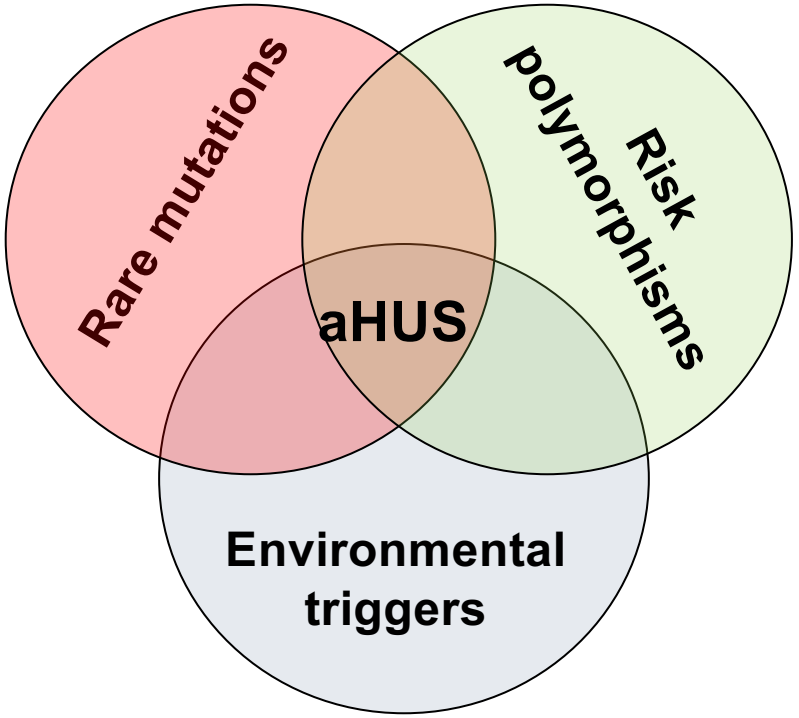
Loirat C et al. Pediatr Nephrol, 2008.

Concurrence of multiple risk factors to develop aHUS

- The overall genetic predisposition to aHUS of an individual results from the combination of different inherited and environmental factors

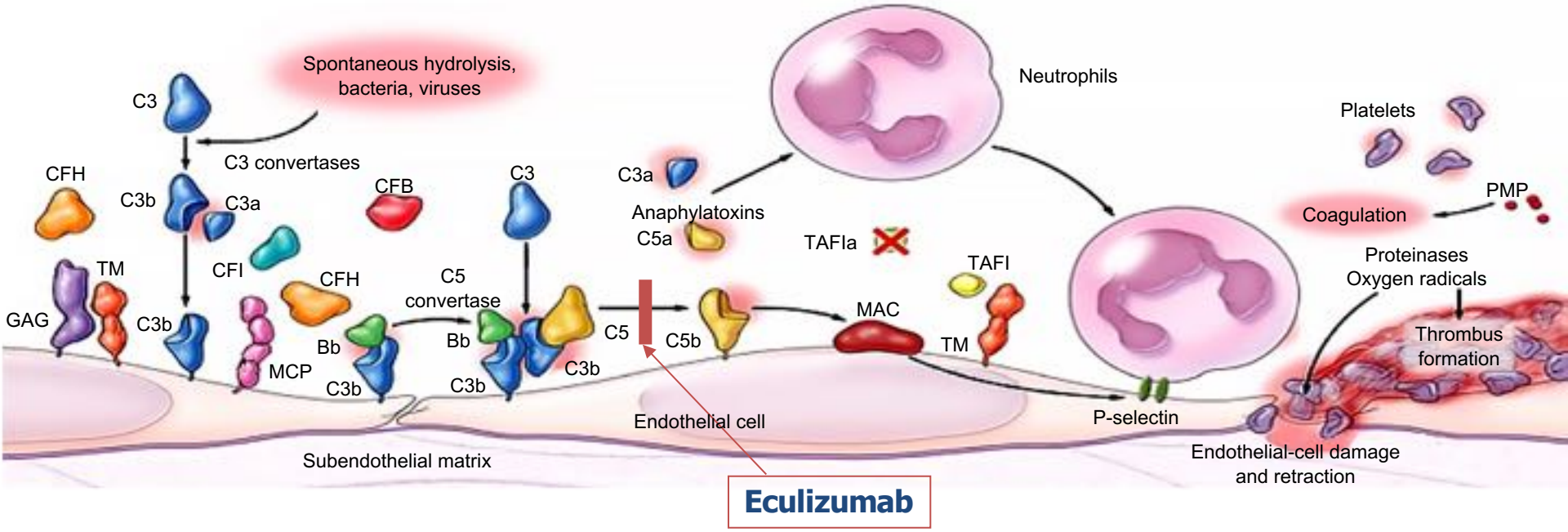
- Incomplete penetrance of aHUS in carriers of mutations is common to all aHUS-associated complement genes: ~50%

- **Combined mutations or concurrence of mutations with risk polymorphisms increase disease penetrance and influence clinical phenotype**



Bresin E et al. J Am Soc Nephrol. 2013;24:475-86.
Caprioli J et al. Hum Mol Genet. 2003;12:3385-95. Esparza-Gordillo J et al. Hum Mol Genet. 2005;14:703-12.
Esparza-Gordillo et al. Mol Immunol. 2006;43:1769-75. Goicoechea de Jorge E et al. Proc Natl Acad Sci USA. 2007;104:240-5.
Martinez-Barricarte et al. J Am Soc Nephrol. 2008;19:639-46. Pickering et al. J Exp Med. 2007;204:1249-56.

Eculizumab: Terminal Blockade of the Alternative Complement Pathway



Noris, Remuzzi. *N Engl J Med.* 2009;361:1676-87.

is aHUS diagnosis based on the detection of C' gene mutations ?

• In aHUS there is no difference in severity of disease for patients with an Identified mutation compared to those with no identified mutation

•aHUS patients present C' activation, despite gene mutation and even in those without an identified mutation

•aHUS diagnosis and treatment is an life-emergency

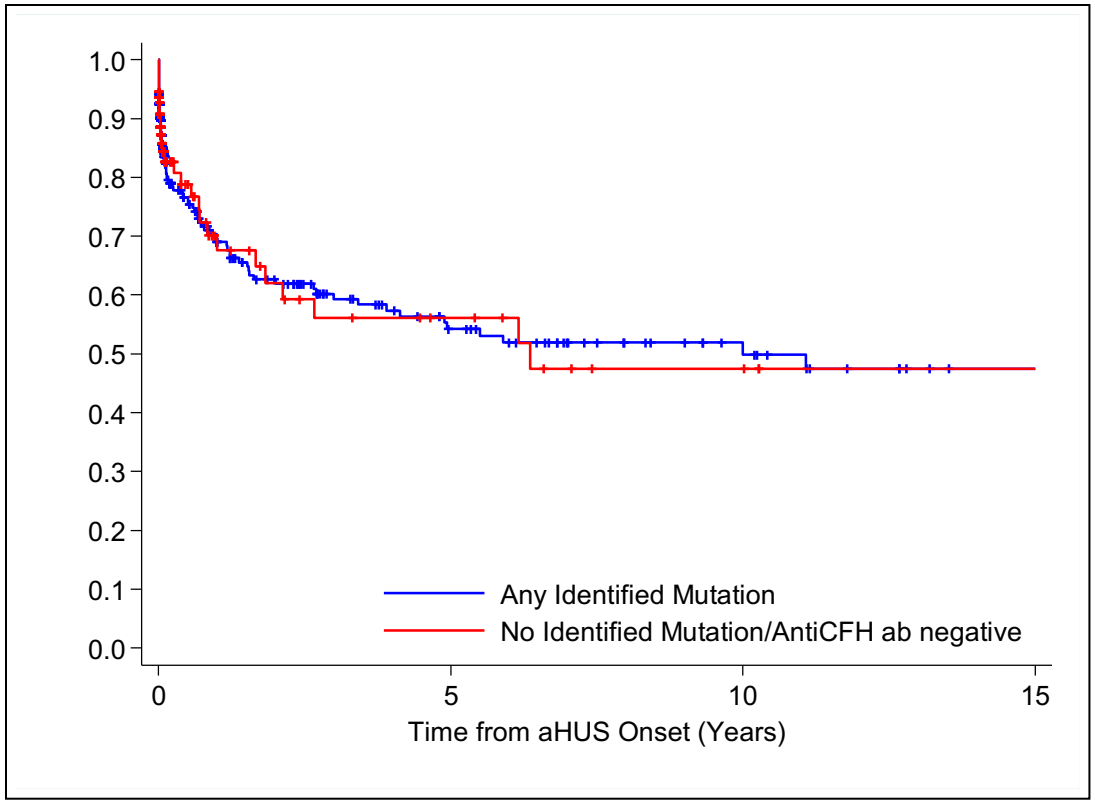
•In aHUS, response to complement blockage treatment (eculizumab) is similar in patients with and without mutations

• response to treatment is time-dependent

•at least 40% patients with aHUS and non-identified mutation or abnormalities

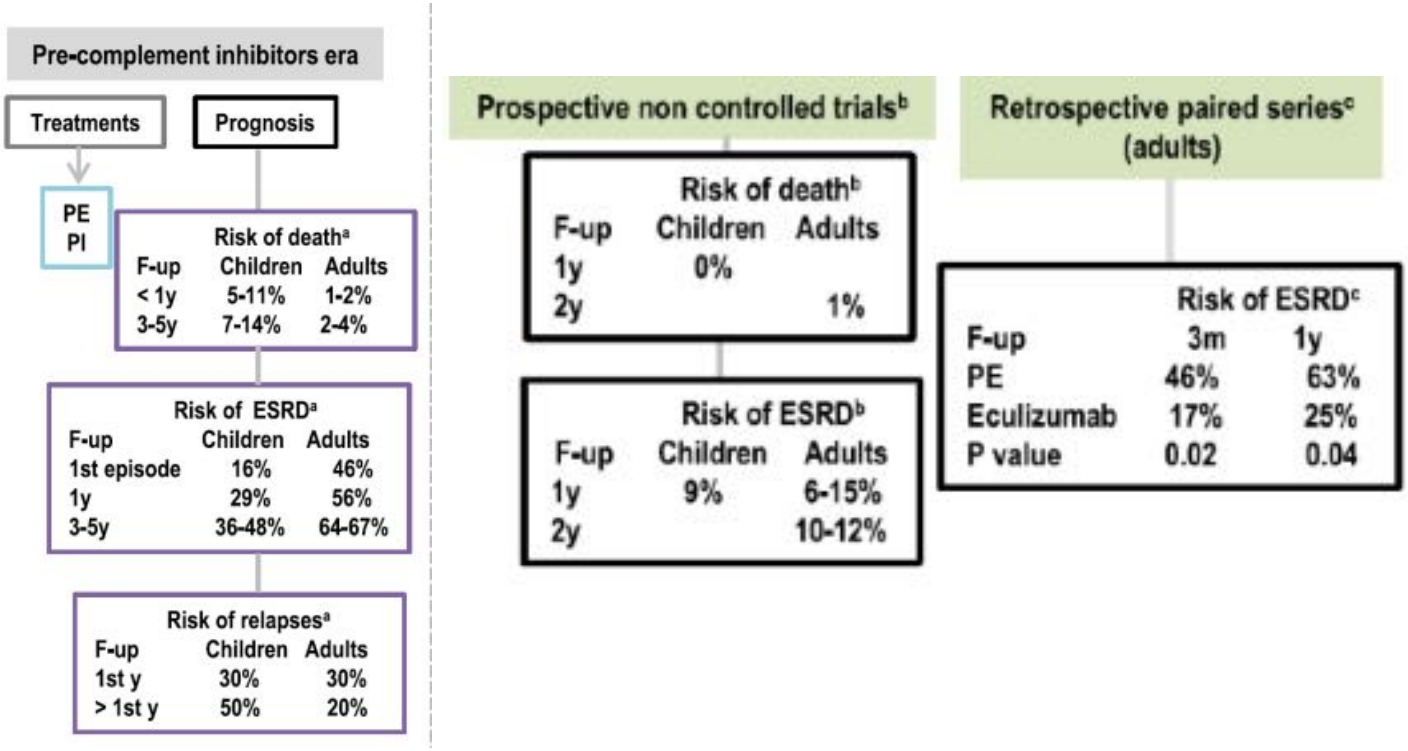
Loirat C et al. Pediatric Nephrology, 2015, Fakhouri F et al. Lancet, 2017)

Renal survival in aHUS patients treated with eculizumab and complement genetic pathogenic variants / anti CFH antibodies



Schaefer et al, Kidney Int, 2019

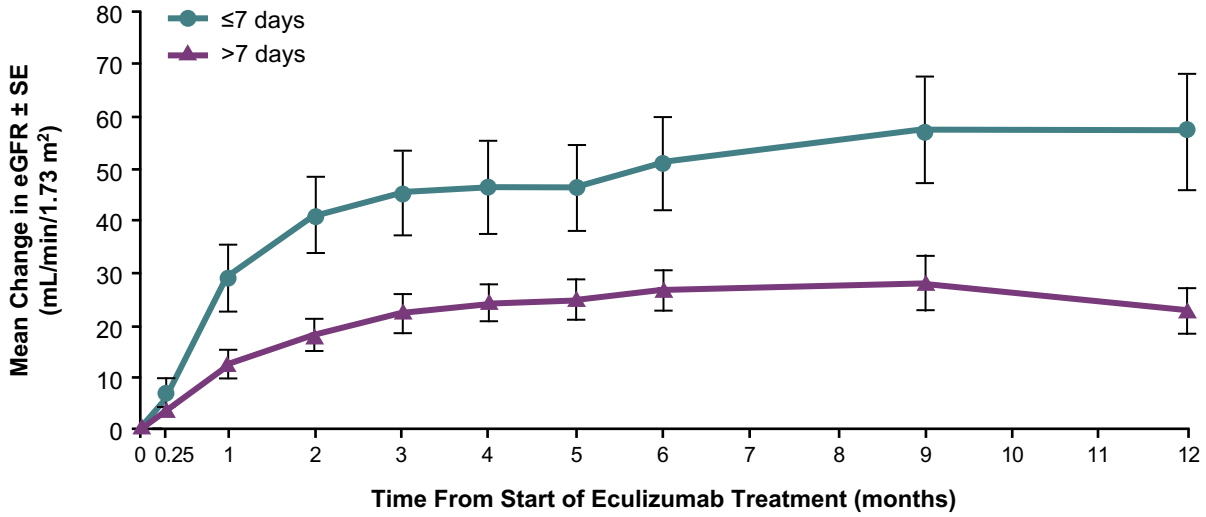
aHUS outcome before and after eculizumab



Fakhouri F, Loirat C. Semin Hematol. 2018

Earlier Eculizumab Initiation Leads to Improved Renal Recovery

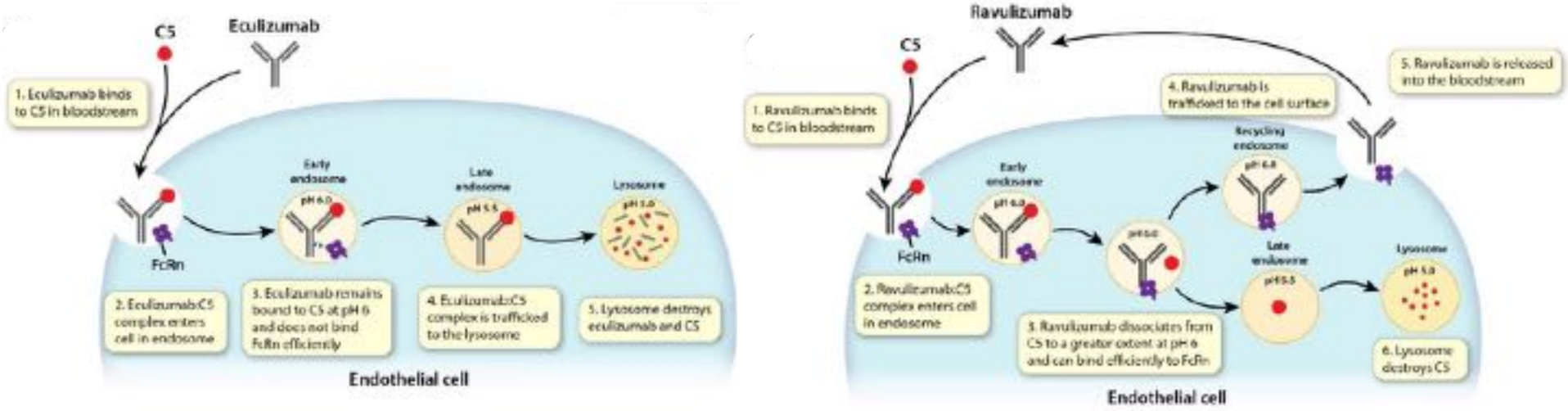
- Retrospective analysis with pooled data from 4 prospective clinical studies
- Evaluated changes in eGFR in patients initiating eculizumab ≤7 days or >7 days after onset of last TMA manifestation



Patients (N)												
Treatment Initiated in	≤7 days	21	20	18	20	20	19	19	20	17		14
	>7 days	76	74	69	74	74	75	72	74	60		54

Vande Walle et al. *J Nephrol*. 2017;30(1):127-34.

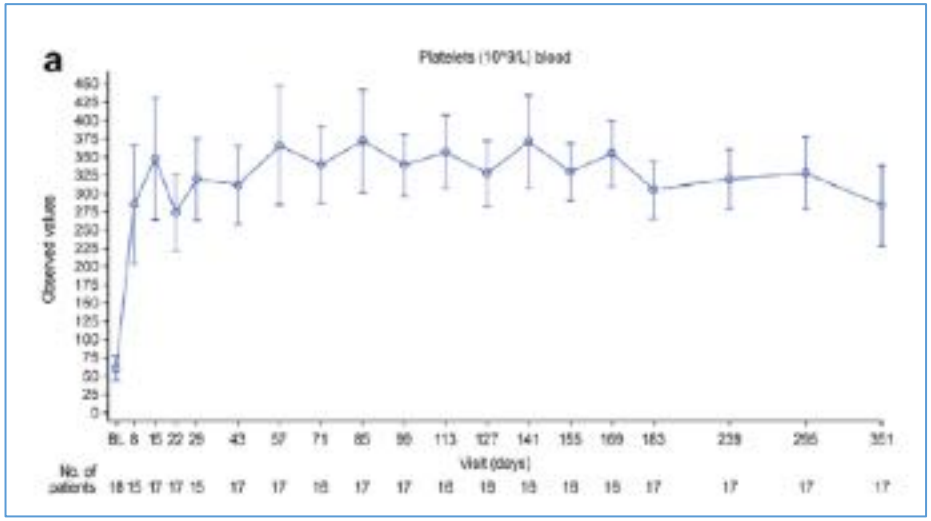
Eculizumab and Ravulizumab mechanism of action



Ravulizumab, is a new long-acting next-generation C5 inhibitor approved for treatment of PNH and aHUS, was engineered from eculizumab. The mean terminal half-life of ravulizumab is 53.7 (SD = 16.7) days, whereas the mean elimination half-life of eculizumab is 11.3 (SD = 3.4).

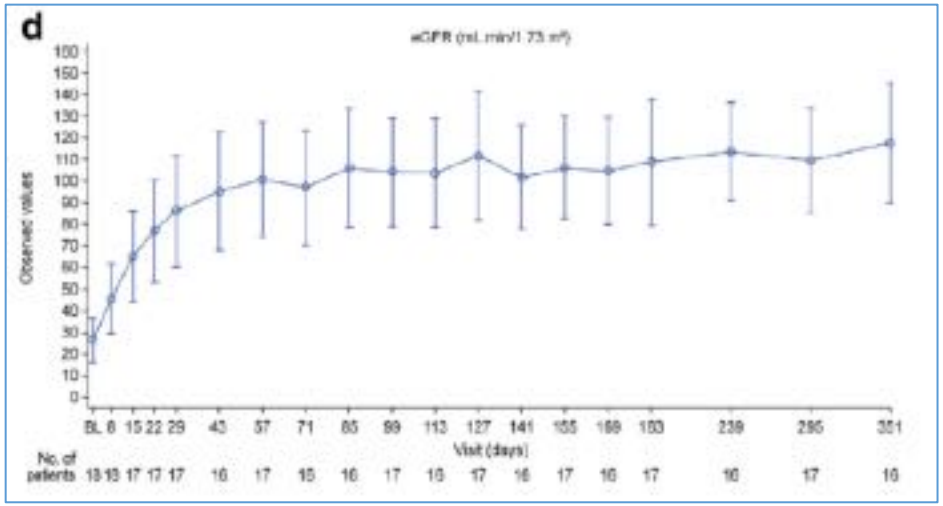
Dixon BP. J Clin Pharm Ther. 2022

Ravulizumab new next generation long-life C5 inhibitor is approved for aHUS



median Δ eGFR **79.0 mL/min/1.73 m²** day +183

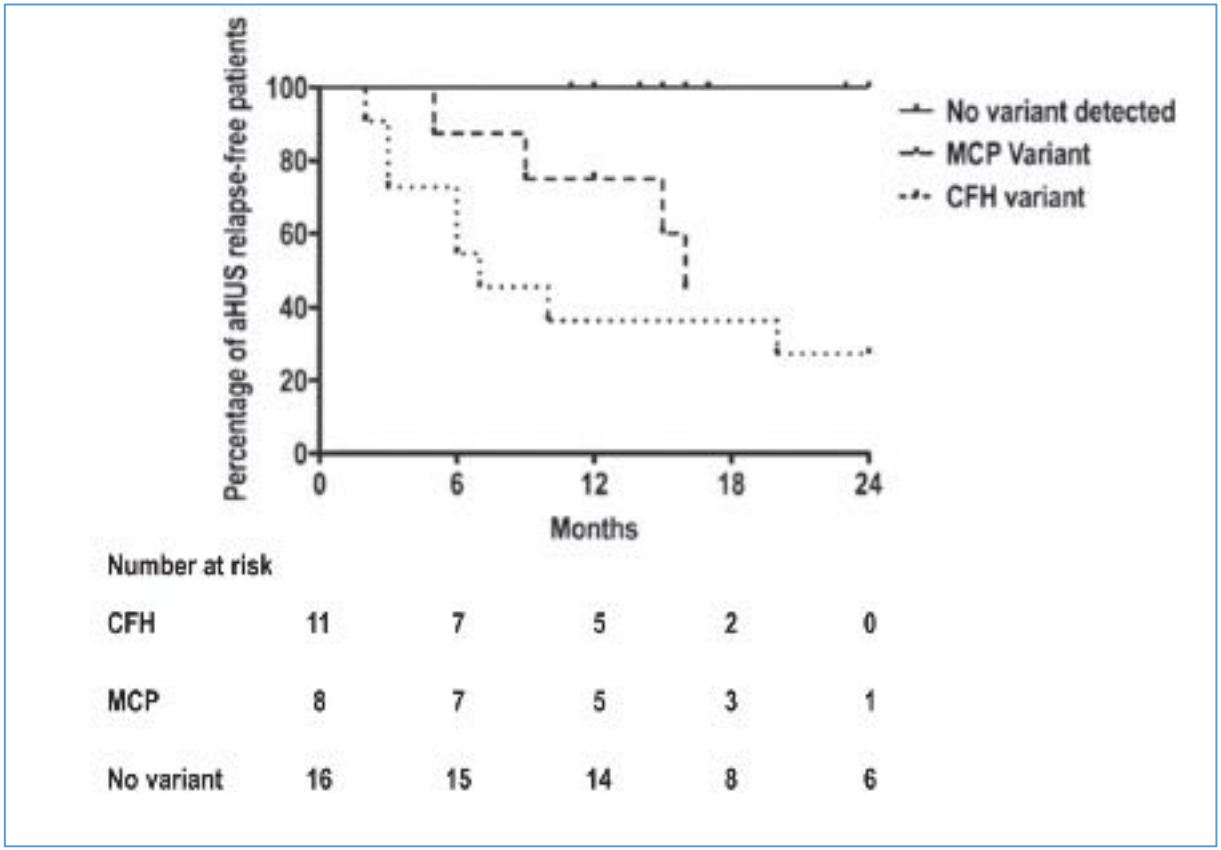
4 out 5 patients on dialysis at baseline, discontinued dialysis within the first month receiving ravulizumab



Ariceta et al Kidney Int. 2021

genotype and recurrence risk after Ecu cessation

Pathogenic variants in complement genes were associated with higher risk of aHUS relapse after eculizumab discontinuation



Number at risk					
CFH	11	7	5	2	0
MCP	8	7	5	3	1
No variant	16	15	14	8	6

Fakhouri F et al. CJASN 2017

How to minimize the infection risk associated with Eculizumab/Ravulizumab ?

1) **Meningococcal vaccination is mandatory 2 weeks before treatment**

   Quadrivalent conjugate vaccine (anti-A, C, Y, W) + Anti-B vaccine

In case of emergency: antibiotics

2) **Other vaccines:**

   - regular vaccination is recommended and there is not contraindication of varicella, measles, rubella, or attenuated virus
   - vaccination against capsulated bacteria is mandatory:
   - Strep. Pneumoniae
   - Haemophilus influenzae B

3) **influenza**

4) **Patient safety card and alert to fever**

Loirat et al. *Pediatr Nephrol.* 2016;31:15-39. US Food and Drug Administration. Soliris (eculizumab) [prescribing information]. Cheshire, CT: Alexion Pharmaceuticals, Inc., 2015. Eculizumab Summary of Product Characteristics. Alexion Europe SAS, 2014.

Thank you very much for your attention

Questions ?