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Microangiopatia trombotica (MAT) e Sindrome emolitico-uremica atipica (SEUa): Basi patogenetiche, inquadramento diagnostico e principi del trattamento

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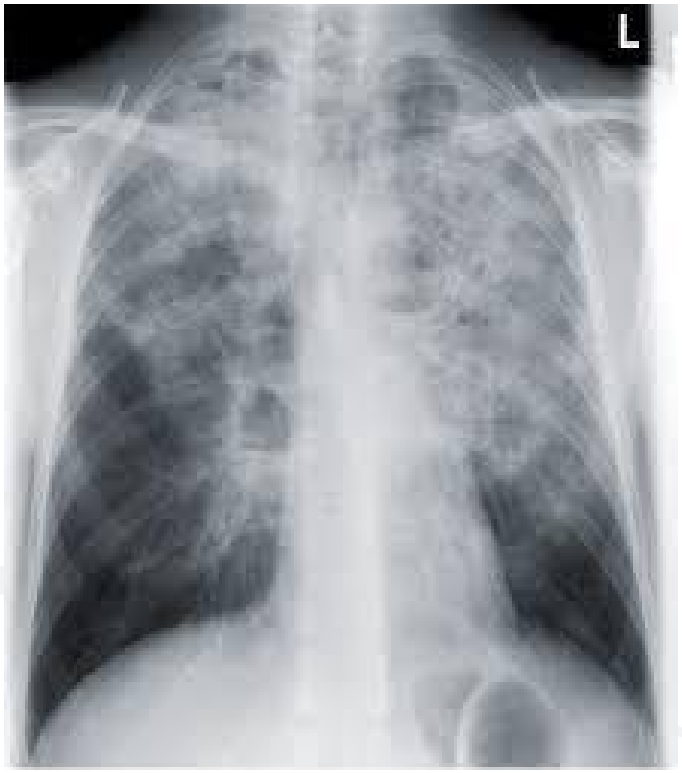
U.O. Nefrologia
Azienda Ospedaliera “Pia Fondazione Card. G. Panico” Tricase (LE)

Caso Clinico

Paz M 42 aa. SM dal 1994 – IFN-β 250 μg a dì alterni (1997)

- PA 200/110 mmHg
- FC 95 bpm
- TC 38,5° C

All'Rx torace 2P: infiltrati parenchimali in entrambi i campi polmonari



Veniva impostata terapia antipertensiva, terapia antibiotica con meropenem, claritromicina e teicoplanina, e terapia antivirale con oseltamivir.

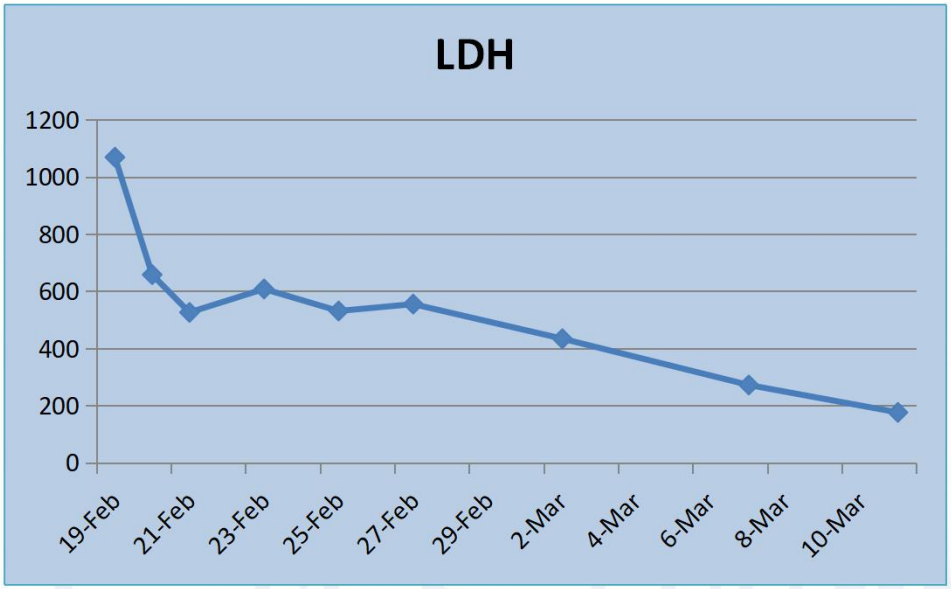
Biochimica (Diagnosi)

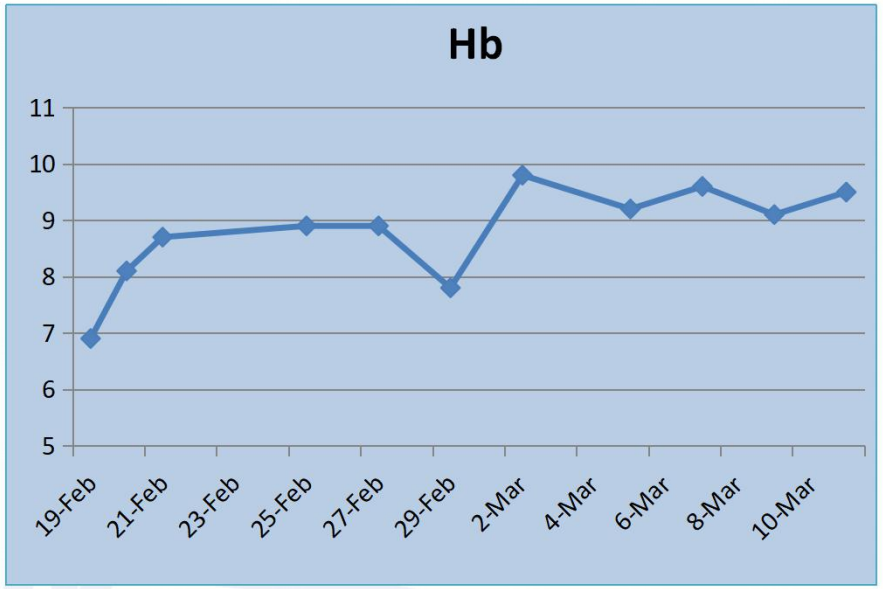
- **anemia** (Hb 7,9 g/dl)
- **piastrinopenia** (102 x 10^3/µL),
- incremento dell'**LDH** (1208 U/L)
- presenza di **schistociti** nel sangue periferico
- **insufficienza renale acuta** (sCr 3,69 mg/dl)
- Aptoglobina <0,08 g/L

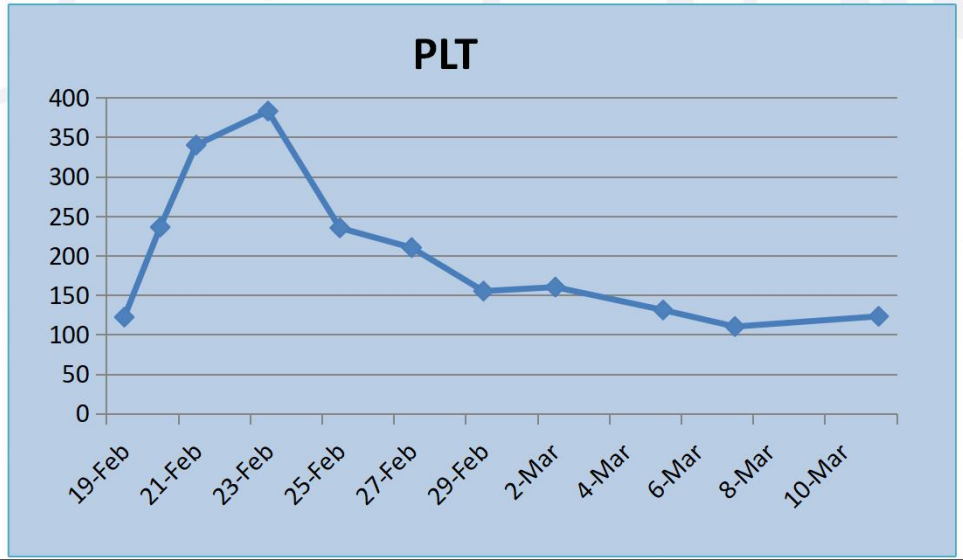
Microangiopatia trombotica

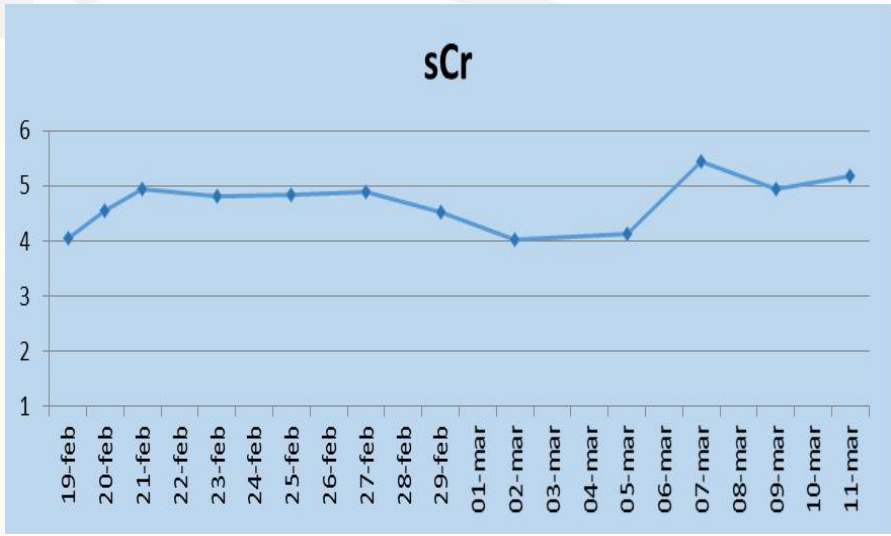
- C3 ridotto
- ADAMTS 13 normale
- Pannello autoimmunitario e infettivologico negativo
- Verotossina di E. Coli negativa
- Biopsia renale: Aspetto tipico di microangiopatia trombotica

Approccio terapeutico – PEX (12 sedute)

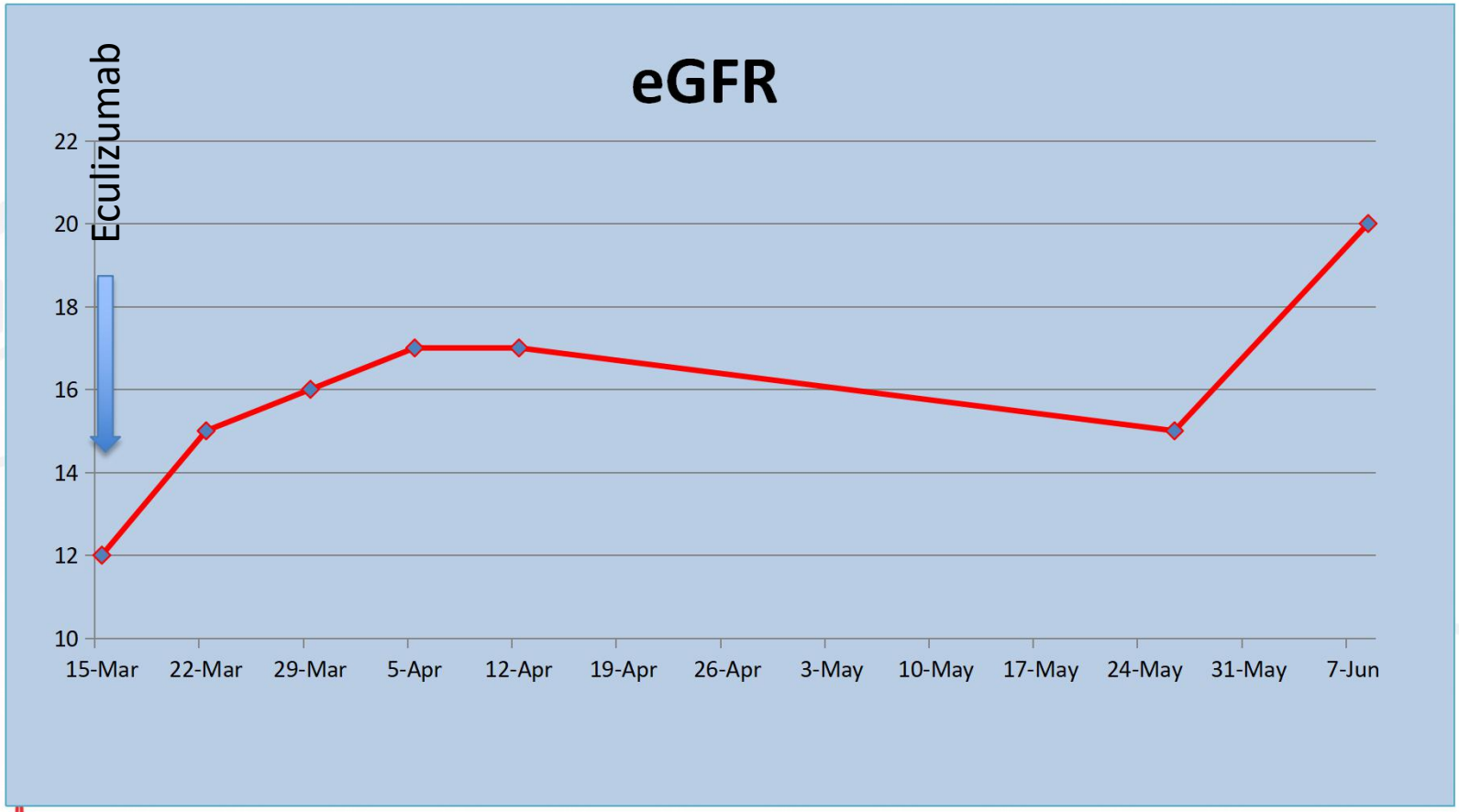




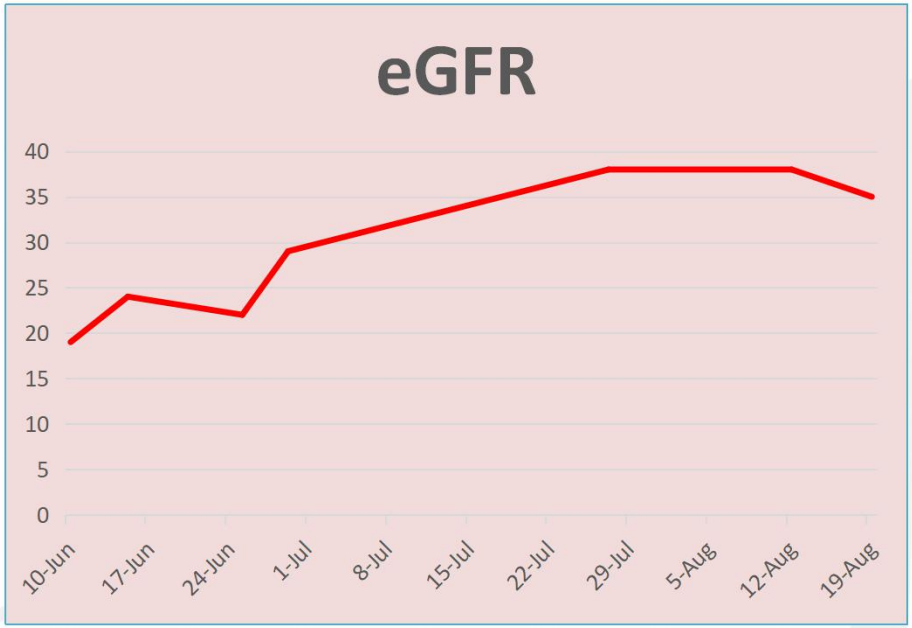




Terapia - Eculizumab



Follow-up


eGFR
40
35
30
25
20
15
10
5
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17-Jun
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29-Jul
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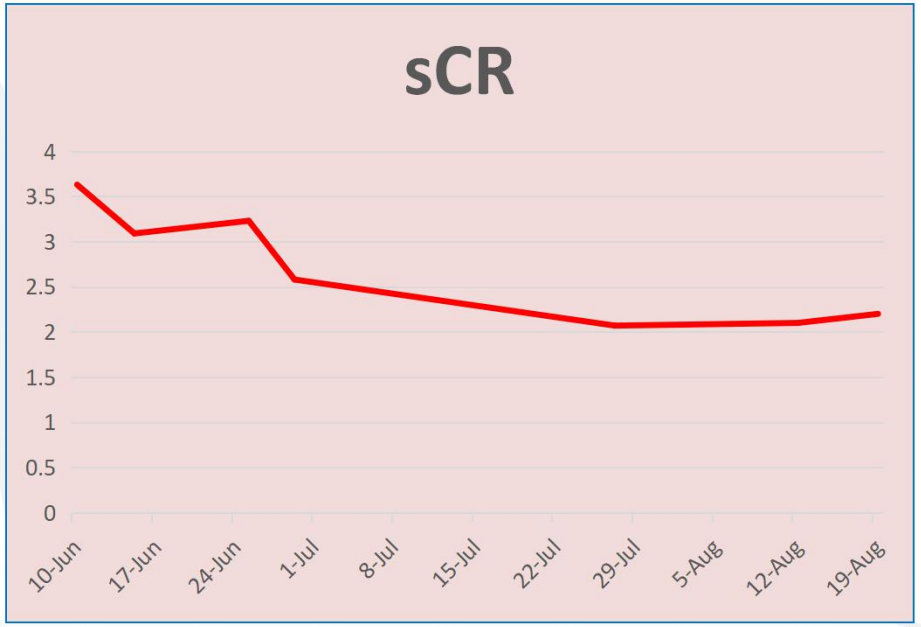
12-Aug
19-Aug


sCR
4
3.5
3
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10-Jun
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8-Jul
15-Jul
22-Jul
29-Jul
5-Aug
12-Aug
19-Aug

aHUS – Definition, Epidemiology

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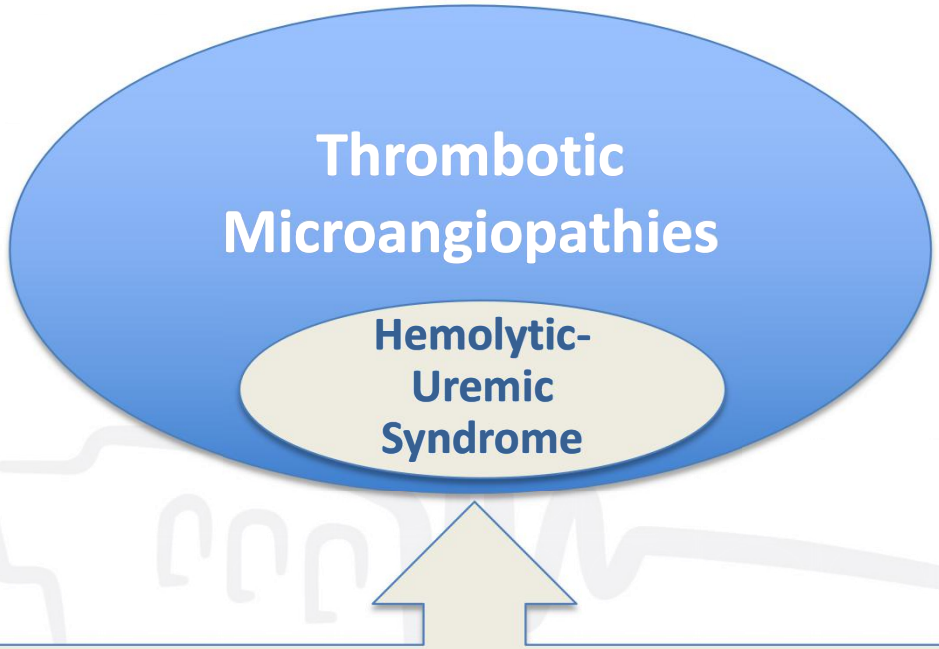
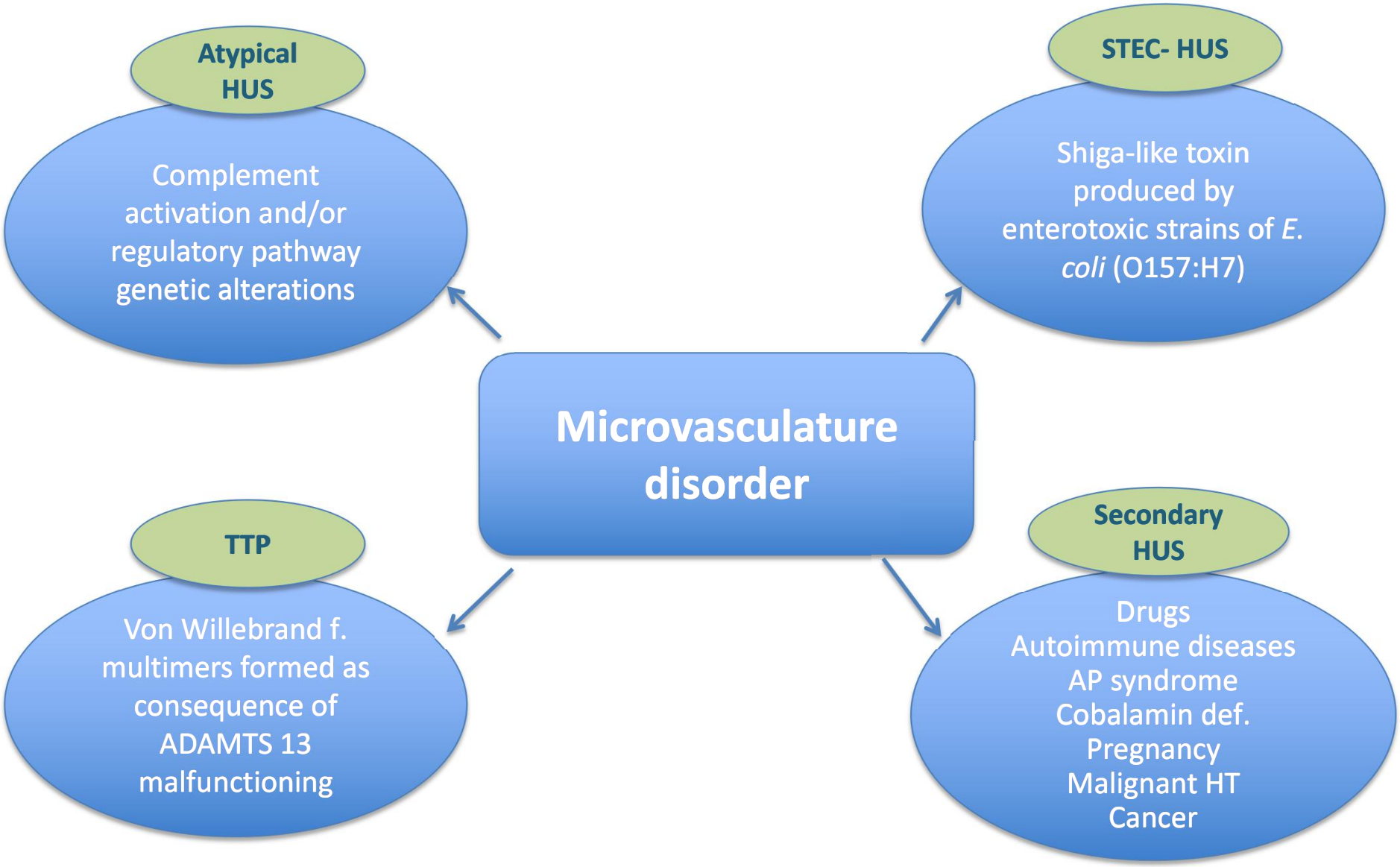
HUS and TMA - Definition



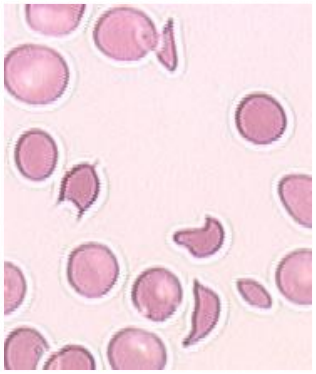
- Non-immune microangiopathic hemolytic anemia (MAHA)
- Thrombocytopenia
- Multiple organ involvement
- Potential fatal evolution

TMAs – Pathogenetic classification



TMA – Initial Diagnosis

- Microangiopathic hemolytic anemia(Hb < 12 g/dl)
- Peripheral thrombocytopenia (< 150 x 10^9/L)
- Organ failure of variable severity



TTP

- Acquired
- Congenital

4 cases/million/year

HUS

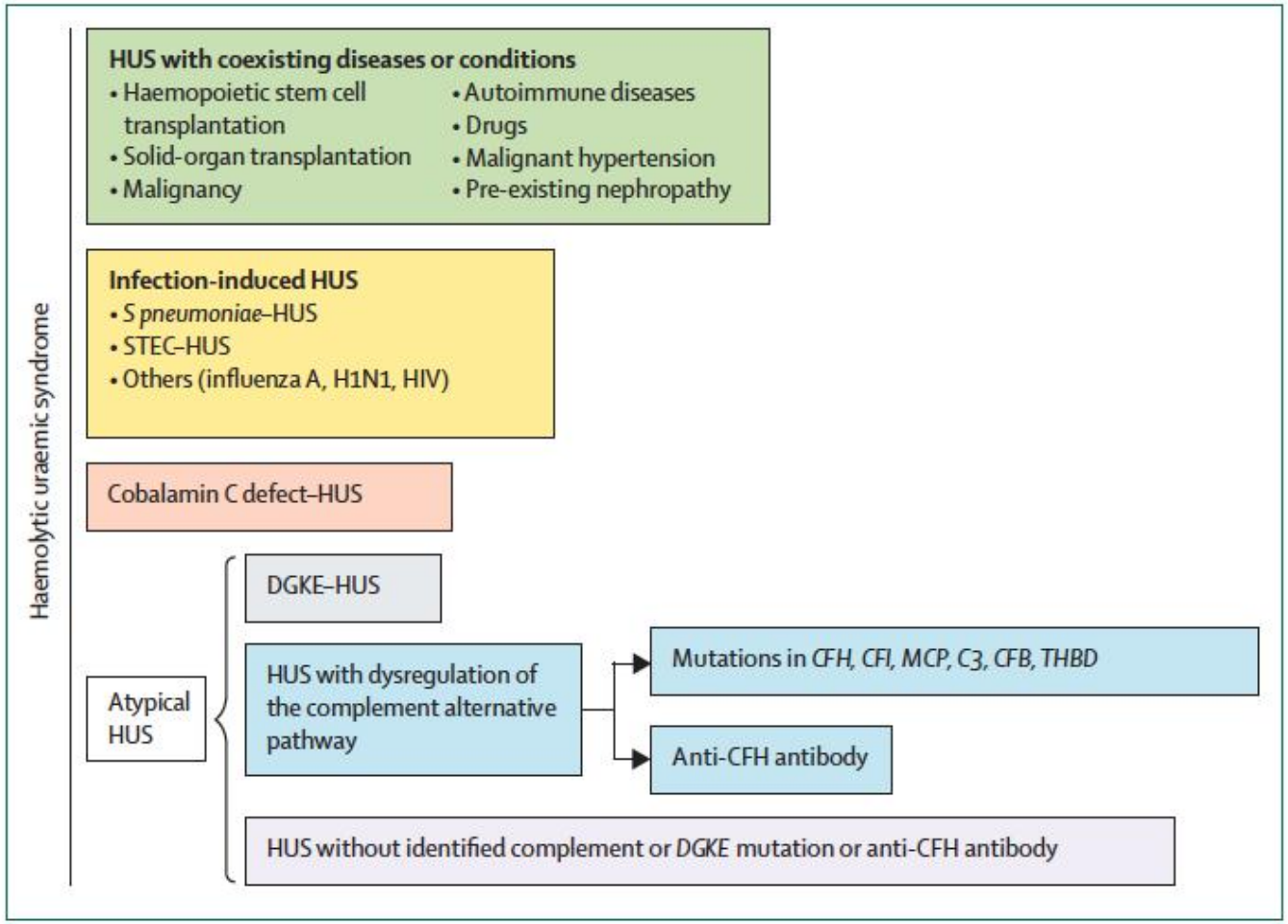
- STEC
- Atypical (0.23-0.42)

2-4 cases/million/year

Others

- HELLP Syndrome
- Malignant HT
- Cancer
- Transplantation

TMA – Initial Diagnosis



Fakhouri F et al: *Lancet* 2017; 390:681-6

Typical and Atypical HUS

Typical HUS (STEC-HUS)

- More frequent
- Predominates in, but is not exclusive of, the age range 6 mo. – 5 yrs
- Enteroemorrhagic diarrhea
- ST-producing E. coli (O157:H7, O104:H4)
- Full recovery in > 80%
- Death or ESRD in 12%
- Single episode (No recurrence)

Atypical HUS (aHUS)

- More rare
- Complement-mediated can be observed in 0-6 mo. age or adulthood
- Triggered by stressing factor (operation, infection)
- Bloody diarrhea may be present in 30%
- ESRD in 50% within 1 year
- Frequent relapses

TMA and aHUS – Pathogenesis

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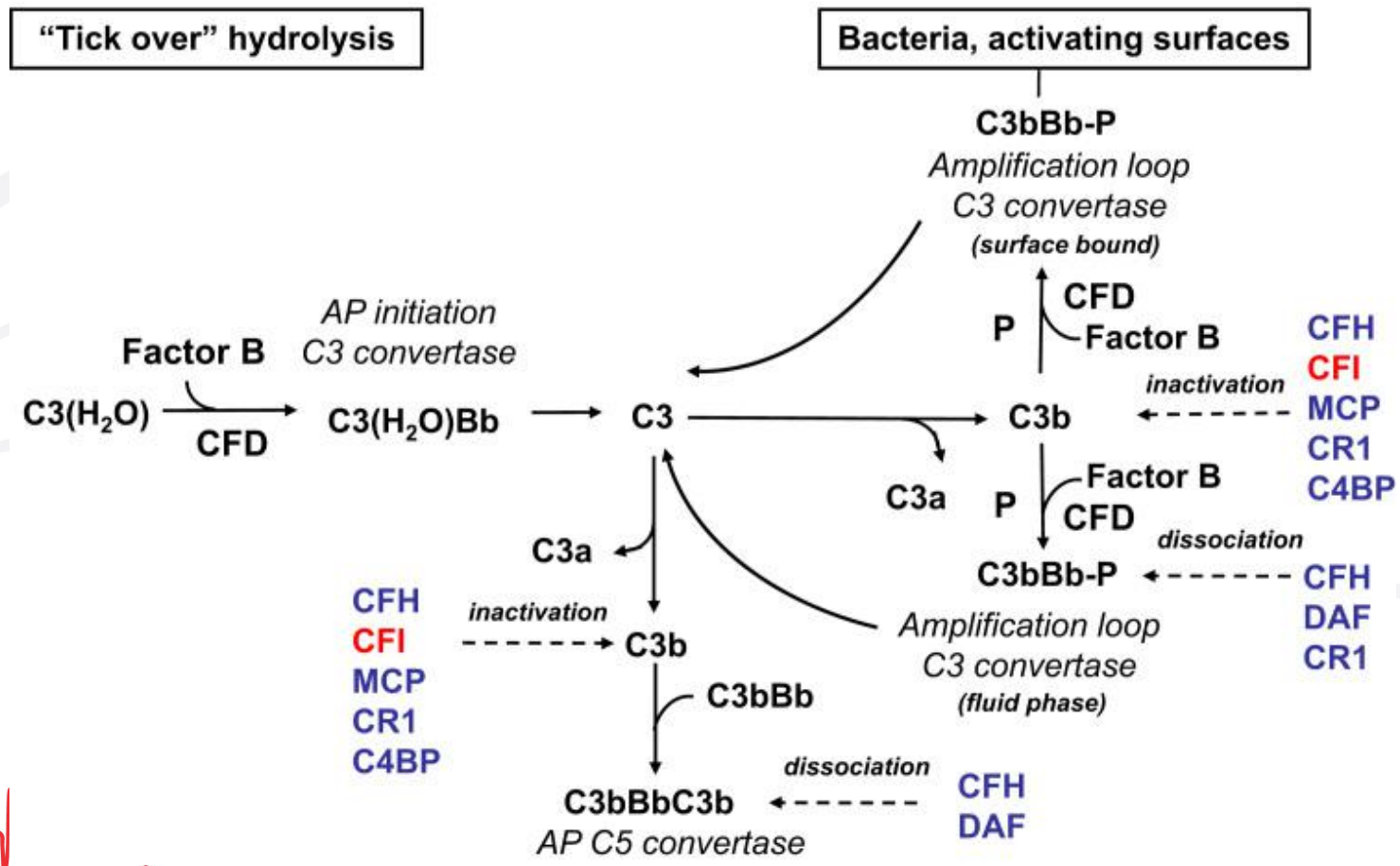
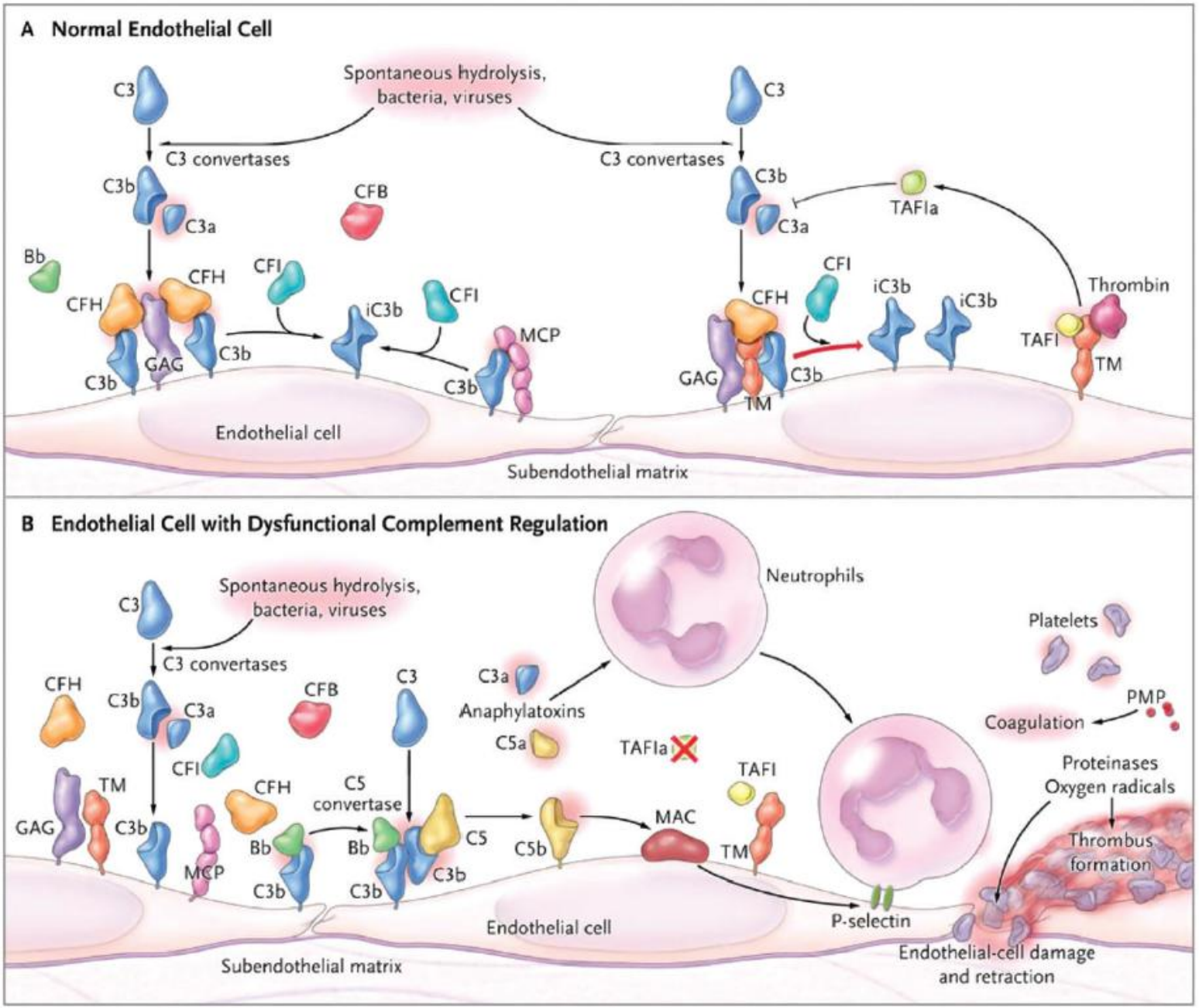
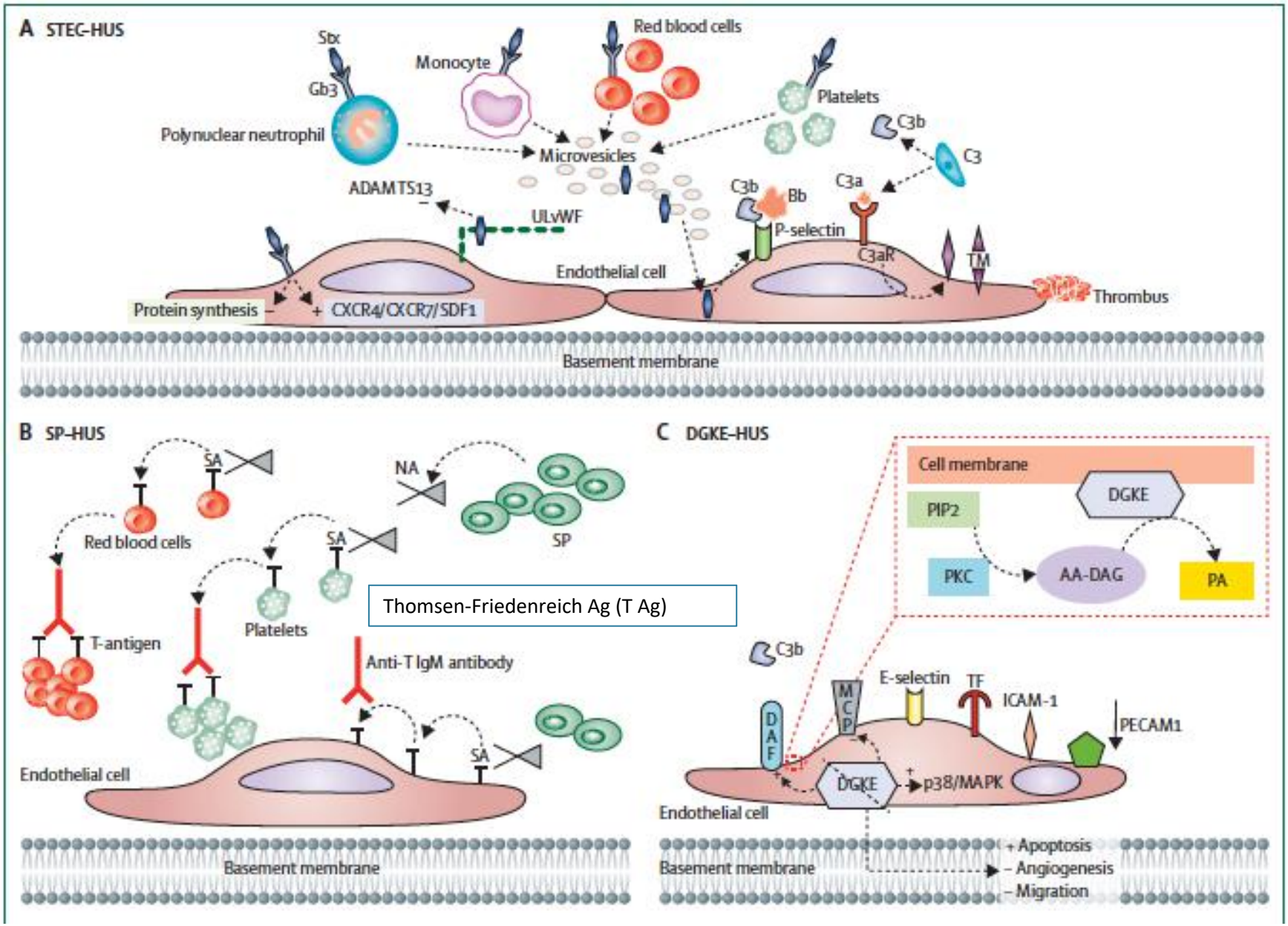
Alternative pathway of complement





Franchini M: *Clin Chem Lab Med* 2015; 53:1679-88

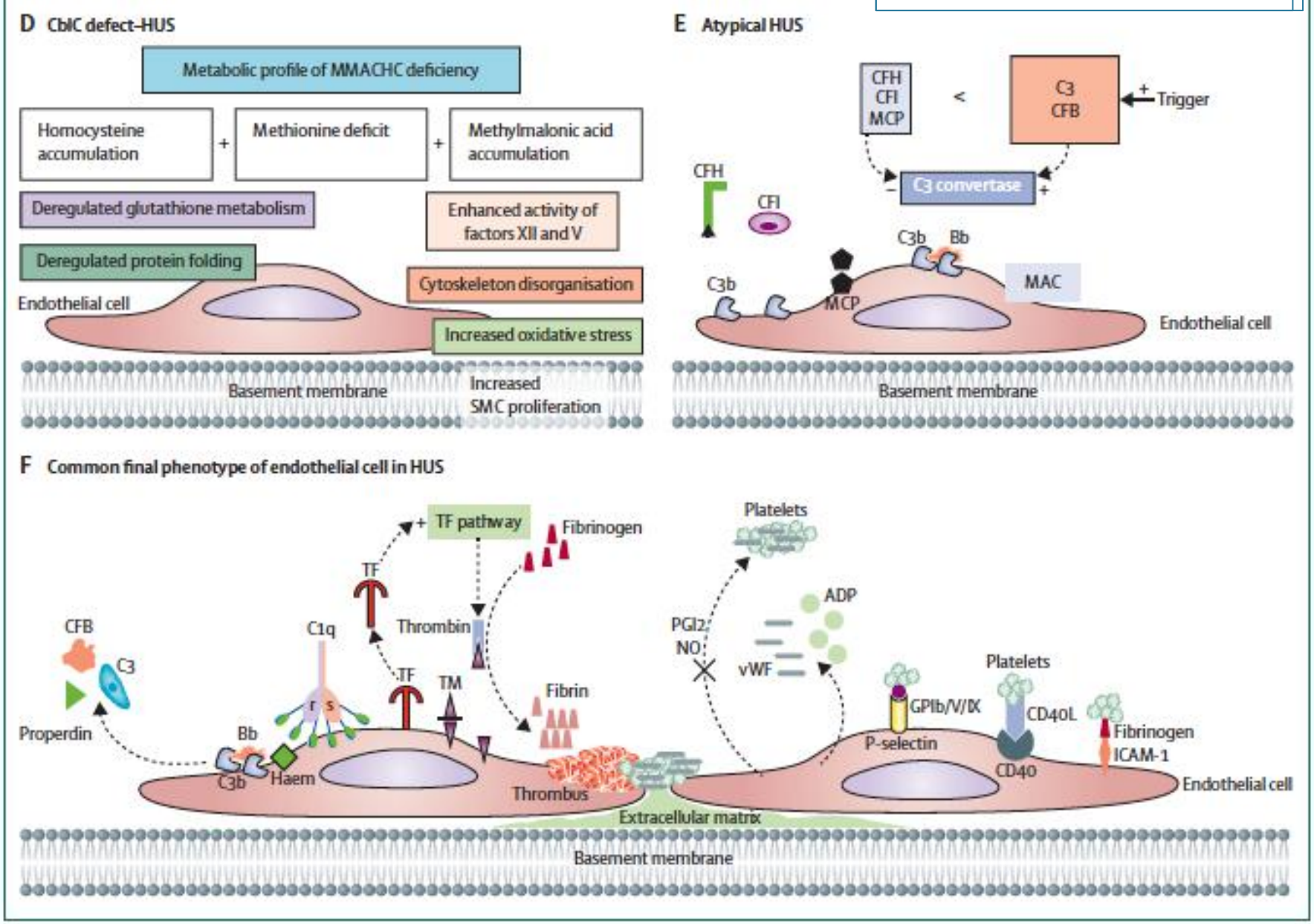
HUS – Pathogenesis - I



Thomsen-Friedenreich Ag (T Ag)

Fakhouri F et al: *Lancet* 2017; 390:681-6

HUS – Pathogenesis - II



Fakhouri F et al: *Lancet* 2017; 390:681-6

aHUS – Genetic deficiencies

Table 2. Genetic Abnormalities Associated With aHUS

Gene	Abnormality	Main Effect	Frequency in aHUS
CFH	Heterozygous and (rarely) homozygous mutations mainly in the last 2 exons	Impaired cell-surface complement regulation	25%-30%
*CFH/CFHR*s	Nonallelic homologous recombinations	Impaired cell-surface complement regulation	3%-5%
CFHR1	Deletion and formation of anti-CFH antibodies	Impaired cell-surface complement regulation	5%-10%
CD46[a]	Heterozygous and (rarely) homozygous mutations	Reduced surface expression	8%-10%
CFI	Heterozygous mutations	Low cofactor activity	4%-8%
C3	Heterozygous mutations	Resistance to C3b inactivation, C3 convertase stabilization	4%-8%
CFB	Heterozygous mutations	C3 convertase stabilization	1%-4%
THBD	Heterozygous mutations	Reduced TAFI activation, reduced C3b inactivation	3%-4%
DGKE	Homozygous or compound heterozygous mutations	Protein truncation, proinflammatory and prothrombotic endothelial phenotype, increased endothelial apoptosis	2%-27% of infantile cases[b]

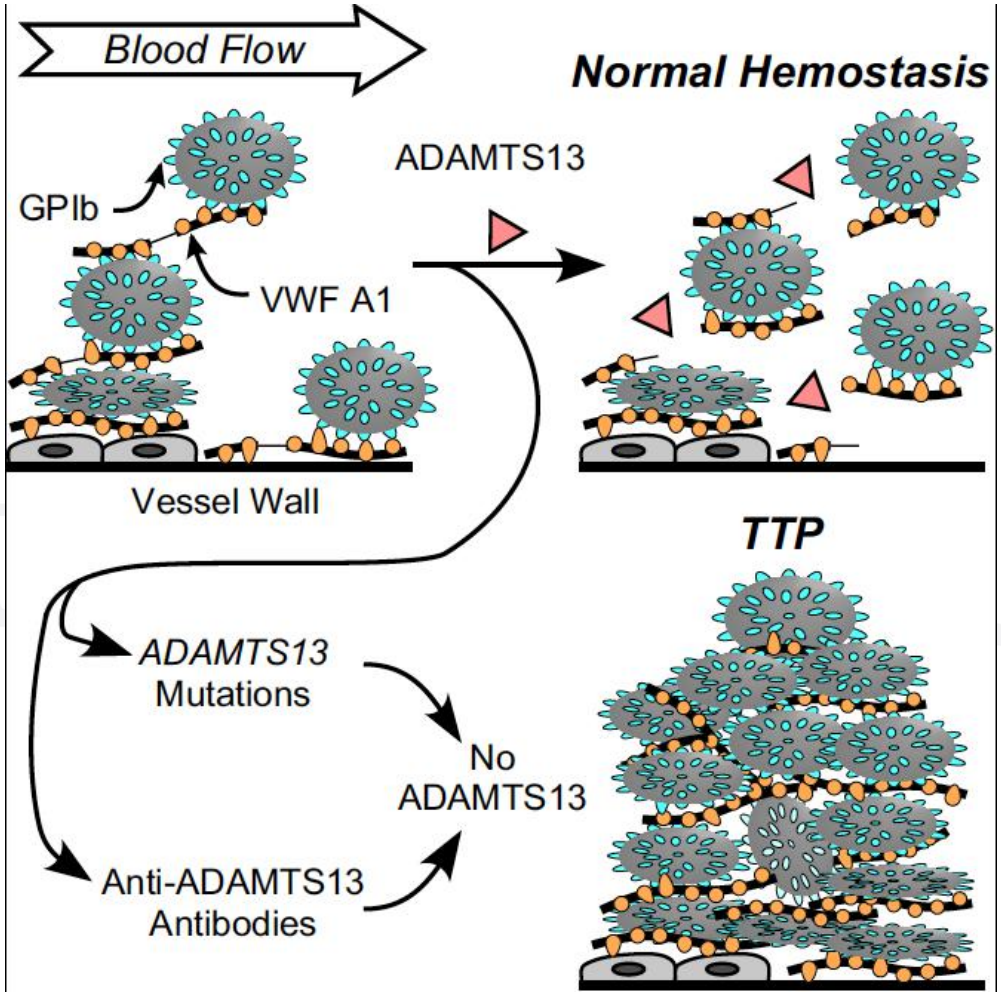
Abbreviations: aHUS, atypical hemolytic uremic syndrome; CFB, complement factor B; CFH, complement factor H; CFHR, complement factor H–related; CFI, complement factor I; DGKE, diacylglycerol kinase ε; MCP, membrane cofactor protein; TAFI, thrombin-activatable fibrinolysis inhibitor; THBD, thrombomodulin.

[a] *CD46* encodes MCP.

[b] Onset of the disease before 1 to 2 years of age.

Noris M, Remuzzi G, *Am J Kidney Dis* 2015; 66:359-75

TTP – Pathogenesis



Sadler JE: *Blood* 2017; 130:1181-8

TMA and aHUS – Clinical Presentation

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TMA – Laboratory features

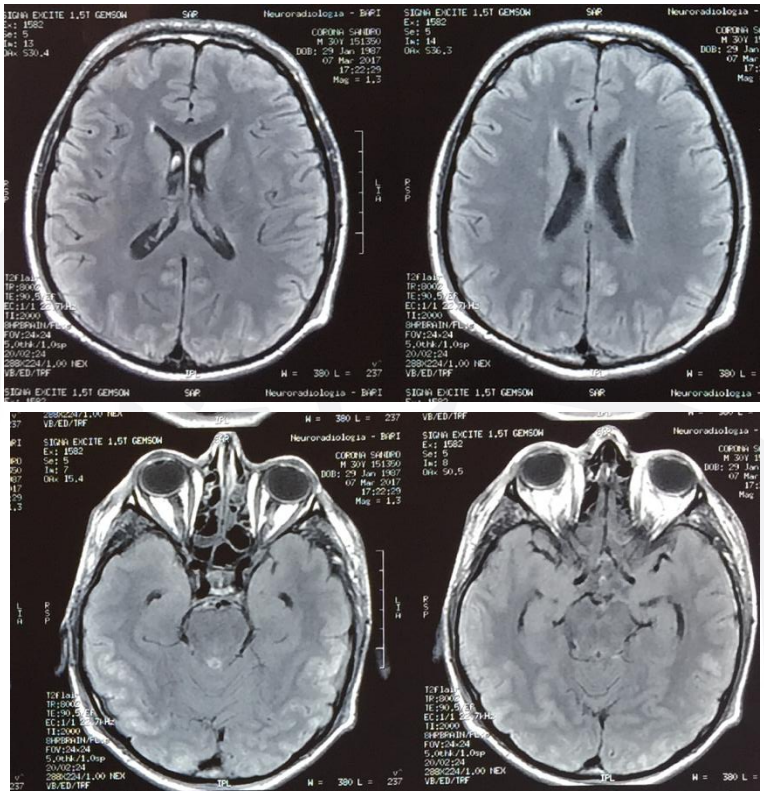
- **DIC:** need to be excluded. Normal value for INR and aPTT in TMAs
- **Schistocytes**: *sine qua non* for a diagnosis of TMA. May be absent in the first days. **Search for repeatedly** (daily blood smear)
- **LDH**: increase 2x NV or more: declines after initiation of PE (no normalization in aHUS)
- **Aptoglobin**: reduced levels in hemolytic anemia. As a reactant phase protein may be in the normal range even in TMA. **No diagnostic criterion for TMA**!
- **Median PLT**
  - < 20,000/mm^3 in TTP
  - > 40,000/mm^3 in aHUS
    - In 15-20% aHUS patients, PLT count can be normal (>150,000/mm^3), but show a decrease in PLT count > 25% vs. basal

Renal involvement in aHUS

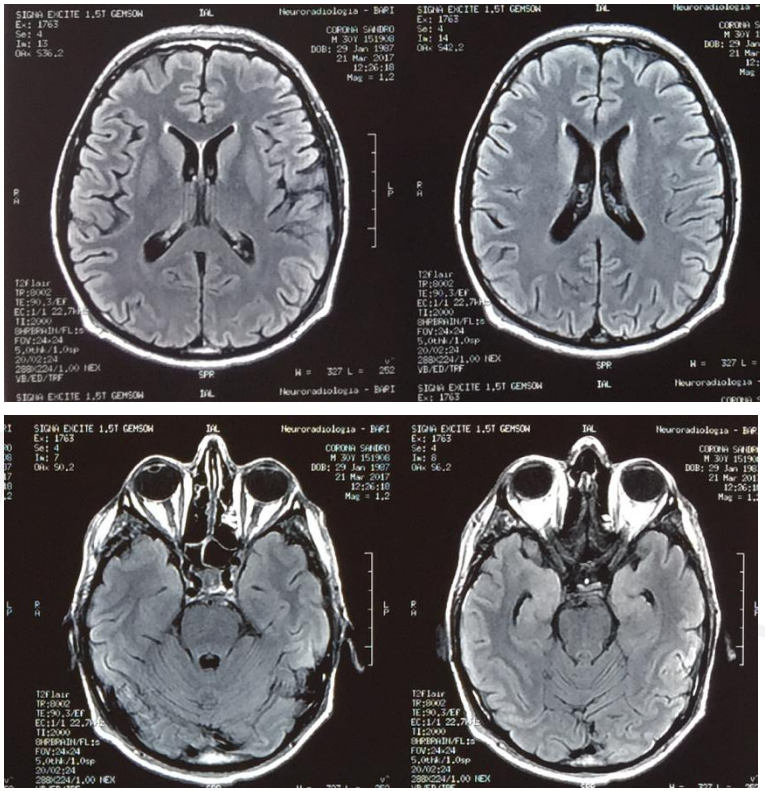
- Proteinuria mild-moderate
- In some cases nephrotic range proteinuria due to GBM damage (capillary C3 deposits → mixed aHUS/C3 GN)
- Renal failure requiring HD in > 75% of adult aHUS
- In some cases inaugural **malignant HT** → Control of HT rapid amelioration of thrombocytopenia and hemolysis

Neurologic involvement in aHUS

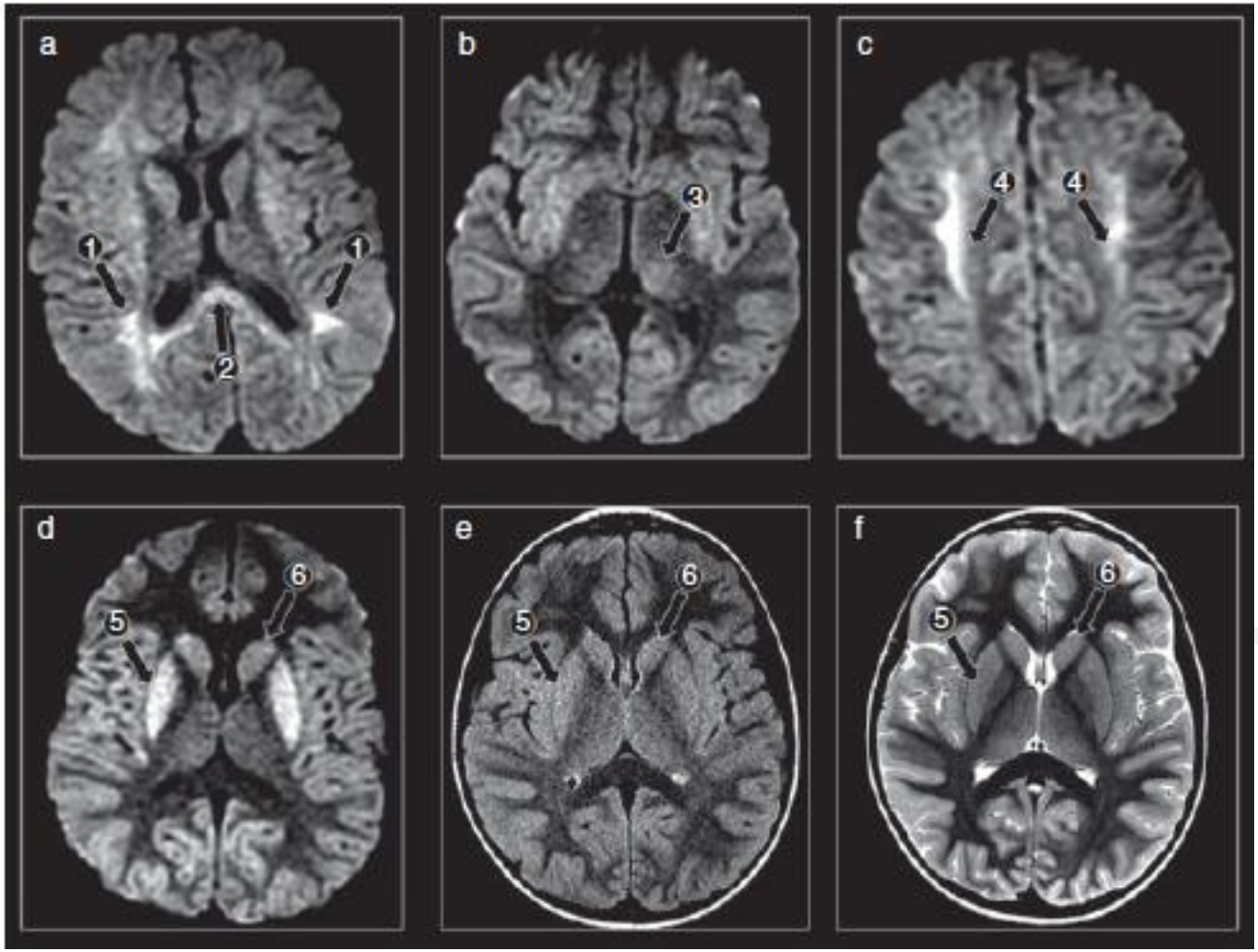
PRES



2 Weeks later



Neurologic involvement in aHUS (TMA)



Gitiaux C et al, *Dev Med Child Neurol* 2013; 55:758-65

Patient characteristics and ADAMTS13 deficiency

Table 4. Association Between Patient Characteristics and ADAMTS13 Deficiency Using Multivariate Analysis.

Patient Characteristics	Adjusted Odds Ratio	95% CI	*P* Value
Creatinine level ≤200 µmol/L (2.26 mg/dL)	23.4	8.8–62.5	<.001
Platelet count ≤30×10^9/L	9.1	3.4–24.2	<.001
Positive ANA	2.8	1.0–8.0	<.05

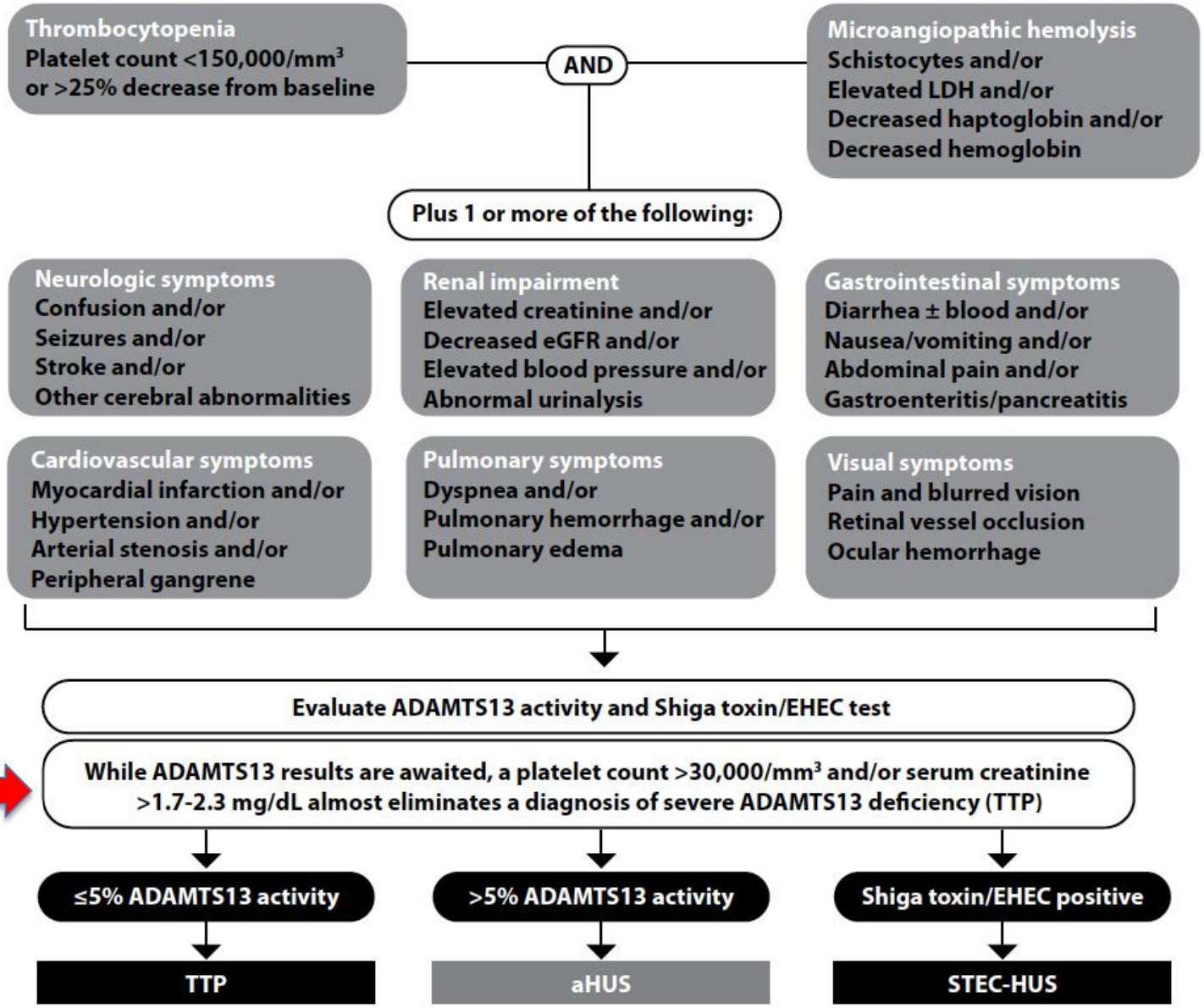
Table 5. Internal Validation to Predict Severe ADAMTS13 Deficiency at Clinical Presentation.

	At Least 1 Positive Criterion	All 3 Criteria Positive
Sensitivity	98.8 (96.9–100)	46.9 (41.3–53.1)
Specificity	48.1 (38.9–59.3)	98.1 (94.4–100)
Positive predictive value	85.0 (82.6–87.7)	98.7 (96.4–100)
Negative predictive value	93.3 (85.2–100)	38.6 (35.8–41.9)

361 pats. with TMA

Coppo P et al, *PLOSOne* 2010; 5:e10208

Differential Diagnosis for TMAs: aHUS, TTP, and STEC-HUS



Laurence J et al: *Clin Adv Hemathol Oncol* 2016; 14: 2-15

TMA and aHUS – Therapy

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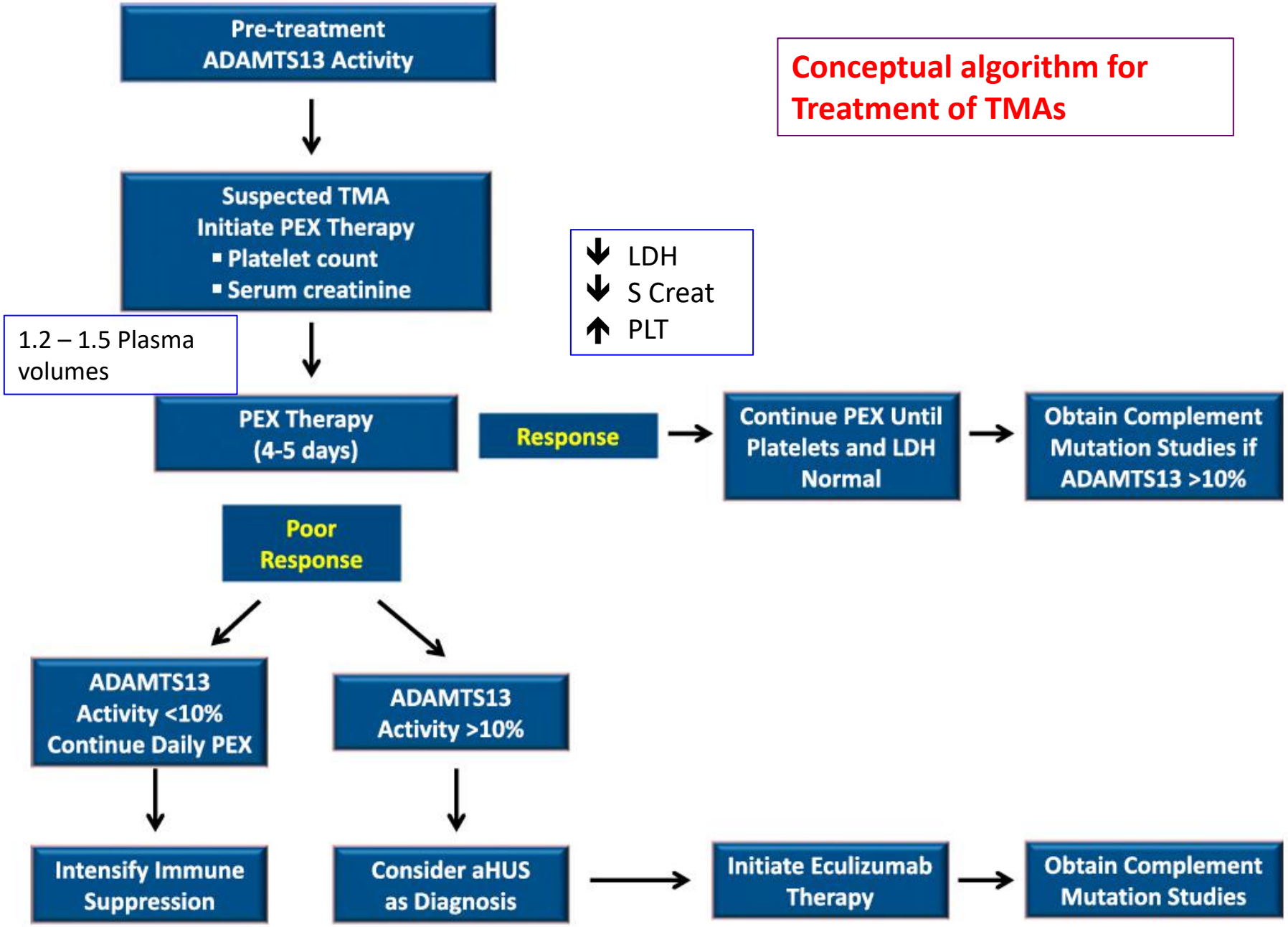
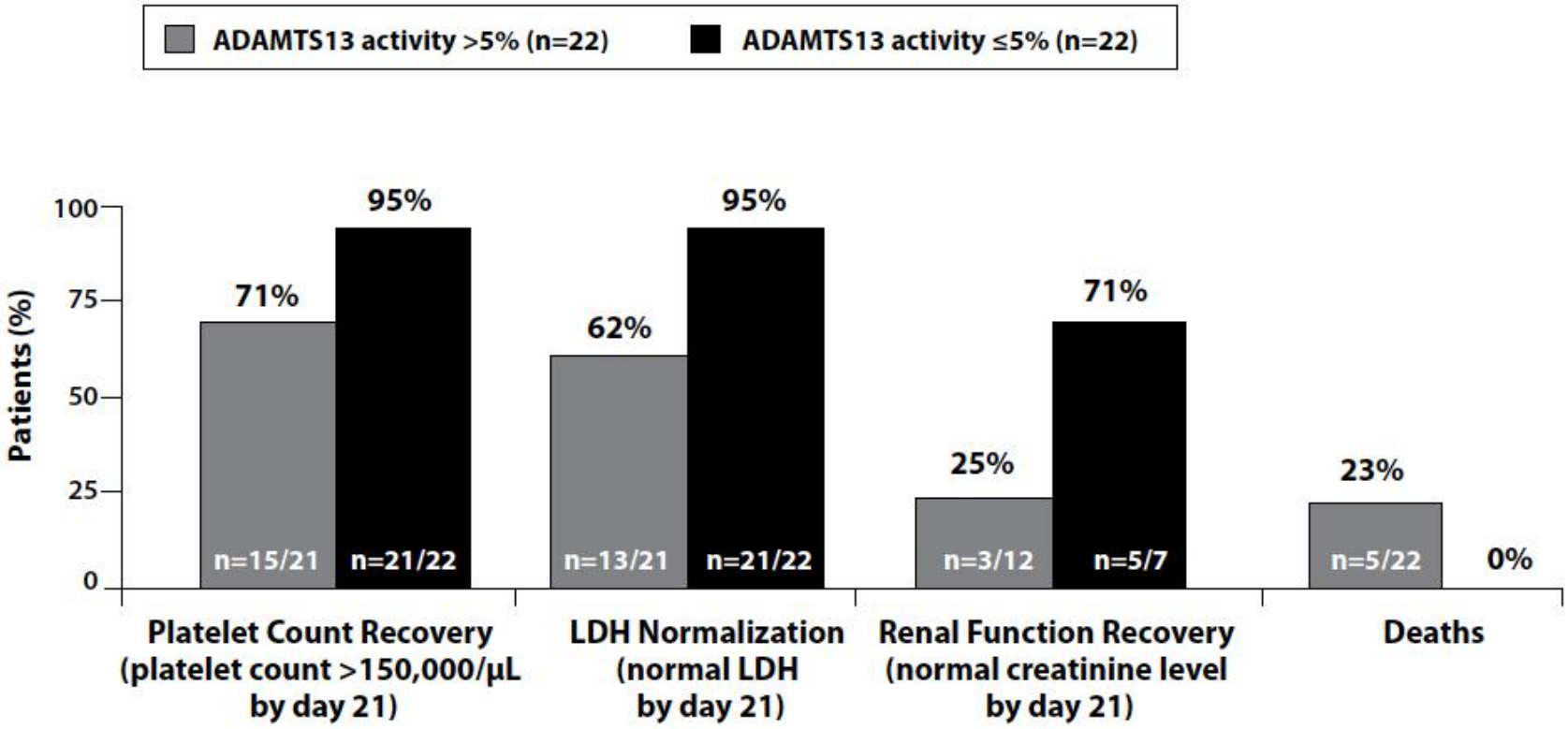
Conceptual algorithm for Treatment of TMAs



Cataland SR and Wu HM: *Blood* 2014; 123: 2478-84

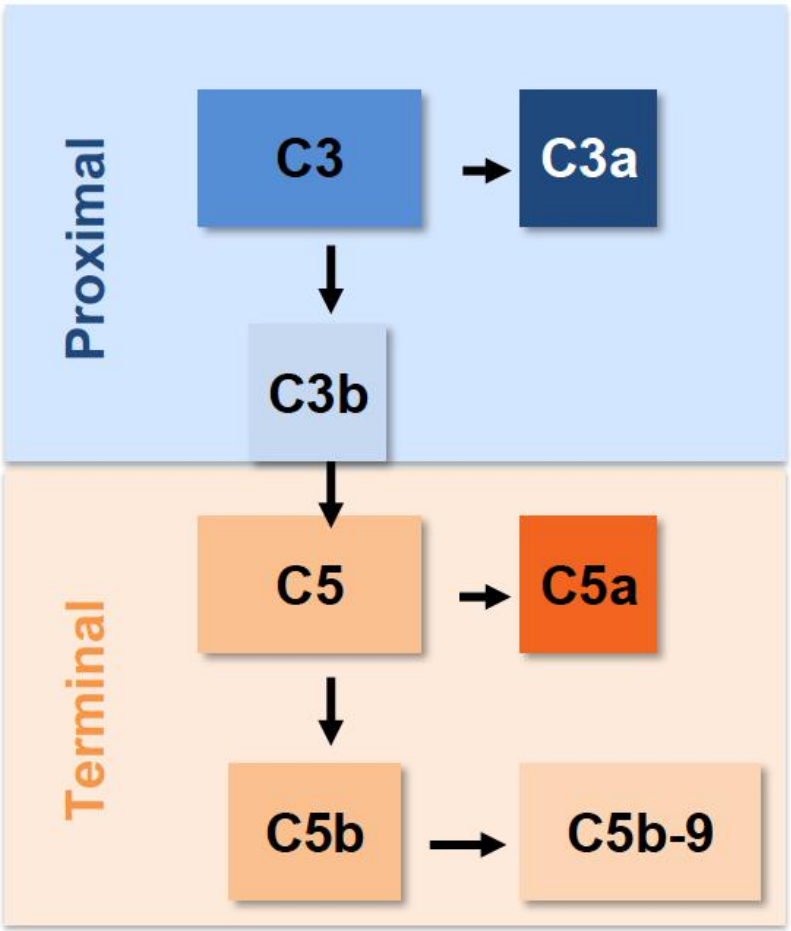
Effect of PE in pats. with TTP and aHUS

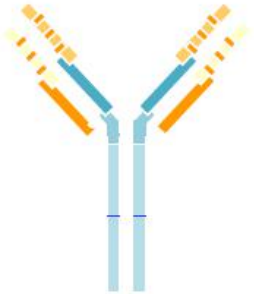


Laurence J et al: *Clin Adv Hemathol Oncol* 2016; 14: 2-15

Effects of Eculizumab on Complement cascade

Complement cascade[2,3]





Eculizumab

- Eculizumab binds with high affinity to C5[1,2]
- Terminal complement – C5a and C5b-9 formation blocked[1,2]
- Proximal functions of complement remain intact[1,2]
  - Weak anaphylatoxin[2,4]
  - Immune complex clearance[2]
  - Microbial opsonisation[2]

1. Alexion Europe SAS. Eculizumab Summary of Product Characteristics, 2015; 2. Rother RP et al. Nat Biotechnol 2007;25:1256-64; 3. Walport MJ. N Engl J Med 2001;344:1058-66; 4. Figueroa JE, Densen P. Clin Microbiol Rev 1991;4:359-95

Effects of Eculizumab on renal outcomes (ESRD) and death

	Children			Adults				
	Pre-eculizumab era		Eculizumab	Pre-eculizumab era		Eculizumab		
	French cohort[2] (n=89)	Italian cohort[3] (n=149)	Trial 3[139,140] (n=22)	French Cohort[2] (n=89)	Italian cohort[3] (n=149)	Trial 1[141,142] (n=17)	Trial 2[141,142] (n=20)	Trial 4[143,144] (n=41)
First episode	16%	..	..	46%	..	..	..	..
6-month follow-up	..	..	9%	..	..	6%	10%	15%
1-year follow-up	29%	..	9%	56%	..	6%	10%	15%
2-year follow-up	..	..	..	..	..	12%	10%	..
3-year follow-up	..	48%	..	..	67%	..	..	..
5-year follow-up	36%	..	..	64%	..	..	..	..

For a detailed table legend see the appendix (pp 27,28). HUS=haemolytic uraemic syndrome.

Table 2: **Percentage of patients with atypical HUS who progressed to end-stage renal disease or who died in four prospective trials of eculizumab compared with the Italian and French registries of the pre-eculizumab era**

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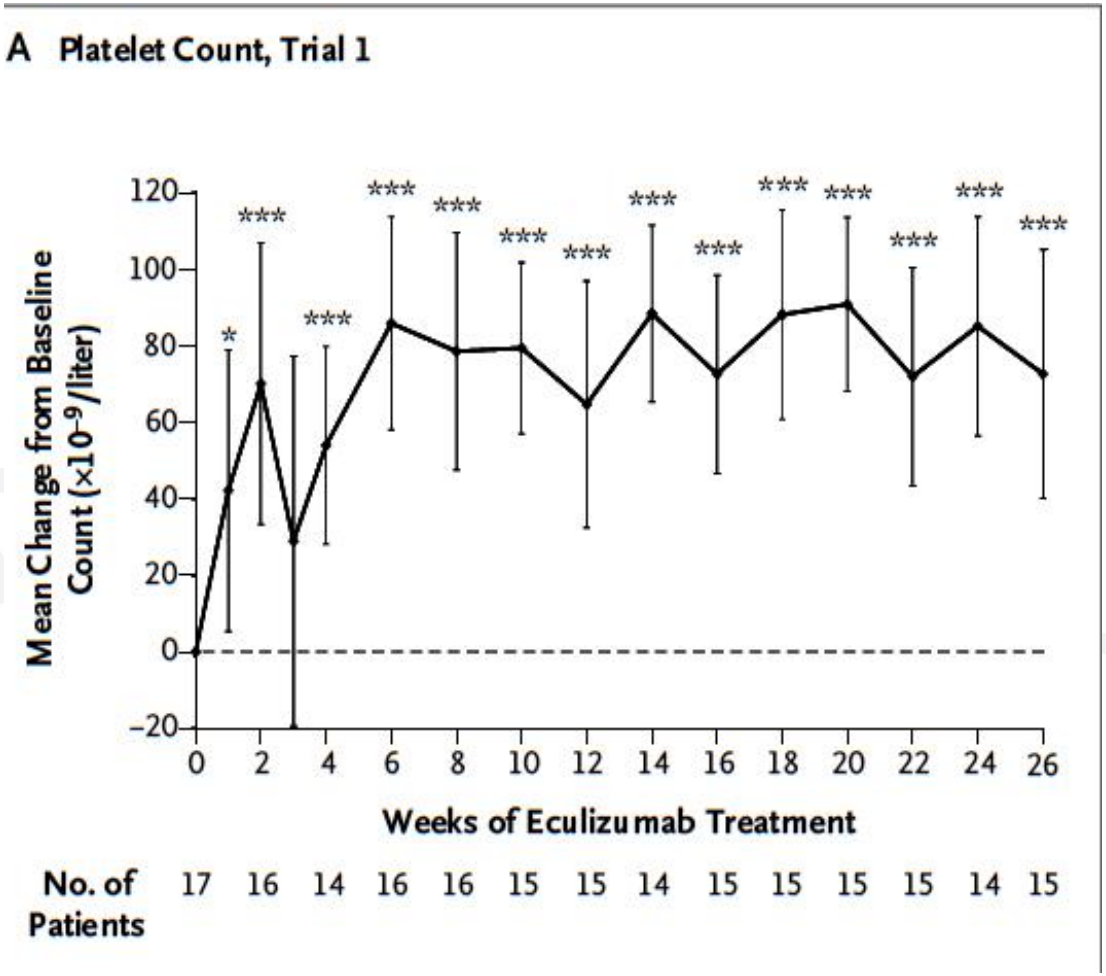
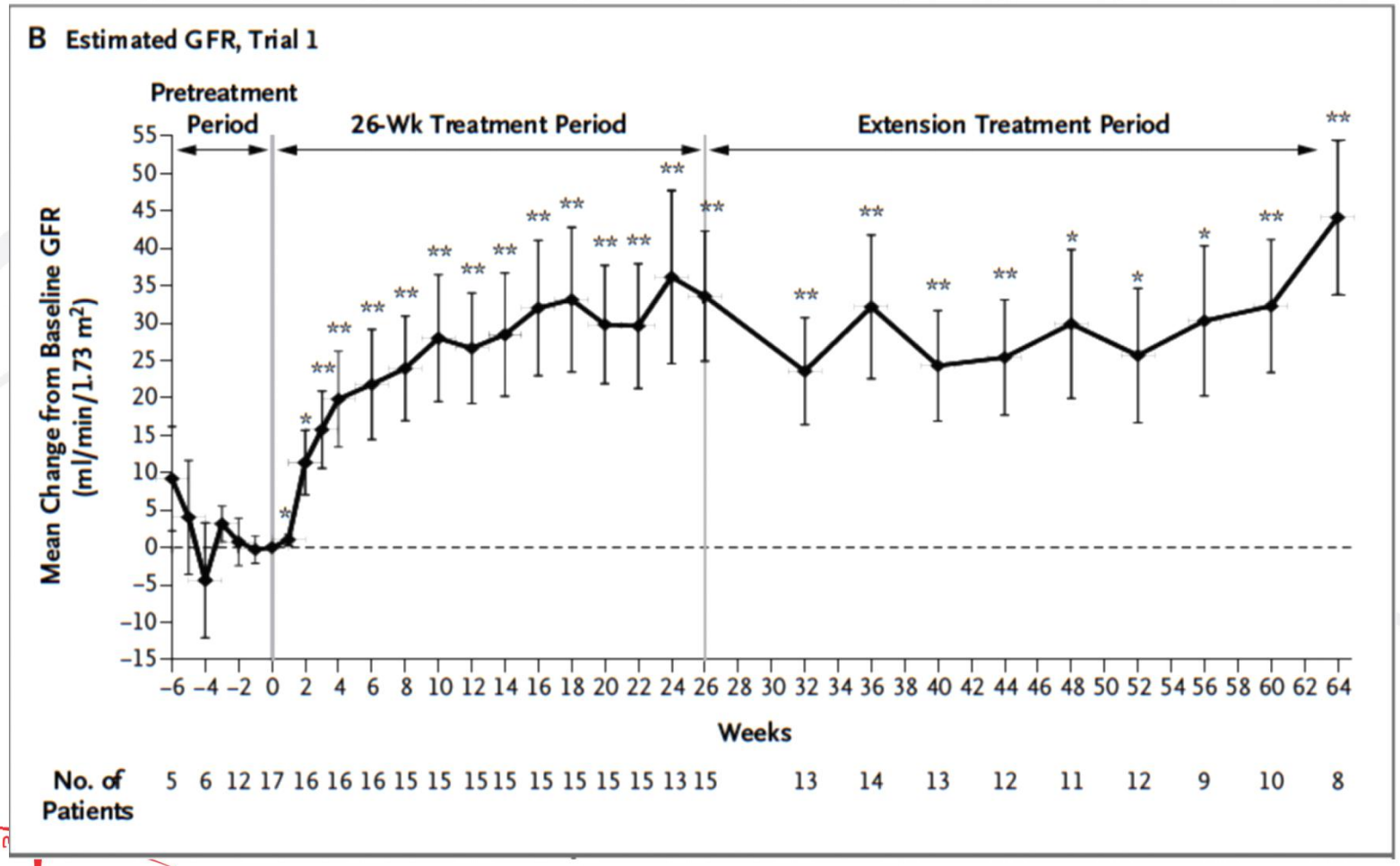
Effects of Eculizumab on PLT count in aHUS



Legendre CM et al, *N Engl J Med* 2013; 368:2169-81

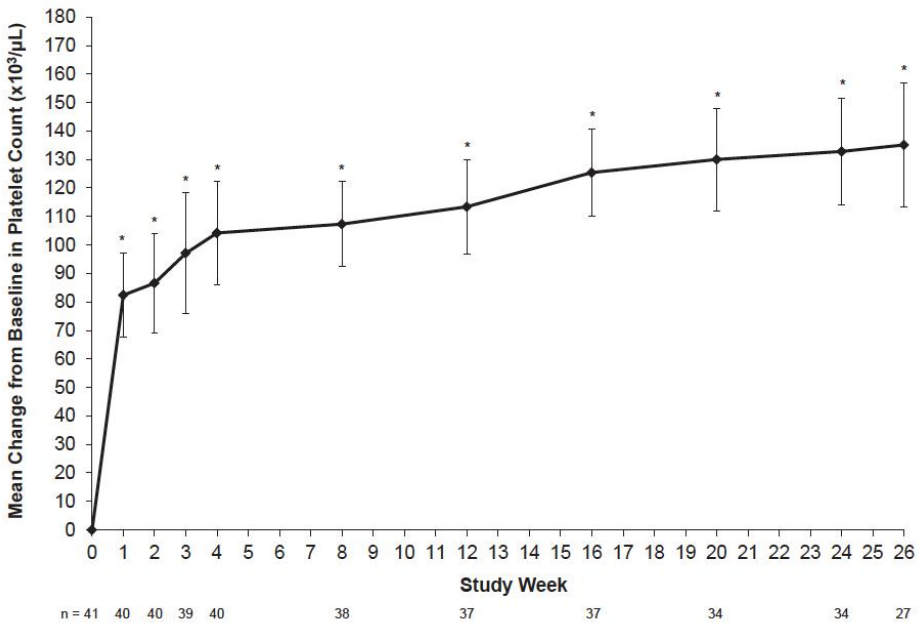
Effects of Eculizumab on eGFR in aHUS



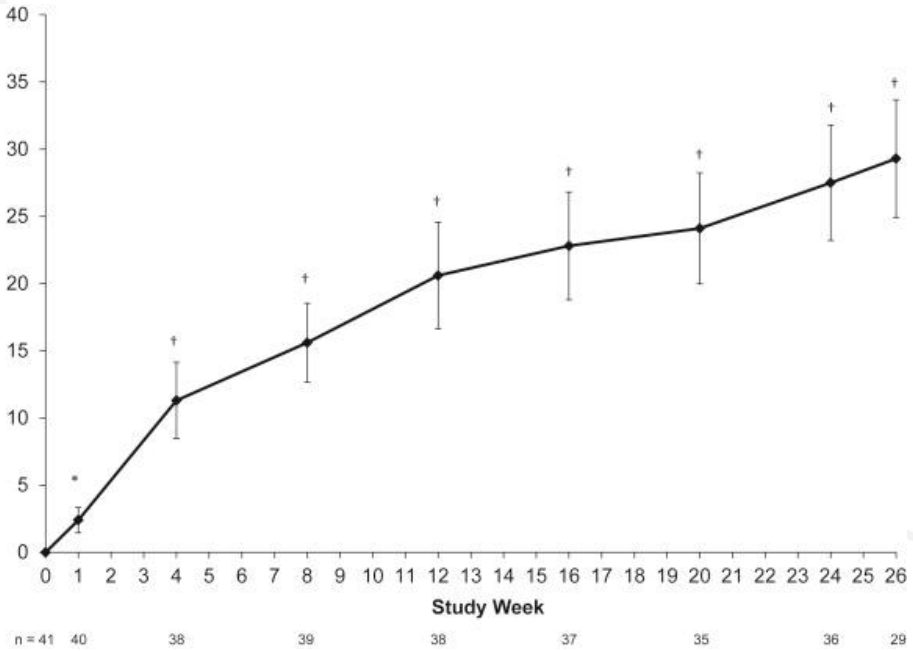
Legendre CM et al, *N Engl J Med* 2013; 368:2169-81

Eculizumab and clinical outcomes in aHUS

PLT

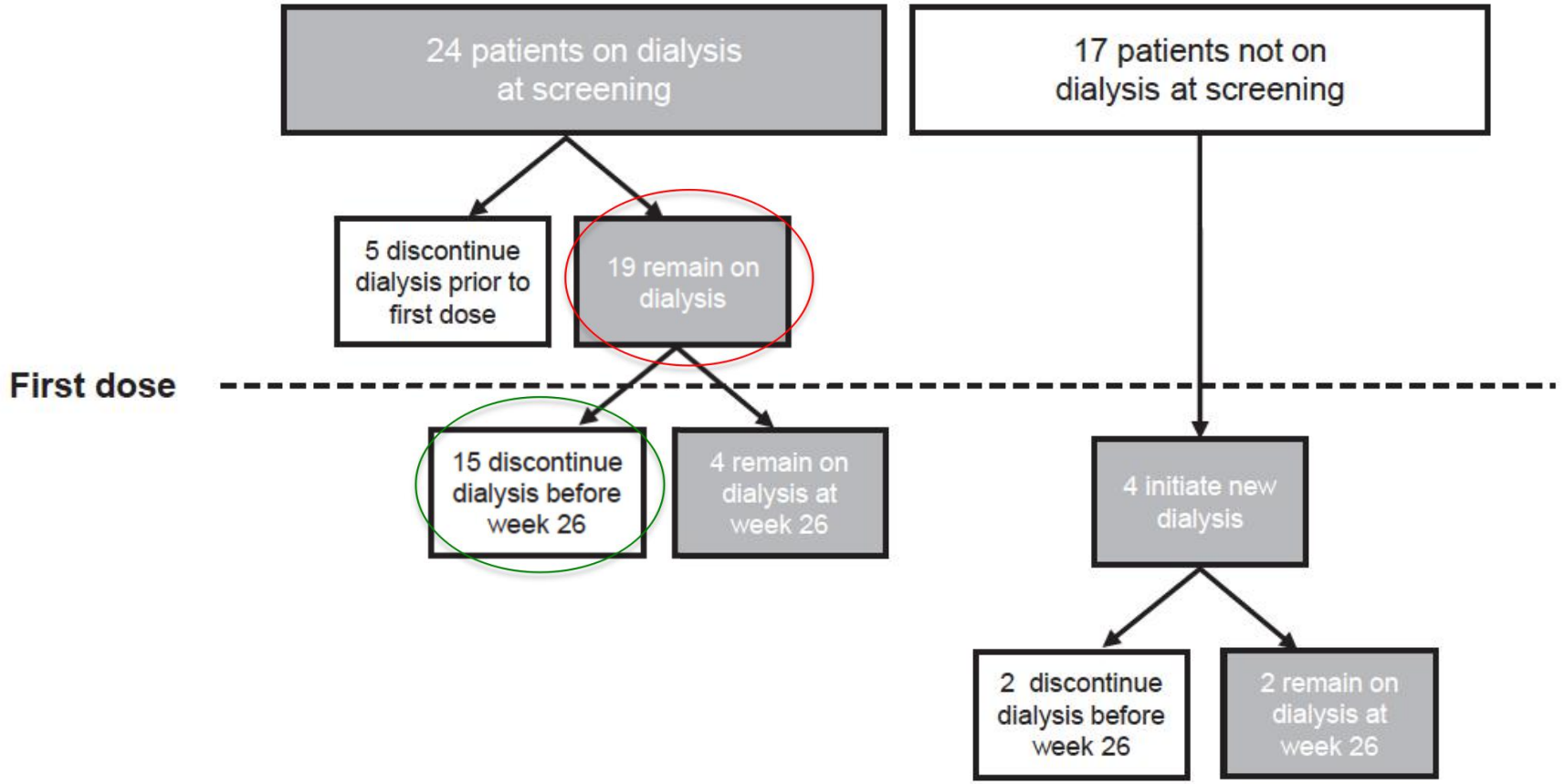


eGFR



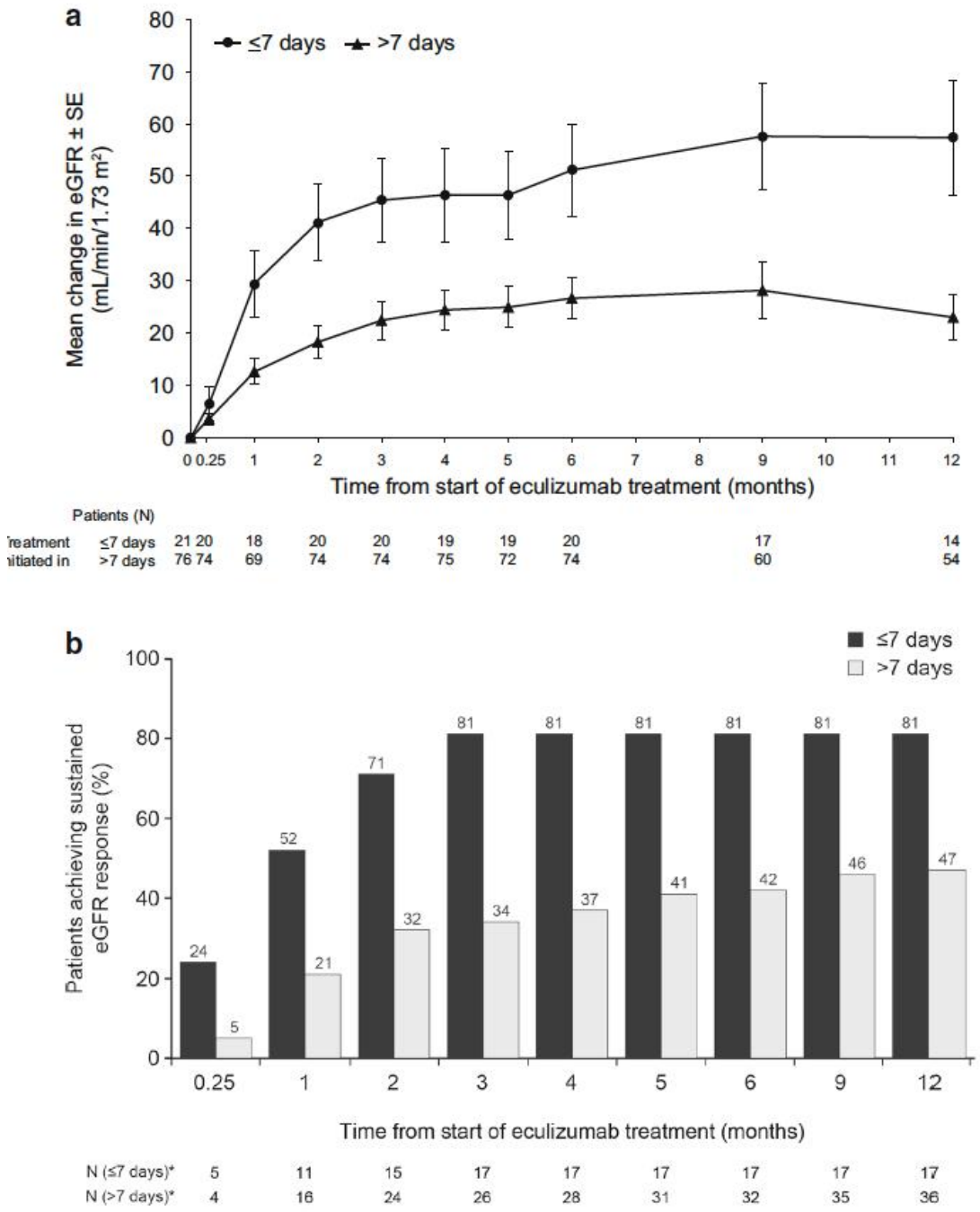
Fakhouri et al.: *Am J Kidney Dis* 2016; 68:84-93

Eculizumab and HD discontinuation in aHUS



Fakhouri et al.: *Am J Kidney Dis* 2016; 68:84-93

Effect of early vs. late Eculizumab treatment on eGFR recovery



Vande Walle J et al: *J Nephrol* 2016; 30:127-34

Eculizumab treatment and TMA episode relapses in aHUS

Table 5. TMA manifestation rates

Parameter	Eculizumab treatment status		Eculizumab dosing		Excluding single laboratory change criterion	
	Off treatment ($n=39$)	On treatment ($n=76$)	Non-labelled regimen ($n=33$)	Labelled regimen ($n=65$)	Off treatment ($n=39$)	On treatment ($n=76$)
Patients with manifestation, *n* (%)	11 (28)	10 (13)	4 (12)	7 (11)	8 (21)	2 (3)
Total number of manifestations	14	14	7	7	11	2
Total patient-years	70.5	192.8	57.9	135.0	70.5	192.8
TMA manifestation rate/ 100 patient-years	19.9	7.3	12.1	5.2	15.6	1.0
Fold change in rate[a]	2.7	Ref	2.3	Ref	15.6	Ref
Per cent change compared with off treatment[b] (%)	Ref	−63	−39	−74	Ref	−94
HR (P value)[c]	4.7 (P = 0.0008)	Ref	1.3 (P = 0.7000)[d]	Ref	16.8 (P = 0.0010)	Ref

[a]Off treatment compared with on treatment (overall) or non-labelled compared with labelled regimen for the same analysis.
[b]On treatment (overall), non-labelled or labelled regimen compared with off treatment for the same analysis.
[c]HRs were based on Cox proportional hazards model of time to first TMA manifestation, with treatment status as a time-dependent explanatory variable and complement abnormality status as a covariate.
[d]Compared with the labelled dosing regimen of eculizumab.
Ref, reference value.

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Menne J et al: *Clin Kidney J* 2018; 1-10 https://doi.org/10.1093/ckj/sfy035

Treatment with Eculizumab in aHUS
Special recommendations

- All patients treated with Eculizumab need anti-Meningococcal vaccination two weeks prior of starting mAb infusion, tetravalent against A, C, Y, W135 strains; better if also vaccination against B type meningococcal strains is performed
- Make sure also that there is no evidence of invasive Aspergillosis
- In the need of immediate start of Eculizumab treatment, a prophylaxis with proper antibiotics can be performed till vaccination is operative.

Summary

- aHUS and TMAs are rare diseases with a relevant morbility and mortality
- Different forms of TMAs involve different pathogenic mechanisms (ADAMTS 13 deficit in TTP, Complement dysfunction in many cases of aHUS)
- Kidney damage in aHUS is relevant and often ends-up in ESRD requiring dialysis
- A pathophysiology-driven approach for therapy of TMAs is warranted
- Rituximab and immune suppressors for cases with ADAMTS 13 inhibitors and Eculizumab for aHUS linked to complement activation (start Eculizumab early on)