Eculizumab in aHUS: where do we stand in 2016

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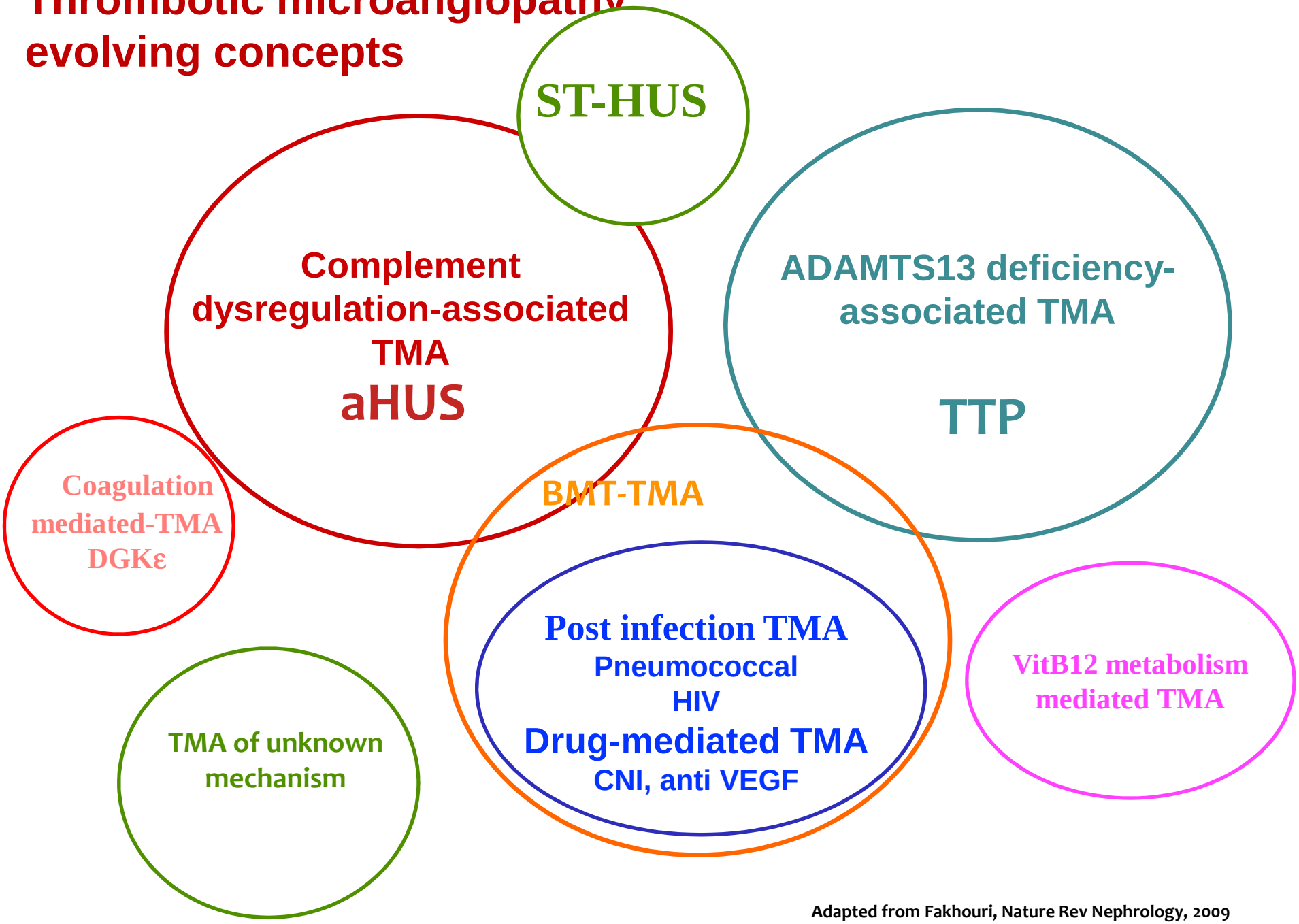
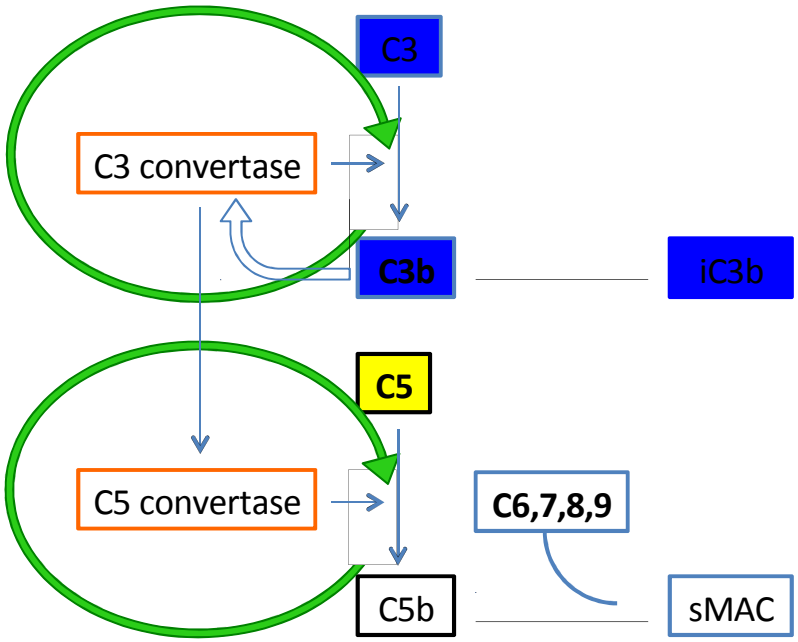
INSERM UMR S-1064

Thrombotic microangiopathy: evolving concepts



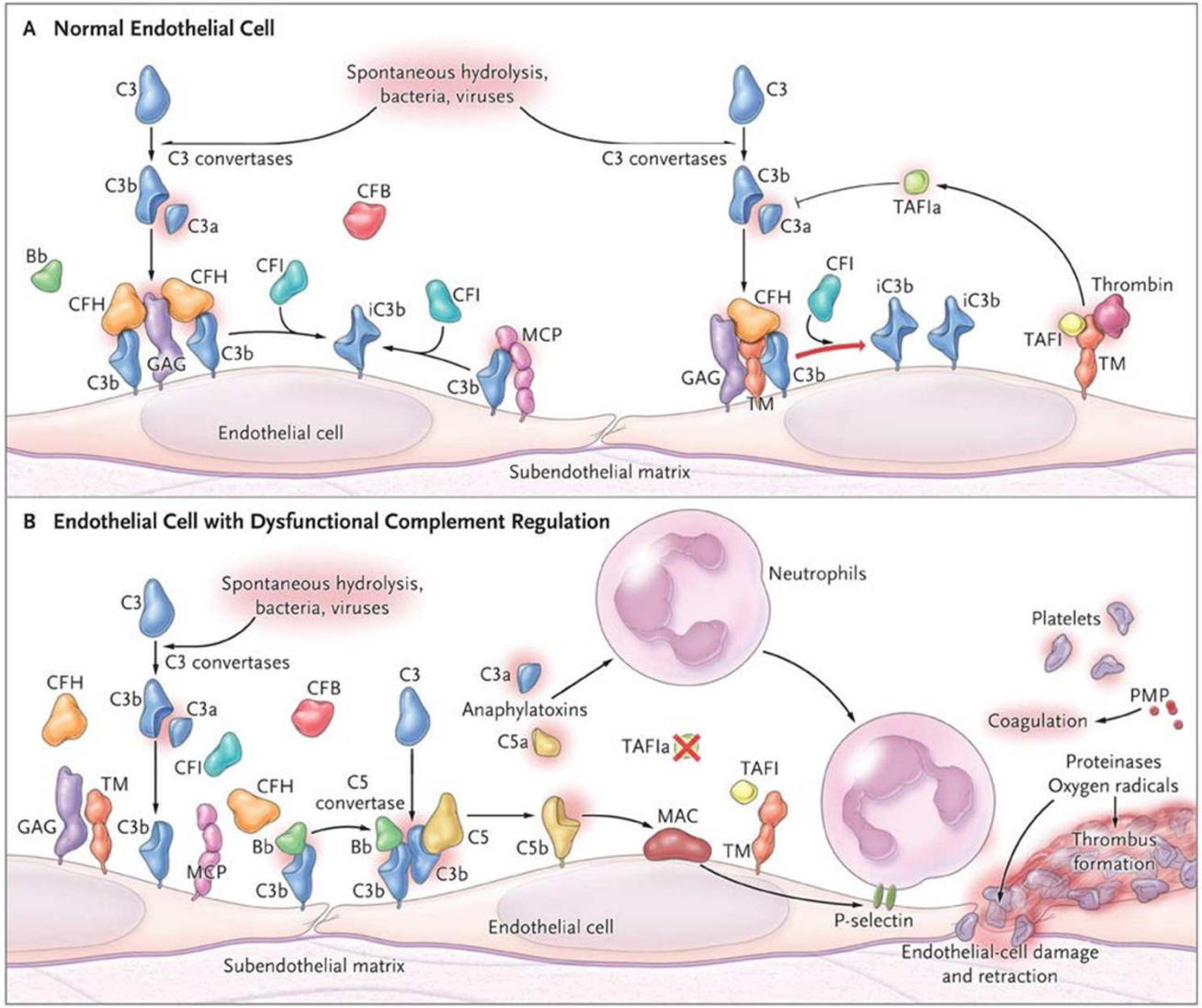
Adapted from Fakhouri, Nature Rev Nephrology, 2009

Complement system



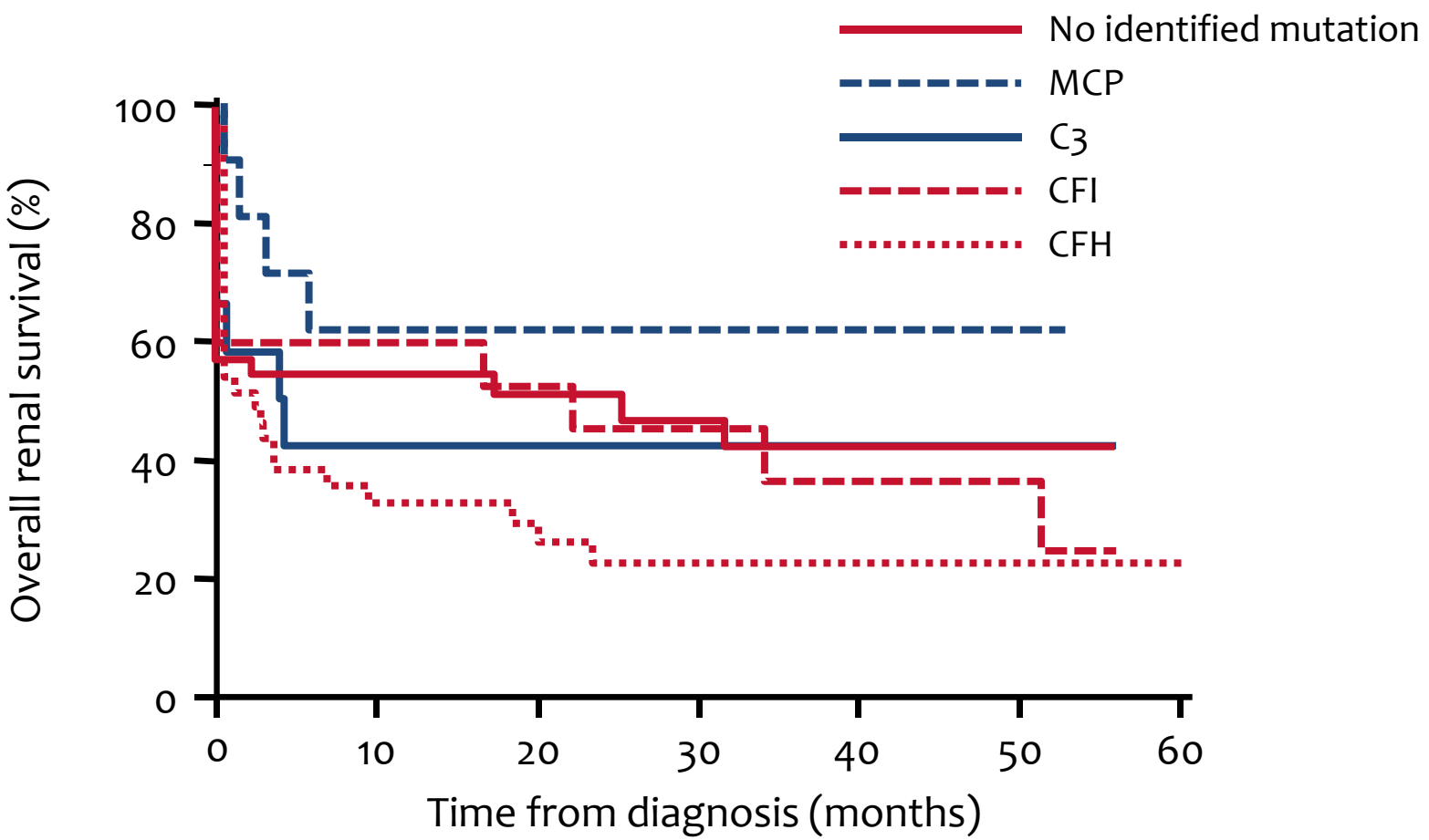
Thrombotic microangiopathy

CAP dysregulation in aHUS



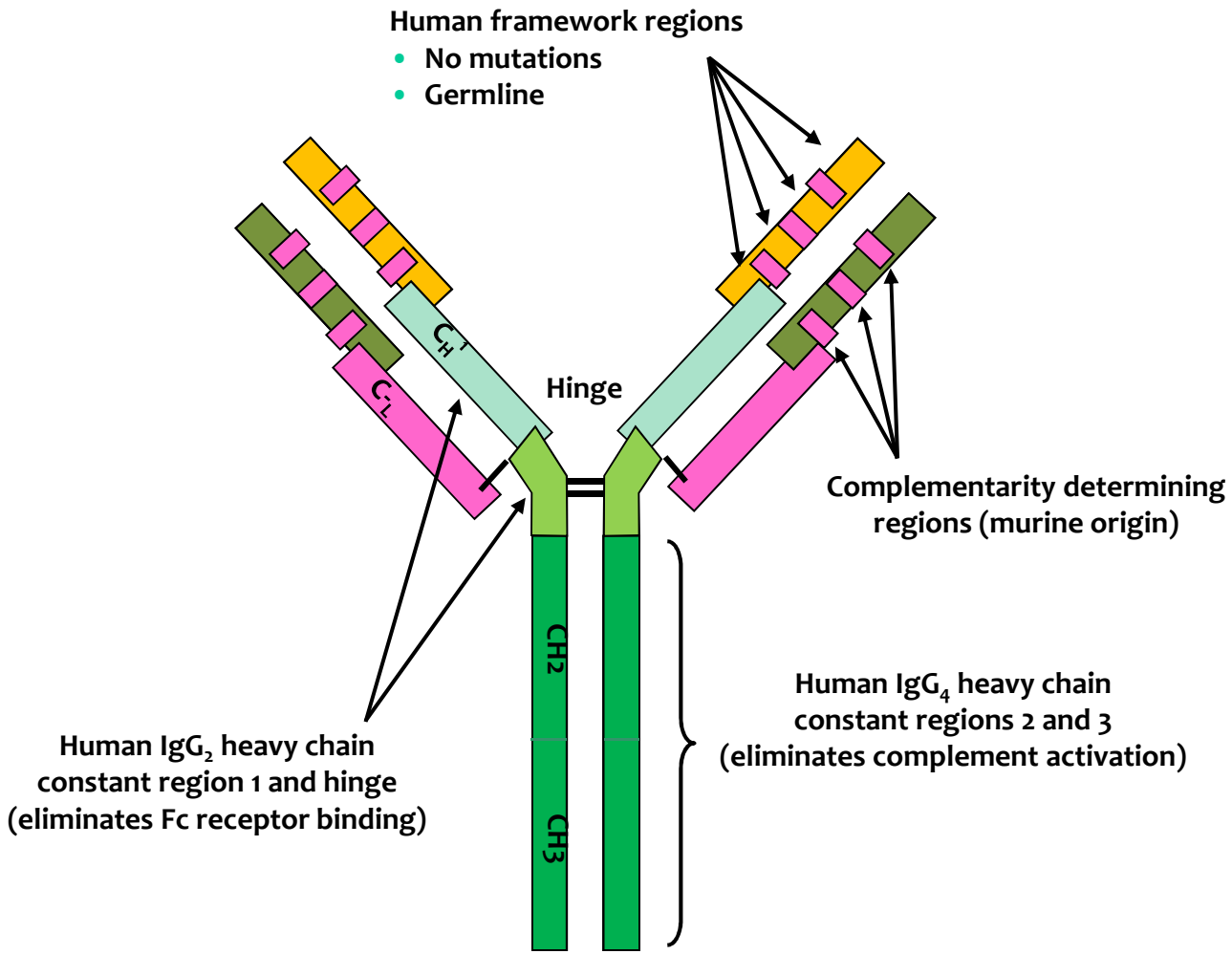
Noris M, NEJM 2009

French aHUS registry (adults): effect of mutational status on survival



65% of patients were treated with plasma exchange / plasma infusion

Eculizumab: humanised 1st-in-class anti-C5 antibody



Eculizumab dosing regimen

Adults and children ≥40 kg: Induction: 900 mg weekly for 4 doses; Maintenance: 1200 mg at week 5, then 1200 mg every 2 weeks.
Children < 40 Kg: Dose adjusted to weight.

Monitoring of complement blockade

CH50 <10% (or AP50 < 10%)
Eculizumab trough level >100 mg/ml

Meningococcal vaccination

Mandatory before eculizumab initiation.
Q**uadrivalent conjugate vaccines (anti-A, C, Y, W)** + **Anti-B serotype vaccine** .

Antibioprophylaxis

Methylpenicillin (in case of allergy to penicillin, macrolides).

Mandatory during the **first 2 weeks** after vaccination.
Maintained throughout eculizumab treatment (and up to 2 months after discontinuation) in some countries.

Patients' **education** and **information card**.

Terminal Complement Inhibitor Eculizumab in Adult Patients With Atypical Hemolytic Uremic Syndrome: A Single-Arm, Open-Label Trial

Fadi Fakhouri, MD, PhD,[1] Maryvonne Hourmant, MD, PhD,[1] Josep M. Campistol, MD,[2] Spero R. Cataland, MD,[3] Mario Espinosa, MD,[4] A. Osama Gaber, MD,[5] Jan Menne, MD,[6] Enrico E. Minetti, MD,[7] François Provôt, MD,[8] Eric Rondeau, MD, PhD,[9] Piero Ruggenenti, MD,[10] Laurent E. Weekers, MD,[11] Masayo Ogawa, MD,[12] Camille L. Bedrosian, MD,[12] and Christophe M. Legendre, MD[13]

AJKD 2016

The largest prospective study with eculizumab in aHUS (adults)

n= 41

≥18 years

Inclusion criteria

Plts <150 × 10^9/L

Hb ≤ LLN

LDH ≥1.5 × ULN

SCr ≥ ULN

No specification for **PE / PI** prior to enrolment

ADAMTS13 activity > 5%

No evidence of **STEC-HUS**

Identification of C genes **mutations** / polymorphisms or **autoAbs**, not required.

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AJKD 2016

Primary outcome:

- Platelet ≥150 × 10^9/L
- LDH ≤ ULN
- <25% increase in SCr from baseline

Secondary outcomes included:

- Modified complete TMA response
  - Plts + LDH normalisation
  - ≥25% decrease in SCr from baseline
- Haematological normalisation (Pltsand LDH normalisation)
- Change from baseline in eGFR

n=41	
Identified complement genes mutation or autoantibody, n (%)	20 (49)
Median duration of current clinical manifestation, months (range)	0.5 (0.0–19.2)
Mean SCr, µmol/L (SD)	411.0 (264.6)
Mean eGFR, mL/min/1.73 m² (SD)	17.3 (12.1)
Dialysis at baseline, n (%)	24 (59)
Prior renal transplant, n (%)	9 (22)

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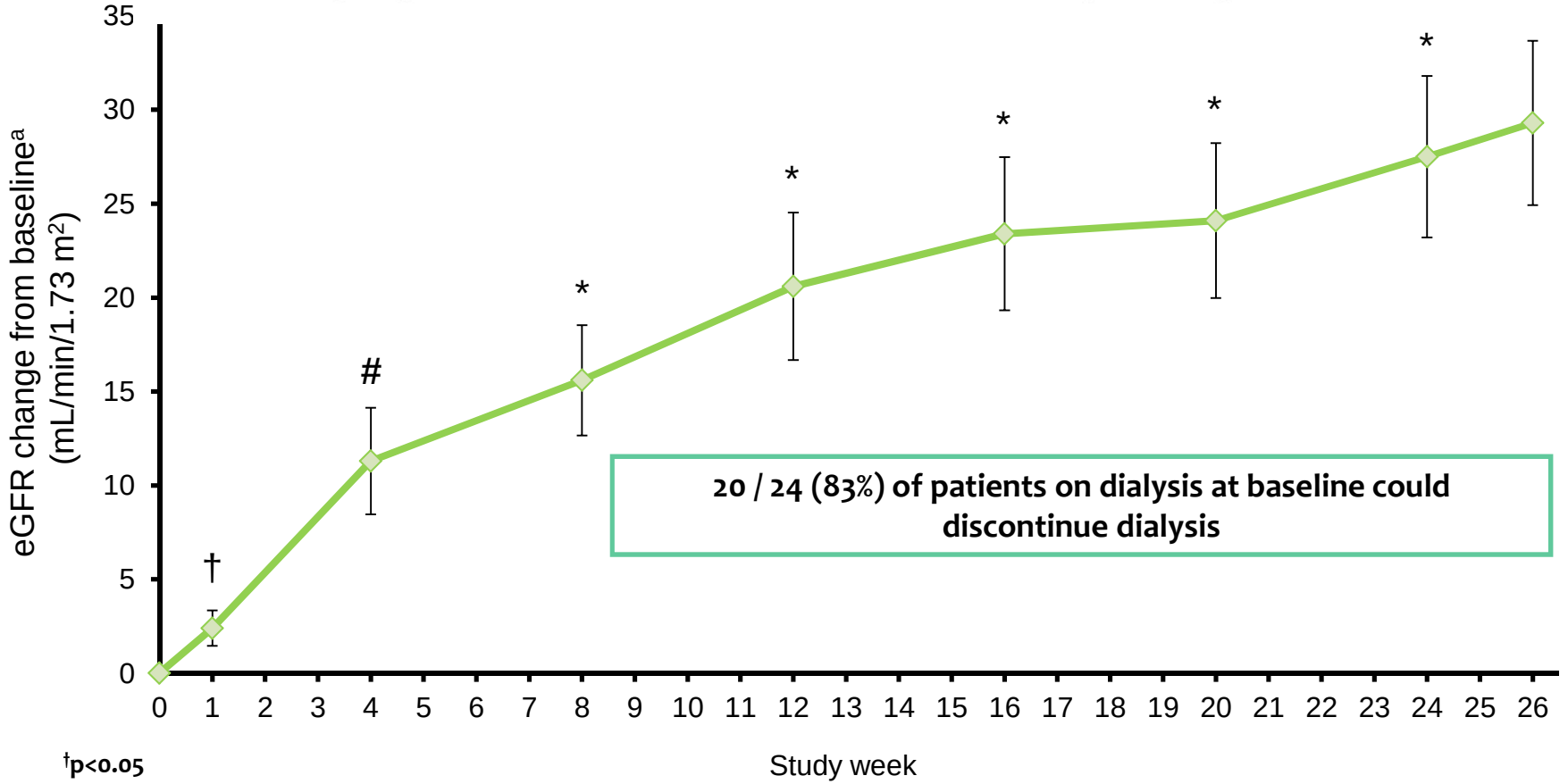
AJKD 2016



†p<0.05
#p<0.001
*p<0.0001
vs baseline

F. Fakhouri, ASN 2013

Terminal Complement Inhibitor Eculizumab in Adult Patients With Atypical Hemolytic Uremic Syndrome: A Single-Arm, Open-Label Trial

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AJKD 2016

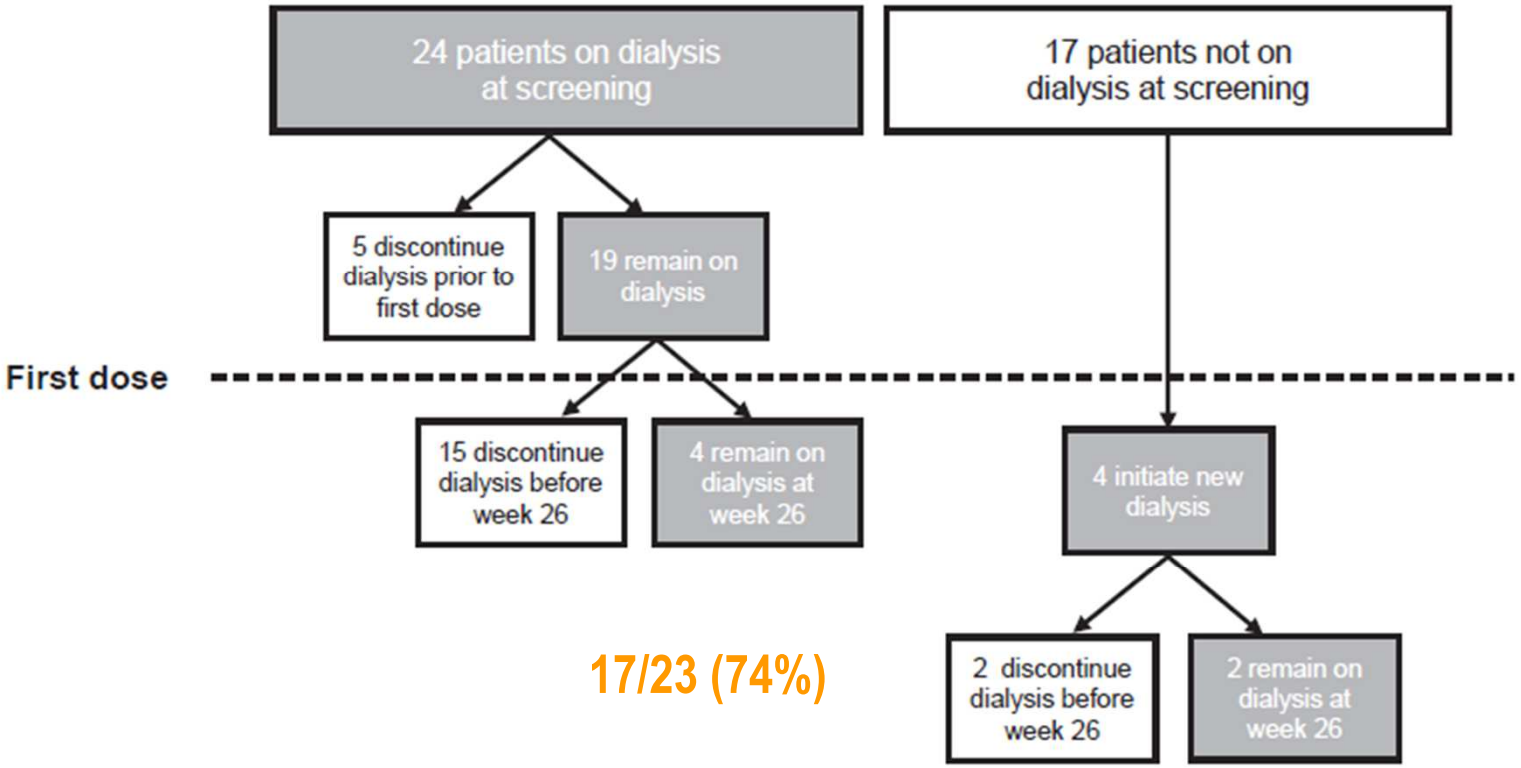


Figure 4. Dialysis use at baseline and during the study.

Insights from use in clinical practice of eculizumab in adult patients with aHUS affecting the native kidneys: an analysis of 19 cases

	Eculizumab-treated aHUS cases (n=18)*	p-value
Female	13 (72%)	0.8
Age	27 (19-53)	0.4
Complement genes mutations	13 (72%)	0.2
Hemodialysis	12 (63%)	0.8
Platelet count > 150 G/L	4 (21%)	0.6
Plasma exchanges	15 (83%)	0.1
End-stage renal disease within 3m of aHUS flare	3 (17%)	0.02
End-stage renal disease at 1 year	2/8 (25%)	0.04

Fakhouri F et al. Am J Kidney Dis 2014;63:40-48

Insights from use in clinical practice of eculizumab in adult patients with aHUS affecting the native kidneys: an analysis of 19 cases

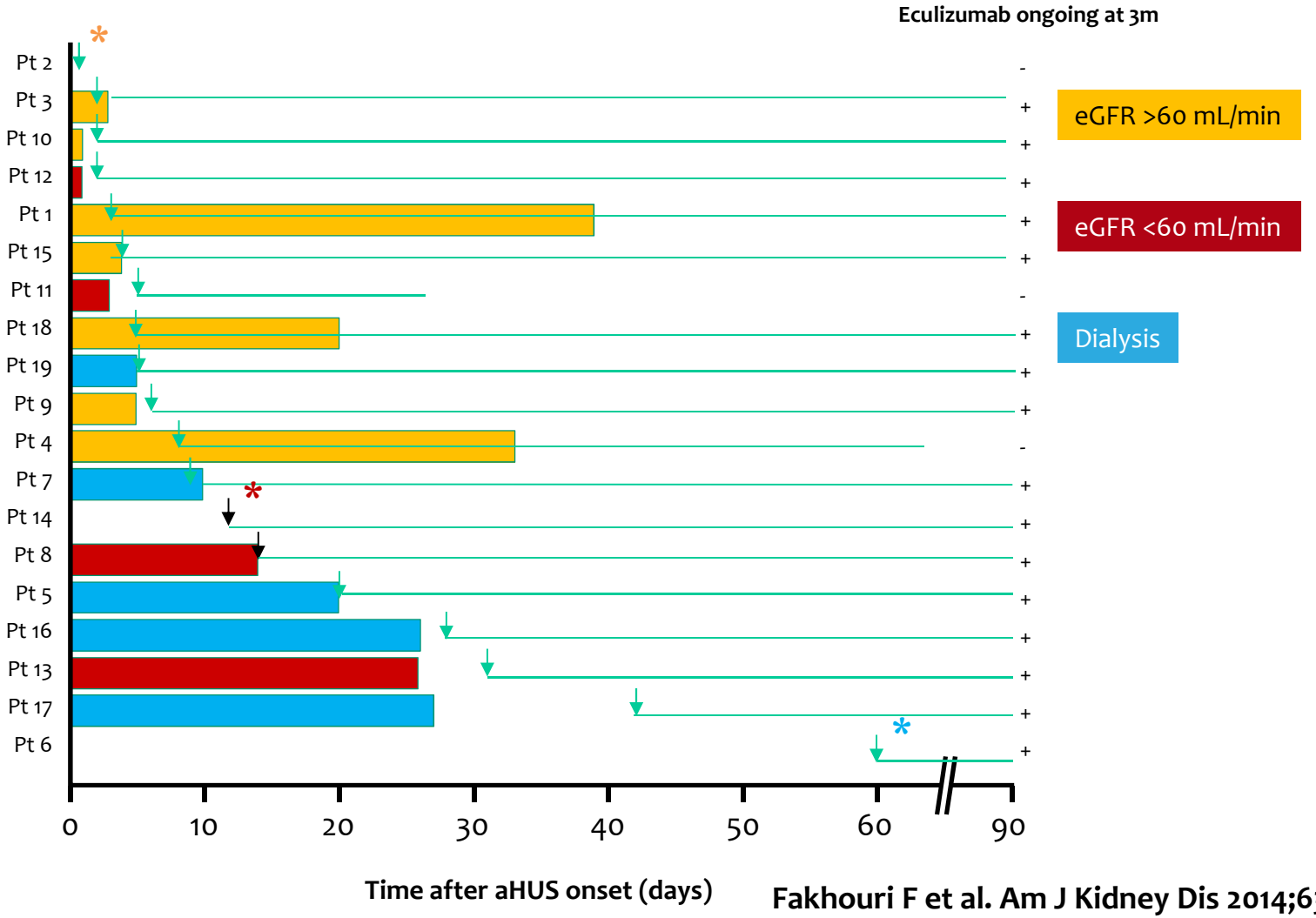
(2004-2008)

	Historical controls (n=41)	Eculizumab-treated aHUS cases (n=18)*	p-value
Female	28 (68%)	13 (72%)	0.8
Age	34 (18-85)	27 (19-53)	0.4
Complement genes mutations	28 (68%)**	13 (72%)	0.2
Hemodialysis	29 (71%)	12 (63%)	0.8
Platelet count > 150 G/L	6/36 (17%)	4 (21%)	0.6
Plasma exchanges	24/38 (63%)***	15 (83%)	0.1
End-stage renal disease within 3m of aHUS flare	20 (46%)	3 (17%)	0.02
End-stage renal disease at 1 year	23/36 (63%)	2/8 (25%)	0.04

Fakhouri F et al. Am J Kidney Dis 2014;63:40-48

Insights from use in clinical practice of eculizumab in adult patients with aHUS affecting the native kidneys: an analysis of 19 cases

Early Ecu intiation = Better renal outcome



Fakhouri F et al. Am J Kidney Dis 2014;63:40-48

Percentage of patients on chronic dialysis in the 4 trials of eculizumab, compared to the French cohort (pre- eculizumab)

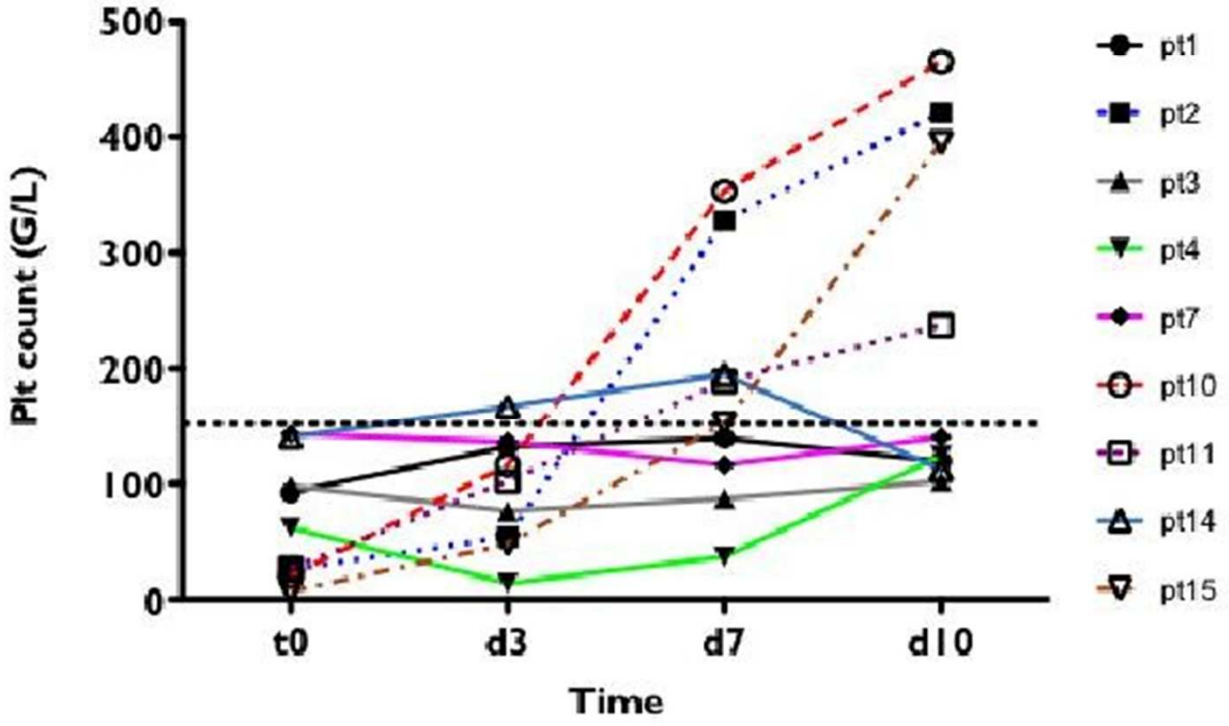
Adults

ESRD (% patients)				
Follow-up	**French cohort N= 125**	**Trial 1 N=17**	**Trial 2 N=20**	**Trial 4 N=41**
First episode	46%			
6 months		6%	10%	15%
1 year	56%	6%	10%	12%
2 years		12%	10%	
5 years	64%			

French cohort: Fremeaux-Bacchi *et al*, CJASN 2013

Insights from the use in clinical practice of eculizumab in adult patients with aHUS affecting the native kidneys: an analysis of 19 cases.

Figure 3



F. Fakhouri, AJKD

Genetics and Outcome of Atypical Hemolytic Uremic Syndrome: A Nationwide French Series Comparing Children and Adults

Véronique Fremeaux-Bacchi, Fadi Fakhouri, Arnaud Garnier, Frank Bienaimé, Marie-Agnès Dragon-Durey, Stéphanie Ngo, Bruno Moulin, Aude Servais, François Provot, Lionel Rostaing, Stéphane Burtey, Patrick Niaudet, Georges Deschênes, Yvon Lebranchu, Julien Zuber, and Chantal Loirat

Defining a new clinical picture of aHUS

Table 1. Patients' characteristics at onset

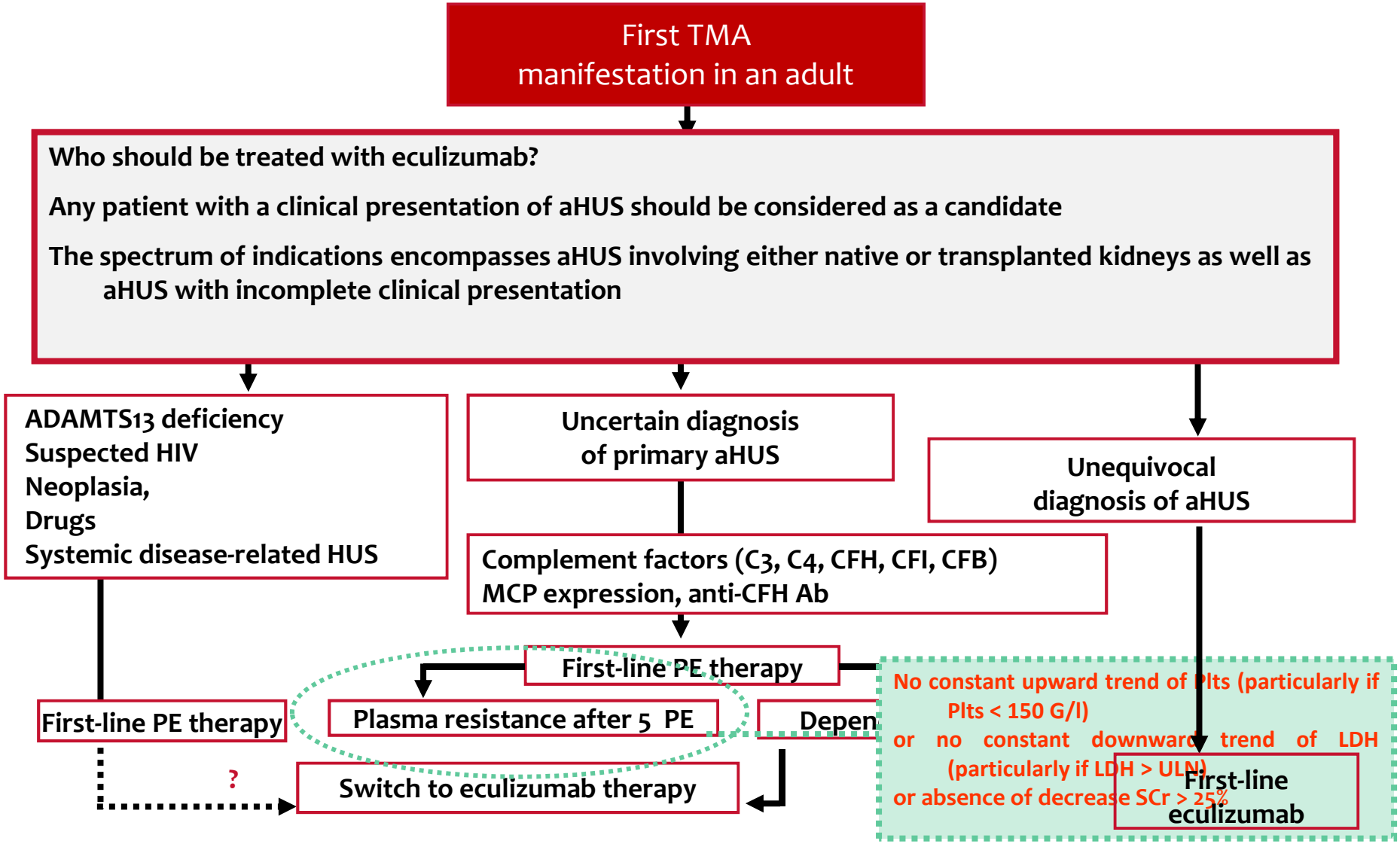
Characteristic	Children	Adults	*P* Value
Patients (*n*)	89	125	
Female/male (*n*/*n*)	42/47	93/32	<0.001
Mean age at onset (yr)	1.5 (0 to <15)	31 (15–85)	
Familial HUS history, *n* (%)	24 (26.9)	18 (14.4)	0.02
Triggering events, *n* (%)	42 (47)	41 (33)	0.03
Diarrhea	35 (39)	19 (15)	<0.001
Respiratory 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

Values are given as means with ranges in parentheses or as percentages. HUS, hemolytic uremic syndrome.

[a]In children, extrarenal manifestations also included pancreatitis (increase of pancreatic enzymes with or without clinical/radiologic signs) in six cases (7%), hepatitis (increase in hepatic enzymes) in five cases (6%), multiorgan failure in three cases (3%), intra-alveolar hemorrhage in two cases (2%), and pericarditis in one case (1%). Extrarenal manifestations other than neurologic are not documented in adults.

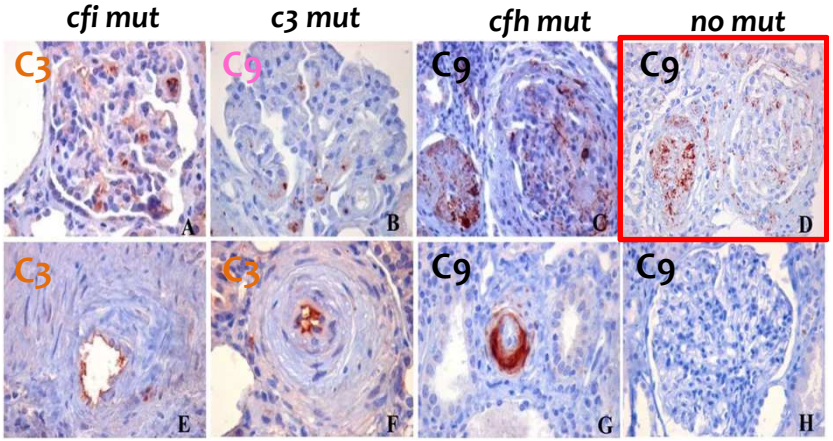
[b]Complete triad: hemoglobin < 10 g/dl plus platelet count < 150 G/L plus serum creatinine above the upper limit of normal.

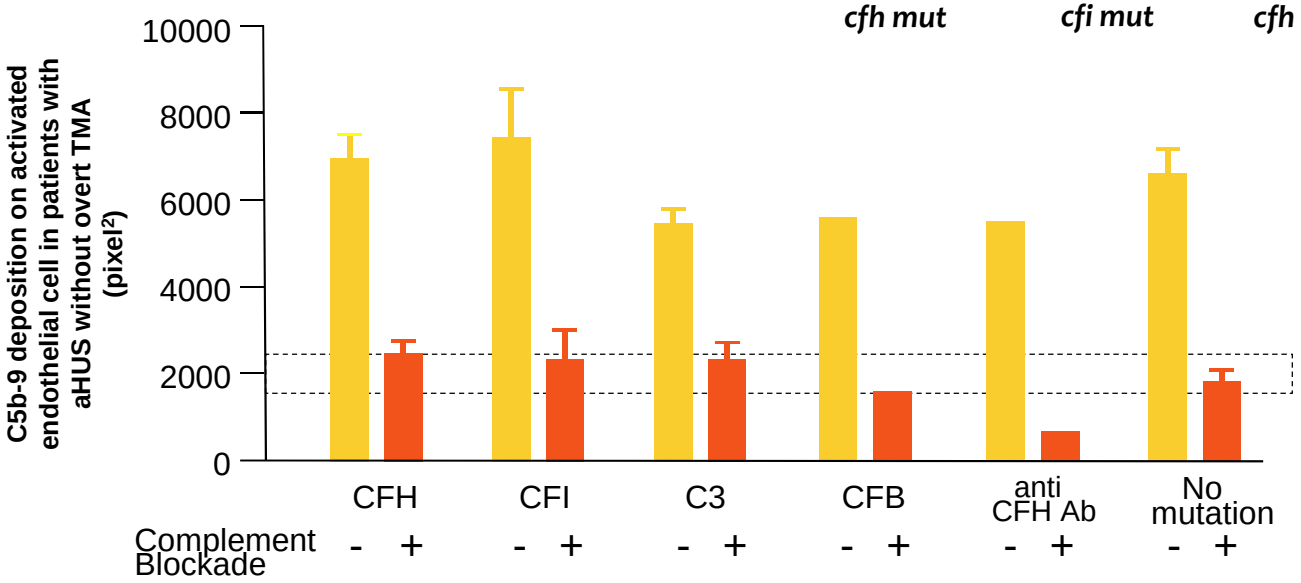
Recommendations for managing adult patients with aHUS



Absence of complement genes mutations does not exclude aHUS

	aHUS phase	Overall	Mutations anti-CFH Ab	No mutations
Reduced serum C3	Acute	10/18	5/9	5/9
Increased serum C5a	Acute	9/19	3/10	6/9
Increased sC5b-9	Acute	10/19	4/10	6/9



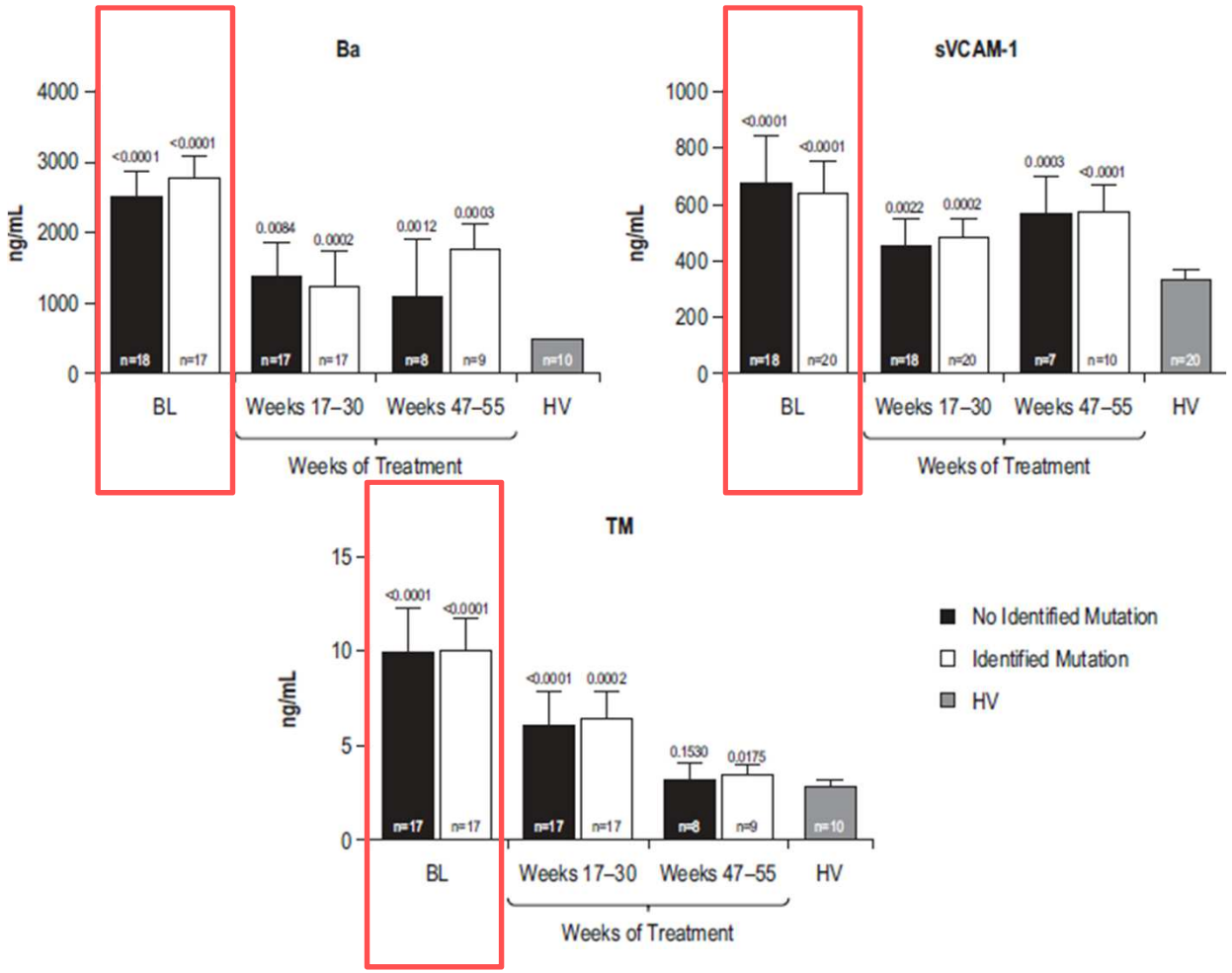


Adapted from Noris et al., *Blood*, 2014

Eculizumab reduces complement activation, inflammation, endothelial damage, thrombosis, and renal injury markers in aHUS

Roxanne Cofiell, Anjli Kukreja, Krystin Bedard, Yan Yan, Angela P. Mickle, Masayo Ogawa, Camille L. Bedrosian and Susan J. Faas

Blood, 2015



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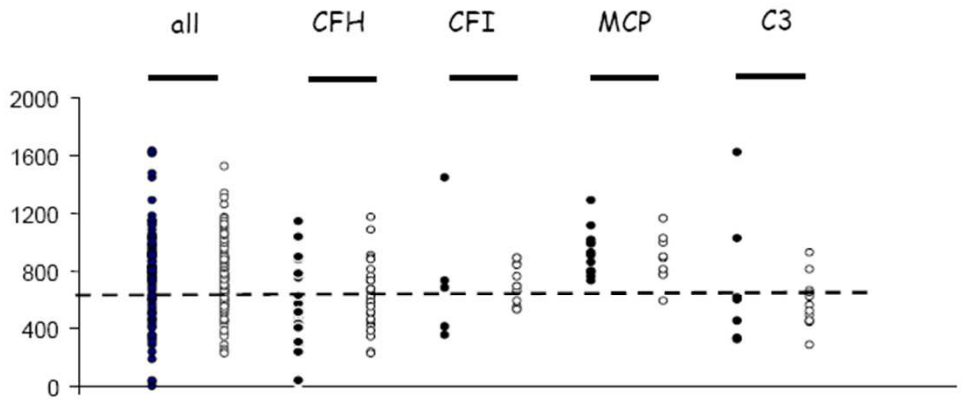
Complement assays

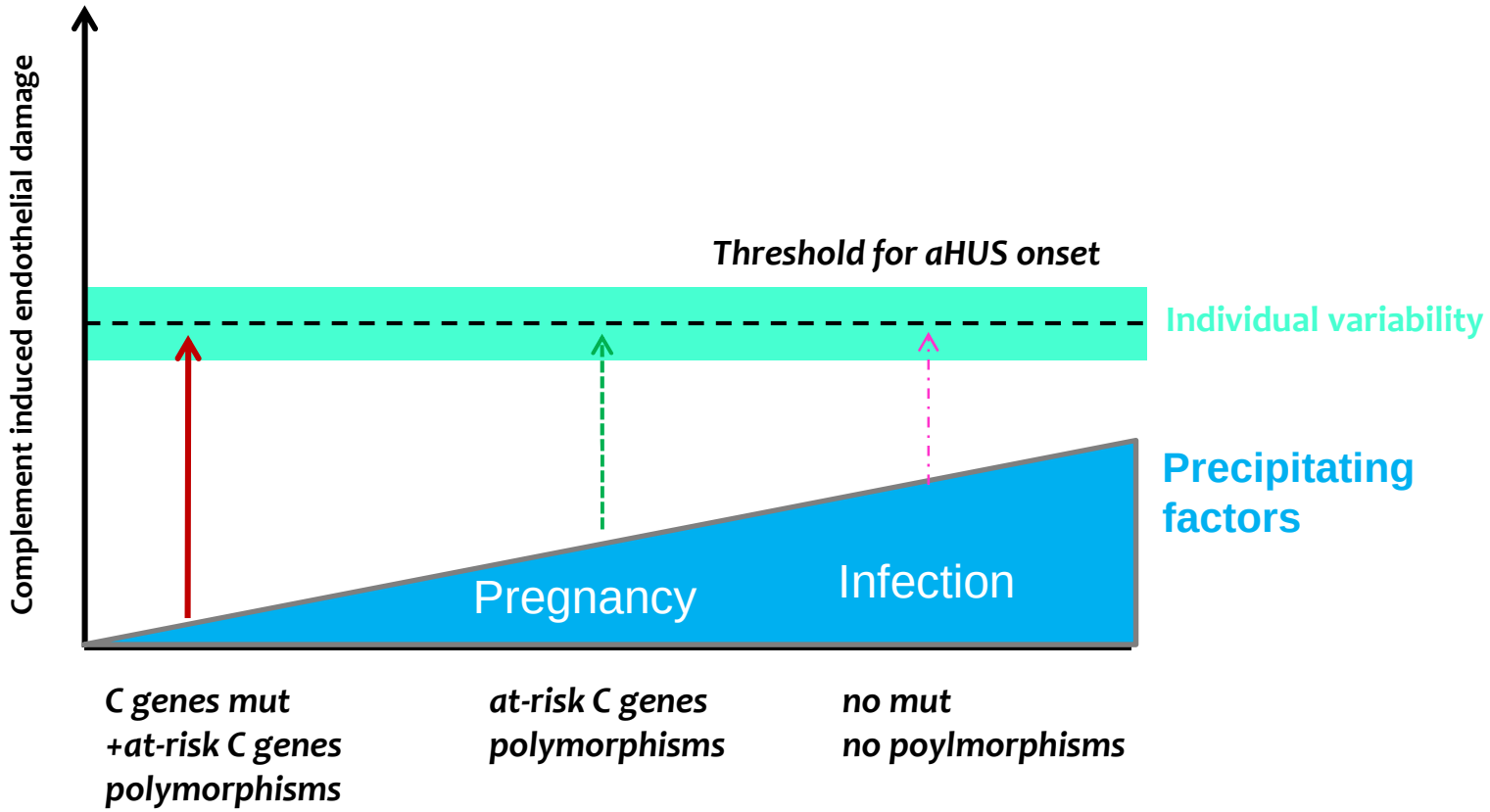


Pediatric onset	+		+		+		+		+	
Adult onset		+		+		+		+		+
Low C3 (%)	31	39	70	52	60	50	0	11	70	85

Normal complement levels do not exclude aHUS diagnosis

Complement activation and aHUS

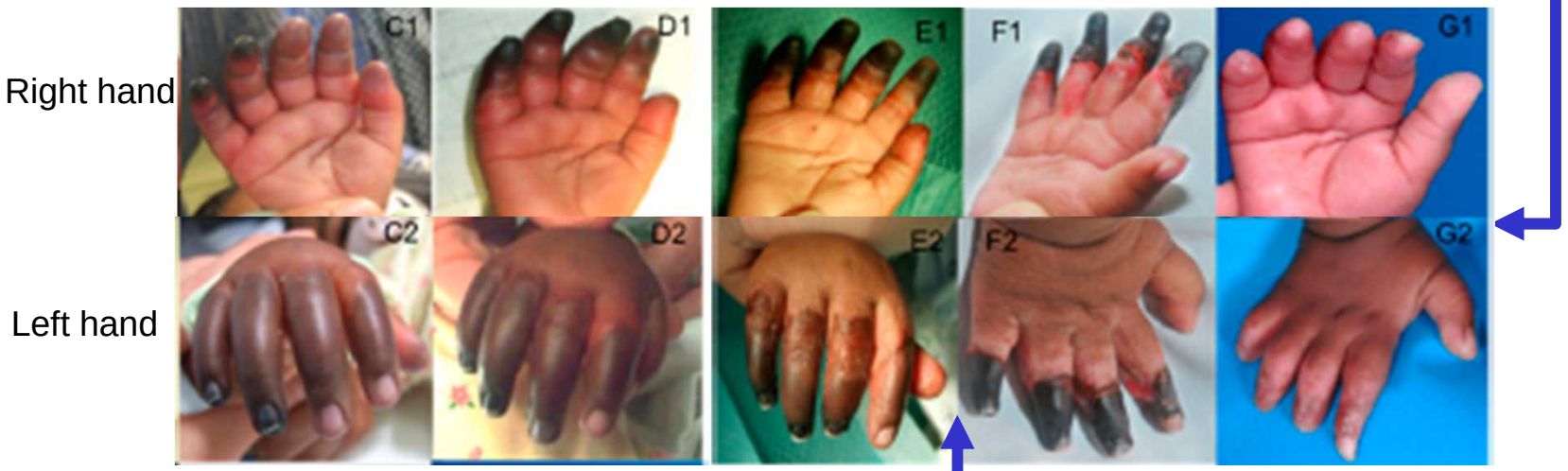
A hypothesis…



Eculizumab rescues distal ischaemic manifestations of aHUS

Ariceta *et al.* AJKD 2012
28-day-old child, 3.6 kg
- No mutation
- Leg skin necrosis, intestinal perforation
- **Eculizumab → remission within 3 days**
- Recovery of skin lesions and renal function
- **Follow-up 18 months, Screatinine 23 µmol/L, remission**

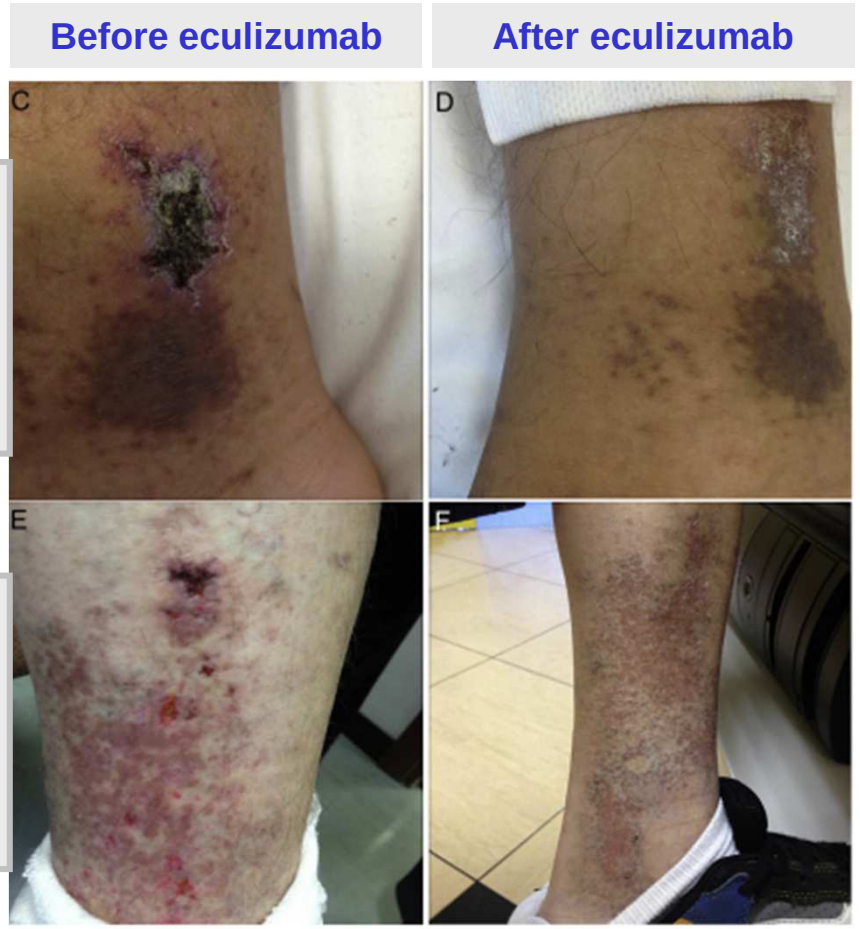
Malina *et al.* Pediatrics 2013
2-month-old child
- ESRD, multiple relapses despite plasma infusions
- C3 gain of function mutation
- At 9 months, acute ischaemia of feet and hands, resistant to PE
- **Eculizumab → immediate reversal of distal ischaemia**
- **Follow-up 22 months, remission**



Ulcerative-necrotic skin lesions in aHUS
Recovery under eculizumab

19-year-old man (no mutation)
- On dialysis
- **Skin lesions for 10 months** + thrombocytopenia
- Skin biopsy: TMA lesions
- **Recovery after one dose of eculizumab**

19-year-old man (factor H mutation)
- Functioning kidney graft under PE/PI
- **Skin lesions for several months**
- → Switch from PE to eculizumab
- **Improvement of skin lesions after first dose with further complete reversal**



Ardissino G *et al.* Am J Kidney Dis 2013

Eculizumab appears efficient to rescue CNS involvement in aHUS

10 case reports (PE resistant:8; 1st line eculizumab:2)

Author	Age,yrs (Mutation/ Anti-FH)	Neurological manifestations	MRI	Time to eculizumab initiation (days)	Outcome
Pu 2013	85 (None)	Seizures, mental disturbances	ND	18	Improvement over 2 weeks Full recovery
Salem 2012	66 (C3)	Seizures, mental disturbances, coma	Focal lesions	3	Awoke and verbal after 8 weeks Nearly complete recovery
Beye 2013	64 (None)	Status epilepticus, focal defects, nystagmus, confusion	Normal CTS	9	Improvement within 24 hours Full recovery
Ohanian 2011	50 (None)	Seizures, unresponsiveness	Right parietal infarction	3	Improvement after 1 week Full recovery
Avila 2015	27 (None)	Decreased intellectual performance, self-limited episode of loss of consciousness	Several high-intensity subcortical white matter lesions in frontal lobes	7	Full recovery within a few days
Chaudhary 2014	20 (None)	Seizures, lethargy	ND	42	Slow initial improvement (subtherapeutic doses) Full recovery after dose increase
Gulleroglu 2013	11 (None)	Seizures, visual loss, confusion	Bilateral occipital and posterior parietal hyperdensities/oedema	2	Improvement after 4 days Full recovery after 1 month
Gulleroglu 2013	6 (MCP)	Seizures, visual loss	Bilateral occipital and posterior parietal hyperdensities	<1	Normal vision within 24 hours Full recovery after 5 weeks
Diamante Chiodini 2014	8 (Anti-FH)	Confusion, delirium Persistant psychocognitive impairment under PE/PI	Multifocal hypersignals	20	Full recovery within 2 weeks
Hu 2013	1.7 (None)	Seizures, hemiparesis, lethargy, unresponsiveness	Subtle bilateral anomalies	<1	Improvement over 3 weeks Full recovery with residual weakness of right thumb/index

Eculizumab appears efficient to rescue ischemic cardiomyopathy in aHUS

4 case reports in children

Author	Age,yrs (mutation/ anti-FH)	Cardiac manifestations	Response to PE	Time to eculizumab initiation (days)	Outcome
Vilalta 2012	1.5 (CFH)	Day 60 under PE: Dilated cardiomyopathy Cardiorespiratory arrest	Resistance to PE	80	Improvement of cardiac function over 6 days. Subsequent full recovery.
Hu 2013	1.6 (None)	Day 0: Dilated cardiomyopathy EF 30% Cardiovascular instability, hypotension	First line eculizumab	< 12 hours	Recovery over 9 days
Diamante Chiodini 2014	8 (Anti-FH)	Day 20 under PE: Dilated cardiomyopathy EF 37% Repolarization anomalies High troponine level	Resistance to daily PE + plasma intolerance	37	Normalization of LV volume and function over 2 weeks
Michaux 2014	11 days (Homozygous CFH)	Day 11:Myocardial imcompetence Increased troponin Hemodynamic instability Respiratory failure	PE not tolerated	2	Recovery within a few days

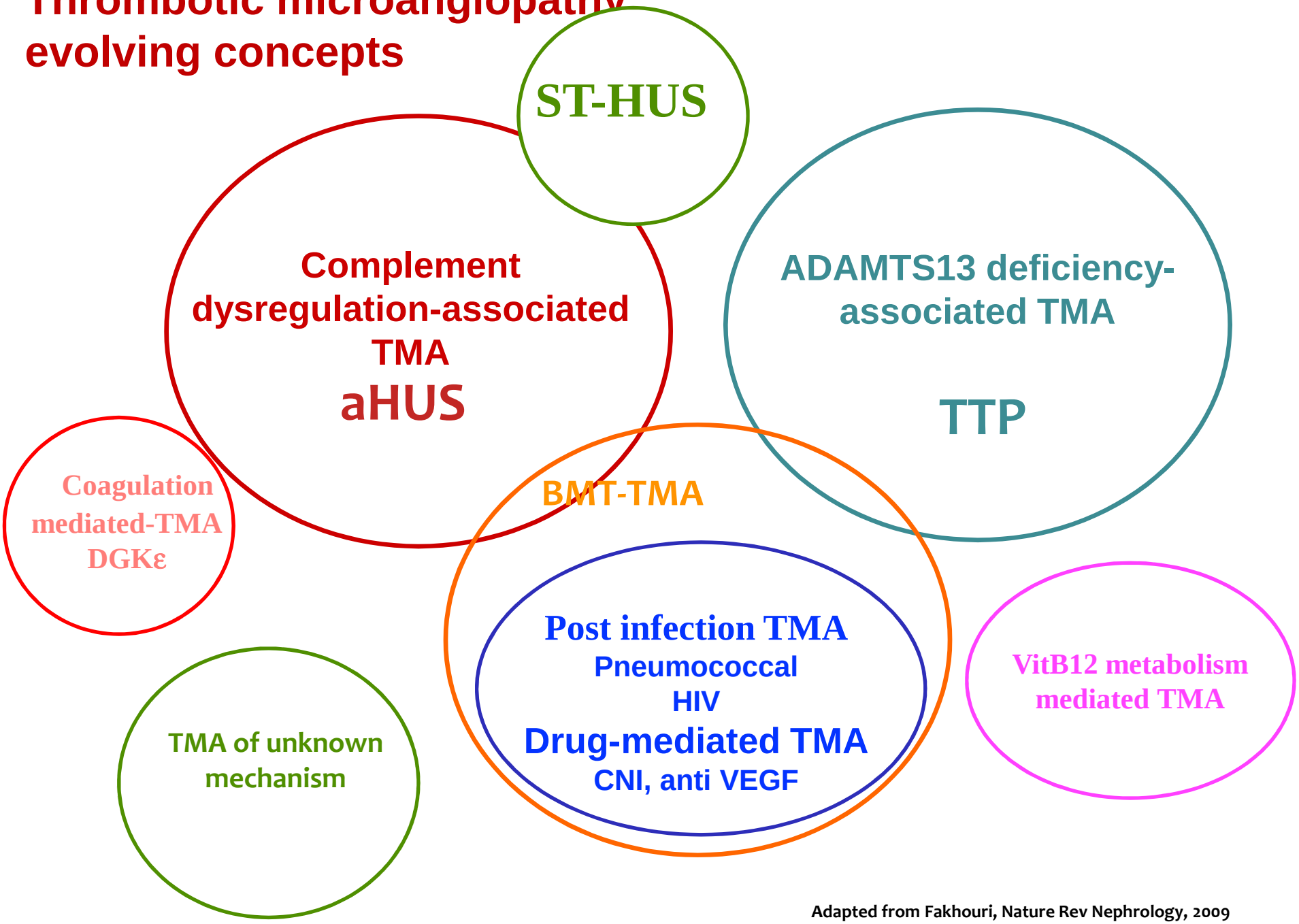
aHUS: a chronic disease

Relapse pattern in adult aHUS patients

	All (n=66)	*CFH* (n=20)	*CFI* (n=8)	*MCP* (n=6)	*C3* (n=7)	*No Mut* (n=21)
F-up (M)	52	55	58	11	50	42
> 1R	35%	30%	38%	33%	71%	33%
1st R < 1y	29%	30%	38%	33%	43%	25%
1st R > 1y	6%	0	0	0	28%	5%
R > 1y	20%	19%	25%	33%	20%	20%

Fremeaux-Bacchi et al, CJASN 2013

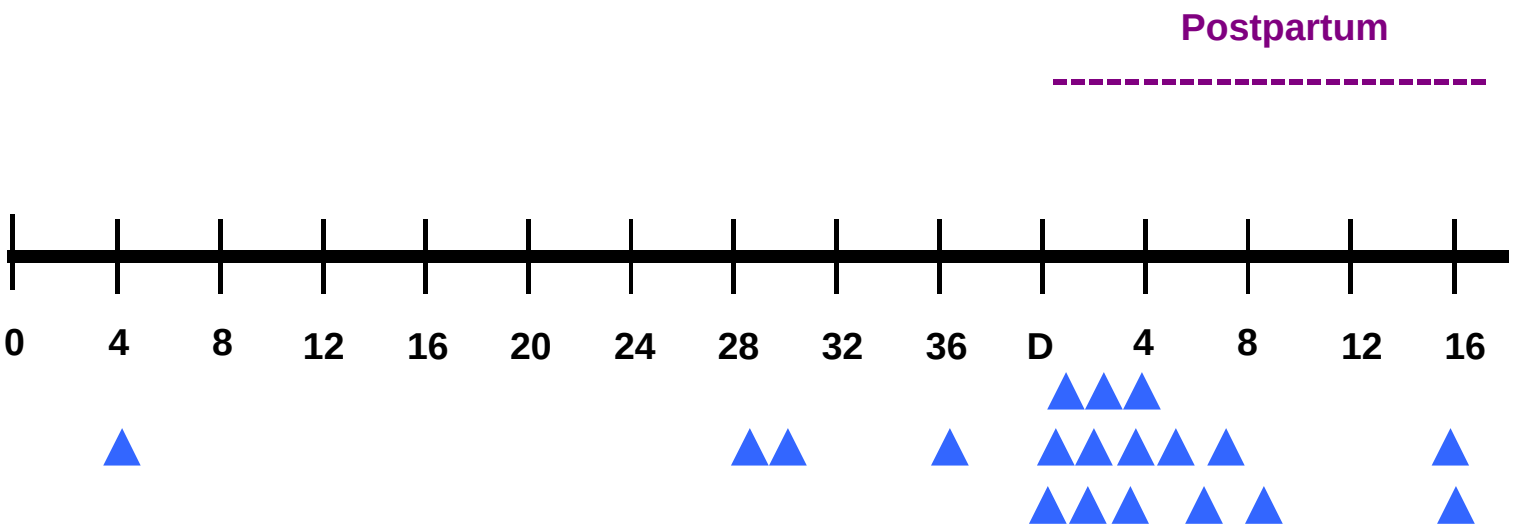
Thrombotic microangiopathy: evolving concepts



Adapted from Fakhouri, Nature Rev Nephrology, 2009

TMA in pregnancy

F, 34 y
2nd uneventful pregnancy
3 weeks PP
SCr 650 mmol/l
Plts 110 G/L
LDH 2.5 ULN
Hb 10 g/dl
Haptoglobin undetectable
Schizocytes neg
Puria 2 g/l



1 woman/5 had aHUS during pregnancy
79% of cases occurred during the post partum

Fakhouri F, JASN, 2010

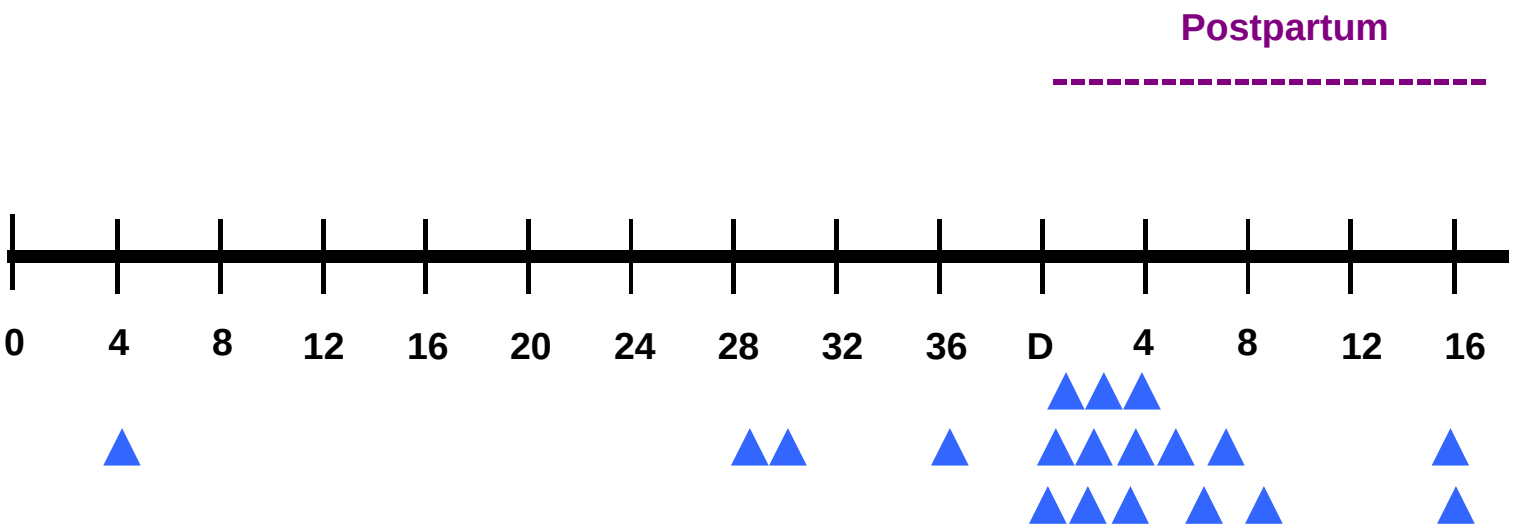
Complement dysregulation-related TMA in pregnancy

Fakhouri F, JASN, 2010

	Patients with P-associated aHUS (n=21)	Patients with aHUS non related to pregnancy (n=35)	
Age at aHUS onset (years)	26 ± 5	33 ± 12	p < 0.05
Nb of pregnancies	2 ± 0.8	2.3 ± 1.5	NS
Nb of patients reaching ESRD < 6 months after aHUS	11 (52%)	20 (57%)	NS
		4 (11%)	NS
Number of patients reaching ESRD at last follow-up	16 (76%)	26 (74%)	NS
Number of patients with complement abnormality	18 (86%)	26 (74%)	NS
CFH	10 (48%)	14 (40%)	NS
CFI	3 (14%)	6 (17%)	NS
MCP	1 (5%)	3 (8.5%)	NS
C3	2 (9.5%)	1 (3%)	NS
FB	0 (0%)	2 (5.5%)	NS
More than one mutation	2 (9.5%)	1 (3%)	NS

TMA in pregnancy

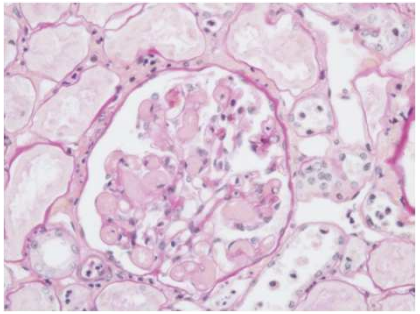
F, 34 y
2nd uneventful pregnancy
3 weeks PP
SCr 650 mmol/l
Plts 110 G/L
LDH 2.5 ULN
Hb 10 g/dl
Haptoglobin undetectable
Schizocytes neg
Puria 2 g/l



P-aHUS = an aHUS precipitated by pregnancy.

Fakhouri F, JASN, 2010

Thrombotic microangiopathy: evolving concepts



Secondary TMA / TMA-like disorders

Kidney-transplantation related TMA

« *CFH* or *CFI* gene mutations found in 7/24 patients (29%) »
Le Quintrec M, AJT 2008

Complement as an amplifying process in secondary HUS.

Mitomycin C

Faguer S, CKJ 2013

APS

Bakhtar O Transplantation, 2014

Gemcitabine

Starck M, BJH, 2013
Al Ustwani, JGO, 2014

HELLP syndrome

Fakhouri F, Blood 2010

Cancer-associated TMA

Favre G, BJH, 2014

SLE

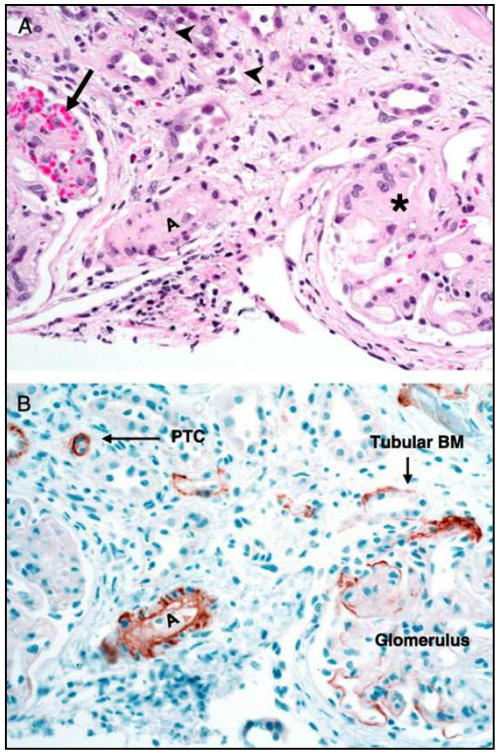
El-Husseini, AJKD 2015

Abnormalities in the alternative pathway of complement in children with hematopoietic stem cell transplant-associated thrombotic microangiopathy

Sonata Jodele,[1] Christoph Licht,[2] Jens Goebel,[3] Bradley P. Dixon,[3] Kejian Zhang,[4] Theru A. Sivakumaran,[4] Stella M. Davies,[1] Fred G. Pluthero,[2] Lily Lu,[2] and Benjamin L. Laskin[5]

Table 2. Complement system analysis in patients with HSCT-TMA

Patient	Transplant type	*CFI,CFH,MCP,CFB,CFR5* (direct sequence analysis)	Recipient *CFH-CFHR5* (MLPA)	Donor *CFH-CFHR5* (MLPA)	CFH antibody (ELISA)	CFHR1 protein analysis (western blot)
1	autologous	normal alleles	**del(CFHR3-CFHR1)*	n/a	absent	present
2	autologous	normal alleles	**del(CFHR3-CFHR1)*	n/a	absent	present
3	autologous	normal alleles	**del(CFHR1-CFHR4)*	n/a	absent	present
4	allogeneic	normal alleles	**del(CFHR3-CFHR1)*	normal allele	present	present
5	allogeneic	normal alleles	**del(CFHR3-CFHR1)*	**del(CFHR3-CFHR1)*	present	present
6	allogeneic	normal alleles	normal allele	normal allele	present	present



Renal Arteriolar C4d Deposition: A Novel Characteristic of Hematopoietic Stem Cell Transplantation-Associated Thrombotic Microangiopathy.

Laskin, Transplantation, 2013

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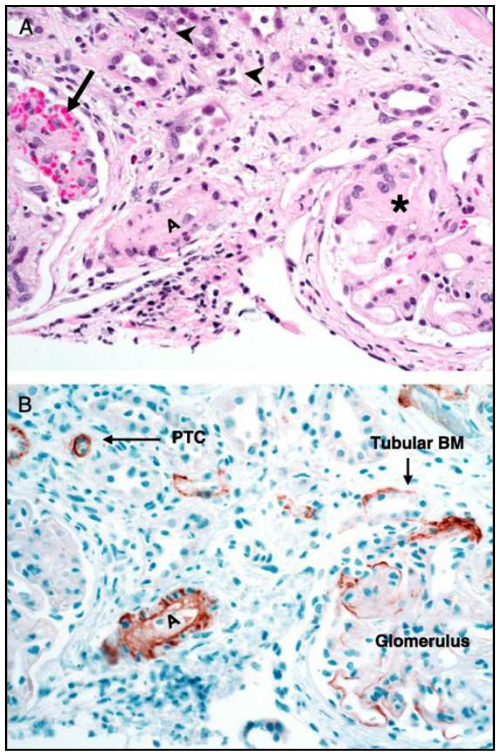

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Laskin, Transplantation, 2013

Eculizumab therapy in children with severe hematopoietic stem cell transplantation-associated thrombotic microangiopathy.
Jodele S, Biol Blood Marrow Transplant, 2014

Successful use of eculizumab in a patient with post-transplant thrombotic microangiopathy.
Peffault de Latour R, Br J Haematol 2013

Eculizumab and typical HUS

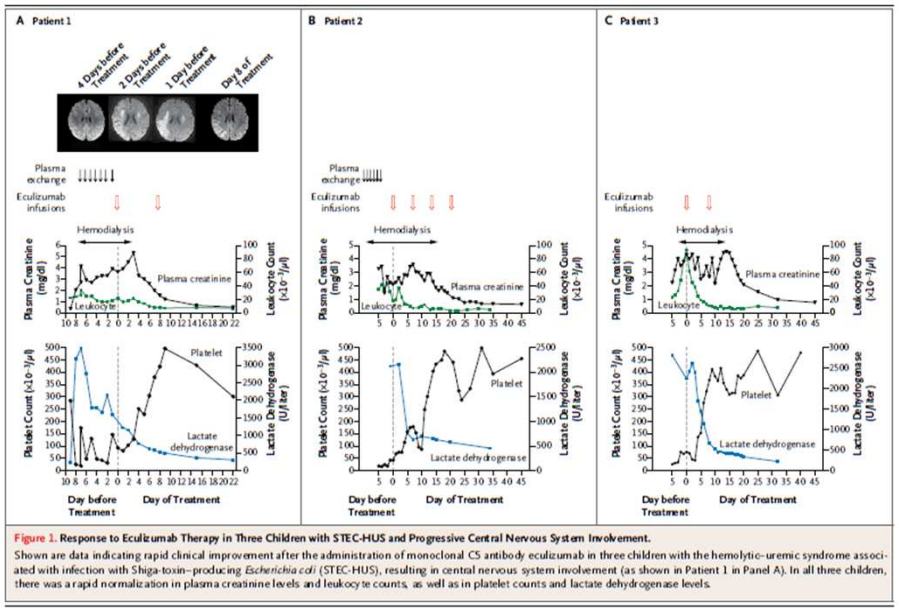
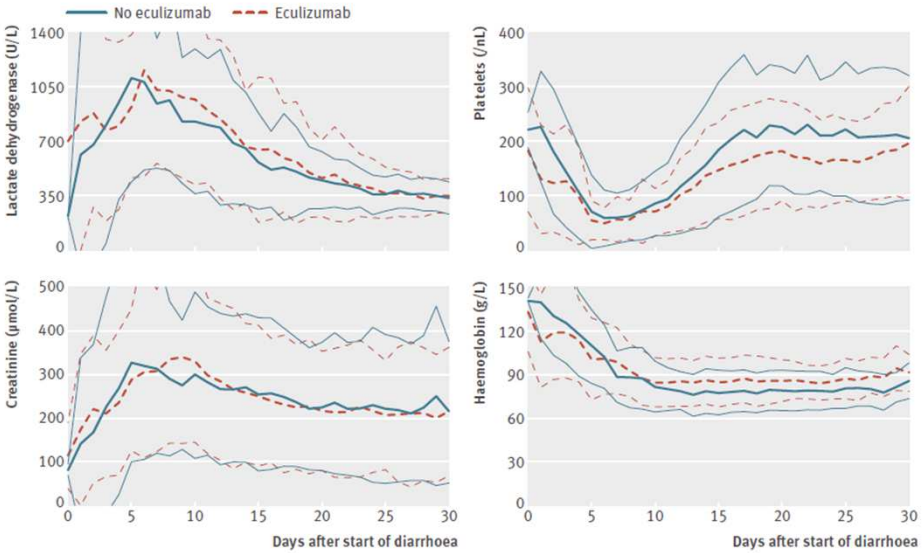


Figure 1. Response to Eculizumab Therapy in Three Children with STEC-HUS and Progressive Central Nervous System Involvement.

Shown are data indicating rapid clinical improvement after the administration of monoclonal C5 antibody eculizumab in three children with the hemolytic–uremic syndrome associated with infection with Shiga-toxin–producing *Escherichia coli* (STEC-HUS), resulting in central nervous system involvement (as shown in Patient 1 in Panel A). In all three children, there was a rapid normalization in plasma creatinine levels and leukocyte counts, as well as in platelet counts and lactate dehydrogenase levels.

Complement Blockade in Severe STEC-HUS.
Lapeyraque AL NEJM 2011



Validation of treatment strategies for enterohaemorrhagic *Escherichia coli* O104:H4 induced haemolytic uraemic syndrome: case-control study

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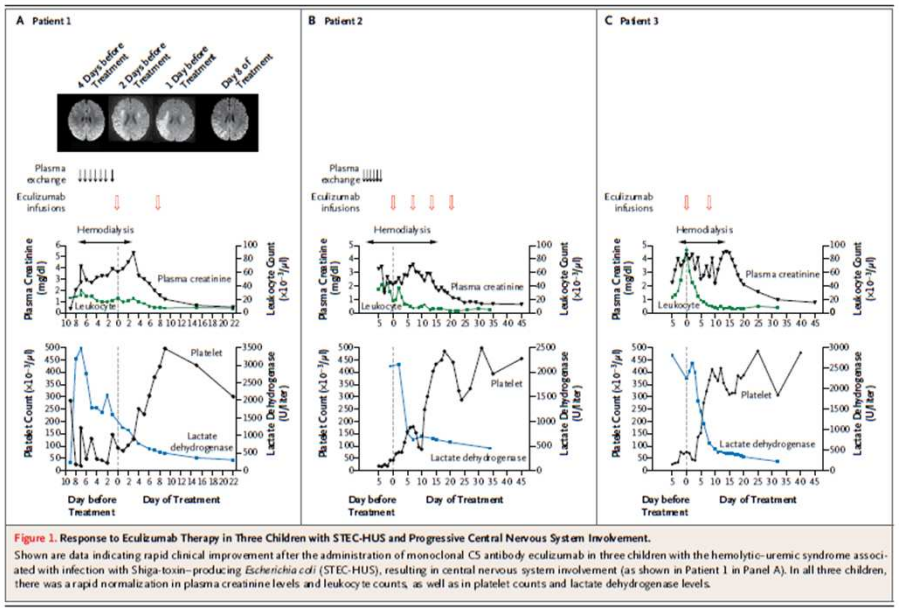
Eculizumab and typical HUS



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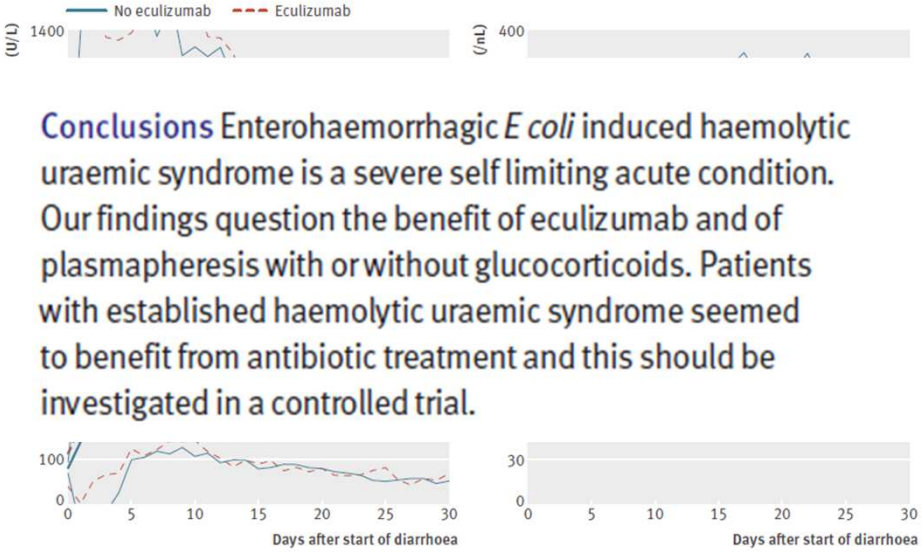

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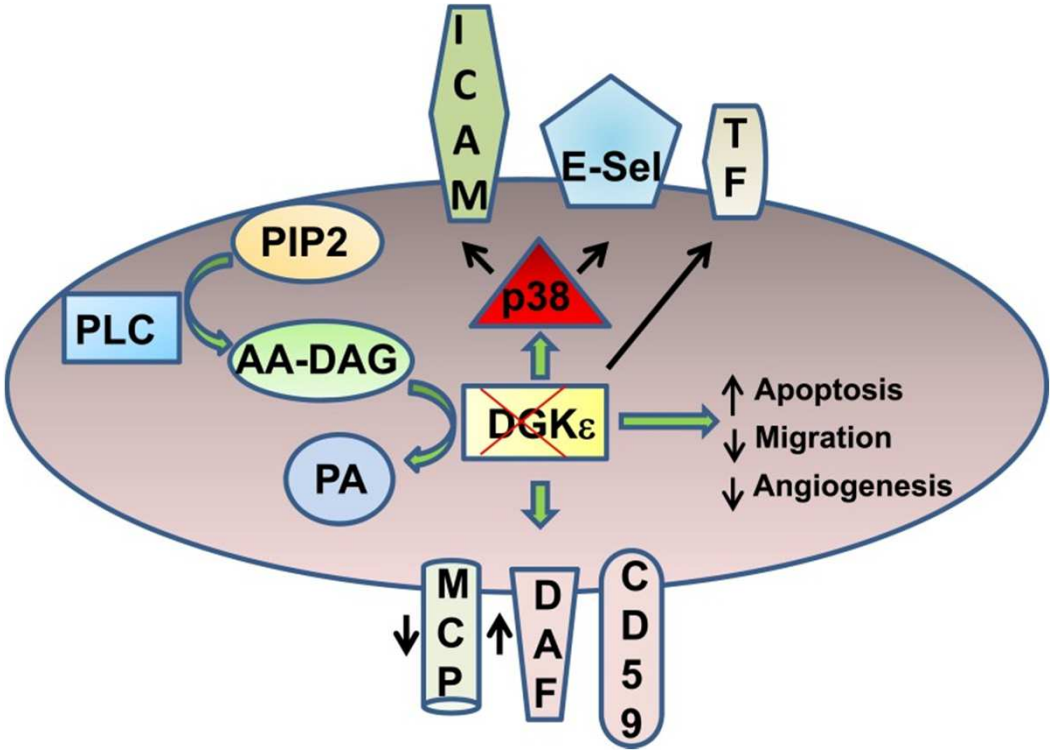
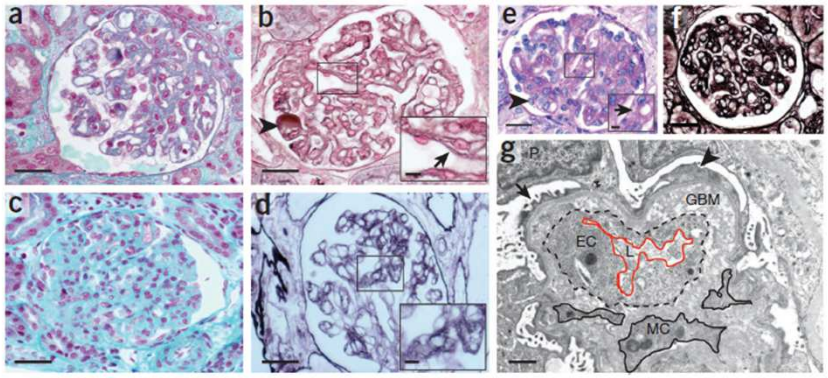
DGKE disruption ditches complement and drives p38 signaling

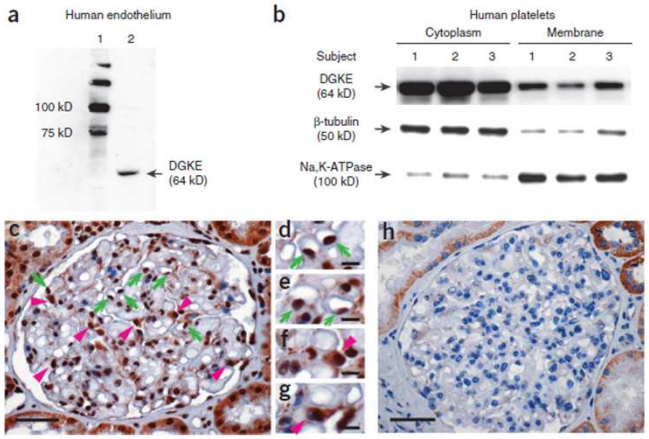
K. Vinod Vijayan BAYLOR COLLEGE OF MEDICINE; MICHAEL E. DEBAKEY VETERANS AFFAIRS MEDICAL CENTER

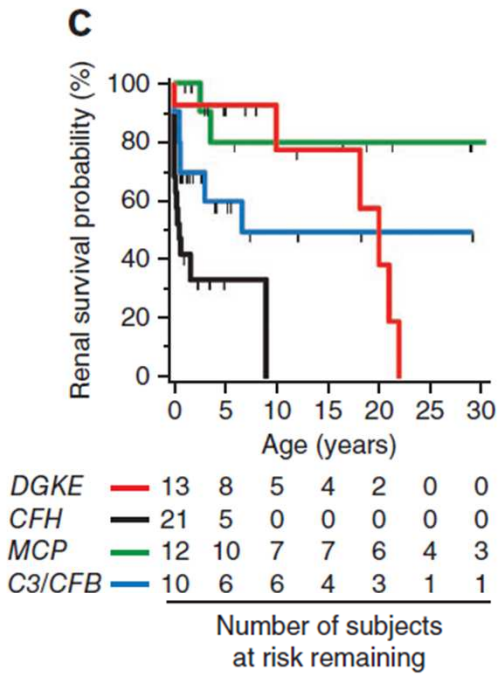


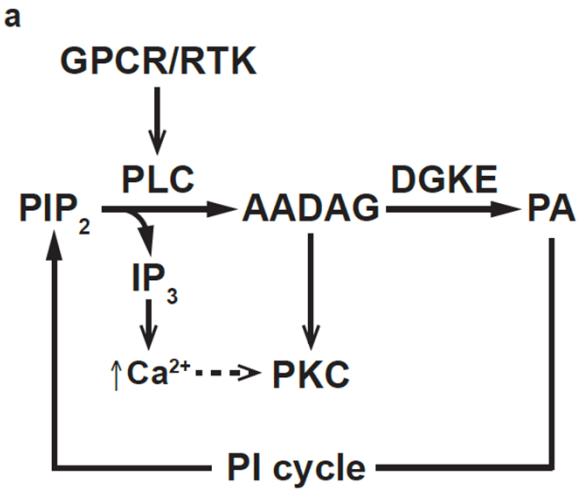
Recessive mutations in *DGKE* cause atypical hemolytic-uremic syndrome

M. Lemaire, V. Frémeaux-Bacchi, Nat Gen 2013.



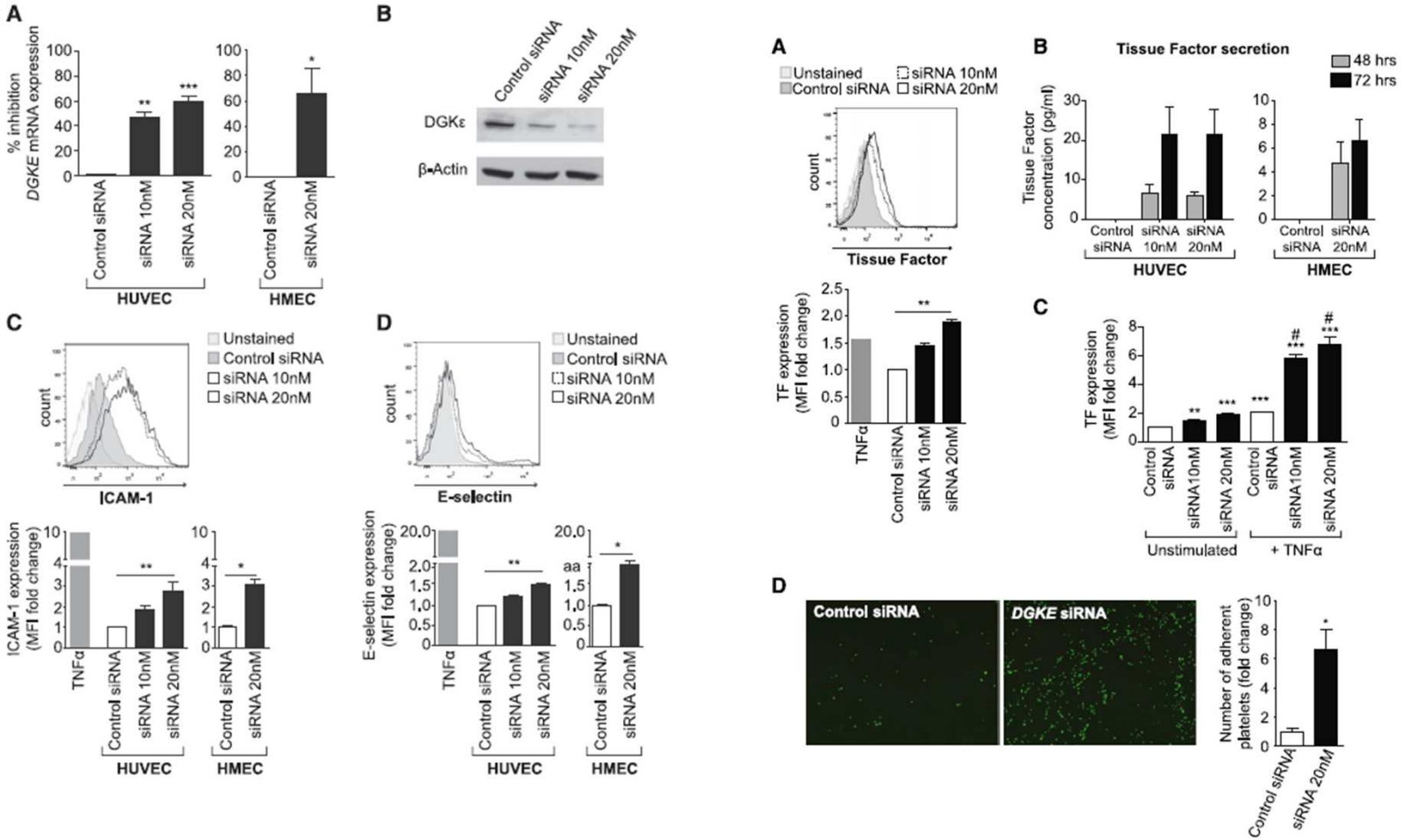






Loss of DGKε induces endothelial cell activation and death independently of complement activation

Sarah Bruneau,[1] Mélanie Néel,[1] Lubka T. Roumenina,[2,3,4] Marie Frimat,[2,5] Lætitia Laurent,[1] Véronique Frémeaux-Bacchi,[2,6] and Fadi Fakhouri[1]



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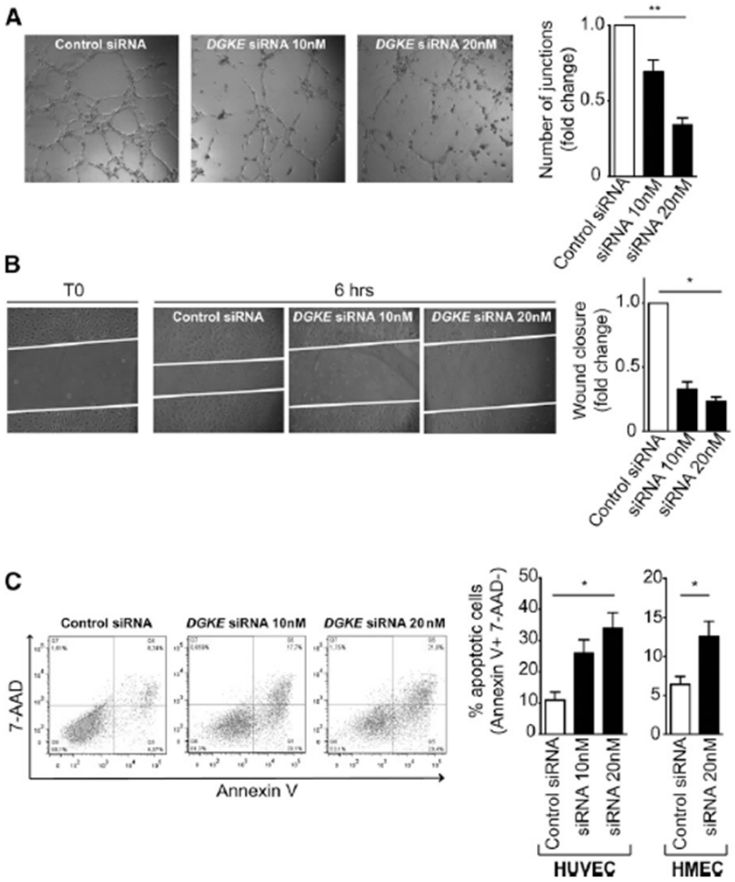
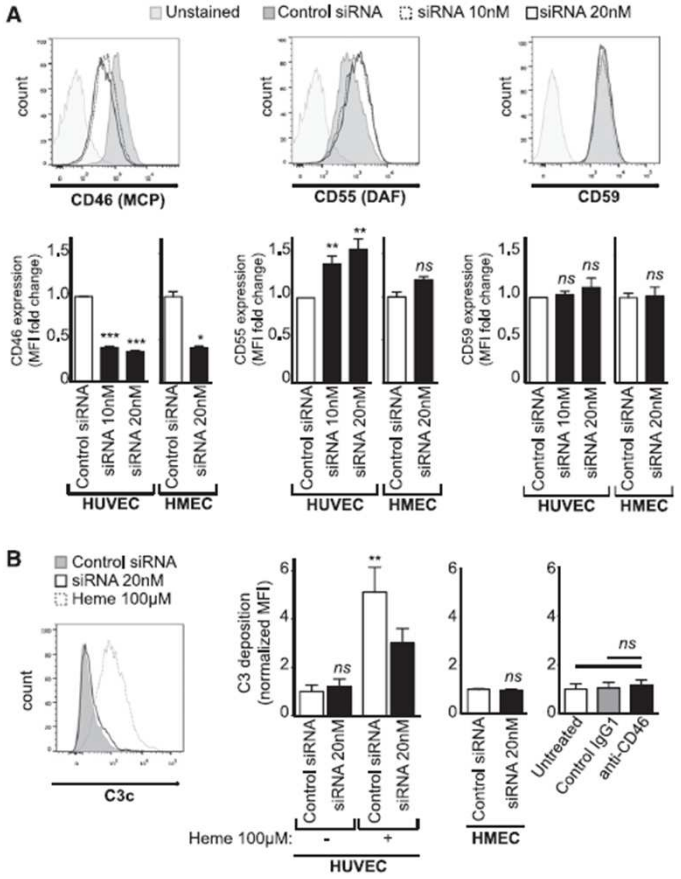
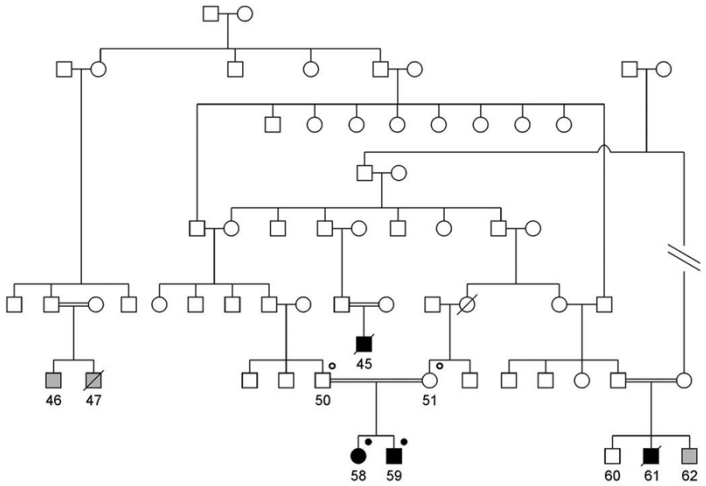
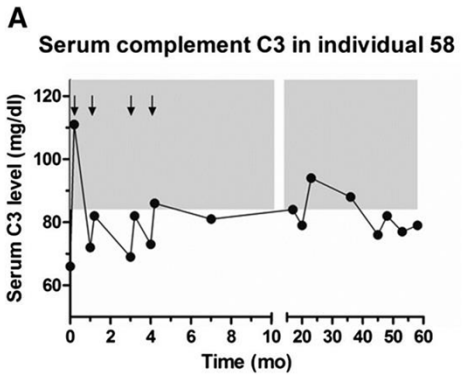


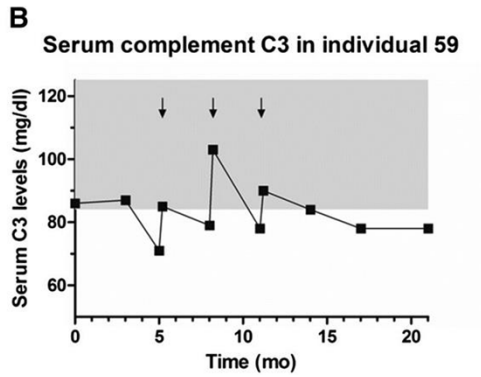


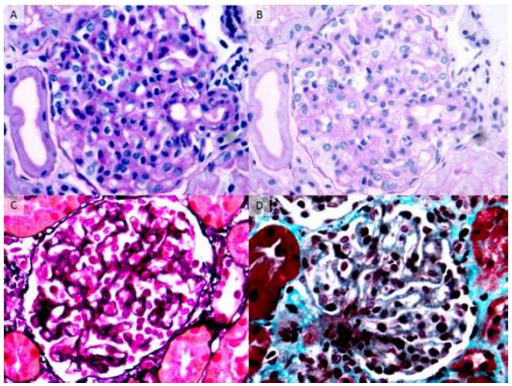
Phenotypic Expansion of *DGKE*-Associated Diseases

Rik Westland,[*†] Monica Bodria,[‡§] Alba Carrea,[‡] Sneh Lata,[*] Francesco Scolari,[‖] Veronique Fremeaux-Bacchi,[¶**] Vivette D. D'Agati,[††] Richard P. Lifton,[‡‡] Ali G. Gharavi,[*] Gian Marco Ghiggeri,[‡] and Simone Sanna-Cherchi[*]





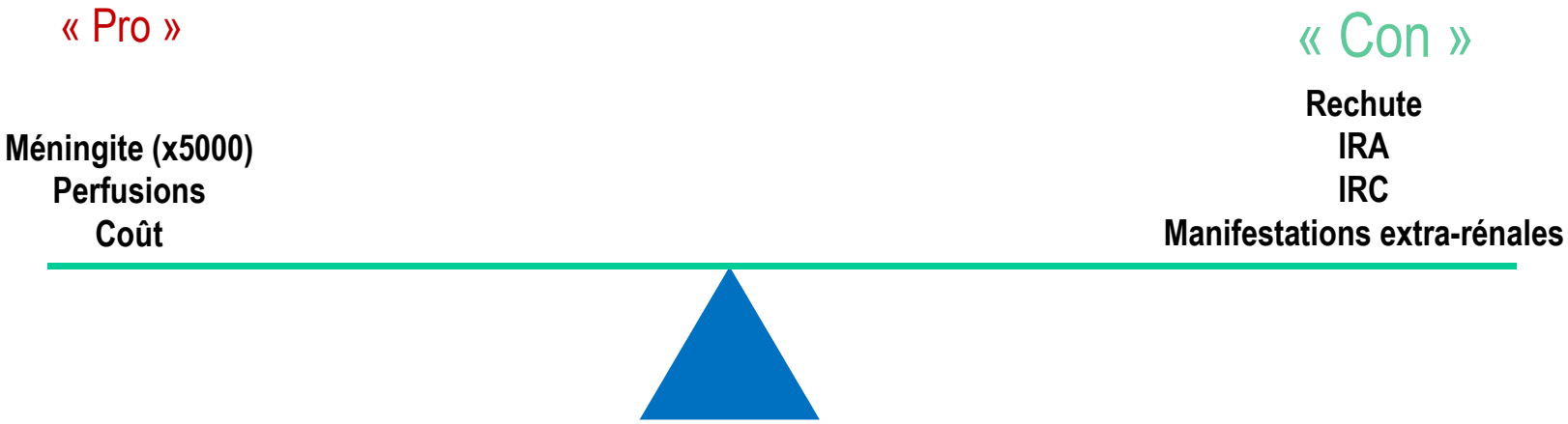




Complement Mutations in Diacylglycerol Kinase-ε–Associated Atypical Hemolytic Uremic Syndrome

Daniel Sánchez Chinchilla,[†] Sheila Pinto,[*†] Bernd Hoppe,[‡] Marta Adragna,[§] Laura Lopez,[§] Maria Luisa Justa Roldan,[‖] Antonia Peña,[¶] Margarita Lopez Trascasa,[†**] Pilar Sánchez-Corral,[†††] and Santiago Rodríguez de Córdoba[*†]*

Activation de la VAC persistante en rémission clinique?



For how long?

Quality of renal recovery

Age

Pregnancy

Psychology patient/doctor

Biomarkers?

For how long?

Quality of renal recovery

Age

COMPLEMENT GENETICS

Pregnancy

Psychology patient/doctor

Biomarkers?

The risk of relapse after eculizumab discontinuation appears to depend on the genetic background

36 patients in the literature (native kidneys)

Courtesy of Mrs Loirat

Mutations	Patients who discontinued N	Patients who relapsed after discontinuation N (%)	Mean duration of eculizumab treatment in relapsers months	Mean delay from eculizumab discontinuation to relapse months
CFH	9 (2 on dialysis)	5* (55)	8 (5.5-14)	2.7 (0.9-6)
MCP	6	1 (16)	6	9
CFI	3	0		
C3	1 (on dialysis)	0		
No mutation identified	17 (4 on dialysis)	1* (6)	6	1.5

7/36 (19.4%) relapsed after discontinuation. Treatment was reinitiated and outcome favourable in all.

* In 1 patient with CFH/CFHR1 hybrid and 1 with no mutation identified, both on dialysis, eculizumab was re-initiated because of significant hemolysis causing hyperkaliemia

Cayci *et al*, 2012; Carr *et al*, 2013; Canigral *et al*, 2013; Pu 2013; Gulleroglu *et al*, 2013; Delmas *et al,* 2013; Fakhouri *et al*, 2014; Chaudhary *et al*, 2014; Sheerin *et al*, 2015; Wetzels *et al*, 2015; Ardissino *et al*, 2015

For how long?

PHRC: ECUSTOP

In all

- Eculizumab has transformed the outcome of aHUS.

- Optimal duration of treatment is unknown.

- Place of eculizumab in secondary HUS remains to be assessed.