Webinars
Thrombotic Microangiopathies
Hemolytic uremic syndrome and other thrombotic microangiopathies

EuroBloodNet Topic on Focus

Title Pregnancy-associated HUS

Speaker Fadi Fakhouri
Prof. of Nephrology
Institution CHUV UNIL
ERN-EuroBloodNet subnetwork TMA
Lausanne – Switzerland
27th October 2020

Co-funded by the Health Programme of the European Union

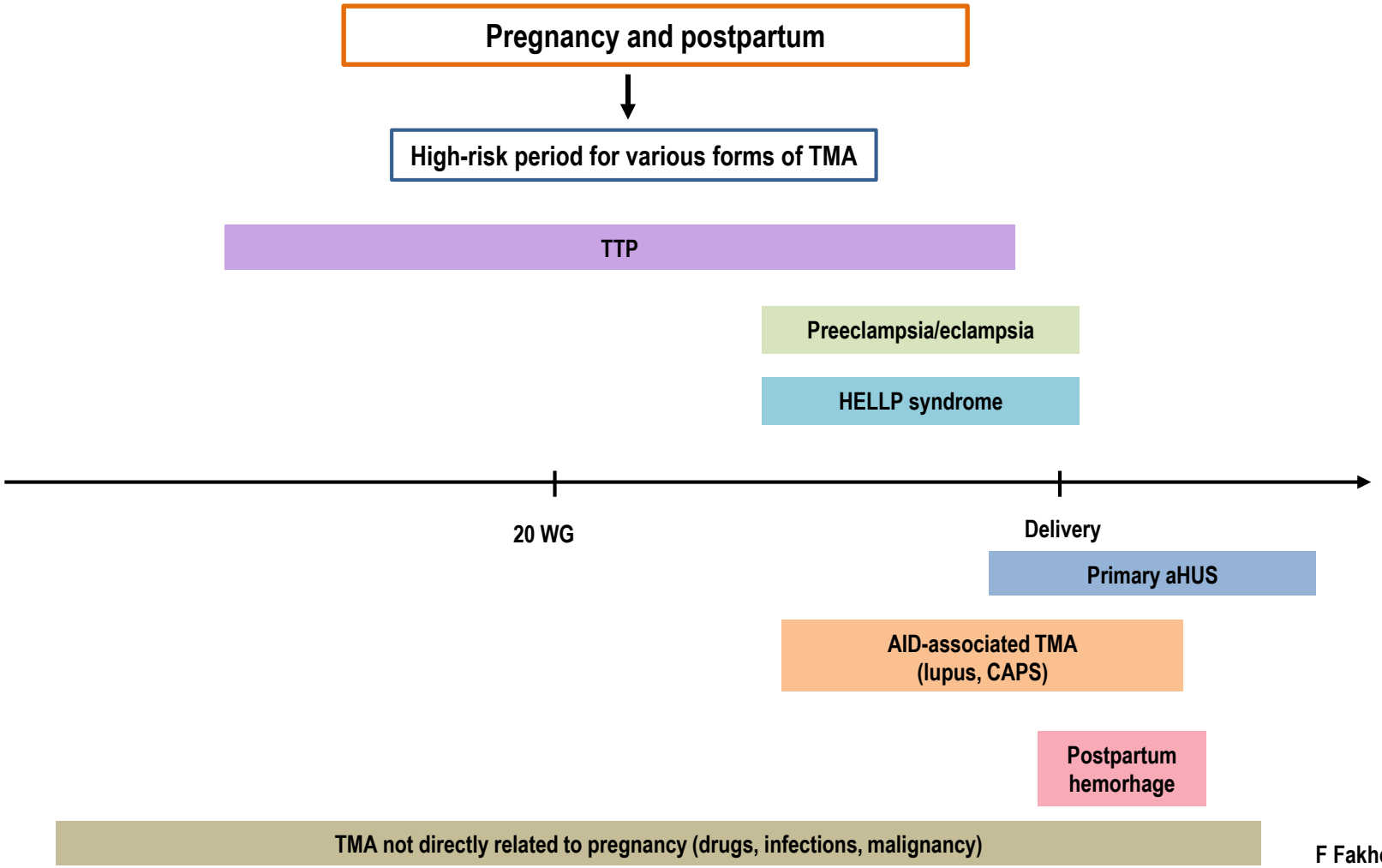
cnr-mat

European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

FF has received consultancy and/or speaker honoraria from Roche, Alexion, Apellis, Achillion, Novartis and Alnylam.

1. To know the spectrum of pregnancy-associated TMA
2. To do the differential diagnosis of the pregnancy-associated HUS.
3. To know the principles of the treatment of pregnancy-associated HUS

Pregnancy and TMA



F Fakhouri, Blood 2020

Complement-mediated atypical HUS: a successful translational research.

A rare severe disease

Atypical HUS

Incidence: 0.25-0.5/10^6 per year

→

Research

Clinical
Genetics
Basic

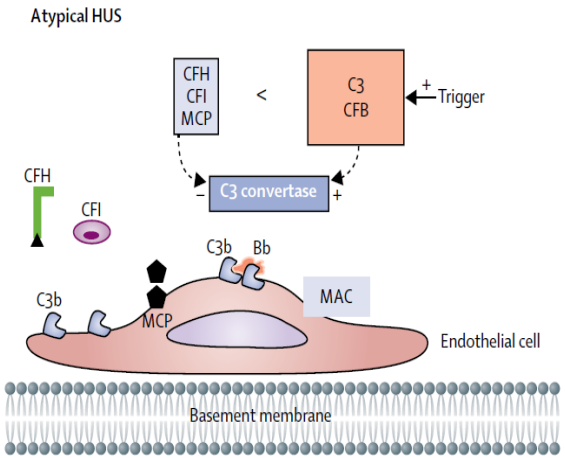
→

Efficacious specific treatment

Complement (C5) blockade

↓

Potential indications in other renal (and extra-renal) diseases



F Fakhouri, Lancet, 2017

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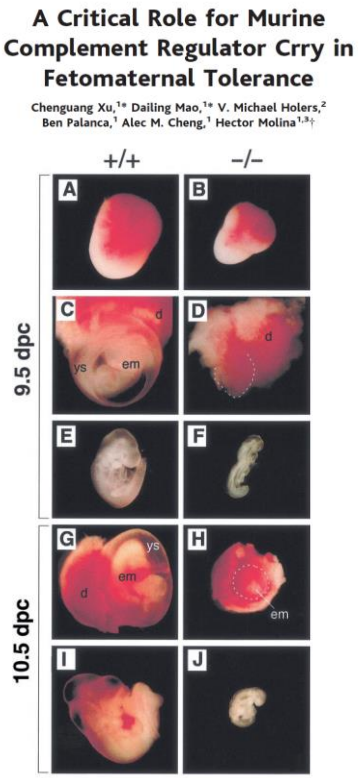
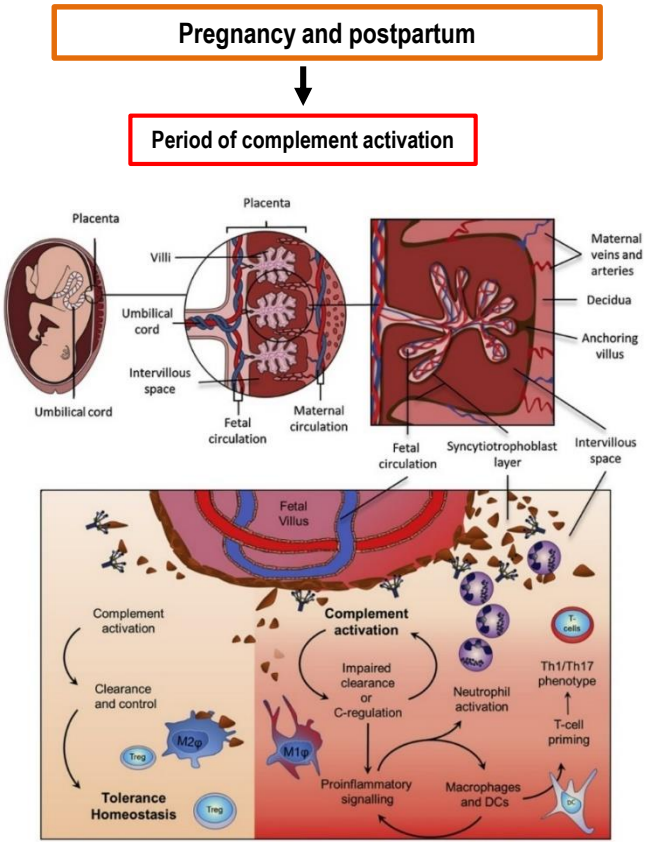
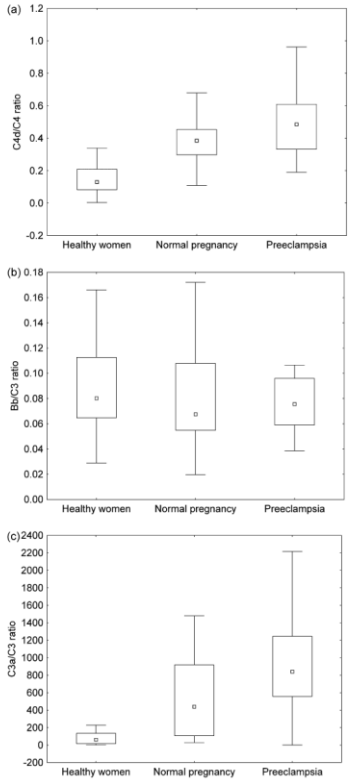
Pregnancy and complement



Science, 2005



Derzsy, Molecular Immunoloy, 2010



Teirilä, Seminars Immunology 2019

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Webinars
Thrombotic Microangiopathies
EuroBloodNet Topic on Focus

Pregnancy and TMA

Hemolytic Uremic Syndrome in Pregnancy and Postpartum

Alexandra Bruel, David Kavanagh, Marina Noris, Yahsou Delmas, Edwin K.S. Wong, Elena Bresin, François Provôt, Vicky Brocklebank, Caterina Mele, Giuseppe Remuzzi, Chantal Loirat, Véronique Frémeaux-Bacchi, and Fadi Fakhouri

Table 1. Characteristics of 87 patients with pregnancy-associated hemolytic uremic syndrome

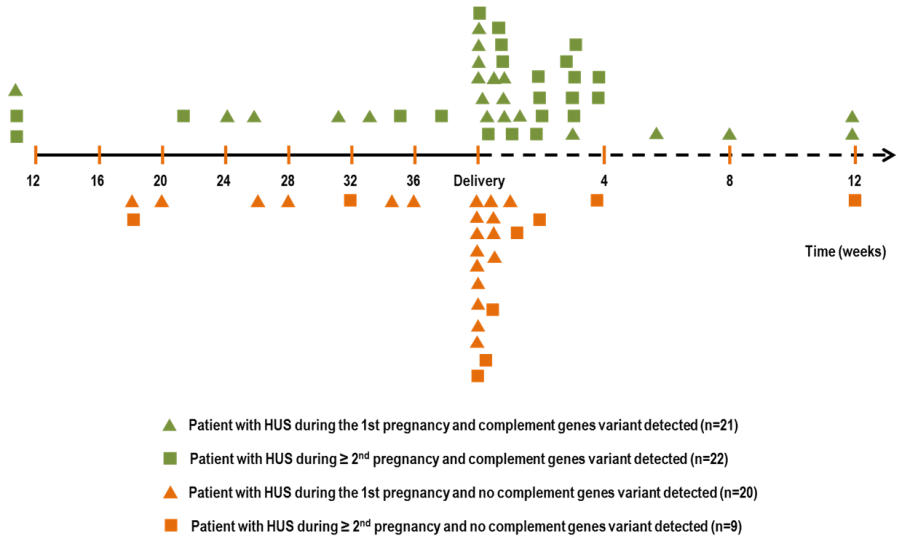
Characteristics	Number (%)/Mean±SD
Number of patients	87
Age at HUS onset, yr	29±6.0
Number of previous pregnancies	0.7±1.2
Rank of pregnancy HUS was diagnosed in (*n*=83)	
First	48 (58)
Second	23 (28)
Third	5 (6)
Fourth or subsequent	7 (8)
Preeclampsia during previous pregnancies (*n*=53)	5 (9)
Fetal loss during previous pregnancies (*n*=49)	10 (20)
Familial history of atypical HUS	14 (16)
Personal history of atypical HUS	7 (8)
Timing of HUS[a]	
Postpartum	63 (76)
During pregnancy	20 (24)
Features at hemolytic and uremic syndrome onset	
Serum creatinine, mg/dl	6.1±5.2
Dialysis	56 (71)
Platelet count $\times 10^3$, per μl	97±99
Hemoglobin, g/dl (*n*=66)	7.8±1.9
Lactate dehydrogenase, U/L (*n*=56)	2225±1617
Neurologic involvement	7 (9)
Other extrarenal manifestations[b]	4 (6)
Treatment	
Number of patients who underwent plasma exchange (*n*=72)	56 (78)
Number of plasma exchange sessions performed per patient (*n*=41)	13±10
Number of patients who received plasma infusion (*n*=51)	21 (41)
Number of patients who received eculizumab	4 (5)
Steroids (*n*=60)	16 (27)
Other[c]	3 (5)

The numbers of patients for whom data are available are reported in brackets. HUS, hemolytic uremic syndrome.
[a]Timing of HUS is unknown for four patients.
[b]Pulmonary edema (*n*=2), pulmonary embolism (*n*=1).
[c]Intravenous Igs (*n*=2), rituximab (*n*=1).

France
UK
Italy

Pregnancy-associated HUS represented 16% (87 out of 547) of HUS cases occurring in women aged 18–45 years reported in the three national registries.

Figure 1



CJASN, 2017

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France
UK
Italy

Table 2. Outcome of 87 patients with pregnancy-associated hemolytic uremic syndrome

Outcome	Number (%)/ Mean±SD
Duration of follow-up, yr (*n*=78)	7.2±5.2
Patients who reached ESRD[a]	41 (53)
ESRD within 3 mo of pregnancy HUS (*n*=78)	25 (32)
Patients with an eGFR<60 ml/min per 1.73 m^2 without ESRD	15 (19)
Patients with an HUS relapse	18 (28)
Relapse in the native kidneys	8 of 62[b] (13)
Number of relapses	1.6±1.4
Patients reaching ESRD after a relapse	6 of 8 (75)
Relapse in the renal graft	10 of 24 (42)

Table 3. Results of complement component assays and complement gene sequencing in patients with pregnancy-associated hemolytic uremic syndrome

Variable	Number (%)
C component assays	
Low serum C3	29 of 74 (39)[a]
Low serum CFH	8 of 54 (15)[b]
Low serum FI	5 of 43 (12)[c]
Low serum FB	0 of 45 (0)
Low MCP expression on granulocytes	6 of 39 (15)[d]
C and THBD genes sequencing (*n*=87)	
Number of patients with a variant detected	49 (56)
Isolated CFH variant	26 (31)
Isolated CFI variant	8 (9)
Isolated MCP variant	3 (3)
Isolated C3 variant	3 (3)
Isolated FB variant	0 (0)
Isolated THBD variant	1 (1)
Combined variants	8 (9)
No variant detected	38 (44)

CJASN, 2017

A retrospective study of pregnancy-associated atypical hemolytic uremic syndrome

Ana Huerta[1,2], Emilia Arjona[3,4], Jose Portoles[1,2], Paula Lopez-Sanchez[1], Cristina Rabasco[2,5], Mario Espinosa[2,5], Teresa Cavero[2,6], Miquel Blasco[2,7], Mercedes Cao[8], Joaquin Manrique[9], Virginia Cabello-Chavez[10], Marta Suñer[10], Manuel Heras[11], Xavier Fulladosa[2,12], Lara Belmar[2,13], Amparo Sempere[14], Carmen Peralta[15], Lorena Castillo[15], Alvaro Arnau[16], Manuel Praga[2,6] and Santiago Rodriguez de Cordoba[3,4]

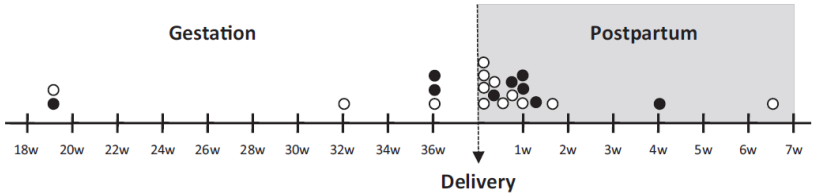

Figure 1 | Timing of onset of the pregnancy-associated atypical hemolytic uremic syndrome event. Black circles represent patients who were carriers of complement pathogenic variants, and white circles represent noncarriers of genetic alterations.

Table 3 | Comparision of clinical parameters between carriers and no carriers of complement pathogenic variants

Clinical parameters	Total (n = 22)	Carriers (n = 9)	No carriers (n = 13)	*P* values
Family history of aHUS	0	0	0	
Diagnosis of aHUS before this event	4	2 (22)	2 (15)	0.7
Previous pregnancies	6	3 (33)	3 (23)	0.6
Not complicated previous pregnancies	4	1 (11)	3 (23)	0.5
Previous complicated pregnancies				
Abortion	2	2 (22)	0 (0)	0.8
Preeclampsia/HELLP	0	0	0	
Prepartum	6	3 (33)	3 (23)	0.6
Postpartum	16	6 (67)	10 (77)	0.6
Cesarean	13	6 (67)	7 (54)	0.6
Severe bleeding	3	1	2	0.6
Fulfill also criteria of preeclampsia?	17	7 (78)	10 (77)	1.0
Fulfill also criteria of HELLP syndrome?	7	3 (33)	4 (31)	0.9
Acute hemodialysis required?	9	3 (33)	6 (46)	0.6
RRT at the end of follow-up	6	3 (33)	3 (23)	0.6
Eculizumab treatment	10	4 (44)	6 (46)	0.10
Discontinuation of eculizumab	7	2 (50)	5 (83)	0.4
Total patients with relapses	7	4 (44)	3 (23)	0.3
Relapses in the group treated with eculizumab	2	1	1	0.7
Average time until the first relapse (mo) (mean [95% confidence interval])		44.5 (17.6–71.4)	305.0 (198.4–411.6)	0.05

aHUS, atypical hemolytic uremic syndrome; HELLP, hemolysis, elevated liver enzymes, and low platelet count; RRT, renal replacement treatment.
Values are n (%) or n unless otherwise indicated.

CJASN, 2017

A retrospective study of pregnancy-associated atypical hemolytic uremic syndrome

Ana Huerta[1,2], Emilia Arjona[3,4], Jose Portoles[1,2], Paula Lopez-Sanchez[1], Cristina Rabasco[2,5], Mario Espinosa[2,5], Teresa Cavero[2,6], Miquel Blasco[2,7], Mercedes Cao[8], Joaquin Manrique[9], Virginia Cabello-Chavez[10], Marta Suñer[10], Manuel Heras[11], Xavier Fulladosa[2,12], Lara Belma[2,13], Amparo Sempere[14], Carmen Peralta[15], Lorena Castillo[15], Alvaro Arnau[16], Manuel Praga[2,6] & Santiago Rodriguez de Cordoba[3,4]

Table 2 | Complement levels, genetics, and autoantibodies in patients with postpartum aHUS

Patient	Genes analyzed[a]	Pathogenic variants	CFH risk haplotype	MCP risk haplotype	Anti FH/FI antibodies	C3 75–135 mg/dl	C4 14–60 mg/dl	FH 90–302 µg/ml	FI 71%–115%	MCP 91%–109%
1	*CFH, MCP, CFI* (Sanger)	None	Hom (H3, H3)	Hom	No	104	19	146	87	ND
2	NGS panel (Ion Torrent)	None	No (H2, H4b)	Hom	No	ND	ND	247	ND	110
3	*CFH, MCP, CFI, CFB* (Sanger)	None	Het (H3, H4b)	No	No	92	15	132	69	100
4	*CFH, MCP, CFI, CFB, C3, THBD* (Sanger)	None	Het (H3, H4a)	No	ND	ND	ND	ND	ND	ND
5	NGS panel (Illumina)	*C3: Exon 4; c.481C>T; p.R161W*	Hom (H3, H3)	Het	No	87	16	79	97	100
6	*CFH, MCP, CFI* (Sanger)	*CFI: Exon 3; c.452 A>G; p.N151S*	Hom (H3, H3)	Het	No	83	25	199	42	103
7	*CFH, MCP, CFI, CFB, CFHR1* (Sanger)	*CFHR1: p.L290S, A296V (CFHR1:CFH hybrid gene)*	Hom (H3, H3)	No	No	64	29	102	100	97
8	*CFH, MCP, CFI* (Sanger)	None	Hom (H3, H3)	Hom	No	94	32	248	ND	ND
9	*CFH, MCP, CFI, CFB, C3, CFP, THBD* (Sanger)	None	Het (H3, H5)	Het	No	106	26	197	113	ND
10	*CFH, MCP, CFI, CFB, C3, CFP, THBD* (Sanger)	None	Het (H3, H4a)	Het	No	104	10	105	109	ND
11	NGS panel (Illumina)	None	No (H4a, H4a)	Hom	No	93	10	138	99	88
12	*CFH, MCP, CFI* (Sanger)	*CFH: Exon2; c.157C>A; p.R53S*	Het (H3, H2)	Hom	No	137	28	242	100	ND
13	NGS panel (Ion Torrent)	None	No (H4a, H4a)	No	No	71	23	174	93	97
14	NGS panel (Ion Torrent)	None	Het (H3, H1)	No	No	82	13	122	70	130
15	*CFH, MCP, CFI, CFB, C3, CFP, THBD* (Sanger)	None	Het (H3, H4a)	Hom	No	51	22	45	113	100
16	*CFH, MCP, CFI, CFB* (Sanger)	*CFH: Exon 16 c.2284G>T; p.E762**	No (H1, H5)	Het	No	63	30	85	93	125
17	*CFH, MCP, CFI* (Sanger)	None	No (H1, H4a)	No	No	106	42	147	120	100
18	NGS panel (Illumina)	*C3: Exon 41; c.4855A>C; p.S1619R*	Het (H3, H1)	No	No	102	40	177	90	119
19	NGS panel (Ion Torrent)	*CFHR1: p.L290S, A296V (CFHR1:CFH hybrid gene)*	Het (H3, H1)	Hom	No	99	20	99	100	ND
20	NGS panel (Ion Torrent)	*CFHR1: p.L290S, A296V (CFHR1:CFH hybrid gene)*	Het (H3, H1)	No	No	91	12	105	100	123
21	NGS panel (Illumina)	*CFH: Exon13; c.1707C>A; p.C569**	No (H1, H7)	No	No	129	27	220	116	104
22	NGS panel (Illumina)	None	No (H1, H1)	No	No	141	38	333	97	113

aHUS, atypical hemolytic uremic syndrome; Het, heterozygote; Hom, homozygote; ND, not done; NGS, next generation sequencing.
[a]NGS panel (Ion Torrent) includes the *CFH, CFI, MCP, C3, CFB, THBD, ADAMTS13, DGKE, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5* and *CFP* genes. NGS panel (Illumina) interrogates as many as 48 genes and includes all complement genes.

9/22 (41%)

CJASN, 2017

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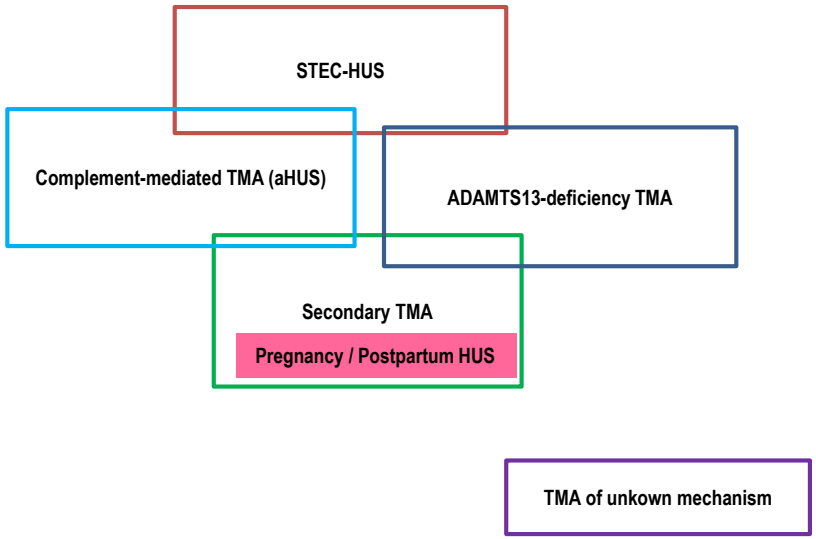
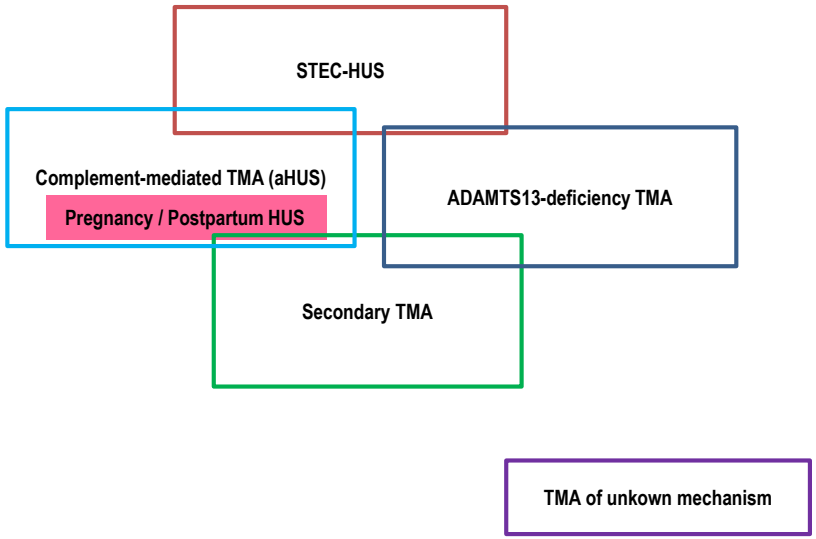
EuroBloodNet Topic on Focus

Reclassifying pregnancy and postpartum-associated HUS



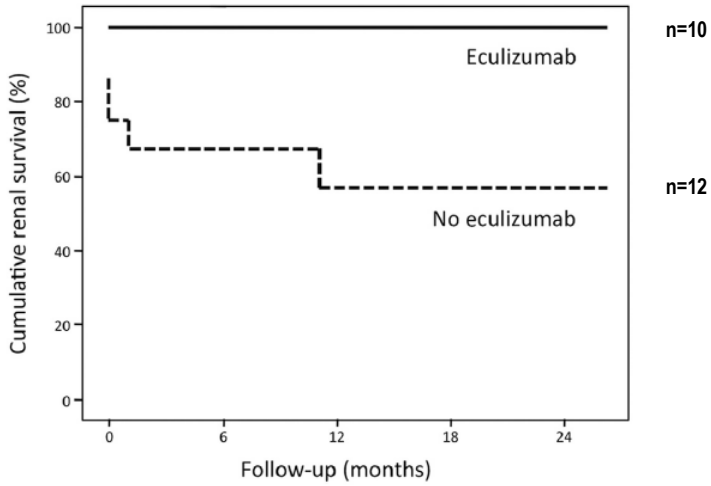
Reclassifying pregnancy and postpartum-associated HUS



Treatment of pregnancy and postpartum-associated HUS

A retrospective study of pregnancy-associated atypical hemolytic uremic syndrome

Ana Huerta[1,2], Emilia Arjona[3,4], Jose Portoles[1,2], Paula Lopez-Sanchez[1], Cristina Rabasco[2,5], Mario Espinosa[2,5], Teresa Cavero[2,6], Miquel Blasco[2,7], Mercedes Cao[8], Joaquin Manrique[9], Virginia Cabello-Chavez[10], Marta Suñer[10], Manuel Heras[11], Xavier Fulladosa[2,12], Lara Belmar[2,13], Amparo Sempere[14], Carmen Peralta[15], Lorena Castillo[15], Alvaro Arnau[16], Manuel Praga[2,6] and Santiago Rodriguez de Cordoba[3,4]



n=10

n=12

CJASN, 2017

Pregnancy and postpartum-associated atypical HUS cases treated with eculizumab

20 individual cases
15 additional patients in 3 series (Bruel et al (2017), Huerta et al (2018), Gaggl et al (2018).
Excellent response in all.

Reviewed in Fakhouri, Blood, 2020

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Thrombotic Microangiopathies
EuroBloodNet Topic on Focus

Reclassifying pregnancy and postpartum-associated HUS

Atypical haemolytic uraemic syndrome and pregnancy: outcome with ongoing eculizumab

Aude Servais[1,2], Nadège Devillard[3], Véronique Frémeaux-Bacchi[4,5], Aurélie Hummel[1,2], Laurent Salomon[2,6], Cécile Contin-Bordes[7], Hélène Gomer[8], Christophe Legendre[1,2] and Yahsou Delmas[9]

Table 2. Data for six pregnancies in three aHUS women

Patient		1		2	3			Mean (range)
Pregnancy		1	2	1	1	2	3	
Eculizumab treatment during pregnancy		Yes	Yes	Yes	No	Yes	Yes	
Age (years)		31	33	29	25	26	27	28.5 (25–33)
Before pregnancy	Serum creatinine (μmol/L)	171	140	130	300	200	194	189.2 (130–300)
	eGFR (mL/min/1.73 m^2)	32	40	45	18	28	29	32 (18–45)
	PU (g/g creatininuria)	1.0	0.4	0.9			0.8	0.8 (0.4–1.0)
	High blood pressure (number of medications)	Yes (2)	Yes (2)	Yes (2)	Yes	Yes	Yes	
During pregnancy	Serum creatinine (μmol/L)	130	115	123			160	135 (115–160)
Foetal complications				Growth retardation	Termination	In utero death	Growth retardation	
Gestational age (weeks)		29	34	30	12	24	30	29.4 (24–34)
Birthweight (g)		1550	2500	1410			1070	1632.5 (1070–2500)
Neonatal complications		Prolonged hospital stay		Prolonged hospital stay				
Maternal complications		HELLP syndrome		Pre-eclampsia	Acute renal failure		Pre-eclampsia	
At delivery	Serum creatinine (μmol/L)	170	115	243	690		169	277.4 (169–690)
	PU (g/g creatininuria)	1.5	0.8	6.8	1.3		1.3	2.3 (0.8–6.8)
Duration of follow-up after delivery (months)		12	24	6	12	5	8	
At last follow-up, after delivery	Serum creatinine (μmol/L)	139	134	140	200	194	170	157.4 (134–194)
	eGFR (mL/min/1.73 m^2)	41	42	41	28	29	33	36.6 (29–42)
	PU (g/g creatininuria)	0.4	0.4	0.6		0.8		0.7 (0.4–1.1)

eGFR, estimated glomerular filtration rate by MDRD formula; PU, proteinuria.

The dose of eculizumab had to be increased during all pregnancies due to incomplete complement blockade.

NDT, 2017

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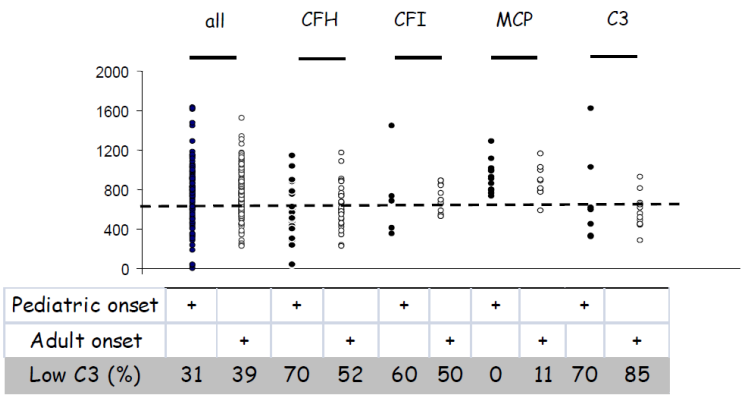
EuroBloodNet Topic on Focus

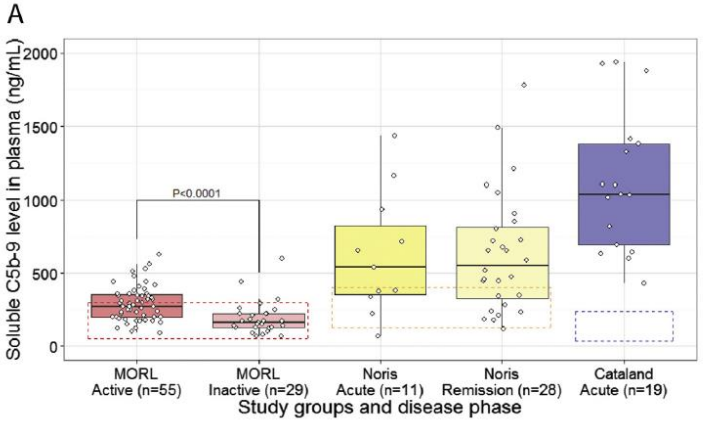
The quest for a diagnostic biomarker/test for aHUS

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



Frémeaux-Bacchi, CJASN, 2013

Soluble C5b-9 as a Biomarker for Complement Activation in Atypical Hemolytic Uremic Syndrome



Bu, AJKD 2015

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EuroBloodNet Topic on Focus

The quest for a diagnostic biomarker/test for aHUS

An Ex Vivo Test of Complement Activation on Endothelium for Individualized Eculizumab Therapy in Hemolytic Uremic Syndrome

Miriam Galbusera, Marina Noris,* Sara Gastoldi,* Elena Bresin, Caterina Mele, Matteo Breno, Paola Cuccarolo, Marta Alberti, Elisabetta Valoti, Rossella Piras, Roberta Donadelli, Marina Vivarelli, Luisa Murer, Carmine Pecoraro, Elisa Ferrari, Annalisa Perna, Ariela Benigni, Valentina Portalupi, and Giuseppe Remuzzi*

AJKD, 2019

HDMEC

Medium + ADP (10 mM)

Serum 1:2

2h 4h

IF (anti-C5b-9 / antiC3c)
Image J (15 fields)

Unstimulated EC (+++)

COMPLEMENT ACTIVATION AND THROMBOTIC MICROANGIOPATHIES

Paloma, CJASN 2019

HDMEC

Medium + ADP (10 mM)

Plasma + control serum (1:1)
Dilution 1:2

4h

IF (anti-C5b-9)
Image J (20 fields)

Stimulated EC (+++)

The quest for a diagnostic biomarker/test for aHUS

Management of thrombotic microangiopathy in pregnancy and postpartum: report from an international working group

Fadi Fakhouri,[1] Marie Scully,[2,3] François Provôt,[4,5] Miquel Blasco,[6] Paul Coppo,[5,7] Marina Noris,[8] Kathy Paizis,[9-11] David Kavanagh,[12,13] Frédéric Pène,[5,14,15] Sol Quezada,[16,17] Alexandre Hertig,[18] Sébastien Kissling,[1] Patrick O'Brien,[19] Yahsou Delmas,[5,20] Lorenzo Alberio,[21] Norbert Winer,[22-25] Agnès Veyradier,[5,26-28] Spero Cataland,[29] Véronique Frémeaux-Bacchi,[30] Chantal Loirat,[31] Giuseppe Remuzzi,[8] Vassilis Tsatsaris,[32] and the International Working Group on Pregnancy-Related Thrombotic Microangiopathies

Table 2. Some findings that may help in the clinical management of patients with P-TMA

Findings to aid in management of patients with P-TMA
1. The context (PE/E, HELLP, severe delivery hemorrhage) in which TMA occurs is paramount.
2. aHUS and TTP are rare disorders in general and during pregnancy.[14,17,22,23]
3. PE/E and HELLP syndrome are still the main cause of P-TMA.[22,42]
4. To date, there is no diagnostic test for aHUS and complement assays and results of genetic tests are not required for diagnosis at the acute phase Normal complement assays do not rule out pregnancy-associated aHUS[36,37]; conversely, features of complement activation are not synonymous with pregnancy-associated aHUS (transient complement activation may be the consequence of endothelial damage).
5. A pregnancy-associated aHUS or a TTP masquerading as HELLP is a very rare occurrence.[26]
6. Increased levels of serum liver enzymes are extremely rare in aHUS.
7. The absence of thrombocytopenia does not rule out pregnancy-associated aHUS.[23]
8. HELLP syndrome is a TMA affecting mainly the liver and more rarely the kidney (the most frequent renal lesion is acute tubular necrosis).[38,39]
9. PE/E and HELLP syndrome are not predominantly complement-mediated TMA.[41,109]
10. Spontaneous evolution of renal/hematological parameters during the first 48 h after delivery is crucial in the management of P-TMA.[42]
11. Benefit of plasma exchanges is only proven in immune ADAMTS13-deficiency–related TTP.
12. In case of anuria (particularly in context of postpartum hemorrhage), renal cortical necrosis (Doppler, magnetic resonance imaging) should be ruled out.[40]
13. A kidney biopsy, when feasible, may be helpful for the differential diagnosis between acute tubular necrosis, TMA, and other causes of AKI.

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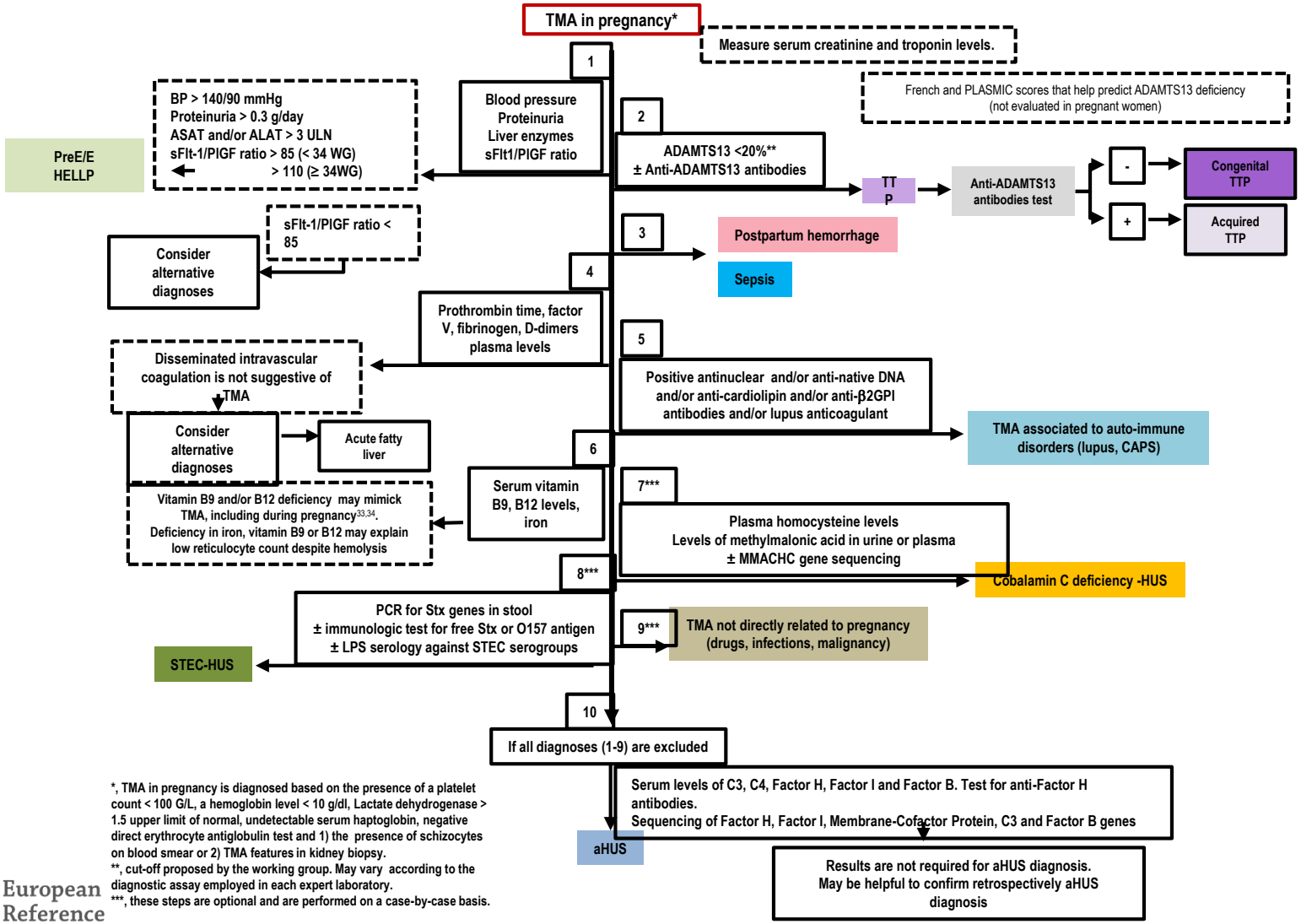
Some clues for the diagnosis of pregnancy-associated HUS



*, TMA in pregnancy is diagnosed based on the presence of a platelet count < 100 G/L, a hemoglobin level < 10 g/dl, Lactate dehydrogenase > 1.5 upper limit of normal, undetectable serum haptoglobin, negative direct erythrocyte antiglobulin test and 1) the presence of schizocytes on blood smear or 2) TMA features in kidney biopsy.
**, cut-off proposed by the working group. May vary according to the diagnostic assay employed in each expert laboratory.
***, these steps are optional and are performed on a case-by-case basis.

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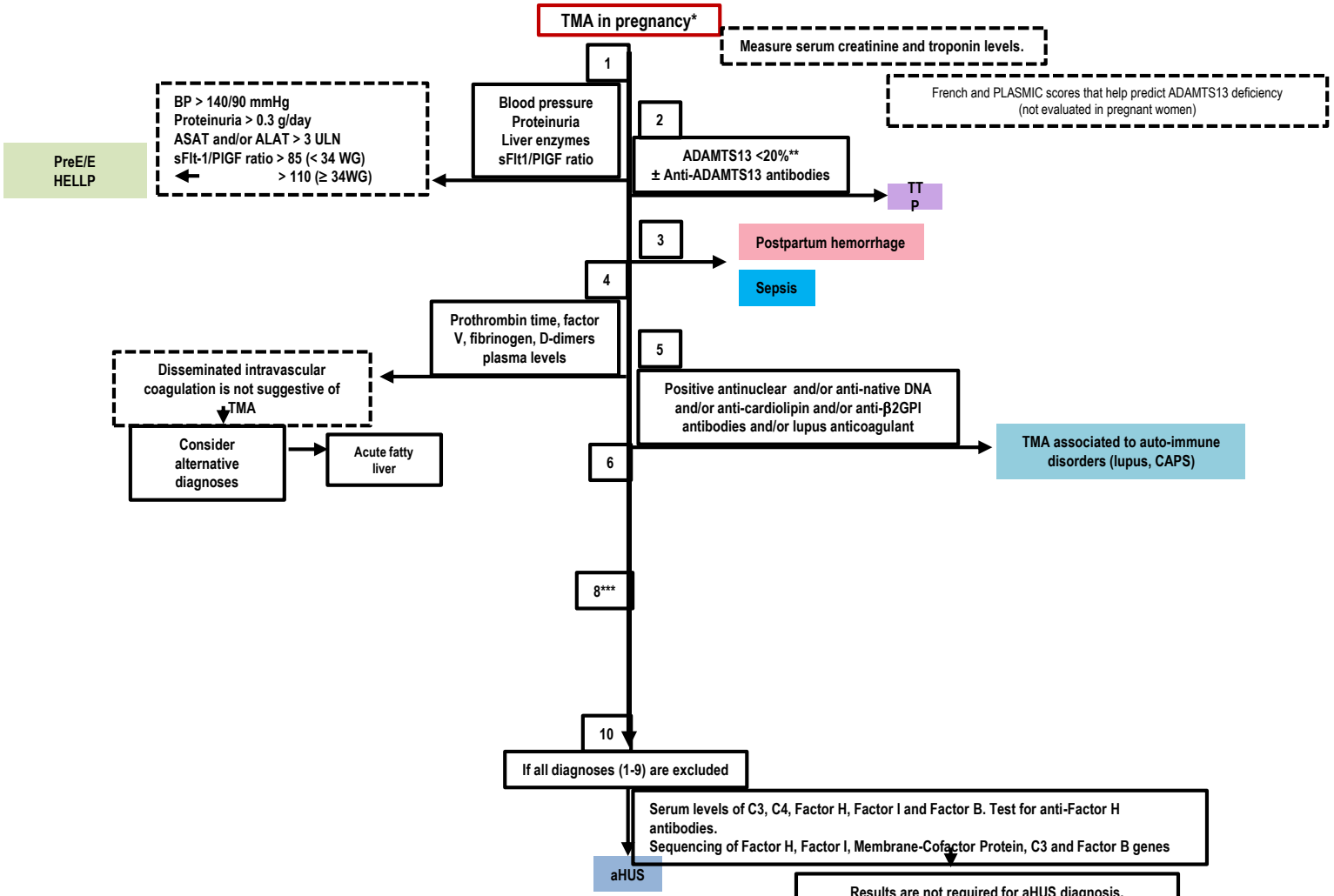

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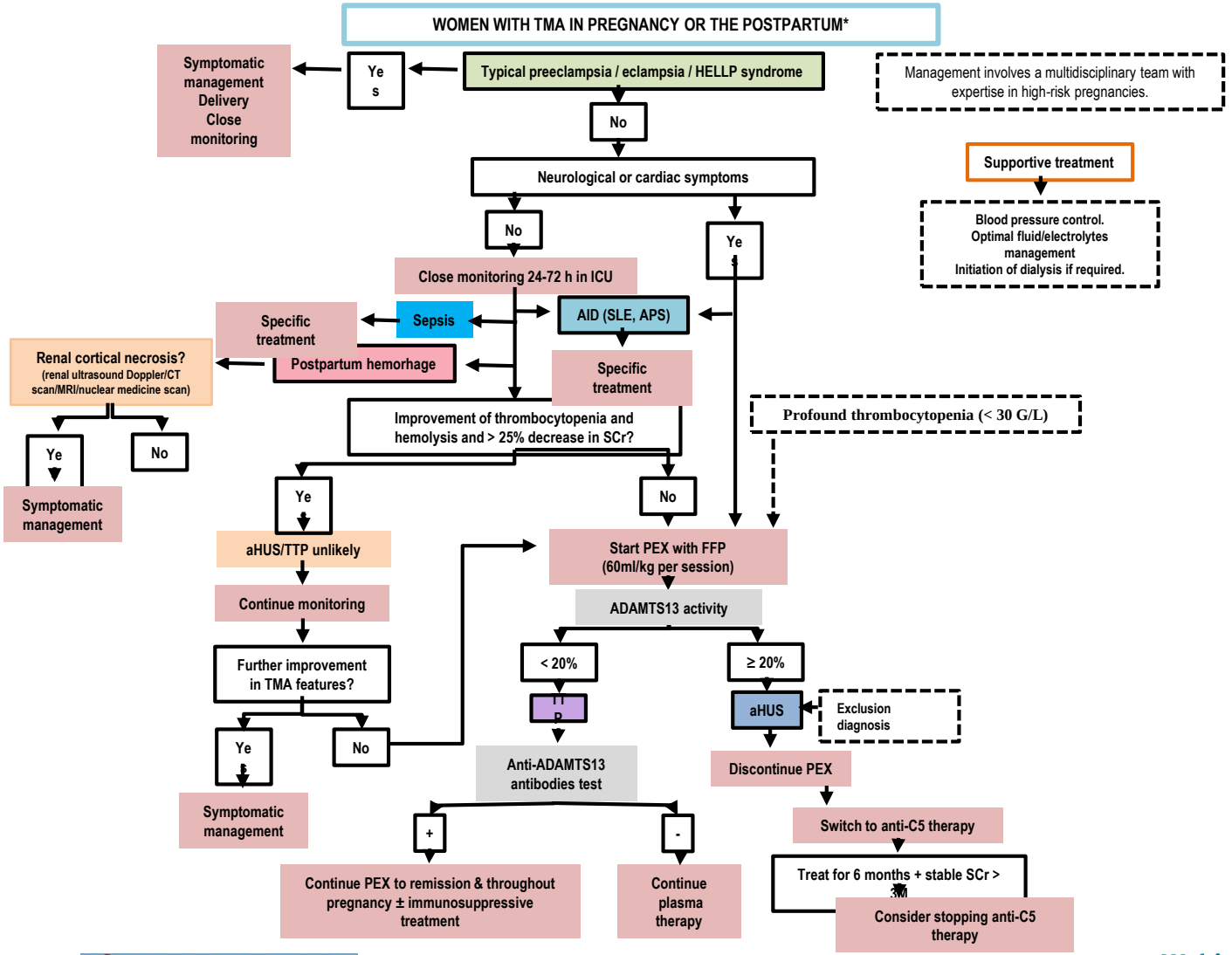

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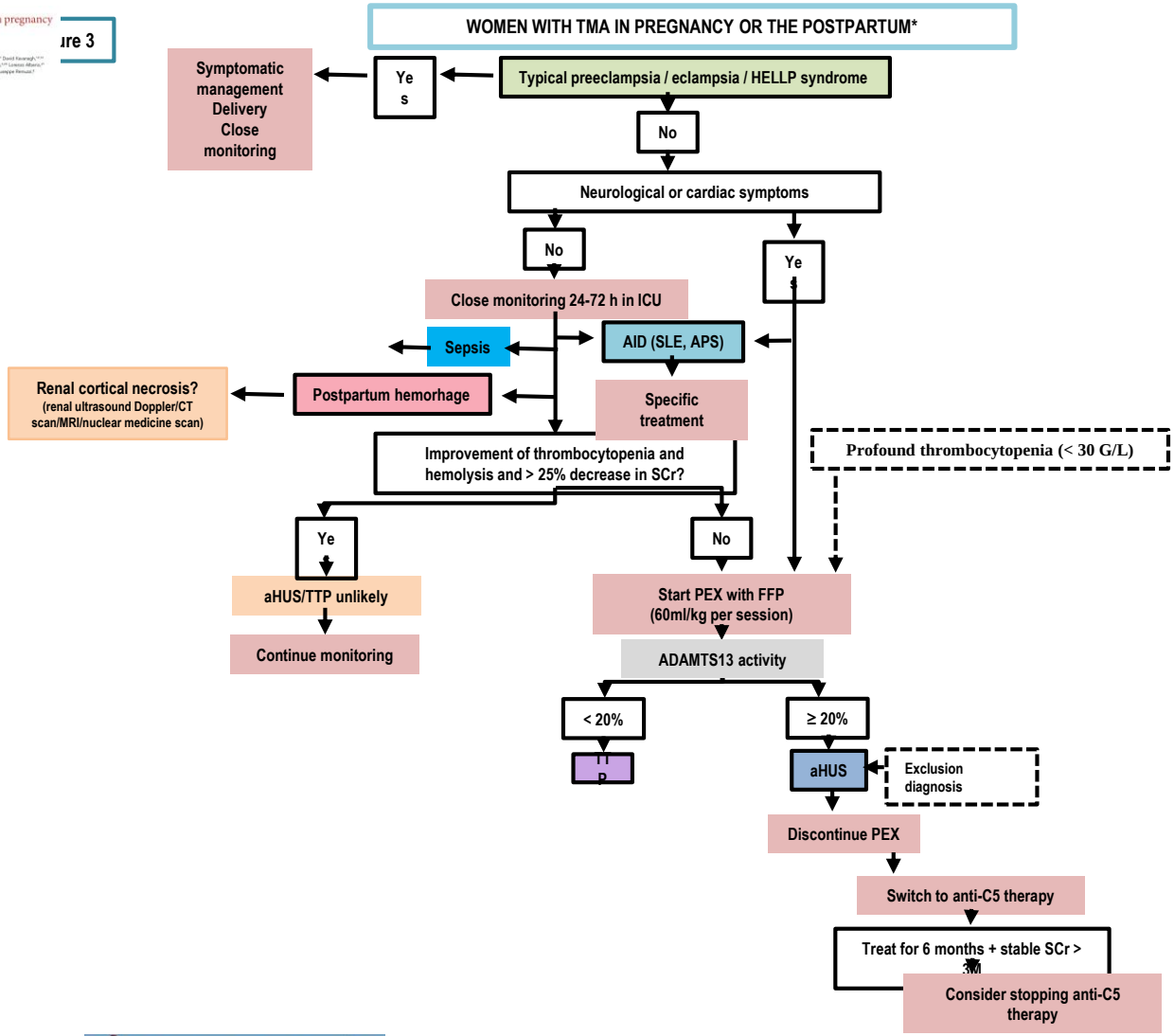

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Renal Cortical Necrosis in Postpartum Hemorrhage: A Case Series

Marie Frimat, MD, PhD,[1,] Melanie Decambron, MD,[2,*] Celine Lebas, MD,[3] Anissa Moktefi, MD,[4] Laurent Lemaitre, MD, PhD,[5] Viviane Gnemmi, MD, PhD,[6] Benedicte Sautenet, MD,[7] François Glowacki, MD, PhD,[1] Damien Subtil, MD, PhD,[8] Mercedes Jourdain, MD, PhD,[9] Agnes Rigouzzo, MD,[10] Isabelle Brocheriou, MD, PhD,[4] Jean-Michel Halimi, MD, PhD,[7] Eric Rondeau, MD, PhD,[11] Christian Noel, MD, PhD,[1] François Provôt, MD,[1] and Alexandre Hertig, MD, PhD[11]*

Am J Kidney Dis. 2016;68(1):50-57

Table 1. Characteristics of the 18 Patients

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Clinical features																		
Age, y	32	32	31	38	29	30	39	27	35	29	34	35	39	28	34	36	40	33
Gestational age, wk[a]	37	36	38	18	38	41	41	37	38	37	39	33	41	37	41	41	38	38
Peripartum data																		
Pregnancy disorders	PE	PE	—	Sepsis	—	—	—	—	—	HELLP	—	PE	—	—	—	—	—	—
Blood loss, L	3	1.7	1.9	1.3	2.6	1.5	2.1	4.2	1.7	2.6	2.2	1.8	2.5	3.5	2.1	1.9	5.6	4.6
Hemodynamic instability	−	−	−	+	−	−	−	+	−	−	−	−	+	+	−	+	−	−
First 24-h urinary volume, L	0.2	0.25	0	0.15	0.3	1.3	0.03	0.5	0.2	0.25	0.3	0.5	0.1	0	0.15	0.1	0	0.03
Laboratory data on ICU admission																		
Creatinine, mg/dL	1.9	2.6	3.7	2.5	1.4	2.9	2	1.5	2	3.2	4.1	1.9	1.8	1.9	2.1	1.9	3.3	1
Hemoglobin, g/dL	9.5	8.5	6.2	8.9	10.5	8.8	8.7	7.3	7.7	8.9	8.3	9.9	10.5	7.4	7.6	9.2	6.7	9.3
Haptoglobin, g/L	<0.07	<0.07	0.72	NA	0.31	1.28	<0.1	<0.07	0.55	<0.07	0.1	2.83	<0.2	0.08	0.37	1.31	<0.07	<0.07
LDH, UI/L	2,256	1,856	1,784	4,076	3,526	4,346	NA	2,318	2,125	4,726	3,222	659	NA	1,593	2,284	1,570	2,152	1,324
Platelet count, $\times 10^9$/L	39	23	93	48	53	43	75	30	51	58	86	63	79	79	55	37	58	57
Hepatic cytolysis	−	+	+	+	−	+	−	−	+	+	+	−	−	+	−	+	+	−
DIC	+	+	+	+	−	+	−	+	−	+	+	−	+	+	+	−	−	−
Postpartum hemorrhage treatment																		
Tranexamic acid treatment																		
Loading dose, g	4	2	1	2	2	4	2	2	1	1	2	1.5	1	1	1	1	2[b]	2.5[b]
Maintenance dose, g/h	1	0.5	1	0.5	1	1	1	0.5	0.5	0.5	0.5	0.5	0.5	1	1	1	0	0
Exposure duration, h	7	4	5	16	2	3	8	2	14	2	6	3	7	4	3	4	0	0
Other treatments																		
Red blood cells, L	2.1	0.9	0	1.2	1.5	1.2	1.2	2.1	0.6	1.2	0.9	0	2.4	1.5	2.1	3.6	1.8	1.8
Crystalloid, L	0	1	3	1.5	1.5	0	1	0	4	2	1.5	1	0.5	4	1	2.5	2.5	2.5
Colloid, L	2	2	1	2	4.5	5	2	3.5	1	1.5	3	0	1	0	1	1	1.5	0
Fibrinogen, g	9	6	3	6	6	4.5	3	7.5	4.5	6	0	0	9	6	0	3	4.5	3
Invasive procedures	L	−	−	H	L	EA	−	H	−	−	−	−	L	L/H	L/H	EA	L	L
RCN characteristics																		
Diagnostic tool used	MRI	MRI/B	MRI	MRI	MRI	MRI	CECT	MRI	MRI	MRI	MRI/B	MRI	MRI/B	MRI	MRI/B	B	CEUS/B	CEUS
Type	D	D	D	D	P	P	P	NA	NA	D	D	D	D	D	D		D	P
Kidney disease outcome																		
Follow-up, mo	36	28	22	34	36	28	55	27	21	12	12	26	16	14	36	21	12	12
Hemodialysis vintage, d	210	62	NR	NR	NR	7	66	23	NR	17	120	NR	NR	NR	60	13	46	19
eGFR at 6 mo postpartum	DD	22	DD	DD	DD	38	25	43	DD	48	12	DD	DD	DD	38	47	22	52
eGFR at last report	24	35	ESRD	ESRD	ESRD	51	46	70	ESRD	45	18	ESRD	ESRD	ESRD	46	45	49	74

Renal cortical necrosis

Renal Cortical Necrosis in Postpartum Hemorrhage: A Case Series

Marie Frimat, MD, PhD,[1,] Melanie Decambron, MD,[2,*] Celine Lebas, MD,[3] Anissa Moktefi, MD,[4] Laurent Lemaitre, MD, PhD,[5] Viviane Gnemmi, MD, PhD,[6] Benedicte Sautenet, MD,[7] François Glowacki, MD, PhD,[1] Damien Subtil, MD, PhD,[8] Mercedes Jourdain, MD, PhD,[9] Agnes Rigouzzo, MD,[10] Isabelle Brocheriou, MD, PhD,[4] Jean-Michel Halimi, MD, PhD,[7] Eric Rondeau, MD, PhD,[11] Christian Noel, MD, PhD,[1] François Provôt, MD,[1] and Alexandre Hertig, MD, PhD[11]*

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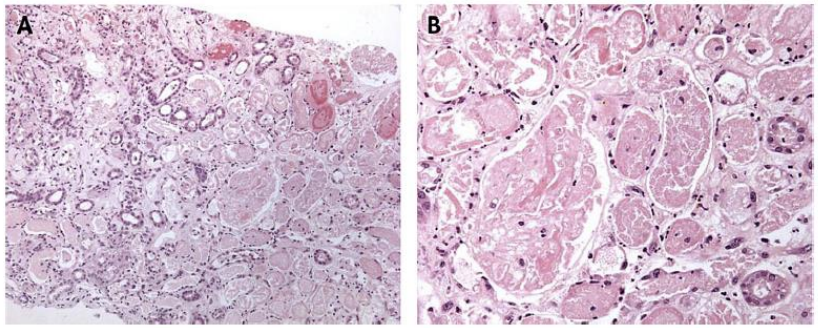

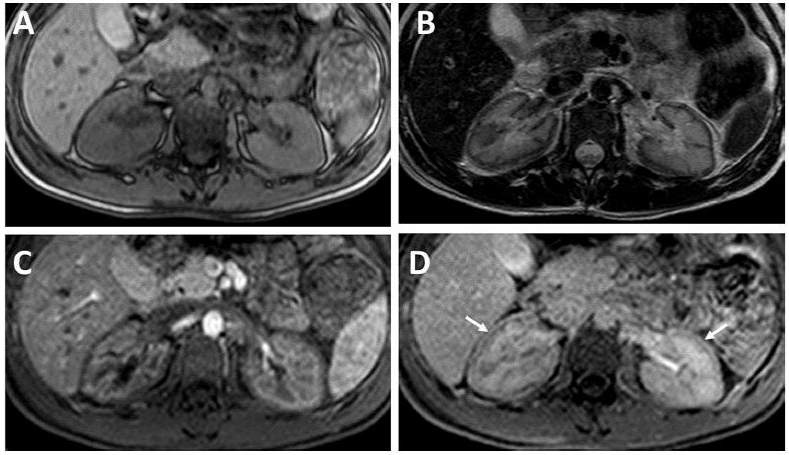

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Table 2. Clinical Parameters and Management According to eGFR at 6 Months Postpartum

	eGFR < 15 (n = 9)	eGFR ≥ 15 (n = 9)	*P*
Obstetric parameters			
Age, y	33.4 ± 3.8	33.3 ± 4.4	0.9
BMI, kg/m^2	25.4 ± 3.6	23.2 ± 3.0	0.2
Twin pregnancy	4/9 (44.4)	3/9 (33.3)	0.5
Gestational hypertension	2/9 (22.2)	2/9 (22.2)	0.7
Gestational age, wk[a]	35.4 ± 6.9	38.9 ± 2.1	0.3
Predelivery disorders	3/9 (33.3)	2/9 (22.2)	0.5
Induction of labor	6/9 (66.7)	6/9 (66.7)	0.7
Cesarean delivery	3/9 (33.3)	7/9 (77.8)	0.08
Uterine atony	6/9 (66.7)	9/9 (100)	0.1
Blood loss, L	2.3 ± 0.7	2.9 ± 1.5	0.6
Hemodynamic instability	3/9 (33.3)	2/9 (22.2)	0.5
Biology			
Hemoglobin, g/dL	8.8 ± 1.5	8.3 ± 0.9	0.5
LDH, UI/L	2,405 ± 1,128	2,572 ± 1,264	0.8
Platelet count, ×10^9/L	65.7 ± 19.1	48.4 ± 16.4	0.06
Hemolysis	3/7 (42.8)	5/8 (62.5)	0.6
PT, %	56 ± 24	64 ± 19	0.4
Hepatic cytolysis	5/9 (55.6)	5/9 (55.6)	0.7
DIC	6/9 (66.7)	5/9 (55.6)	0.5
Renal presentation			
First 24-h urinary volume, mL	114 ± 105	290 ± 409	0.4
Anuria	4/9 (44.4)	3/9 (33.3)	0.5
Early hemodialysis	5/9 (55.6)	6/9 (66.7)	0.5
Creatinine, mg/dL	2.36 ± 0.9	2.28 ± 0.8	0.9
Diffuse cortical necrosis	7/8 (87.5)	4/7 (57.1)	0.3
Therapeutics			
Red blood cells, L	1.13 ± 0.8	1.77 ± 0.8	0.1
Crystalloid loading, L	1.9 ± 1.5	1.4 ± 1	0.4
Colloid loading, L	1.6 ± 1.5	1.9 ± 1.5	0.6
Total loading volume, L	3.5 ± 1.7	3.3 ± 0.9	0.8
Uterotonics	8/9 (88.9)	7/9 (77.8)	0.5
Invasive procedure	5/9 (55.6)	6/9 (66.7)	0.5
Iodinated contrast medium exposure	4/9 (44.4)	4/9 (44.4)	0.7
Fibrinogen, g	4.8 ± 3.3	4.2 ± 2.2	0.6
Tranexamic acid			
Loading dose, g	1.7 ± 1	1.9 ± 0.9	0.5
Cumulative dose, g	6.3 ± 2.8	4.4 ± 2.6	0.2
Treatment duration, h	7.1 ± 4.8	2.9 ± 2.4	0.03

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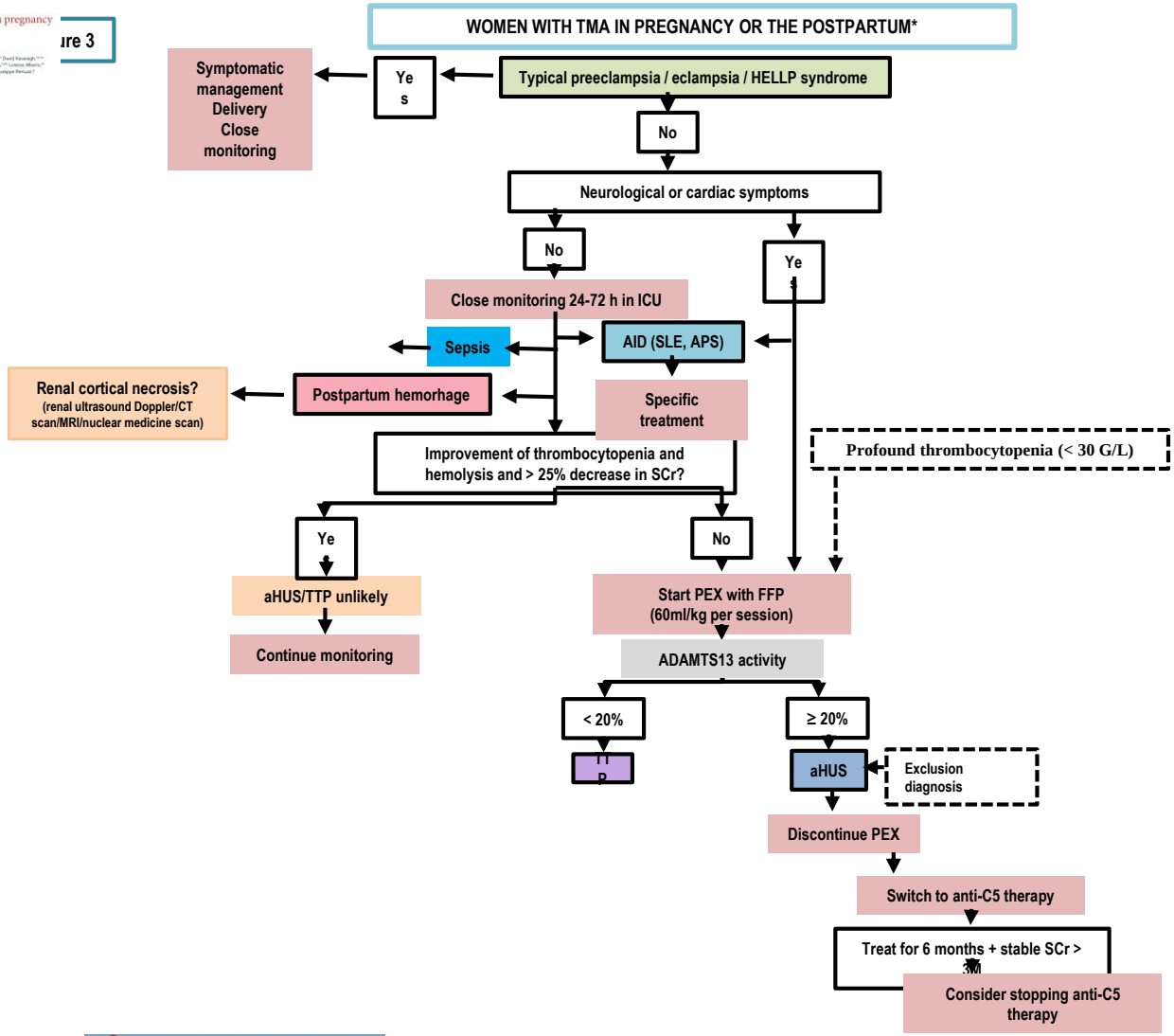

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Pregnancy in a patient with a history of aHUS

Management of thrombotic microangiopathy in pregnancy and postpartum: report from an international working group

Fadi Fakhouri,[1] Marie Scully,[2,3] François Provôt,[4,5] Miquel Blasco,[6] Paul Coppo,[5,7] Marina Noris,[8] Kathy Paizis,[9-11] David Kavanagh,[12,13] Frédéric Pène,[5,14,15] Sol Quezada,[16,17] Alexandre Hertig,[18] Sébastien Kissling,[1] Patrick O'Brien,[19] Yahsou Delmas,[5,20] Lorenzo Alberio,[21] Norbert Winer,[22-25] Agnès Veyradier,[5,26-28] Spero Cataland,[29] Véronique Frémeaux-Bacchi,[30] Chantal Loirat,[31] Giuseppe Remuzzi,[8] Vassilis Tsatsaris,[32] and the International Working Group on Pregnancy-Related Thrombotic Microangiopathies

Table 4. Helpful elements for counseling a patient with a history of aHUS who wishes to plan a pregnancy

Counseling a woman with a history of aHUS about pregnancy relies on the following information:
1. Pregnancy is no longer contraindicated in women with a history of aHUS. The risk of relapse of aHUS during pregnancy or postpartum appears lower (~25%) than formerly appreciated.[83] An efficient treatment (anti-C5 treatment such as eculizumab) is available.
2. The risk of relapse of aHUS triggered by pregnancy is difficult to predict. A prior uneventful pregnancy does not guarantee subsequent pregnancies will be free of relapse.[21,83] Women who do not carry a complement gene variant are not protected from pregnancy aHUS.[21]
3. An interval of ~12 mo of aHUS remission and stabilized renal function is appropriate before pregnancy initiation.
4. In women with prior aHUS, relapse of aHUS occurs more frequently during pregnancy than after delivery.[21,23] In the pre-anti-C5 treatment era, this was associated with a high risk of fetal death or preterm birth.[83]
5. CKD may be a limitation to pregnancy. Residual severe CKD or hypertension after aHUS may worsen during pregnancy, with increased risk of preeclampsia or HELLP syndrome, ESRD, and fetal death.[24,83]
6. In case of aHUS relapse, prompt anti-C5 treatment initiation optimizes chances of patient's full recovery and child's full-term live birth.
7. Prophylactic anti-C5 treatment is currently not recommended. Anti-C5 treatment is usually not discontinued in women already treated prior to pregnancy (particularly renal transplant patients).
8. Pregnancy in a woman with a history of aHUS remains a high-risk pregnancy. Close multidisciplinary (obstetricians, nephrologists, neonatologists, and complement biologists) supervision from the first weeks of pregnancy and up to 3 mo postdelivery in high-risk pregnancy maternity clinic is mandatory.

CKD, chronic kidney disease; ESRD, end-stage renal disease.

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Eculizumab discontinuation in children and adults with atypical hemolytic-uremic syndrome: a prospective multicenter study

Fadi Fakhouri,[1,2] Marc Fila,[3] Aurélie Hummel,[4] David Ribes,[5] Anne-Laure Sellier-Leclerc,[6] Simon Ville,[7] Claire Pouteil-Noble,[8] Jean-Philippe Coindre,[9] Moglie Le Quintrec,[10] Eric Rondeau,[11] Olivia Boyer,[12,13] François Provôt,[14] Djamal Djeddi,[15] William Hanf,[16] Yahsou Delmas,[17] Ferielle Louillet,[18] Annie Lahoche,[19] Guillaume Favre,[20] Valérie Châtelet,[21] Emma Allain Launay,[22] Claire Presne,[23] Ariane Zaloszyc,[24] Sophie Caillard,[25] Stéphane Bally,[26] Quentin Raimbourg,[27] Leïla Tricot,[28] Christiane Mousson,[29] Aurélie Le Thuaut,[30] Chantal Loirat,[31] and Véronique Frémeaux-Bacchi[32]

Table 2. Individual characteristics of 6 children and 7 adults who experienced aHUS relapse after eculizumab discontinuation

Patient	Sex, age, y	Complement gene variant	At eculizumab discontinuation		Precipitating factor of aHUS relapse	At aHUS relapse				At 3 mo after aHUS relapse and eculizumab restart		At last follow-up		
			SCr, µmol/L (eGFR, mL/min/ 1.73 m²)	UP/ Cr, g/ mmol		Time from eculizumab discontinuation, mo	SCr, µmol/ L	Plt × 10⁹/L	UP/ Cr, g/ mmol	SCr, µmol/ L (eGFR, mL/min/ 1.73 m²)	UP/ Cr, g/ mmol	Duration, mo	SCr, µmol/L (eGFR, mL/min/ 1.73 m²)	UP/ Cr, g/ mmol
1	M, 4	*CFI* (p.Gly261Asp)/ *C3* (p.Thr1383Asn)	34.0 (104)	0.018	Bacterial infection	5.4	62	95	0.04	34.0 (107)	0.01	18.0	46.0 (85)	0.012
2*	F, 6. F, 7	*CFH* (p.Ser1191Trp)	32.0 (128) 34.0 (127)	0.03 0.03	Flu-like illness Flu-like illness	11.5 8.1	92 69	63 126	1.28 1.06	33.0 (130) 36.0 (127)	0.04 0.03	3.2 18.3	33.0 (130) 38.0 (126)	0.04 0.08
3†	F, 7	*MCP* (persistently low CD46 level)	52.0 (79)	0.008	Flu-like illness	9.9	105	94	3.08	50 (78)‡	0.01	14.7	53.0 (85)	0.009
4	F, 8	*MCP* (p.Asp33His)/ *MCP* (p.Asp33His)	34.0 (143)	0.01	Gastroenteritis	20.5	188	56	5.66	32.0 (145)	0.02	2.8	32.0 (145)	0.02
5	M, 9	*MCP* (IVS2+2)/*MCP* (IVS2+2)	39.1 (169)	3.0	Gastroenteritis	13.4	214	72	1.21	32.8 (210)	0.05	8.7	35.6 (199)	0.05
6§	M, 9	None	45.0 (109)	0.01	Tonsillitis	17.2	45	62	NA	46 (108)‖	NA	15.0	47.0 (148)	0.01
7	F, 30	*C3* (p.Ala1094Ser)	136.0 (42)	0.08	Sinusitis	2.5	191	138	0.28	131.0 (44)	0.15	18.5	148.5 (37)	0.1
8	F, 34	*CFH* (p.Phe1199Leu)	121.0 (47)	0.03	Tracheitis	20.0	165	209	0.06	125.0 (45)	0.03	6.6	129.0 (43)	0.06
9	F, 34	*MCP* (p.Tyr117Stop)	93.0 (63)	0.13	Diarrhea	1.6	184	57	0.36	89.3 (66)	0.1	23.7	77.8 (77)	0.05
10	F, 38	*MCP* (IVS2+2)/*MCP* (IVS2+2)	121.0 (46)	0.22	Viral tonsillitis	2.5	163	113	0.37	145.0 (37)	0.05	20.9	132.0 (41)	0.08
11	M, 44	*MCP* (IVS2+2)	245.0 (27)	0.15	—	3.6	414	143	0.26	426.0 (14)	0.16	10.8	881.0 (6)¶	0.21
12	F, 53#	*CFI* (p.Pro50Ala)	64.0 (89)	0.01	Pancreatitis	3.7	802	30	0.25	69.0 (82)	NA	21.1	64.0 (89)	0.04
13	F, 56	*CFH* (p.Arg1215Stop)	101 (52)	0.02	—	22.1	232	235	0.26	168.0 (29)	0.07	10.8	167.0 (29)	0.04

F. Fakhouri, Blood, 2021

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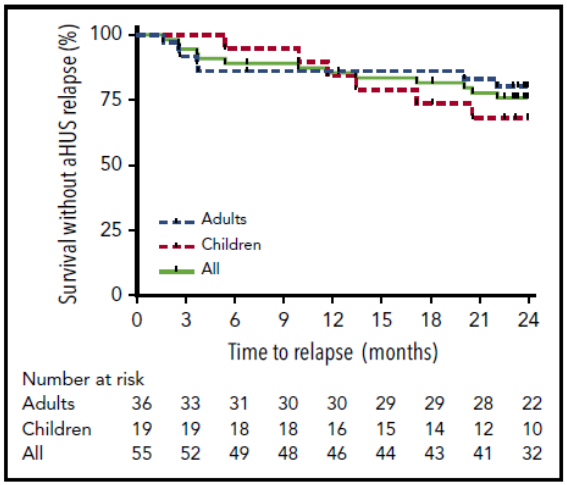

Figure 1. Probability of survival without aHUS relapse after eculizumab discontinuation according to age at eculizumab discontinuation. Risk of relapse was not statistically significant different between children and adults ($P = .39$ by log-rank test).

Table 3. Characteristics at inclusion and during follow-up of 13 patients who relapsed and 42 patients who did not relapse after eculizumab discontinuation

	n (%)		
	Relapsing patients (n = 13)*	Nonrelapsing patients (n = 42)	P
Age, <18 y	6 (46)	13 (31)	.34
Sex			.03
Female	9 (69)	15 (36)	
Male	4 (31)	27 (64)	
>1 aHUS episode before inclusion in study†	5 (38)	3 (7)	.01
Requirement for dialysis during last aHUS episode before eculizumab discontinuation	2 (15)	22 (52)	.02
Extrarenal manifestation	3 (23)	21 (53)‡	.06
Duration of eculizumab treatment, mo			.28
Mean	23.3	14	
Range	3.3-59.3	0.95-57.4	
Complement gene variants	12 (92)	16 (25)	.0009
CFH	3 (23)	3 (7)	.1
MCP	6 (46)	6 (14)	.02
CFI	1 (8)	4 (9)	1
C3	1 (8)	2 (5)	.5
Combined	1 (8)	1 (2)	.4
No variant/positive anti–factor H antibodies	0 (0)	4 (9)	.5
No variant/no anti–factor H antibodies	1 (7)§	22 (53)	.004
No. of relapses after eculizumab discontinuation	14	—	
At eculizumab discontinuation (inclusion)			
Serum creatinine, μmol/L			
All			.12
Mean	82	102	
Range	32-245	26-305	
Children			.15
Mean	39	56	
Range	32-52	26-134	
Adults			.96
Mean	126	123	
Range	64-245	61-305	
eGFR, mL/min/1.73 m²			
All			.57
Mean	87	78	
Range	27-169	19-130	
Children			.19
Mean	123	106	
Range	79-169	55-124	
Adults			.25
Mean	52	65	
Range	27-89	19-130	

Table 3. (continued)

	n (%)		
	Relapsing patients (n = 13)*	Nonrelapsing patients (n = 42)	P
CKD stage 3	4 (30)	13 (31)	.9
CKD stage 4	1 (7)	3 (7)	1
Urinary protein/creatinine ratio, g/mmol			
All			.10
Mean	0.27	0.04‡	
Range	0.01-3	0-0.38	
Children			.39
Mean	0.45	0.03	
Range	0.01-3.00	0.00-0.14	
Adults			.07
Mean	0.10	0.05	
Range	0.01-0.22	0.00-0.38	
Plasma C3 level <660 mg/L at inclusion	2/12 (17)	3/41 (7)	.31
Plasma factor H level <70% at inclusion	1/10 (10)‖	2/40 (5)‖	.49
sC5b-9 ≥300 ng/ml at inclusion	11/12 (92)‖	23/41 (56)‖	.04
sC5b-9 at inclusion			.03
Mean	418	325	
Range	363-499	234-428	
At last follow-up			
Duration of follow-up, mo			
Before relapse			
All			<.0001
Mean	9.3	23	
Range	1.6-22.1	6.7-24	
Children			<.0001
Mean	10.9	23.1	
Range	5.4-17.2	18.1-24	
Adults			<.0001
Mean	8	22.9	
Range	1.6-22.1	6.7-24	
After relapse			
All		—	
Mean	13.2		
Range	2.7-23.7		
Children		—	
Mean	10.9		
Range	2.8-18.3		
Adults		—	
Mean	14.9		
Range	2.7-23.7		
Serum creatinine, μmol/L			
All			.21
Mean	135	107	
Range	32-881	25-287	
Children			.19
Mean	41	59	
Range	32-53	25-144	

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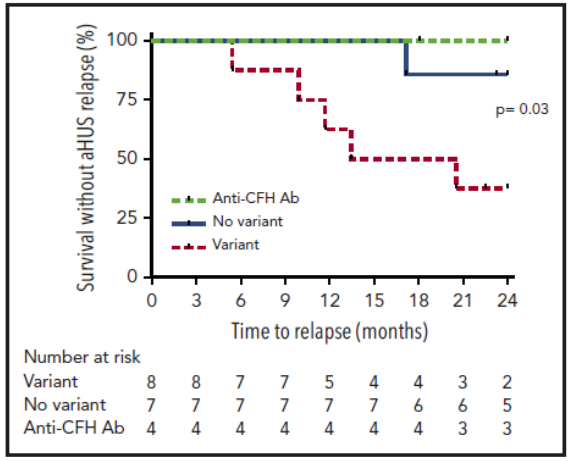

Figure 2. Probability of survival without aHUS relapse after eculizumab discontinuation in children according to presence or absence of detected complement gene variant. Risk of relapse was higher in children with complement gene variants compared with those without variants ($P = .03$ by log-rank test). Ab, antibody.

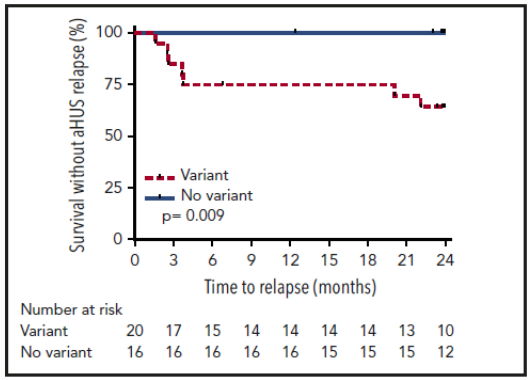

Figure 3. Probability of survival without aHUS relapse after eculizumab discontinuation in adults according to presence or absence of detected complement gene variant. Risk of relapse was higher in adults with complement gene variants compared with those without variants ($P = .009$ by log-rank test).

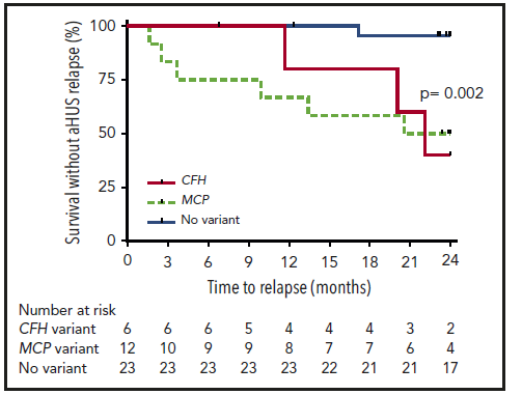

Figure 4. Probability of survival without aHUS relapse after eculizumab discontinuation in children and adults according to type of detected complement gene variant. Risk of relapse was higher in patients with variants in *CFH* and *MCP* genes compared with those without variants ($P = .002$ by log-rank test).

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Table 4. Factors associated with aHUS relapse after eculizumab discontinuation in multivariable analysis

	OR	95% CI	*P*
Analysis including presence of complement gene variant as parameter			
Requirement for dialysis during last aHUS episode before eculizumab discontinuation	0.17	0.03-1.02	.0560
Female sex	4.21	0.85-20.75	.0777
Presence of rare variant in complement gene	16.20	1.78-147.73	.0135
Analysis including sC5b-9 level as parameter			
Requirement for dialysis during last aHUS episode before eculizumab discontinuation	0.07	0.01-0.53	.0101
Female sex	10.06	1.53-66.19	.0163
Plasma sC5b-9 ≥300 ng/mL at inclusion	20.96	1.76-250.12	.0162

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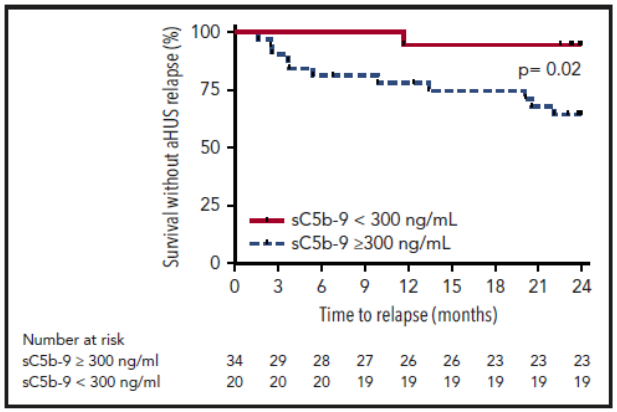

Figure 5. Probability of survival without aHUS relapse after eculizumab discontinuation according to level of sC5b-9 at inclusion in the entire cohort. Risk of relapse was higher in patients with elevated sC5b-9 at inclusion compared with those with normal sC5b-9 levels (P = .02 by log-rank test).

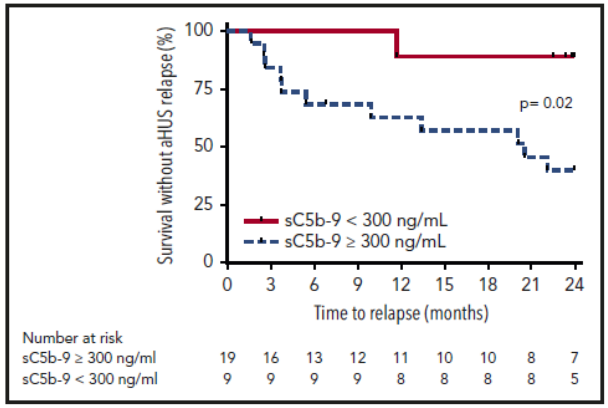

Figure 6. Probability of survival without aHUS relapse after eculizumab discontinuation according to the level of sC5b-9 at inclusion in patients with detected rare variants in complement genes. Risk of relapse was higher in patients with elevated sC5b-9 at inclusion compared with those with normal sC5b-9 levels (P = .02 by log-rank test).

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Table 5. Rate of aHUS relapse after eculizumab discontinuation in 4 previously published retrospective series from Europe and the United States and in Present Prospective Study

	n (%)					
	Ardissino et al[11] (2014)	Fakhouri et al[12] (2016)	Wijnsma et al[13] (2017)	Merrill et al[17] (2017)	Present study	Total
Patients with complement gene screening	16	38	18*	13†	55	140
Adults	8	29	14	13	36	100
Children	8	9	4	0	19	40
Duration of follow-up‡			NS			
Median	13.1 mo	22 mo		239 d	19.8 mo§	
Range	0.4-40	5-43		0-1390	5.4-24	
Patients with no variant and no anti–factor H Ab	5	16	4	8‖	23	56
Relapse rate	0	0	0	1 (13)	1 (4)	2 (3.5)¶
Patients with rare variants (MAF <0.1%)	7	21	13	5	28	74
Relapse rate	3 (43)	12 (57)	5 (38)	2 (40)	12 (43)	34 (46)
Patients with rare pathogenic variant	4	18	9	2	26	59
Relapse rate	3 (75)	10 (56)	3 (33)	2 (100)	10 (38)	28 (47)
Patients with *CFH* rare variant	2	11	7	2	6	28
P/LP	2	9	4	1	6	22
VUS	0	2	3	1	0	6
Relapse rate	2 (100)	8 (72)	4 (57)	1 (50)	3 (50)	18 (64)
P/LP	2	7	2	1	3	15
VUS	0	1	2	0	0	3
Patients with *MCP* rare variant	2	8	0	2	12	24
P/LP	1	7		1	12	21
VUS	1	1		1	0	3
Relapse rate	0	3 (37)	—	0	6 (50)	9 (37)
P/LP		3			6	9
VUS		0			0	0
Patients with *CFI* rare variant	3	2	1	0	7	13
P/LP	1	2	0		6	9
VUS	2	0	1		1	4
Relapse rate	1 (33)	0	0	—	2 (29)	3 (23)
P/LP	1	0			1	2
VUS	0	0			1	1

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Conclusion

1) Pregnancy and postpartum HUS is a complement-mediated atypical HUS.

2) Its (differential) diagnosis remains challenging…
…when specific treatment has become urgent.

3) Discontinuation of C5 blockade is feasible in some patients with pregnancy and postpartum atypical HUS.

4) Pregnancy in a patient with a history of atypical HUS is not contraindicated but remains a high risk pregnancy.

Discussion