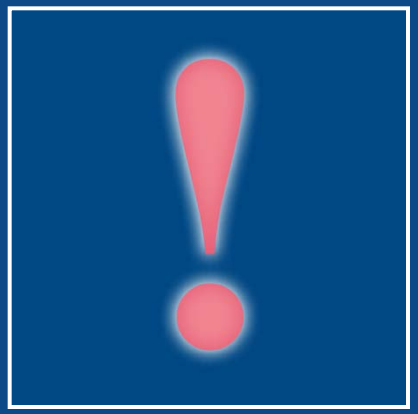
# Nephro Update Europe 2017

## 6-7 October, Vienna

# Hot Topic: Rare Diseases - aHUS & other TMAs

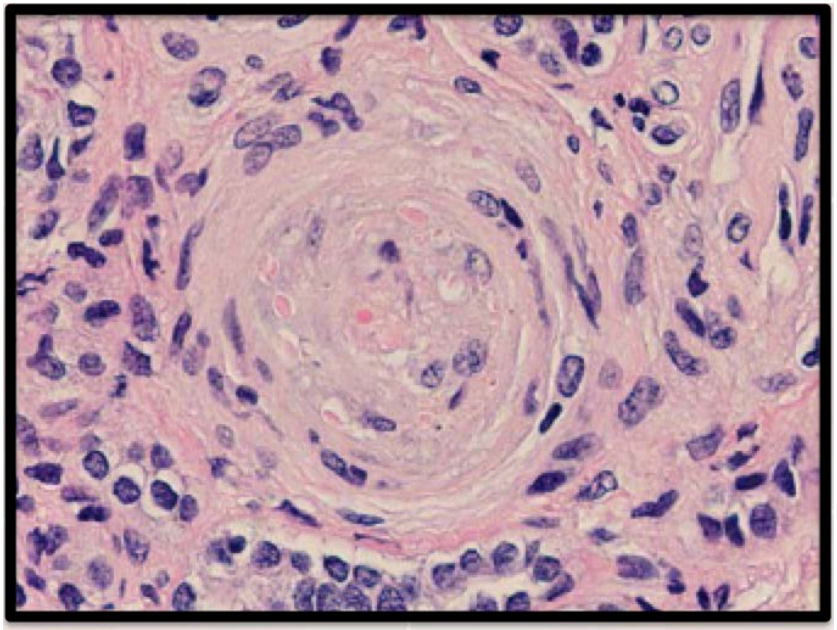


Christophe Legendre, France

# HUS - TMAs: classifications

# State of the Art

## Syndrome of Thrombotic Microangiopathy (TMA)
## =
## Micro-vasculature occlusive diseases
## =
## Microvascular endothelial injury and thrombosis.



JL Moake, N Engl J Med 2002, 347:589-600.
JN George, CM Nester, N Engl J Med 2014, 371: 654-666.

# 1. Classical classification # clinical presentation.

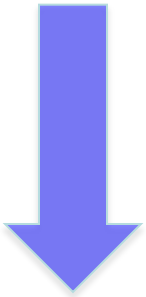
Mechanical hemolytic anemia +
Peripheral thrombocytopenia +
Organ failure due to microvasculature occlusion

→ **3 nosological entities**

A. **Thrombotic thrombocytopenic purpuras (TTP)**
B. **Hemolytic uremic syndromes (HUS)**
C. **« Secondary » Thrombotic Microangiopathies**

# A. Thrombotic Thrombocytopenic Purpura (TTP)

Mechanical hemolytic anemia +
Peripheral thrombocytopenia+
Neurological symptoms.



**Congenital or acquired ADAMTS13 deficit**

E Moschcowitz, Proc N Y Pathol Soc 1924.
JL Moake, N Engl J Med 2002, 347:589-600.

# B. Hemolytic Uremic Syndrome (HUS)

Mechanical hemolytic anemia +
Peripheral thrombocytopenia +
Acute renal failure (AKI).

**Typical**
**Shiga toxin**

**Atypical**
**Complement**

C Gasser, Schweiz Med Wochenschr 1955

# B. Atypical Hemolytic Uremic Syndromes (aHUS)

Mechanical hemolytic anemia +
Peripheral thrombocytopenia +
Acute renal failure (AKI).

**Typical**
**Shiga toxin**

**Atypical**
**Complement**

# Atypical Hemolytic Uremic Syndromes

## Congenital or acquired anomaly in alternate complement pathway

- **Mutation(s) in genes coding for complement regulation molecules +++**
- **Acquired antibodies directed against factor H, I**
- **Mutation(s) in DGKE (diacylglycerol kinase ε)**

**70% of cases of aHUS**

M Noris et al, N Engl J Med 2009, 361: 1676-1687.
V Frémeaux-Bacchi et al, Clin J Am Soc Nephrol 2013, 24: 475-486.
M Lemaire et al, Nat Genet 2013, 310: 45: 531-536.

# C. TMA with « underlying » conditions

**TTP**

- Acquired thrombotic thrombocytopenic purpura (acquired TTP)
- Congenital TTP (Upshaw–Schulman syndrome)

**HUS**

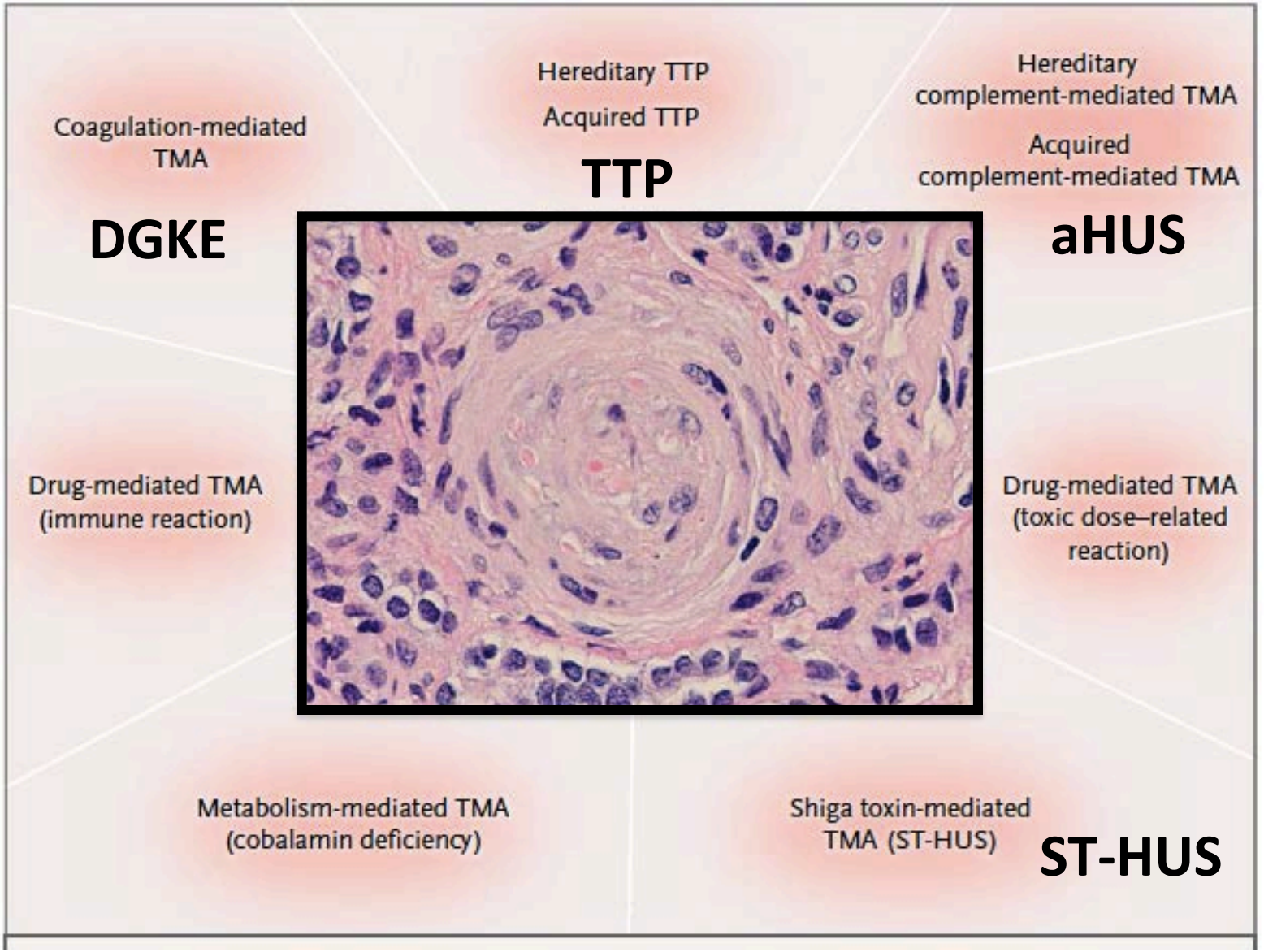
- Diarrhea-associated (Shiga toxin-induced) hemolytic uremic syndrome (Shiga-HUS)
- Atypical hemolytic uremic syndrome (aHUS)

**TMA**

- Pregnancy-associated TMAs
  - HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)
  - Preeclampsia
  - Pregnancy as trigger for acquired or congenital TTP, or aHUS
- Drug-induced TMAs
  - Thienopyridines (ticlopidine and clopidogrel)
  - Calcineurin inhibitors (cyclosporine and tacrolimus)
  - mTOR inhibitors (sirolimus and everolimus)
  - Antineoplastic agents (mitomycin and gemcitabine)
  - Quinine
- TMA after organ transplantation
  - Renal transplantation
  - Lung transplantation
  - Allogeneic hematopoietic stem cell transplantation
- Other conditions resembling or causing TMA
  - Infections
  - Severe pulmonary or systemic hypertension
  - Advanced malignancies
  - Disseminated intravascular coagulation

MH Rosove, Semin Arthritis Rheum 2013, 43:787-805.

# 2. Towards a mechanism-related classification




JN George, CM Nester, N Engl J Med 2014, 371: 654-666.

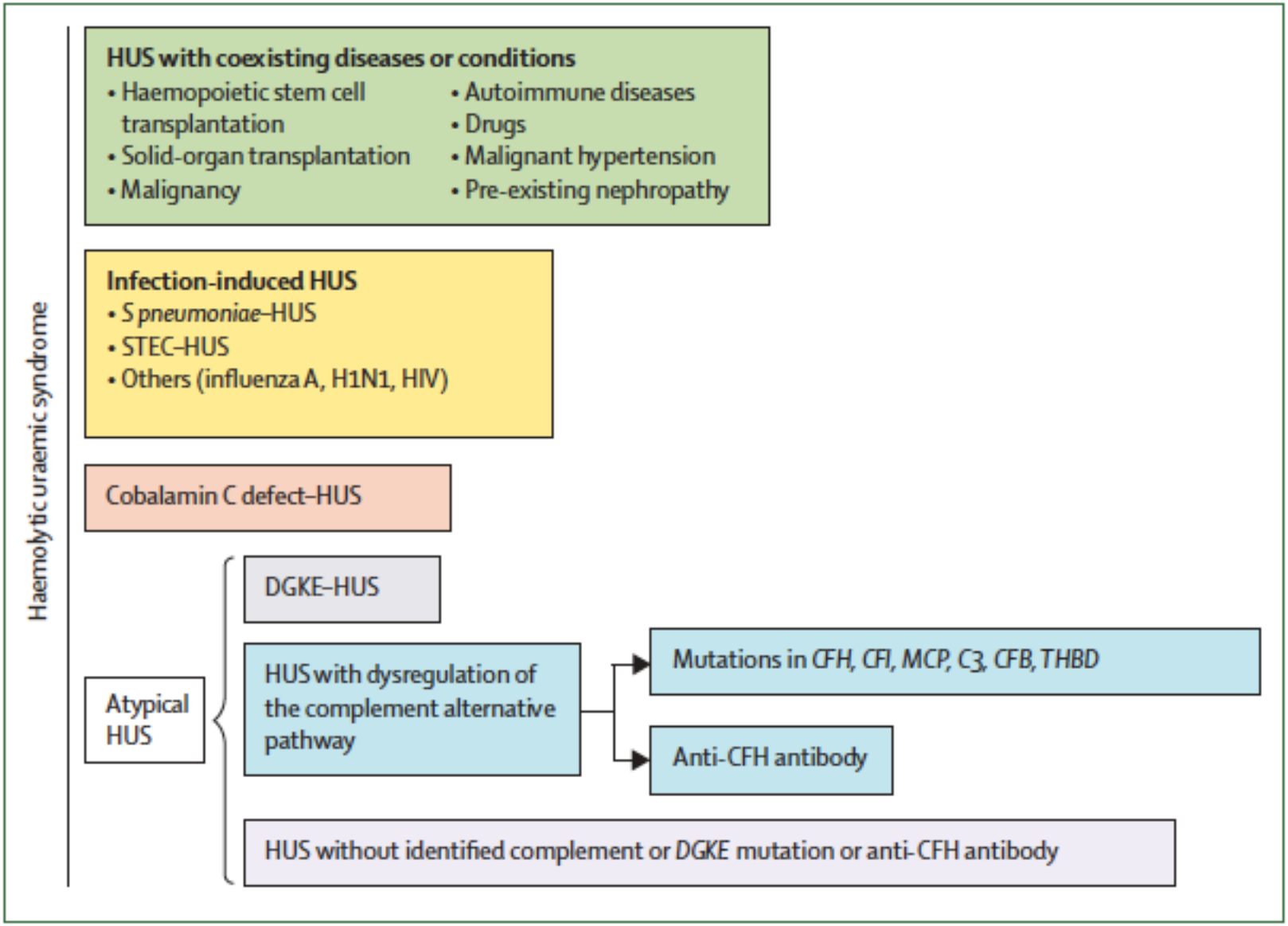
# As yet unknown mechanism: syndrome of Thrombotic Microangiopathy (TMA).

**Table 2. Common Disorders Associated with Microangiopathic Hemolytic Anemia and Thrombocytopenia.***

| |
|---|
| Systemic infection |
| Systemic cancer |
| Severe preeclampsia, eclampsia, HELLP syndrome |
| Severe hypertension |
| Autoimmune disorders (e.g., systemic lupus erythematosus, systemic sclerosis, antiphospholipid syndrome) |
| Hematopoietic stem-cell or organ transplantation |

JN George, CM Nester, N Engl J Med 2014, 371: 654-666.

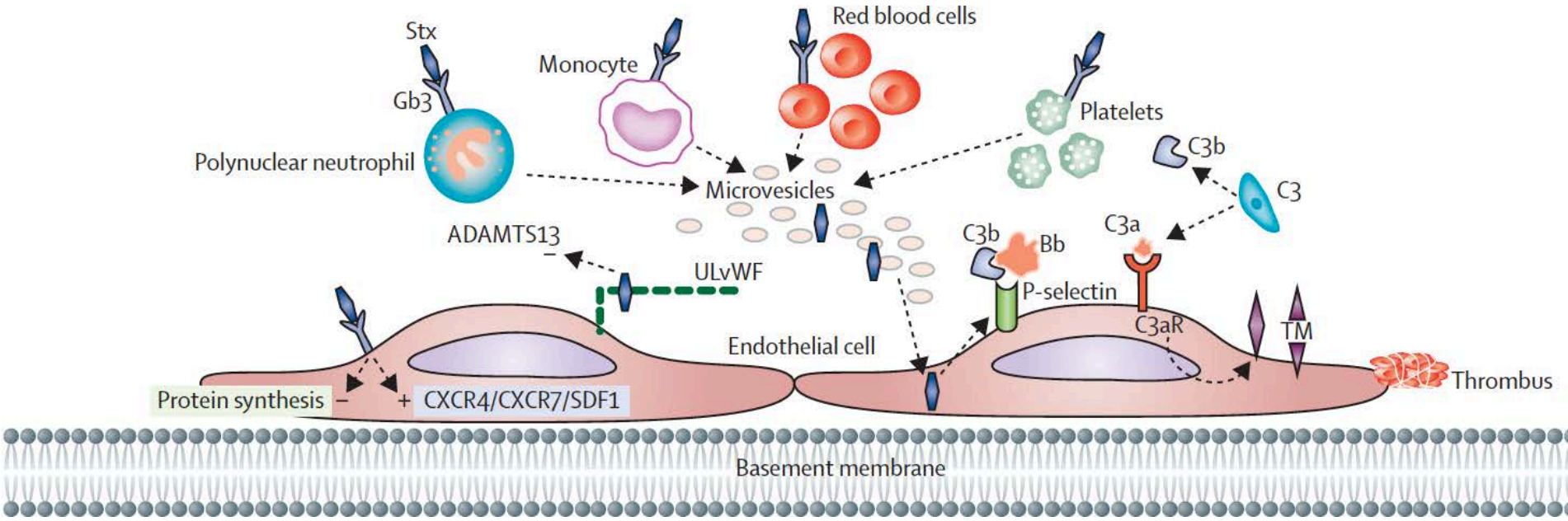
# 2016 International HUS Group Classification




C Loirat et al, Pediatr Nephrol 2016, 31: 15-39.

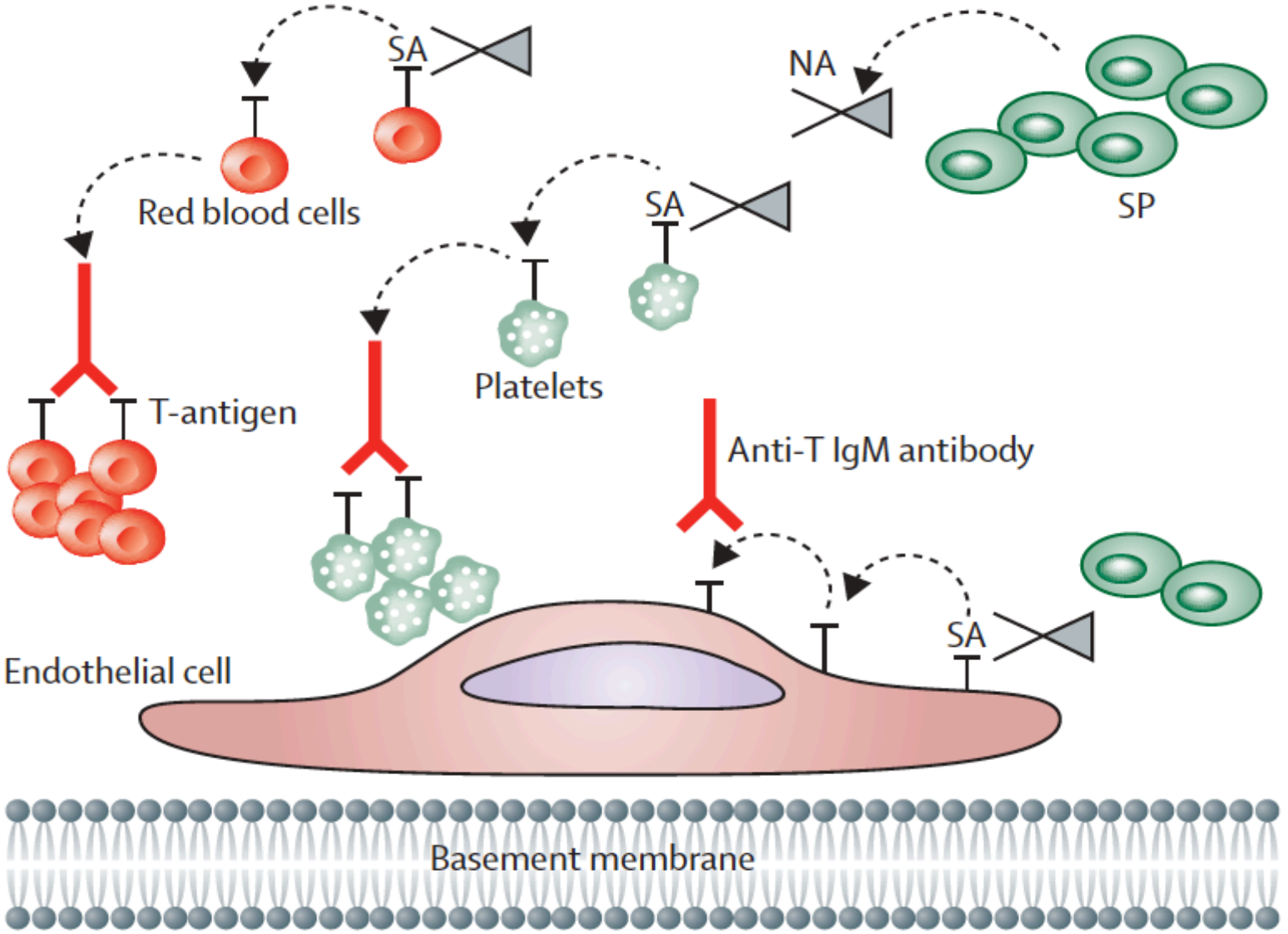
F Fakhouri et al, Lancet 2017, 390: 681-696.

# STEC HUS



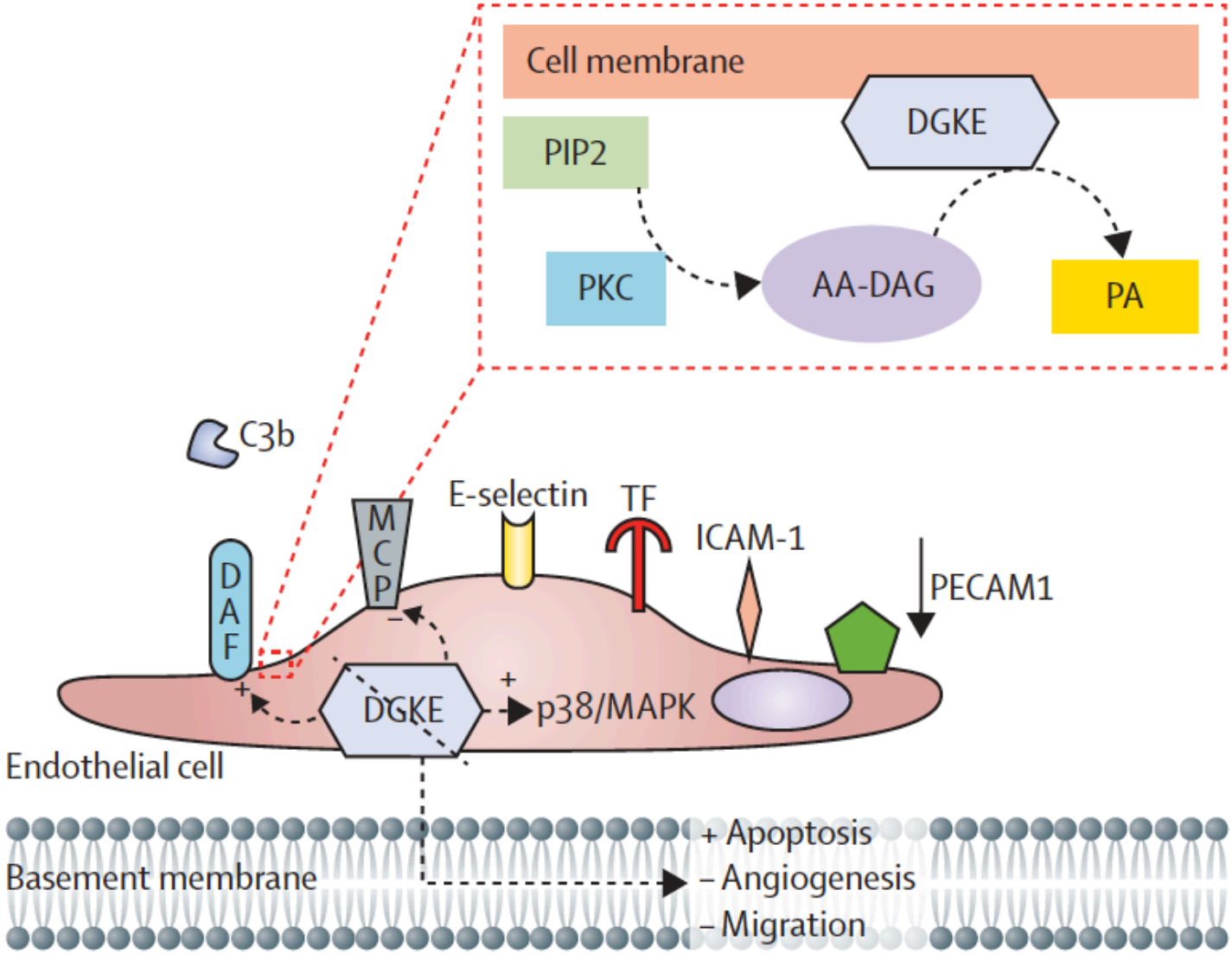

F Fakhouri et al, Lancet 2017, 390: 681-696.

# *S. Pneumoniae*-HUS



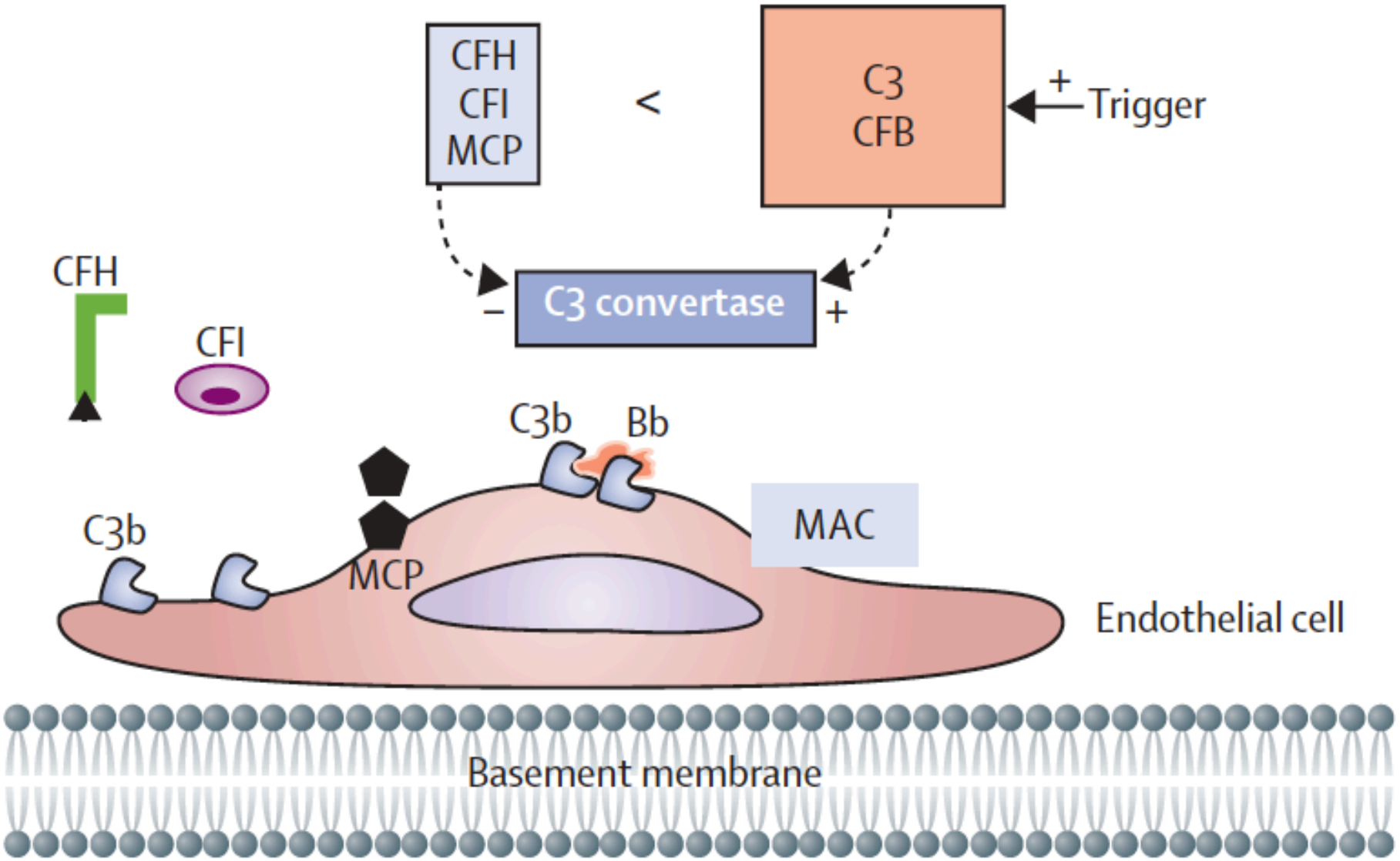

F Fakhouri et al, Lancet 2017, 390: 681-696.

# DGKε-HUS



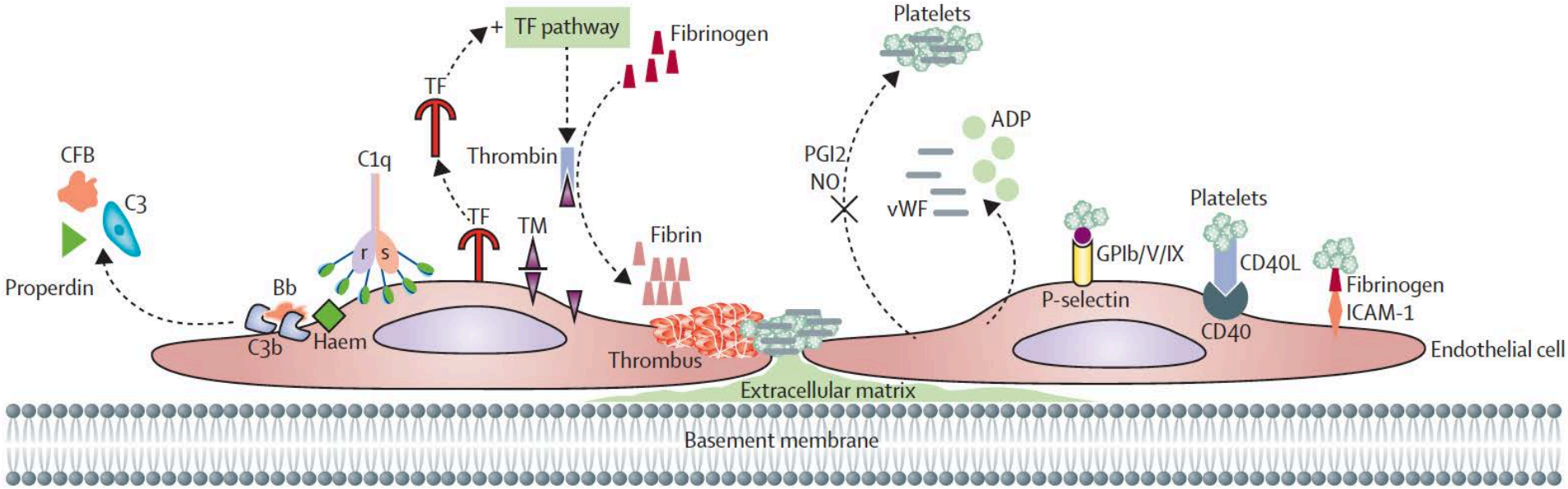

F Fakhouri et al, Lancet 2017, 390: 681-696.

# atypical-HUS

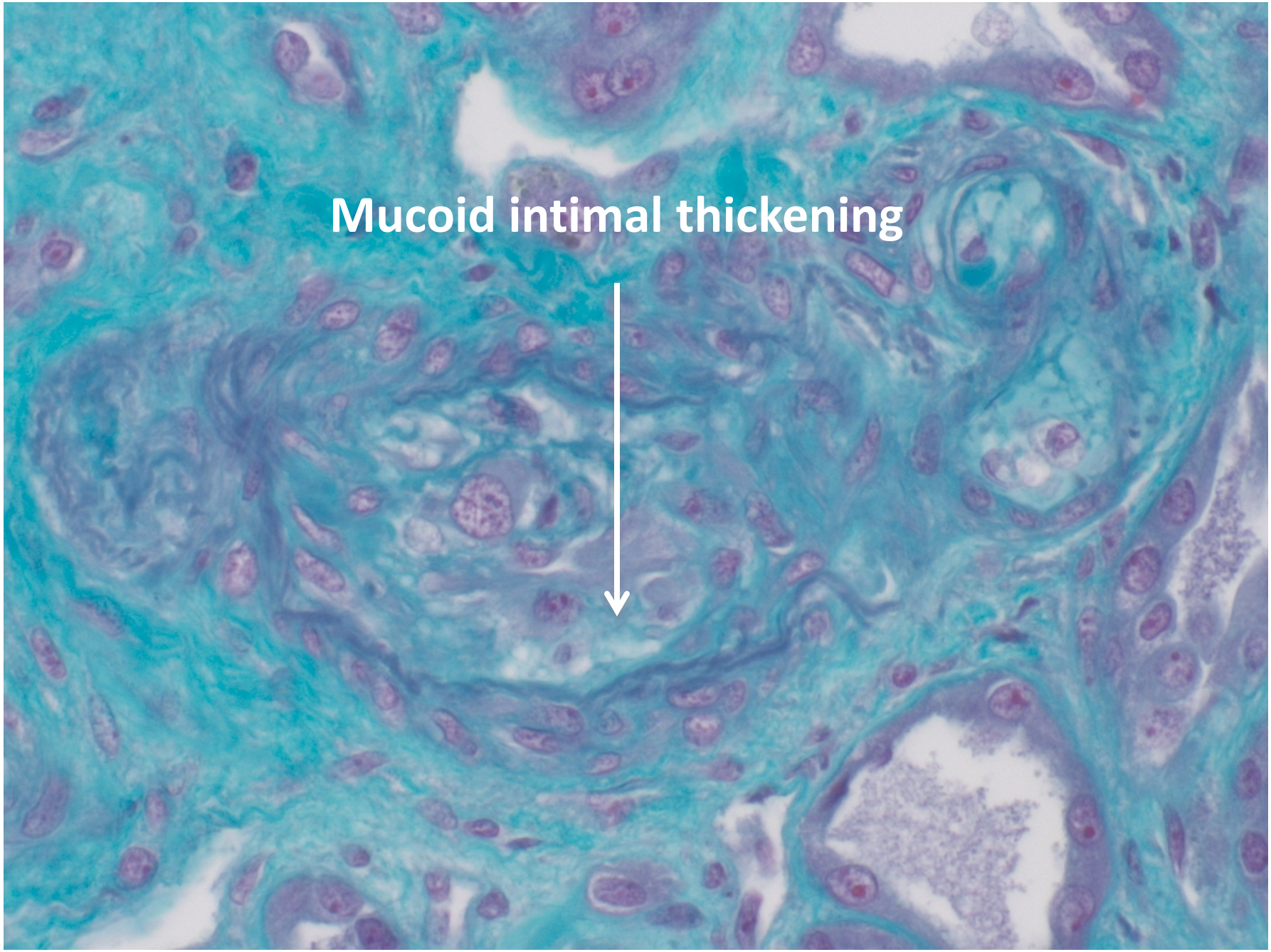



F Fakhouri et al, Lancet 2017, 390: 681-696.

# Common final phenotype of endothelial cell

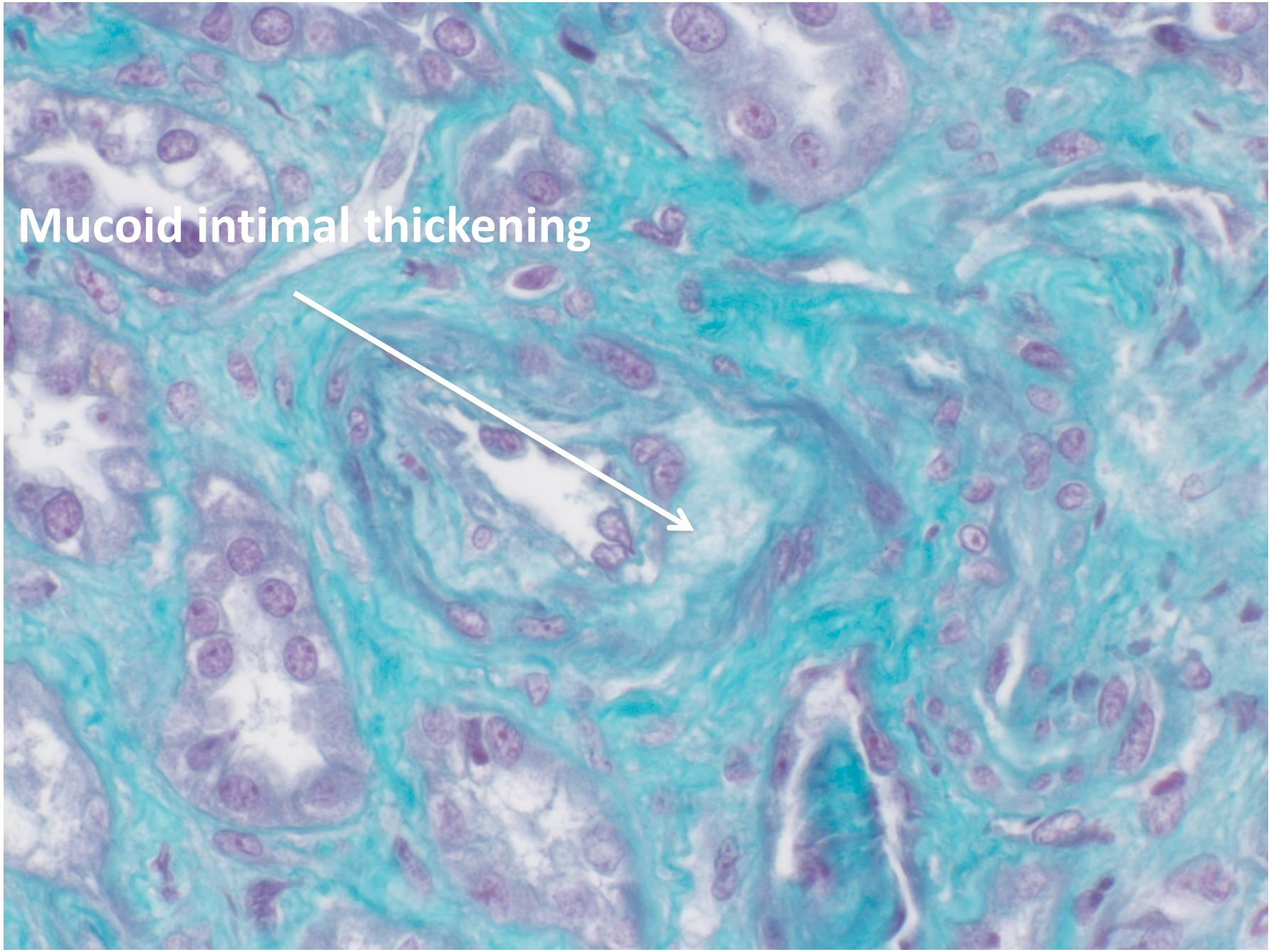



F Fakhouri et al, Lancet 2017, 390: 681-696.



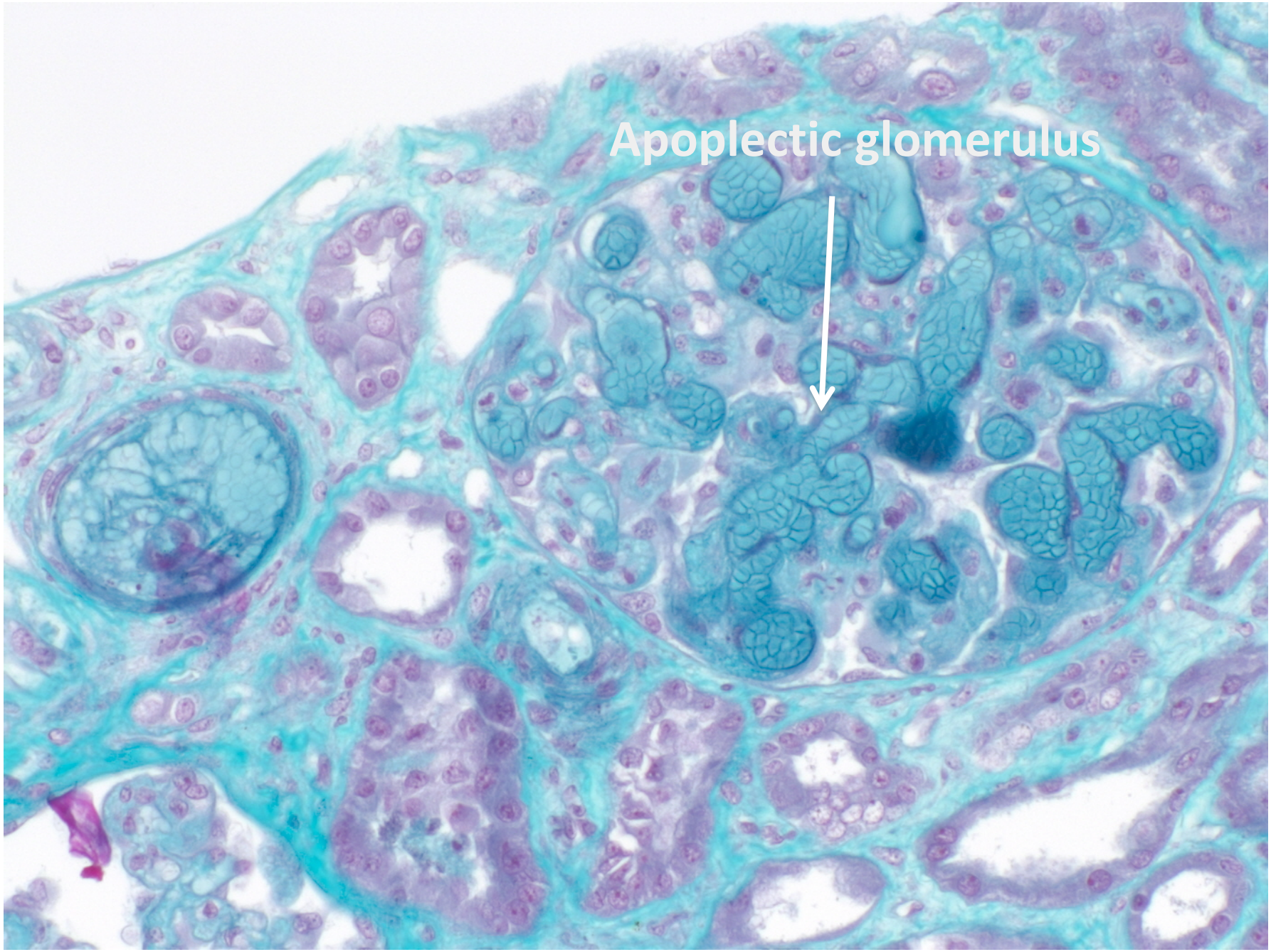



Courtesy of Marion Rabant



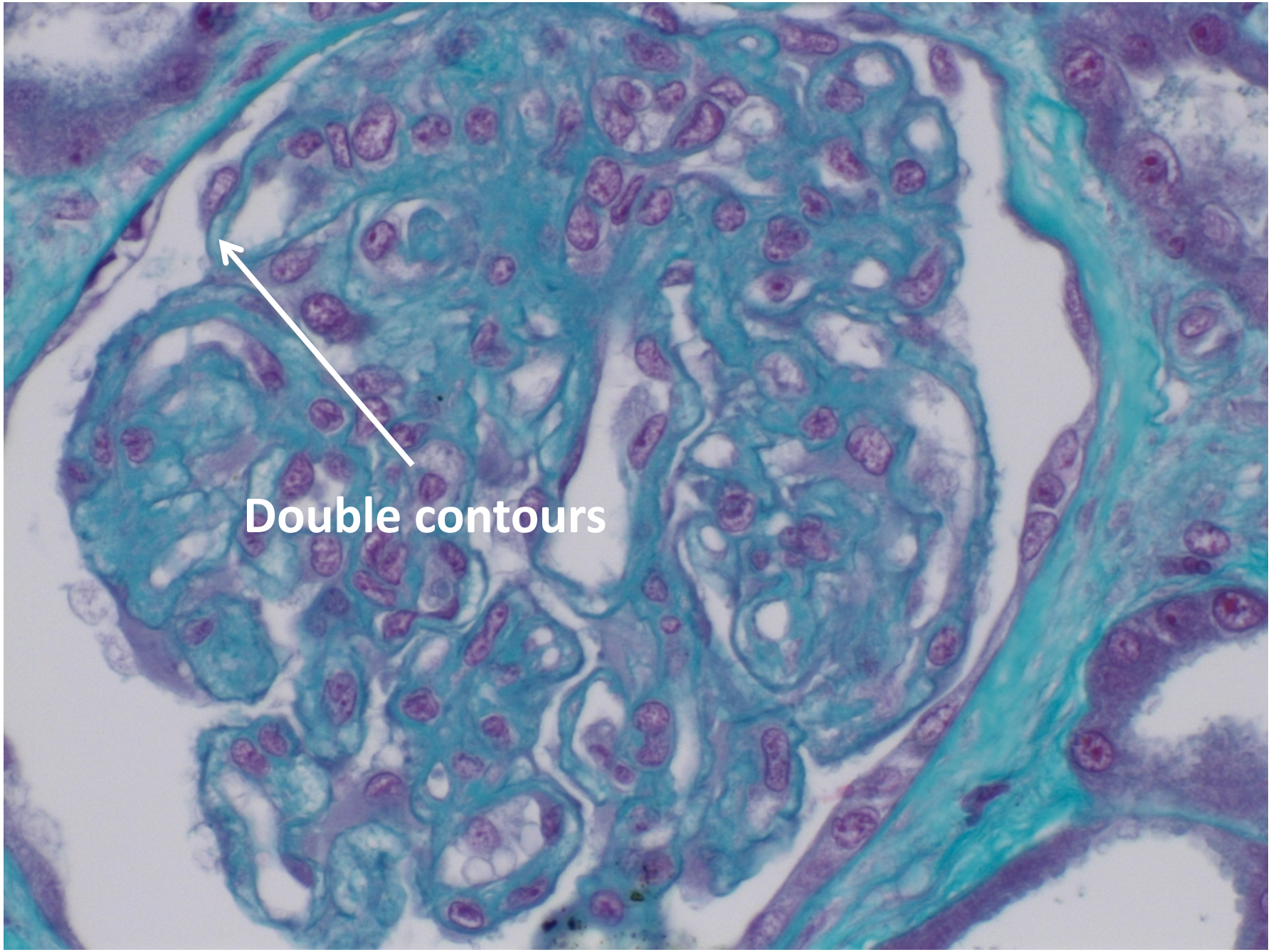



Courtesy of Marion Rabant






Courtesy of Marion Rabant



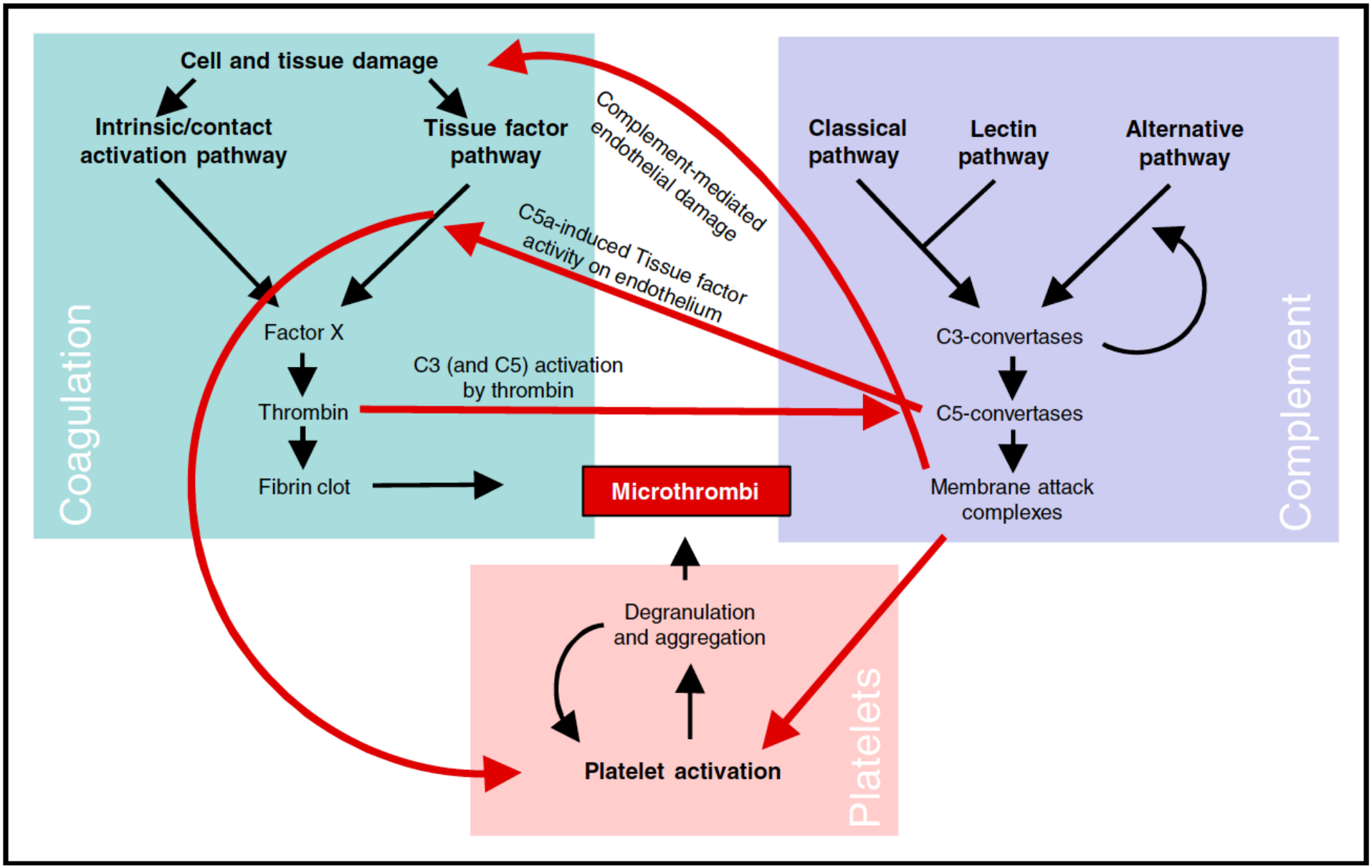



Courtesy of Marion Rabant

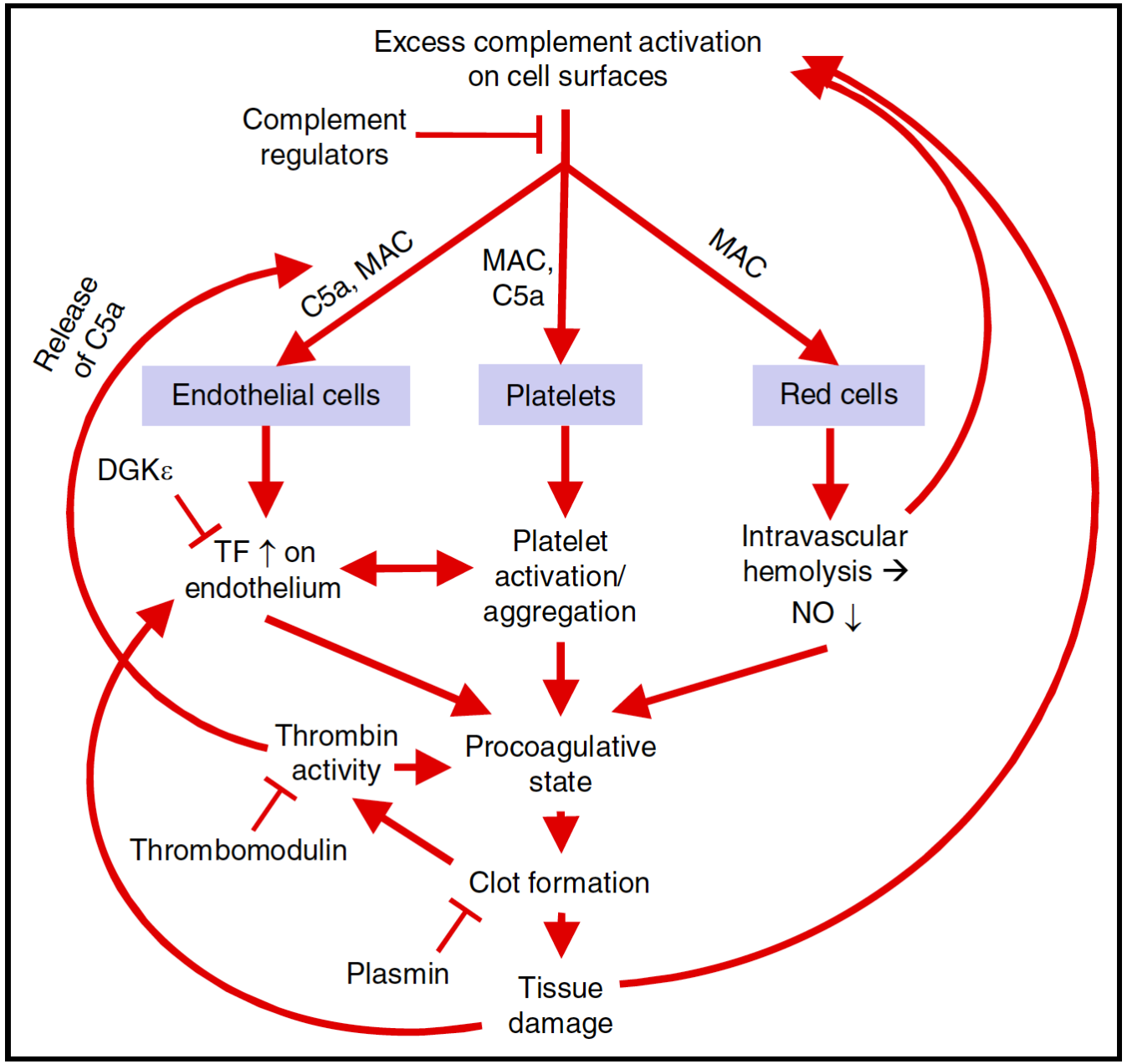
# Take-Home Message #1

**Whatever their mechanisms, known or not yet known, all categories of HUS are due to various endothelial cell injuries and lead to acute kidney dysfunction.**

# aHUS - HUS:
# role of complement




T Sakari Jokiranta, Blood 2017, 129: 2847-2856.



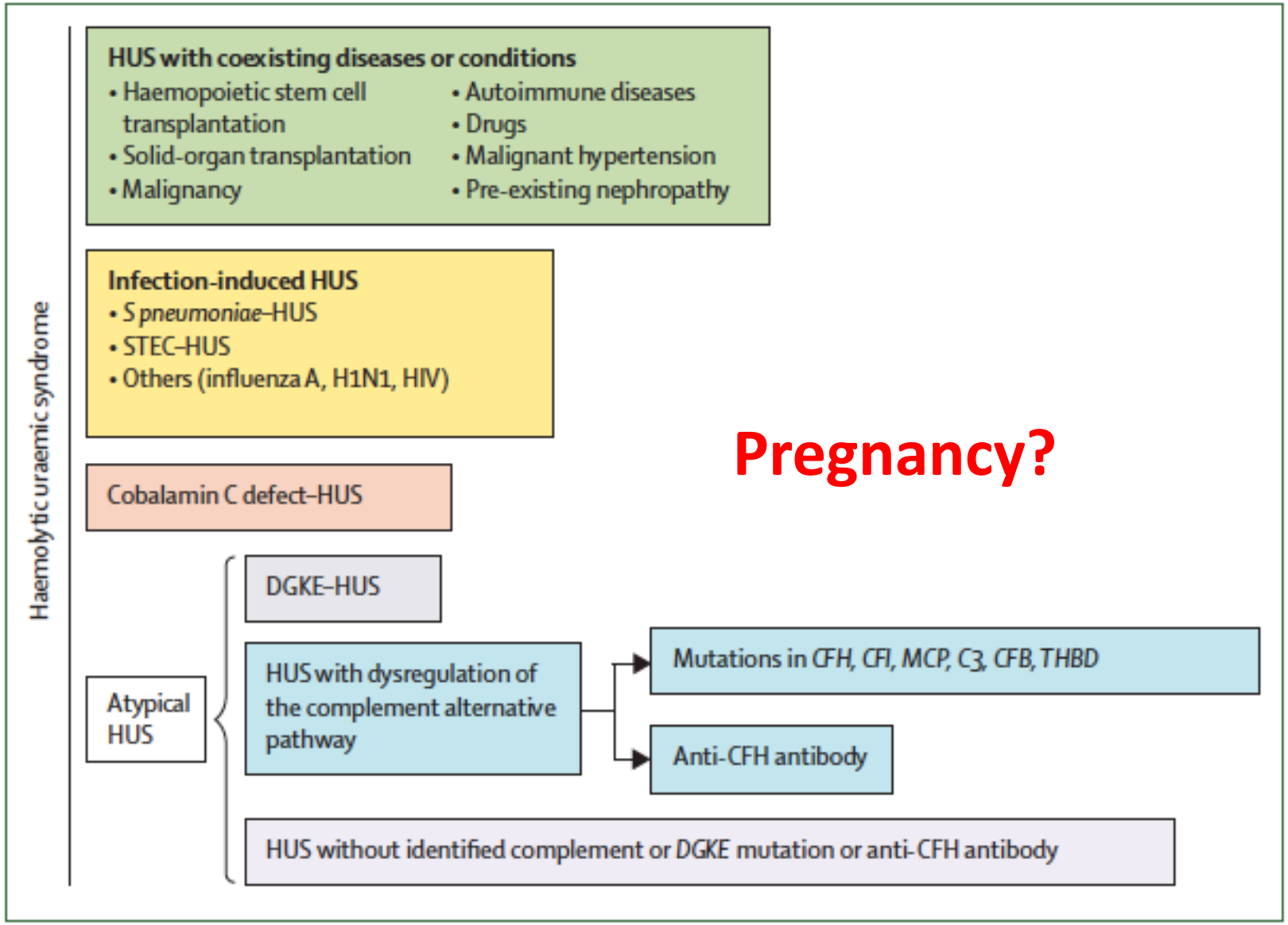

**T Sakari Jokiranta, Blood 2017, 129: 2847-2856.**

# Take-Home Message #2

**Whatever their specific mechanism, known or not yet known, most categories of HUS are characterized by a complex interplay between complement activation, endothelial cell injury and thrombosis.**

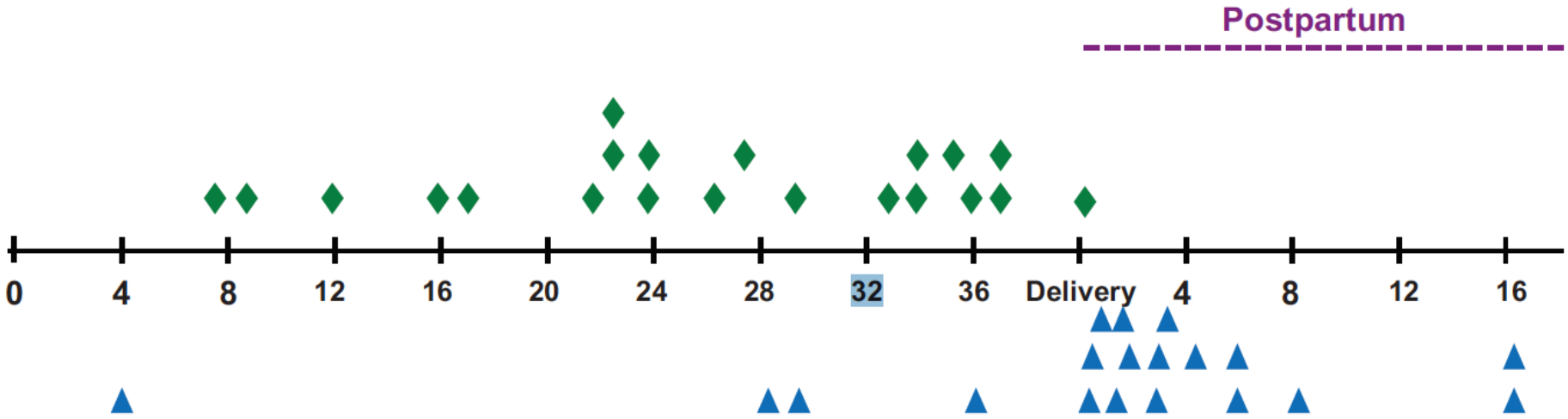
# TMA and Pregnancy

# HUS - TMAs




F Fakhouri et al, Lancet 2017, 390: 681-696.

# Pregnancy-associated aHUS




Complement-dysregulation-TMA in the French aHUS cohort

TTP due to ADAMTS13 deficiency

F Fakhouri et al, J Am Soc Nephrol 2010, 21: 859-867.

# Pregnancy-associated aHUS

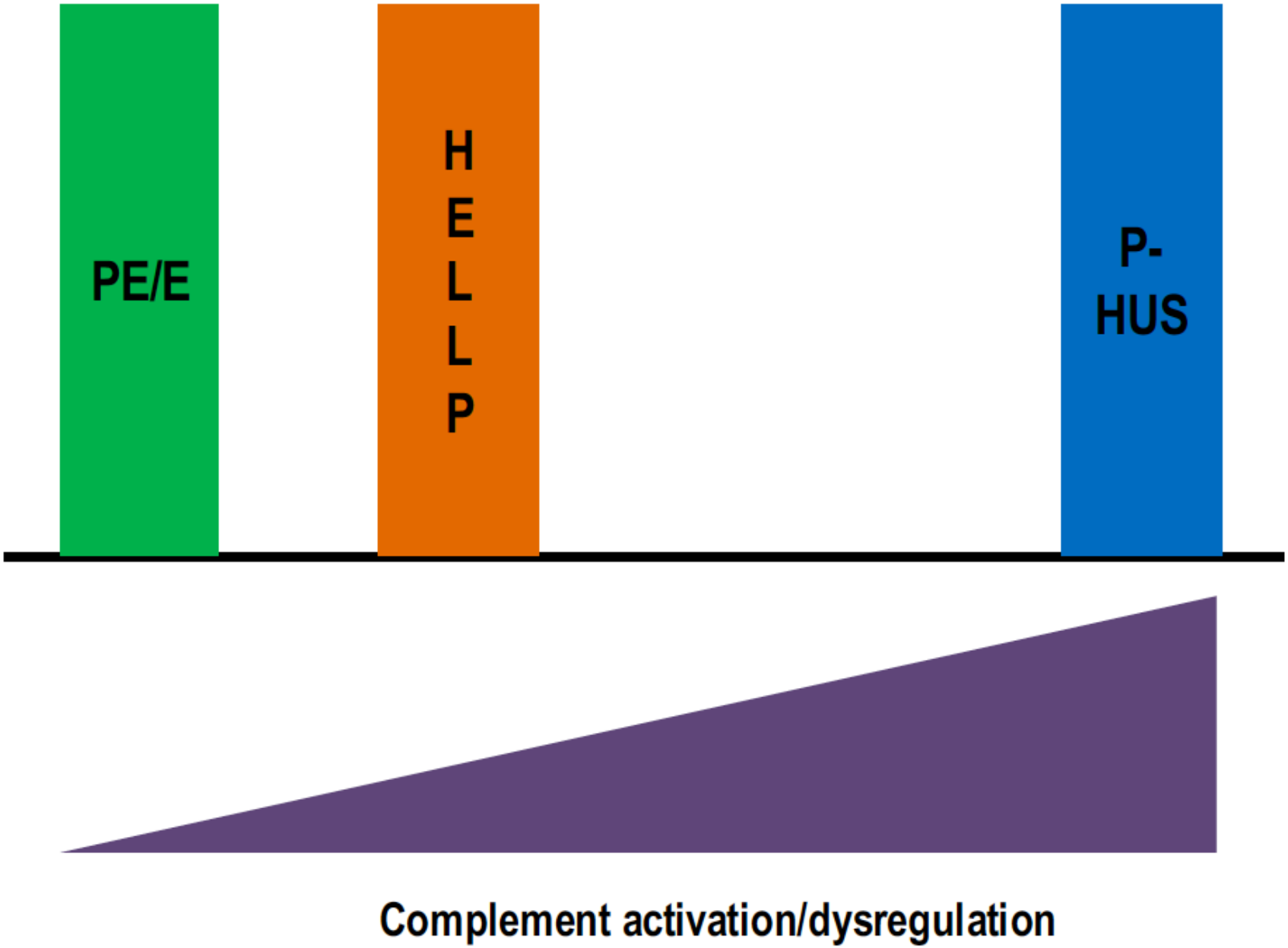
| | Patients with P-associated aHUS (n=21) | Patients with aHUS non related to pregnancy (n=35) | |
|---|---|---|---|
| **Age at aHUS onset (years)** | 26 ± 5 | 33 ± 12 | p < 0.05 |
| **Nb of pregnancies** | 2 ± 0.8 | 2.3 ± 1.5 | NS |
| **Nb of patients reaching ESRD < 6 months after aHUS** | 11 (52%) | 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 |

**F Fakhouri et al, J Am Soc Nephrol 2010, 21: 859-867.**

# TMA and pregnancy

| | |
|---|---|
| Pregnancy–HUS | In a retrospective study,[72] among 21 patients with pregnancy–HUS (79% in post-partum), 52% reached end-stage renal disease within 6 months of onset *vs* 57% in women with non-pregnancy-related atypical HUS, and 86% had mutations of complement genes *vs* 74% in female patients with non-pregnancy-related atypical HUS. Patients with pregnancy–HUS might have disease relapse outside pregnancy.[73] Few cases of eculizumab efficacy in pregnancy–HUS or post-partum–HUS.[73,74] |
| Differential diagnosis of pregnancy–HUS | |
| HELLP syndrome, pre-eclampsia, or eclampsia | Endothelial cell injury results from an imbalance between antiangiogenic (soluble Flt1 and endoglin) and angiogenic factors (placental growth factor).[75] Initial cause of the disease is unknown but probably multifactorial. Variants of complement genes reported in 10–12% of patients with HELLP syndrome,[76] in 18% of patients with SLE-associated or APS-associated pre-eclampsia, and in 8% of patients with non-immune pre-eclampsia.[77] |
| Post-partum haemorrhage | High risk of renal cortical necrosis in the setting of gravid renal endothelium.[78] Current data not supportive of a definitive role of complement. |

**F Fakhouri et al, Lancet 2017, 390: 681-696.**




F Fakhouri, Tranfus Apher Sci 2016, 54: 199-202.

**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) |

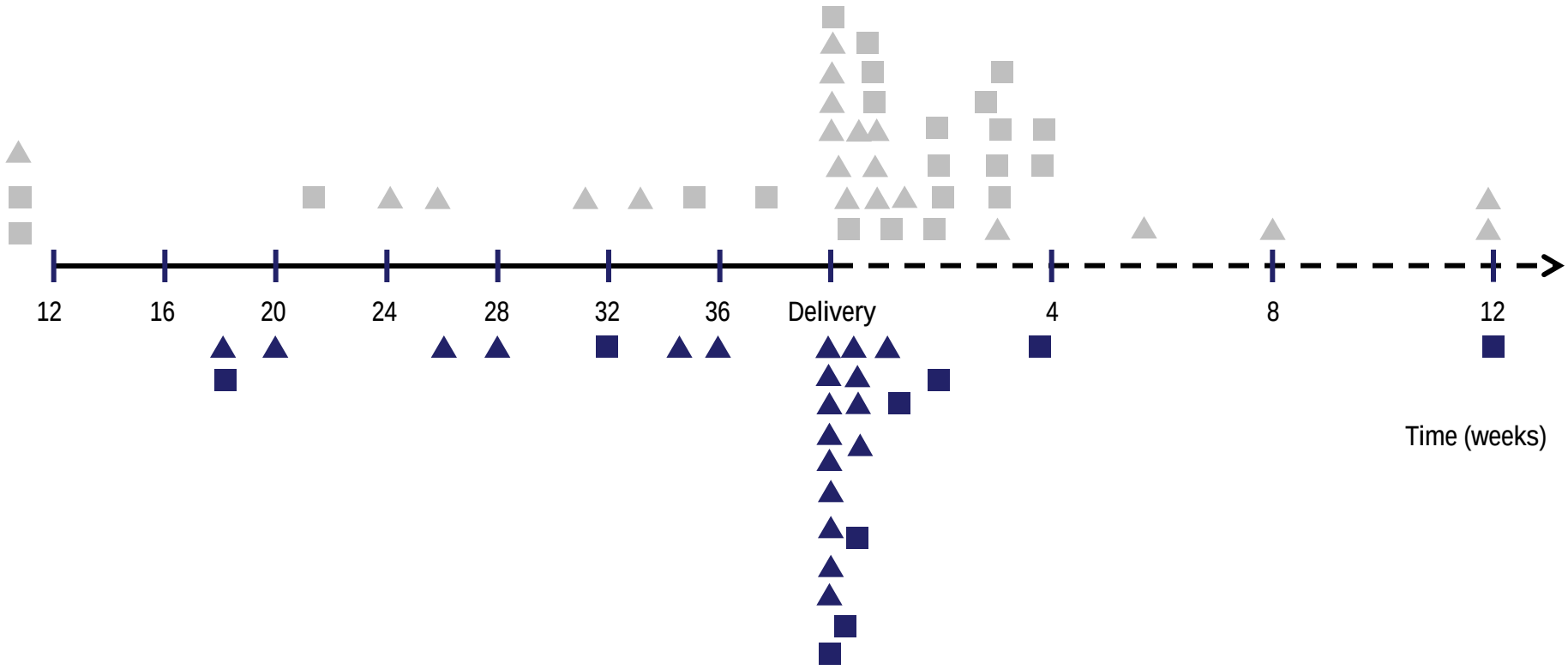
**A Bruel et al, Clin J Am Soc Nephrol 2017, 12: 1237-1247.**

**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) |

**A Bruel et al, Clin J Am Soc Nephrol 2017, 12: 1237-1247.**

Figure 1




**A Bruel et al, Clin J Am Soc Nephrol 2017, 12: 1237-1247.**

**Table 5. Main characteristics of 87 patients with pregnancy-associated hemolytic uremic syndrome with (*n*=49) or without complement gene variants (*n*=38)**

| Characteristics | Complement Gene Variant Detected (*n*=49) | No Complement Gene Variant Detected (*n*=38) | *P* Value |
|---|---|---|---|
| **At presentation** | | | |
| Age, yr | 28±6 | 30±6 | 0.06 |
| Personal history of HUS | 4 (8%) | 3 (9%) | 1 |
| Onset in the postpartum | 39 (79%) | 28 (72%) | 0.49 |
| Need for dialysis | 35 (81%) | 21 (58%) | 0.02 |
| Neurologic involvement | 5 (12%) | 2 (6%) | 0.38 |
| Plasma exchange | 30 (79%) | 26 (77%) | 0.80 |
| **During follow-up, *n*=74** | | | |
| Duration of follow-up, yr | 6.2±3.6 | 6.7±4.1 | 0.75 |
| Relapse | 13 (38%) | 5 (16%) | 0.04 |
| CKD | 9 (21%) | 6 (18%) | 0.81 |
| ESRD | 29 (64%) | 12 (36%) | 0.01 |

Data are mean ± SD for continuous variables, and *N* (%) for categorical variables. HUS, hemolytic uremic syndrome.

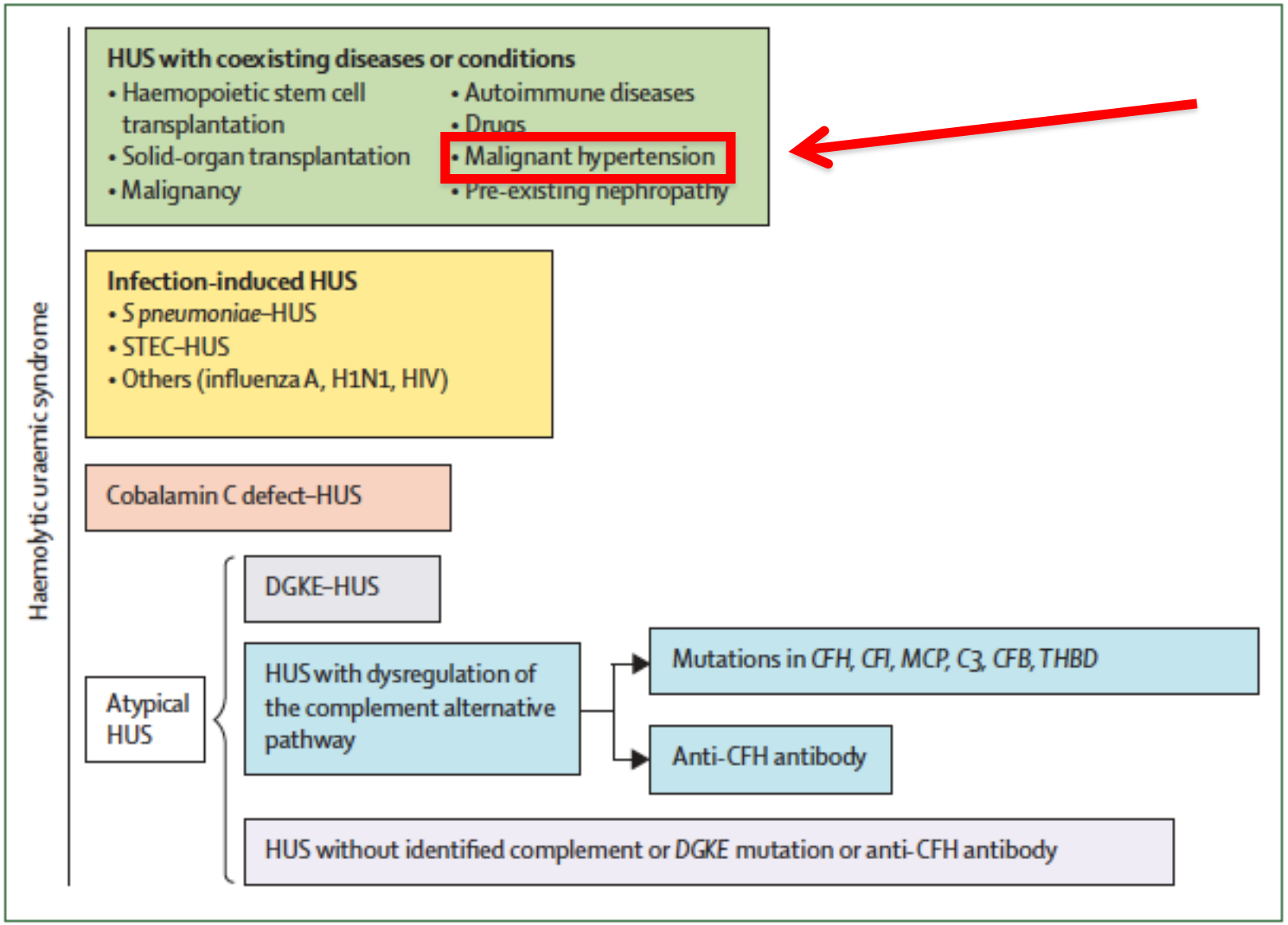
**A Bruel et al, Clin J Am Soc Nephrol 2017, 12: 1237-1247.**

# Take-Home Message #3

**Currently, aHUS occurring during pregnancy or the post-partum period is considered to be similar to aHUS occurring in a non-pregnant woman.**

# aHUS - HUS:
# role of complement

# HUS - TMAs




F Fakhouri et al, Lancet 2017, 390: 681-696.

# Hypertension-MOD

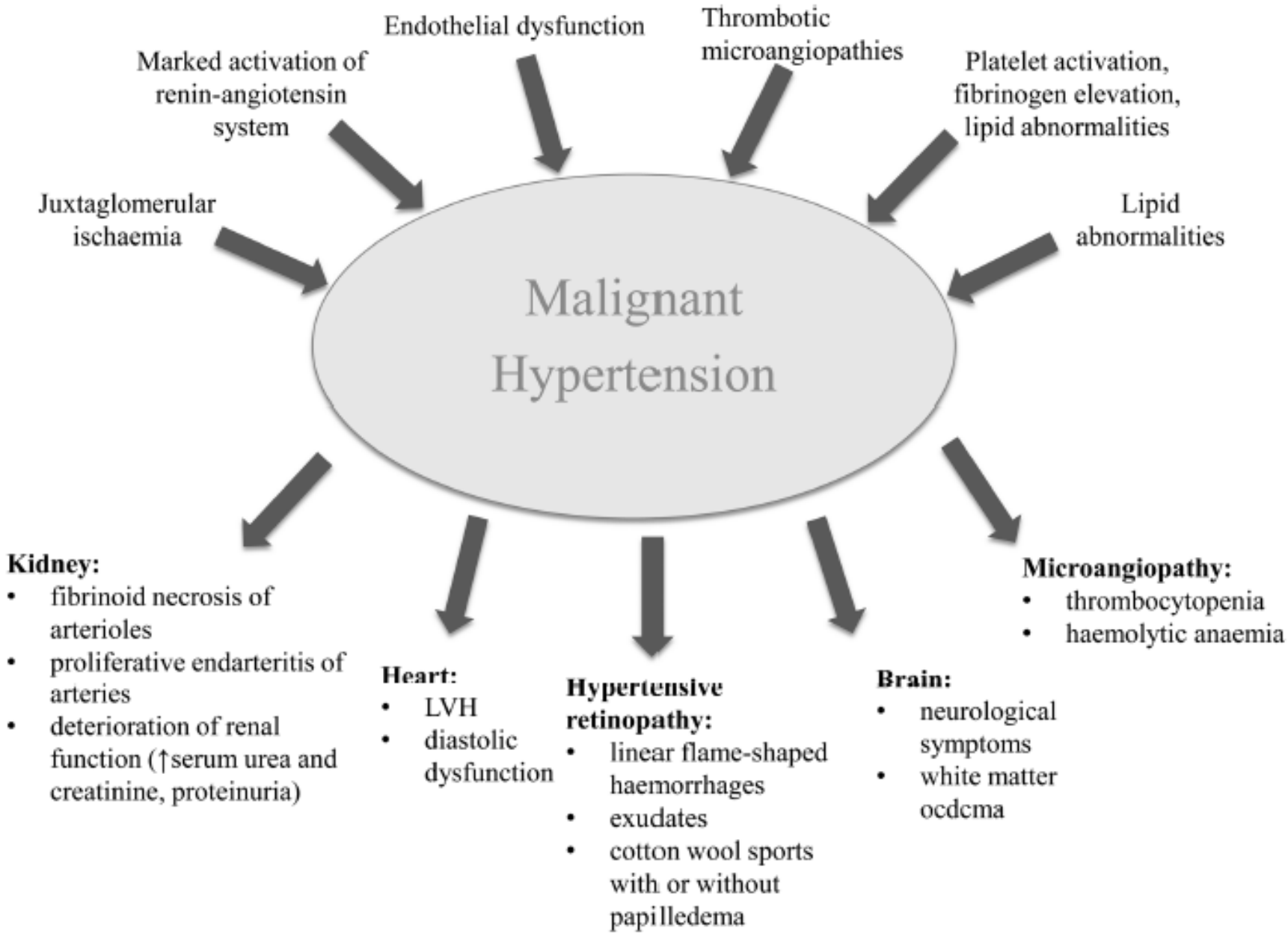
**Table 1.** Main criteria for target organ involvement in hypertension-MOD

| | *Criteria* |
|---|---|
| Kidney | Impaired renal function<br>Creatinine elevation >30% with respect to recent assay in the absence of obvious cause<br>Proteinuria (usually modest and non specific) |
| Heart | Marked LVH<br>Impaired systolic function (especially global longitudinal stain)<br>Abnormalities of repolarization on ECG. Increased troponin |
| Brain | Ischaemic or haemorrhagic stroke<br>Extensive white matter lesions, microbleeds before 60 years<br>PRES |
| Microangiopathy | Haemolysis |

Abbreviations: ECG, electrocardiogram; LVH, left ventricular hypertrophy; PRES, posterior reversible encephalopathy syndrome.



A Cremer et al, J Hum Hypertens 2015, 8:463-466






A Shantsila et al, Am J Hypertens, 2017, 30: 543-549

# TMA and malignant hypertension

**Table 1 | Baseline clinical features and laboratory evaluation**

| Patient No. | Age (yr) | Sex | BP (mm Hg) | SCr (μmol/l) | uProt (g/d) | uRBC | ESRD | Hb (mmol/l) | LDH (U/l) | MAHA[a] | Platelets ($\times 10^9$/l)[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 38.4 | F | 184/140 | 1730 | NA | NA | Y | 5.1 | 1800 | Y | 224 |
| 2 | 40.3 | M | 205/114 | 1195 | 2.3 | Y | Y | 5.7 | 1104 | Y | 158 |
| 3 | 37.7 | M | 200/120 | 586 | 3.9 | Y | Y | 5.3 | 2125 | Y | 100 |
| 4 | 32.0 | F | 180/120 | 1138 | NA | NA | Y | 5.9 | 1486 | Y | 142 |
| 5 | 65.0 | M | 195/105 | 162 | 1.5 | Y | N | 7.9 | 271 | N | 98 |
| 6 | 41.1 | F | 180/120 | 334 | 0.7 | Y | Y | 7.5 | 291 | N | 285 |
| 7 | 28.5 | F | 224/122 | 1065 | 1.6 | Y | Y | 5.1 | 298 | N | 228 |
| 8 | 27.9 | M | 240/150 | 673 | 1.6 | Y | Y | 7.9 | 165 | N | 133 |
| 9 | 44.0 | F | 220/120 | 649 | 0.4 | Y | Y | 8.2 | 339 | N | 340 |

**SAMEG Timmermans et al, Kidney Int 2017, 91: 1420-1425.**

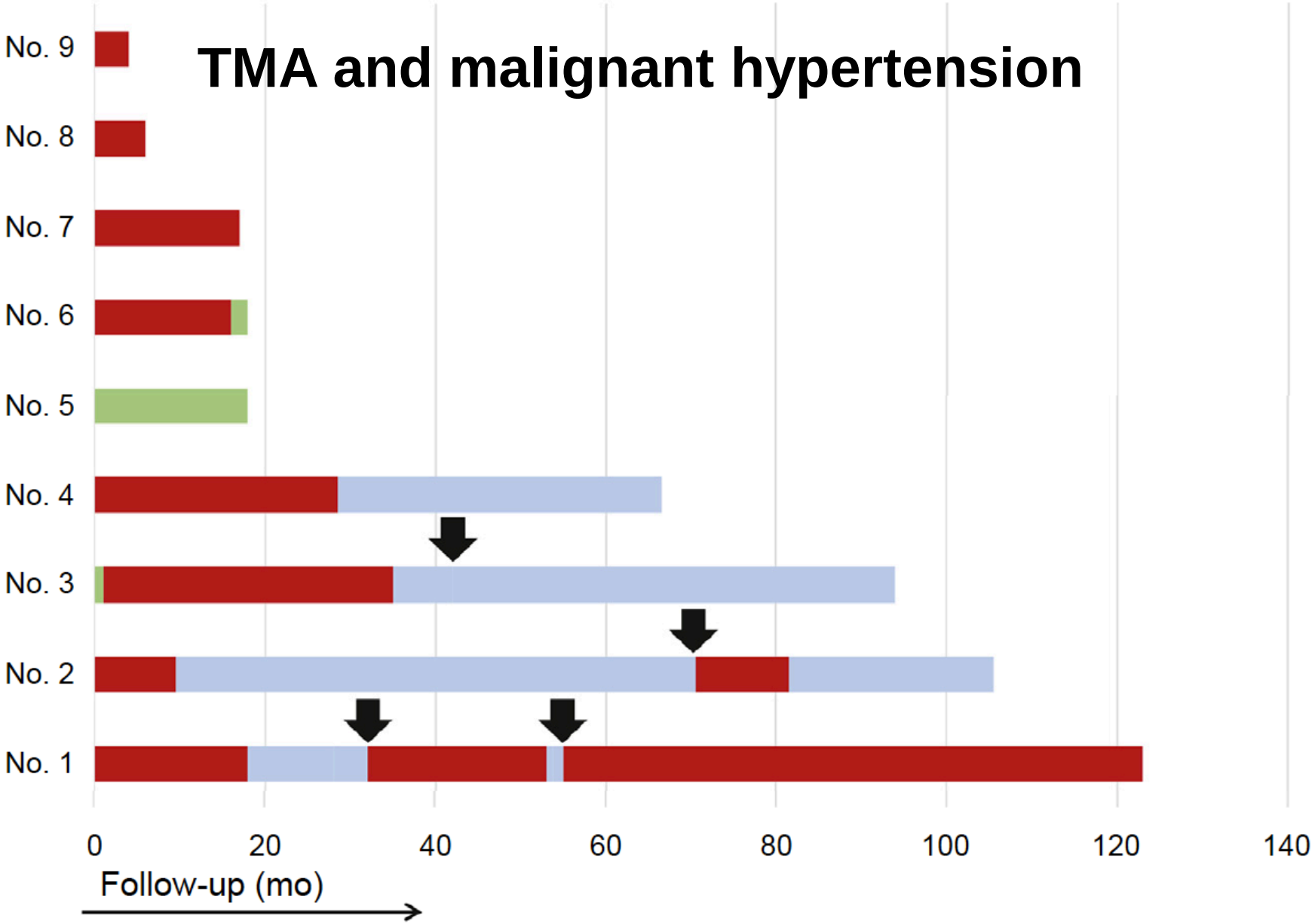
# TMA and malignant hypertension

**Table 2 | Complement abnormalities**

| Patient No. | Mutation(s) | *CFH*-H3[11] | FHAA | CP (%)[a] | AP (%)[b] | sC5b-9 (ng/ml)[c] |
|---|---|---|---|---|---|---|
| 1 | *C3*-R161W[18] | N | Negative | 95 | 64 | 2800 |
| 2 | *CD46*-ΔD237/S238,[15] *CFH*-Q950H[11] | Y | Negative | 97 | 107 | 1000 |
| 3 | *C3*-R161W[18] | Y | ND | 94 | 97 | 640 |
| 4 | *CFH*-C853R[16] | Y | ND | 104 | 71 | 1840 |
| 5 | No mutations | N | ND | 99 | 99 | 1800 |
| 6 | *CFI*-N151S[14] | N | ND | 97 | 87 | 4200 |
| 7 | *C3*-R161W,[18] Δ*CFHR1*-*CFHR3*[d] | N | Negative | 110 | 62 | 1840 |
| 8 | No mutations | Y | Negative | 90 | 74 | 440 |
| 9 | No mutations | N | Negative | 113 | 110 | 3800 |

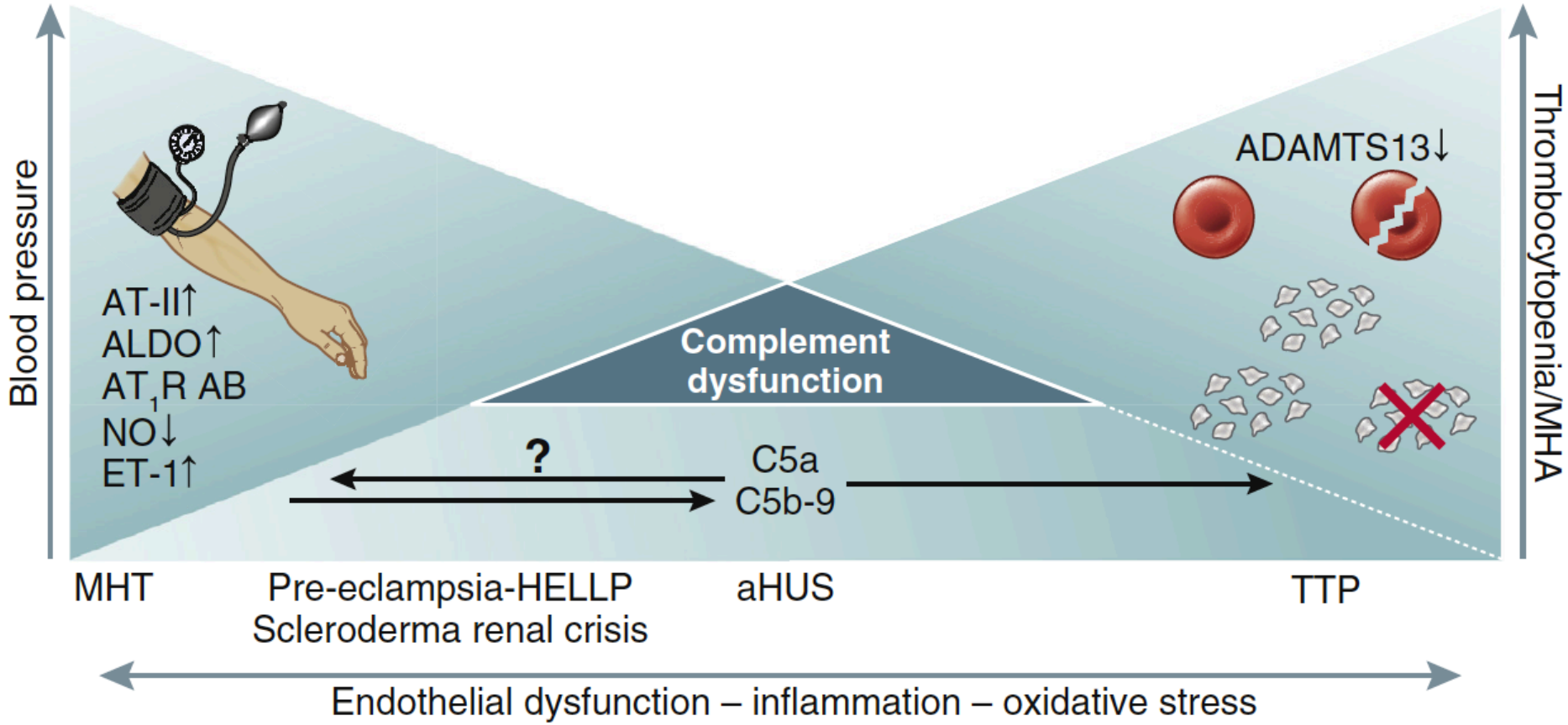
**SAMEG Timmermans et al, Kidney Int 2017, 91: 1420-1425.**

# TMA and malignant hypertension




SAMEG Timmermans et al, Kidney Int 2017, 91: 1420-1425.

# TMA ⇄ Malignant Hypertension





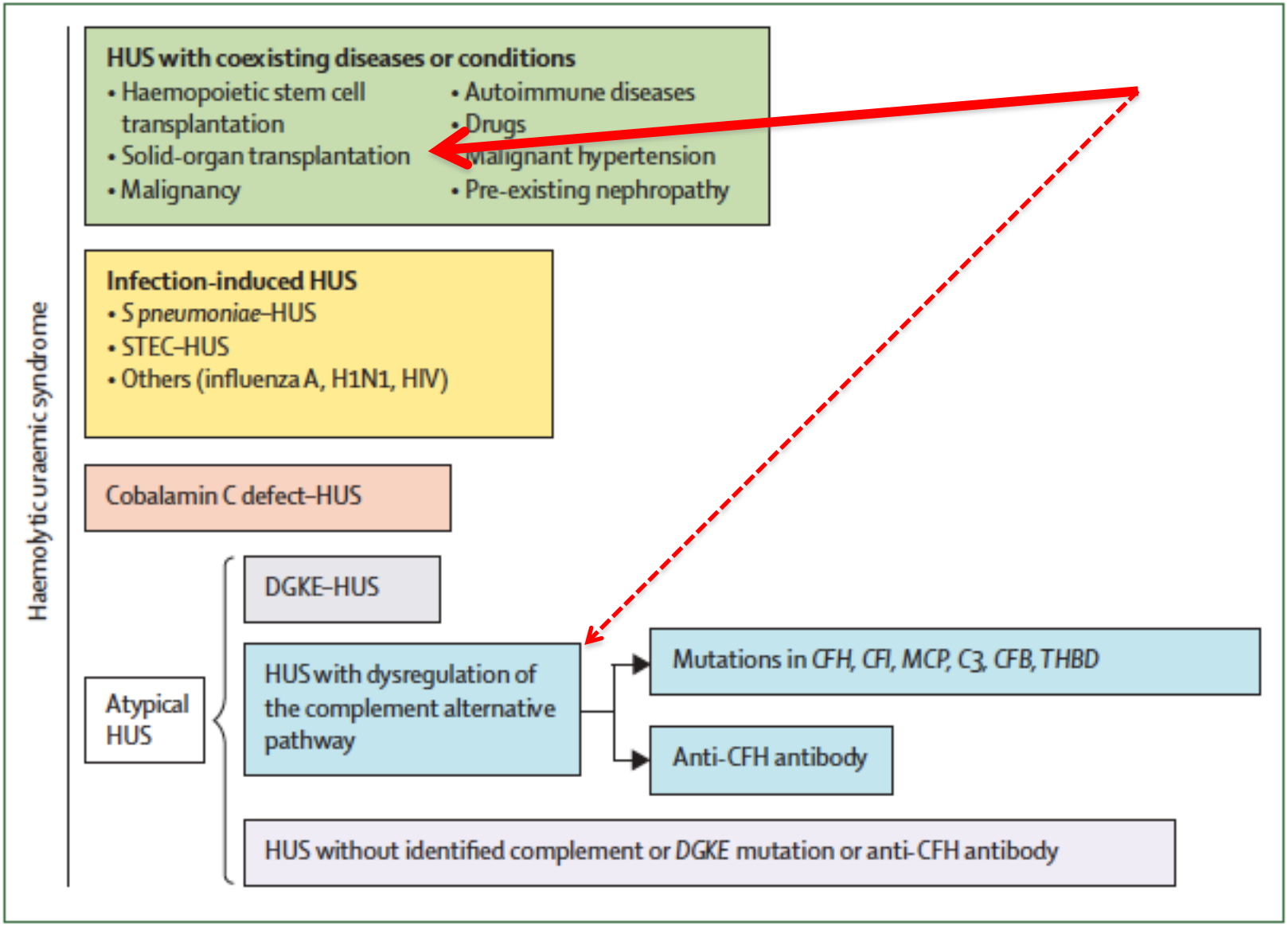

S Van Laecke et al, Kidney Int 2017, 91:1271-1274

# Take-Home Message #4

**There is some evidence, but not yet confirmed, that some patients developing malignant hypertension and TMA do have a genetic susceptibility.**

# TMA and Kidney Transplantation

# HUS - TMAs




F Fakhouri et al, Lancet 2017, 390: 681-696.

# Driving force

*CFH/CFHR1*
*CFH*
*C3*
*CFB*

Isolated *CFI*
Positive anti-CFH Ab
Homozygous *gtgt* CFH
Combined *MCP*

Isolated *MCP*
Negative anti-CFH Ab

Complement activation
Endothelial insults

Brain death

I/R injury

Rejection

IS drugs

Infections

# Precipitating factors

J Zuber et al, Nat Rev Nephrol 2011, 7: 23-35.

# Differential diagnosis of TMA post-KT

**Mechanical hemolytic anemia +**
**Peripheral thrombocytopenia +**
**Acute renal failure (AKI).**

- **Post-transplant anemia**
- **Elevated LDH post-transplantation:**
  - **Severe delayed graft function (acute tubular necrosis),**
  - **Post-transplant lymphoproliferative disease,**
  - ***Pneumocystis jiroveci* pneumonia,**
  - **Partial or patchy infarction/cortical necrosis ( severe ABMR),**
  - **Drugs (CNI, mTOR inhibitors, IVIg etc…).**

**R Boothpur et al, Am J Transplant 2008, 8: 862-865.**

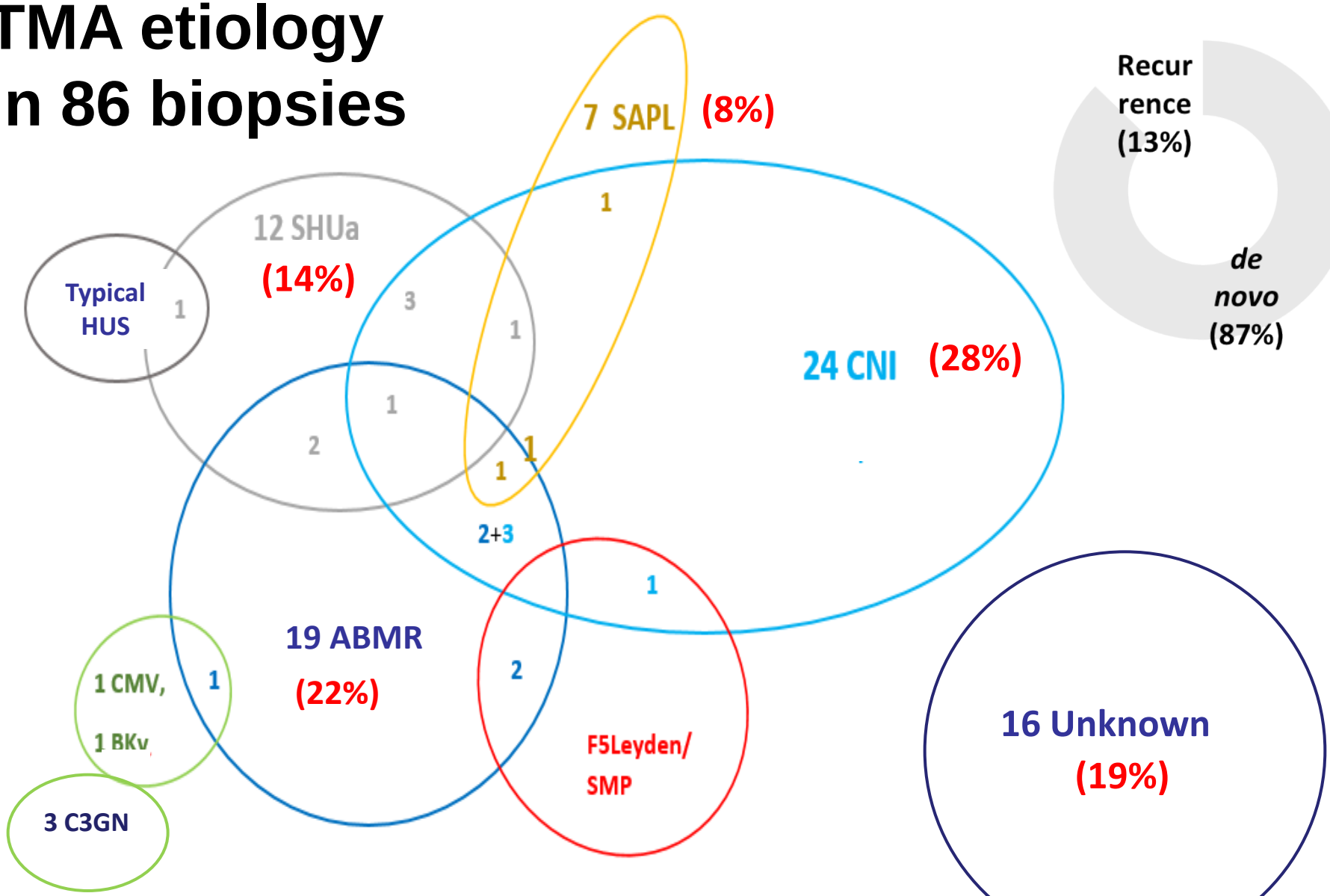
# Differential diagnosis of TMA post-KT

**Mechanical hemolytic anemia +**
**Peripheral thrombocytopenia +**
**Acute renal failure (AKI).**

- **Thrombocytopenia**
- **Acute kidney injury:**
  - **Rejection with vascular lesions,**
  - **CNI nephrotoxicity**
  - **Drug nephrotoxicity**

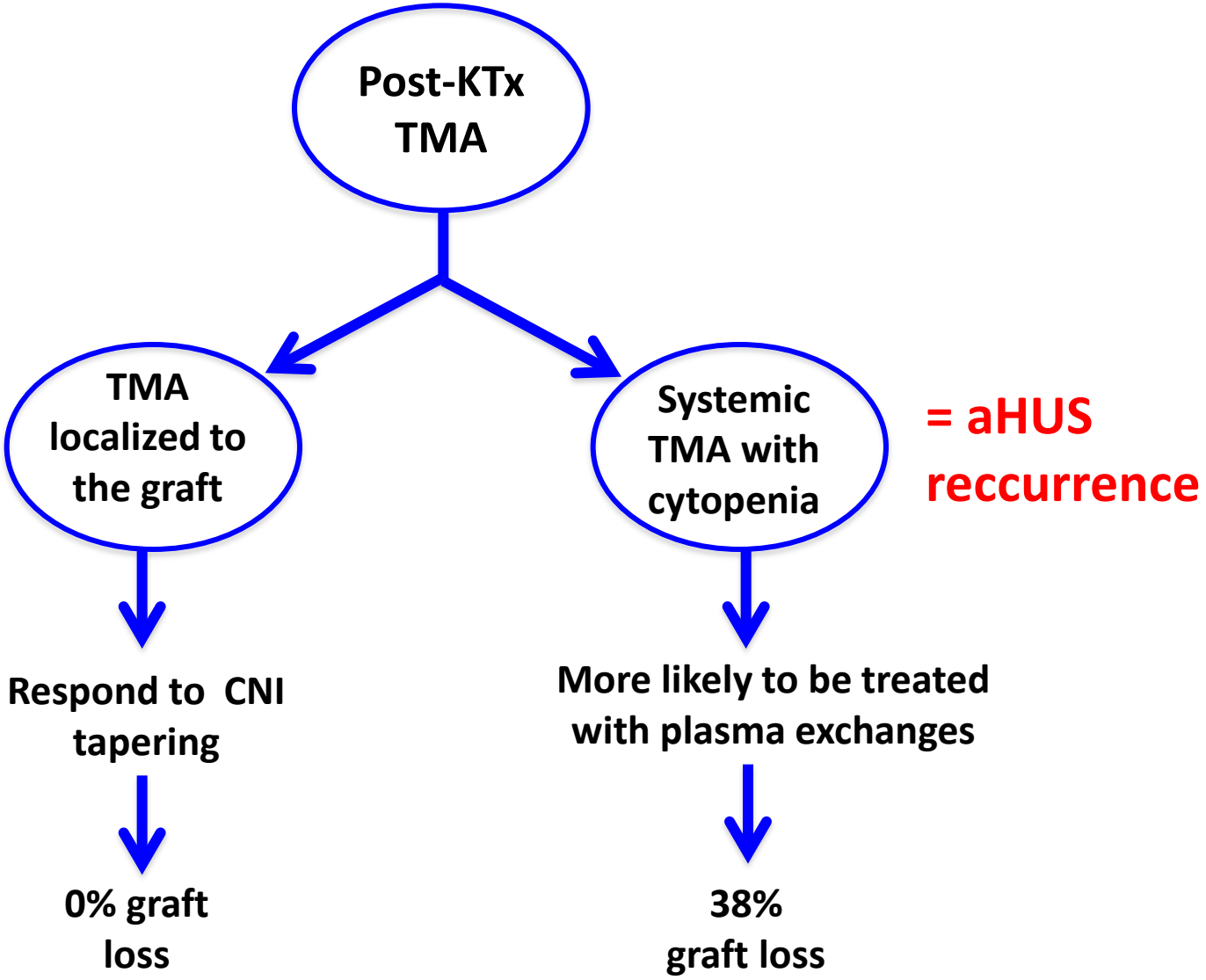
**R Boothpur et al, Am J Transplant 2008, 8: 862-865.**

# TMA etiology in 86 biopsies




**Multiples and associated-etiologies!**

K Dessaix et al, Manuscript in preparation




J Schwimmer et al, Am J Kidney Dis 2003, 41: 471-479.

**Table 1** | Risk of aHUS recurrence according to the implicated genetic abnormality

| Gene | Protein location | Functional impact | Mutation frequency in aHUS (%) | Recurrence frequency after transplantation (%) |
|---|---|---|---|---|
| *Mutation* | | | | |
| CFH | Plasma | Loss | 20–30 | 75–90 |
| CFI | Plasma | Loss | 2–12 | 45–80 |
| CFB | Plasma | Gain | 1–2 | 100 |
| C3 | Plasma | Gain | 5–10 | 40–70 |
| MCP | Membrane | Loss | 10–15 | 15–20 |
| THBD | Membrane | Loss | 5 | 1 case |
| *Genetic polymorphism (frequency in control populations)* | | | | |
| Homozygous *CFHR1*del (3–8%) | Circulating | Undetermined | 14–23 (>90% in patients with anti-CFH antibodies) | NA |

J Zuber et al, Nat Rev Nephrol 2011, 7: 23-35.

# TMA after transplantation: really *de novo*?

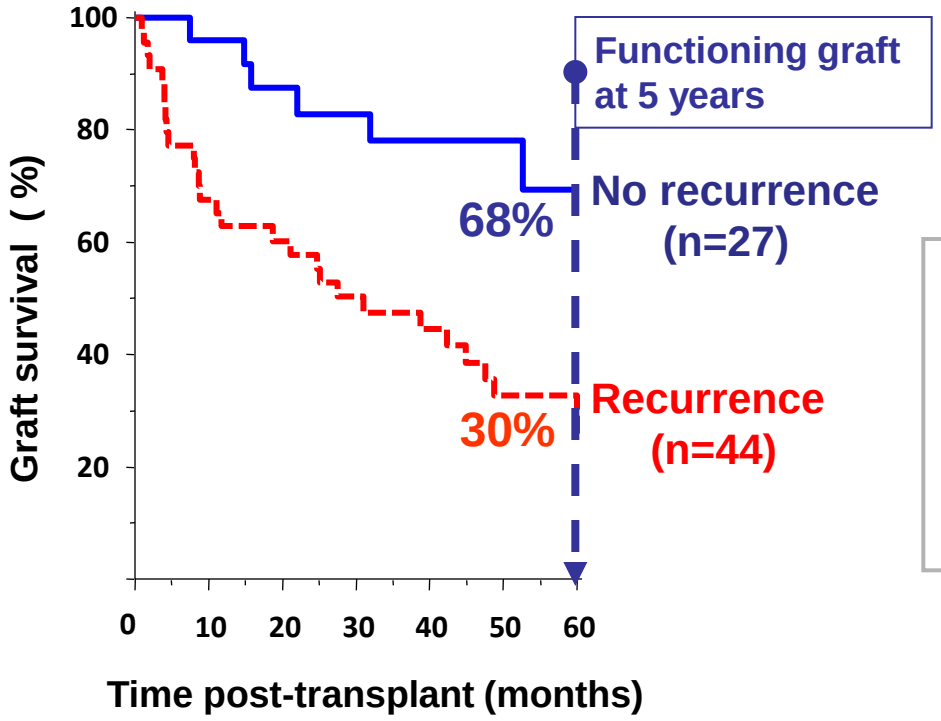
**Table 3:** Genetics abnormalities in the 7 patients

| Patient | Cause of ERSD | Mutation | Protein domain | Mutation characteristic |
|---|---|---|---|---|
| CFH | | | | |
| 1 | NAS | p.Asn516Lys (c.1548T>A) | SCR9 | SCR9 is implicated binding of CFH to the C3c and heparin |
| 2 | CrGN | p.Gln950His (c.2850G>T) | SCR16 | SCR16 is implicated binding of CFH to C3b/C3d, as well as to endothelial cells. Q950H has been reported in one patient with aHUS (28) |
| 3 | CrGN | p.Lys1186His (c.3557A>C) | SCR 20 | SCR20 is highly implicated binding of CFH to C3b/C3d, as well as to endothelial cells |
| CFI* | | | | |
| 4 | IgAN | p.Ser90Asn (c.269G>A); S72N | FIMAC | Associated with a reduced CFI concentration seem to result in quantitative defect |
| 1 | NAS | p.Gly162Asp (c.485G>A); G144D | CD5 | Associated with a reduced CFI concentration seem to result in quantitative defect |
| 5 | NAS | p.Ile416Leu (c.426A>C); I398L | SP | Associated with a normal CFI concentration; presumed functional deficiency has not yet been defined; reported in one patient with aHUS (4) |
| 6 | Und | p.Ile306Val (c.916A>G); I288V | LDLRA-2 | Associated with a normal CFI concentration; presumed functional deficiency has not yet been defined |
| 3 | CrGN | p.Ile340Thr (c.1019T>C); I322T | Between Heavy and light chain | I322T has been reported in one patient with aHUS (32) Complete loss C3b cofactor activity (33) |
| 7 | MPGN | IVS12 + 5 (c.1536 + 5 G>T) | Spice defect | Previously reported in patients with aHUS (4,6) |

**M Le Quintrec et al, Am J Transplant 2008, 8: 1694-1701.**

# 2/3 of aHUS patients experienced post-transplant recurrence which significantly impaired graft outcome

**71 kidney grafts in 57 aHUS patients (>18 y at onset) transplanted in France between 1995 and 2009**



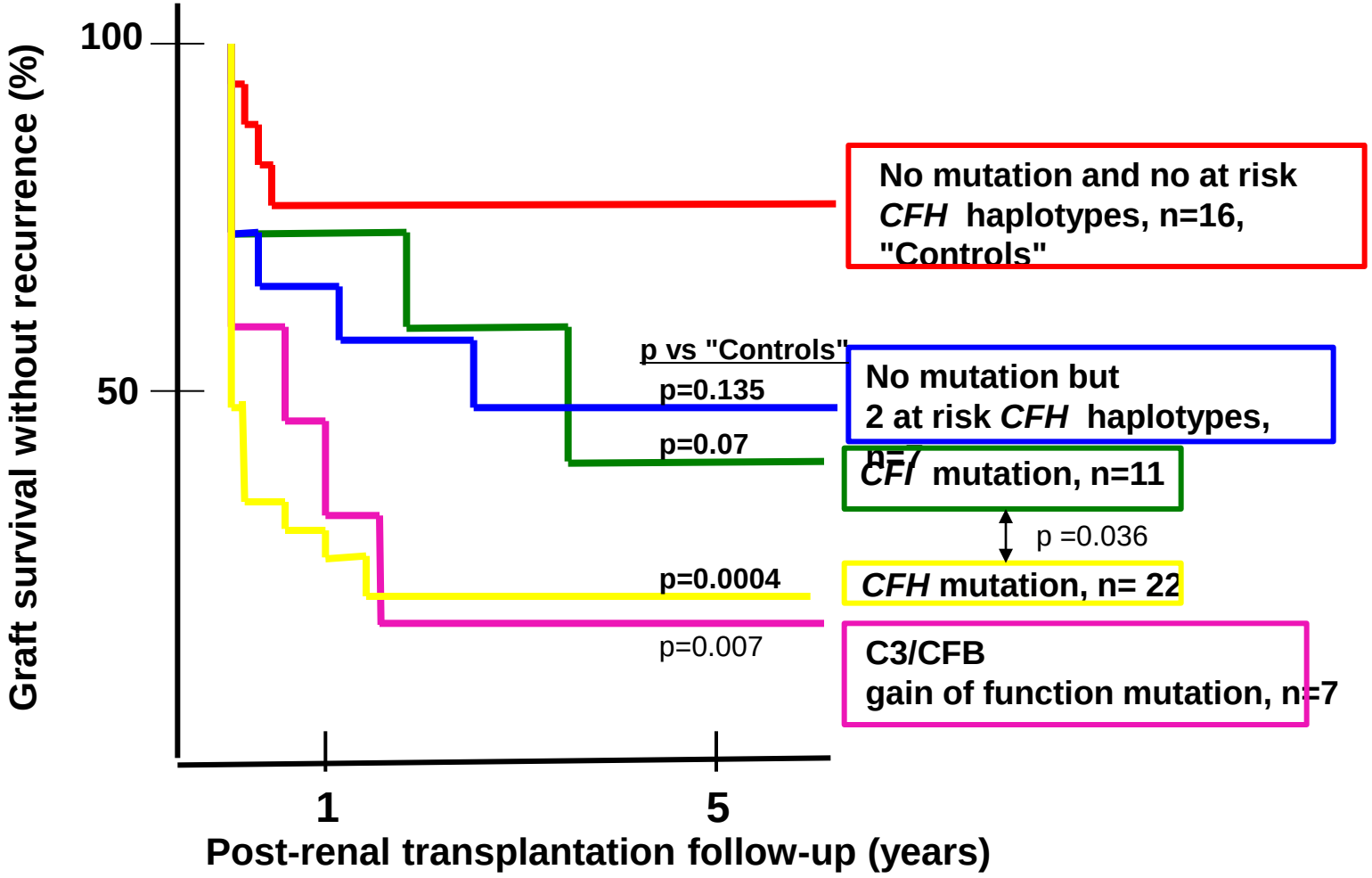

- Post-transplant recurrence occurred in 44/71 grafts (62%)
- At 5 years, graft survival was 30% in patients with recurrence versus 68% in patients without recurrence

**RR 4.89 (1.30-13.81), p=0.001**

M Le Quintrec et al, Am J Transplant 2013, 13: 663-675.

France

# Pre-transplant assessment of post-transplant recurrence risk relies on genetics

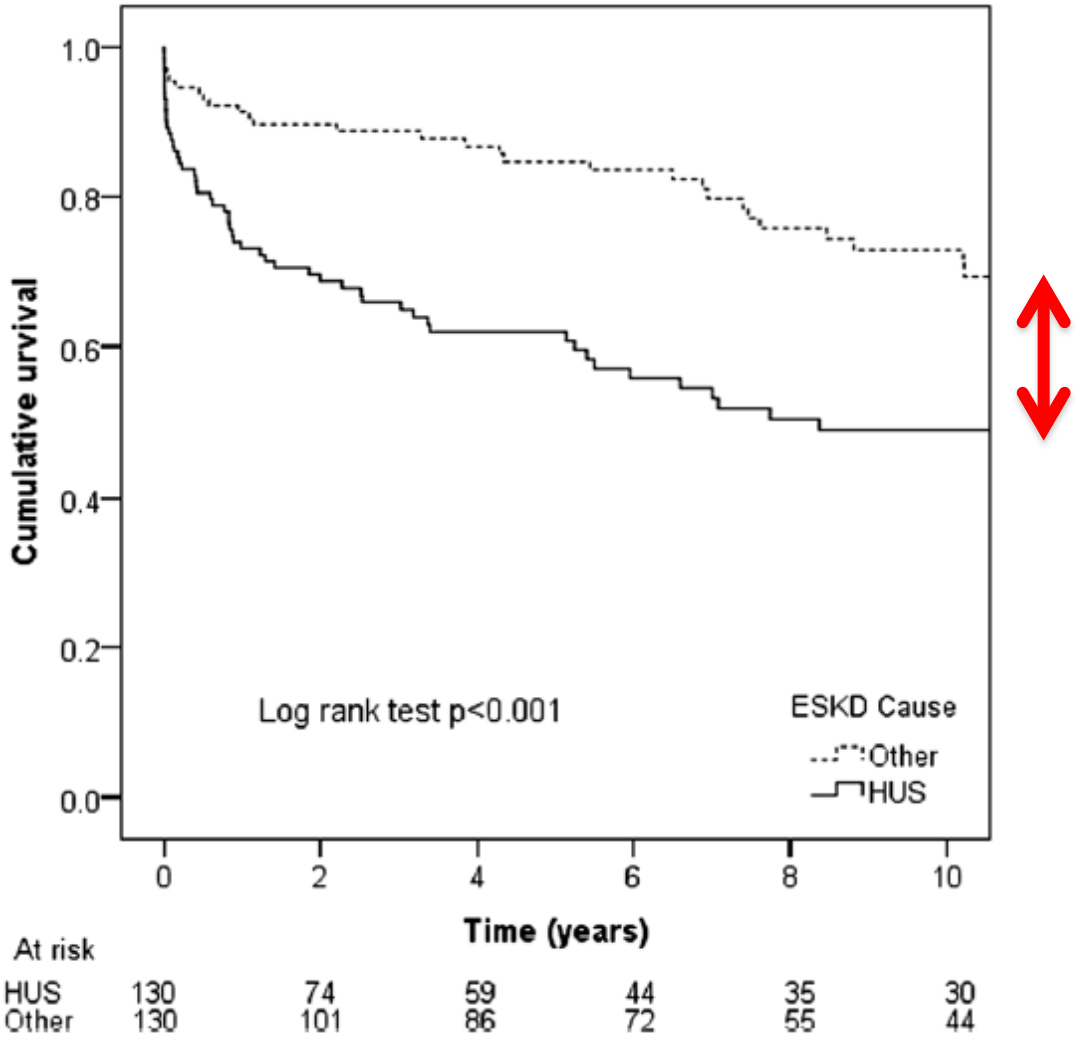



M Le Quintrec et al, Am J Transplant 2013, 13: 663-675.

France

Australia/NZ

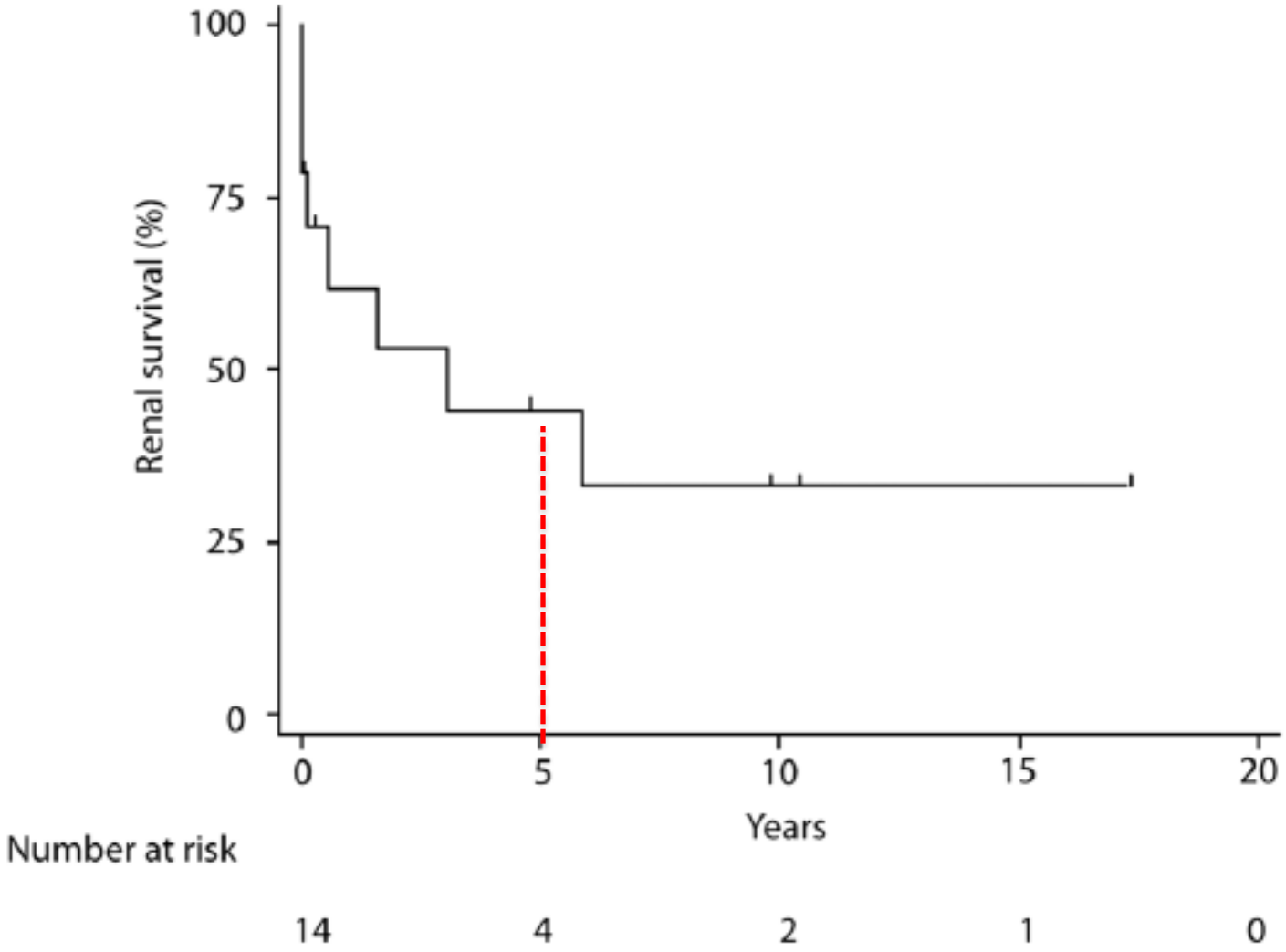
# ANZDATA registry data




A Tang et al, BMC Nephrology 2012

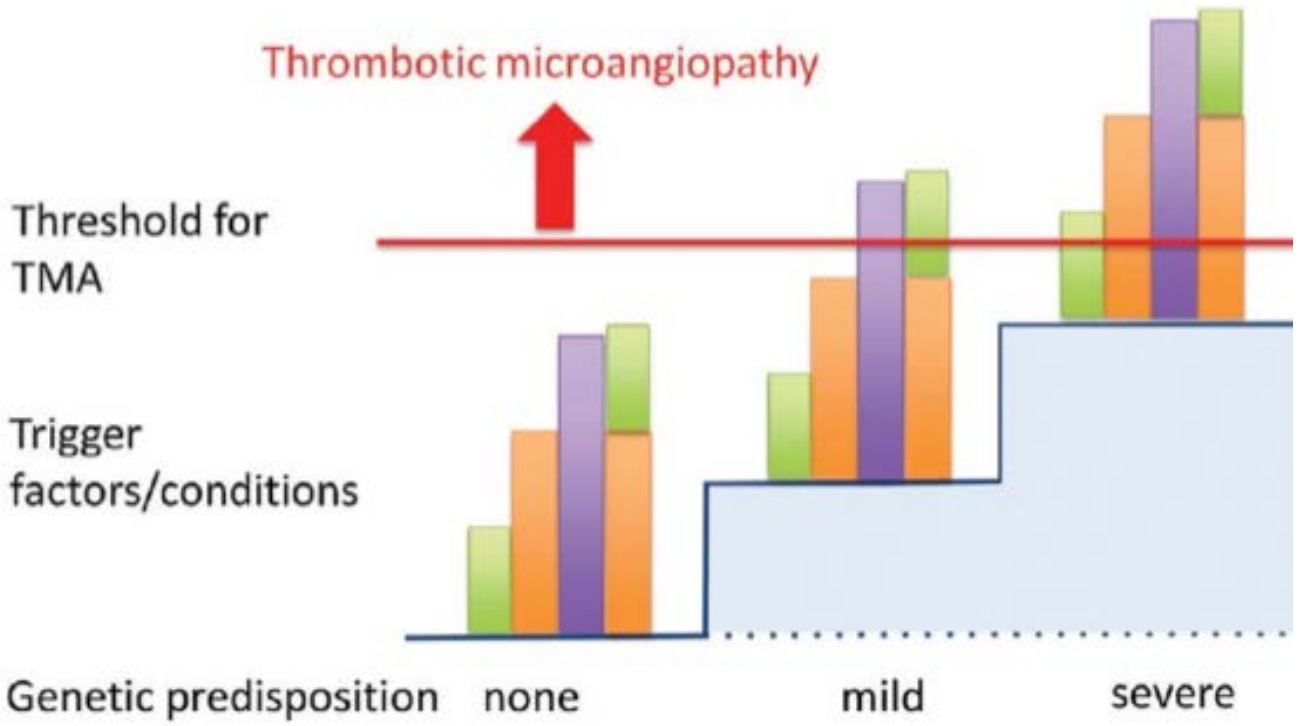
Australia

# Prognosis of aHUS before eculizumab era




AM Durkan et al, Arch Dis Child 2016, 101: 387-391.

# “Multiple hit” hypothesis

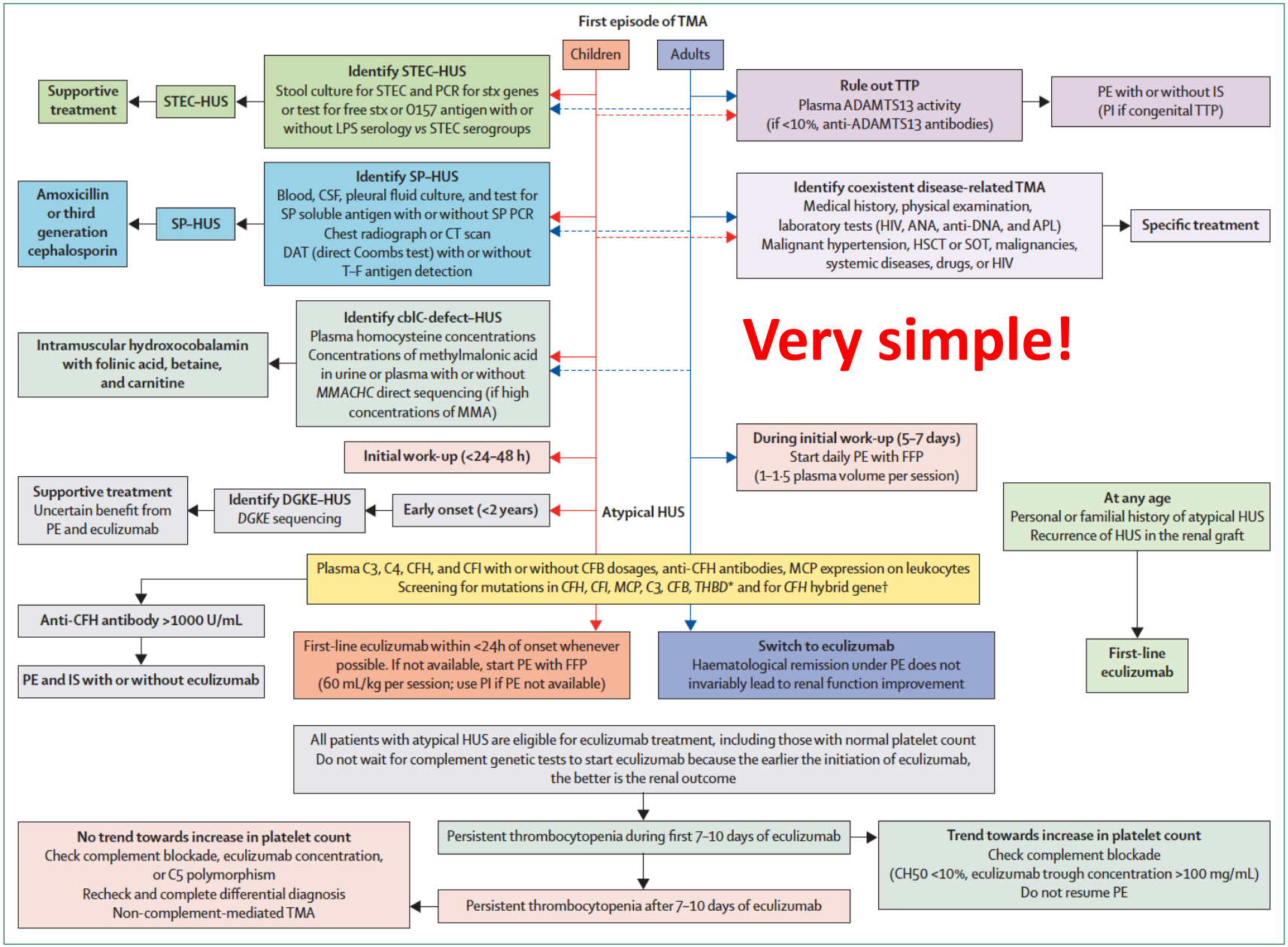



M Riedl et al. Semin Thromb Hemost 2014, 40:413-415.

# Take-Home Message #5

**TMA in the course of kidney transplantation is often related to acute humoral rejection and/or CNI nephrotoxicity but most severe cases are related to recurrence of aHUS.**

# aHUS: current treatment




F Fakhouri et al, Lancet 2017, 390: 681-696.

# The late 2000s: recommended schedule for PE/PI for aHUS at presentation and during the first month

Pediatr Nephrol (2009) 24:687–696
DOI 10.1007/s00467-008-0964-1

EDITORIAL COMMENTARY

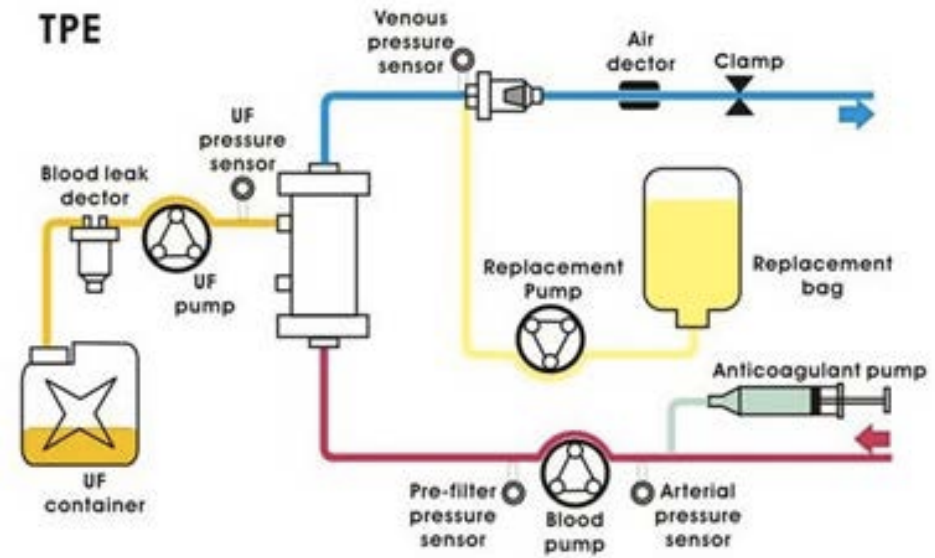
**Guideline for the investigation and initial therapy of diarrhea-negative hemolytic uremic syndrome**

Gema Ariceta · Nesrin Besbas · Sally Johnson · Diana Karpman · Daniel Landau · Christoph Licht · Chantal Loirat · Carmine Pecoraro · C. Mark Taylor · Nicole Van de Kar · Johan VandeWalle · Lothar B. Zimmerhackl · The European Paediatric Study Group for HUS

**Clinical Practice Guidelines for the management of atypical Haemolytic Uraemic Syndrome in the United Kingdom**

C. Mark Taylor, Sam Machin, Stephen J. Wigmore and Tim H. J. Goodship on behalf of a working party from the Renal Association, the British Committee for Standards in Haematology and the British Transplantation Society

*Institute of Human Genetics, Newcastle University, Central Parkway, Newcastle upon Tyne, UK*




**After 5 daily PE :**

**Platelet count < 150 mm3**

**Screat not decreased by ≥ 25%**

**Hemolysis persists (LDH > 2N)**

**G Ariceta et al, Pediatr Nephrol 2009. 24:687-696; C Taylor et al, BJH Guideline 2009**

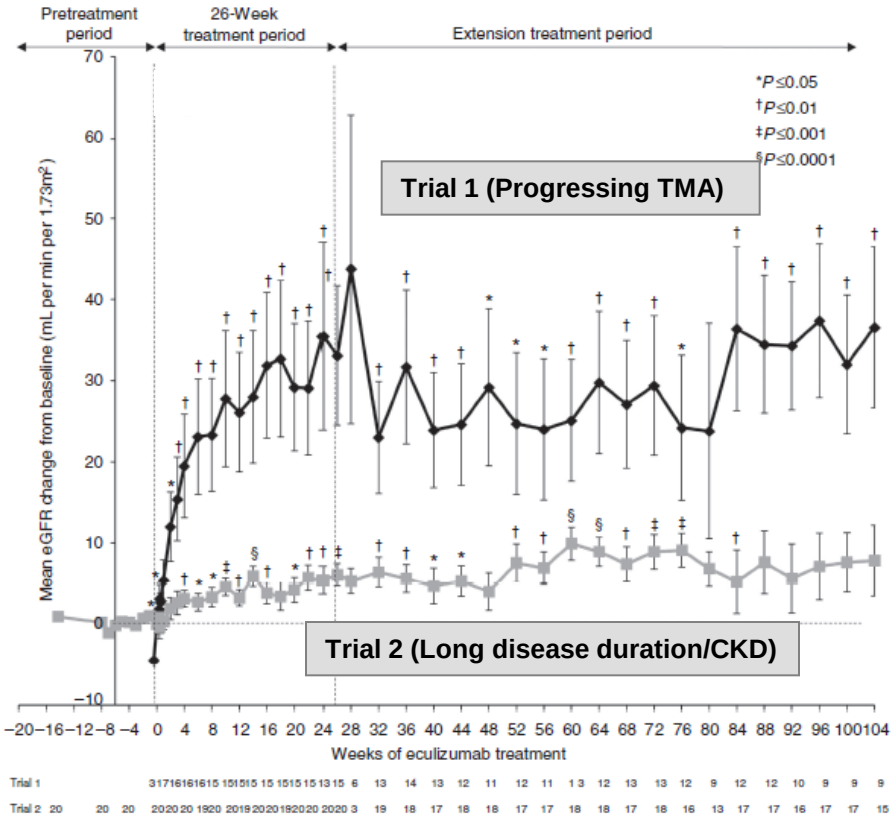
# Prospective aHUS clinical trial patient populations: Baseline

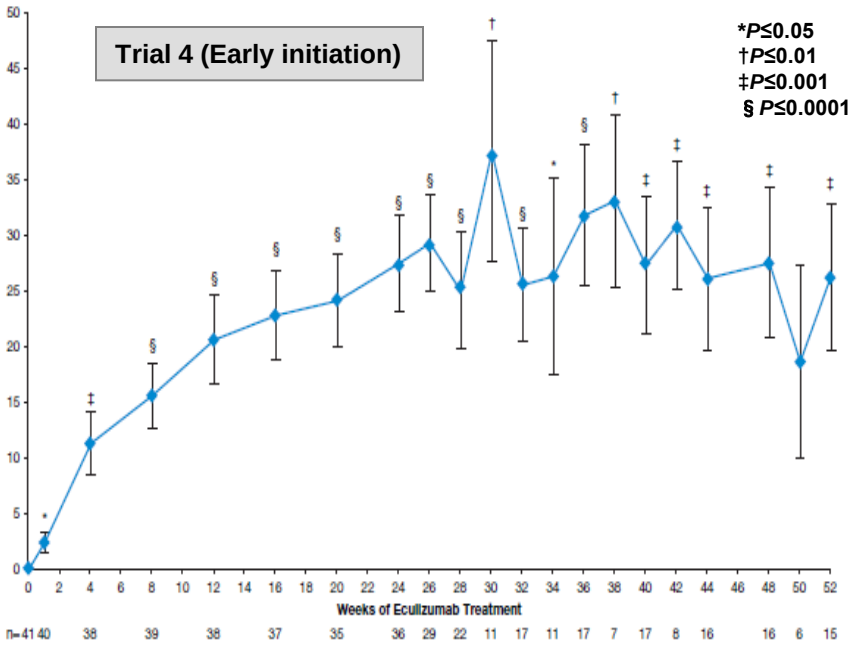
| | KTR = 8 | KTR = 7 | KTR = 9 |
|---|---|---|---|
| **Baseline characteristics** | **Patients with long duration of aHUS and CKD (C08-003; n=20)[1]** | **Patients with aHUS and progressing TMA (C08-002; n=17)[1]** | **Patients with aHUS (C10-004; n=41)[2]** |
| Median duration from aHUS diagnosis to screening, months (range) | 48.3 (0.7–285.8) | 9.7 (0.3–235.9) | 0.79 (0.03–311.3) |
| Median duration of current TMA, months to screening, months (range) | 8.6 (1.2–45.0) | 0.8 (0.2–3.7) | 0.5 (0.0–19.2) |
| PE/PI prior to eculizumab | Median duration: 10.1 months | Median no. 1 week prior: 6 (0–7) | Median no. 1 week prior: 3 (0–8) |
| Platelet count<br>Median × 10⁹/L<br><150 × 10⁹/L, no. (%) | 218 (105–421)<br>3 (15) | 118 (62–161)<br>15 (88) | 125 (16–332)<br>27 (66) |
| Renal damage | 50% of patients with CKD Stage 4–5;<br>2 (10%) patients on chronic dialysis | 70% of patients with CKD Stage 4–5;<br>5 (29%) patients on dialysis | 80% of patients with CKD Stage 4–5;<br>24 (59%) patients on dialysis |
| Genetic mutations or autoantibody | 30% of patients had none identified | 24% of patients had none identified | 49% of patients had none identified |


C. Legendre et al, New Engl J Medicine 2013

F. Fakhouri et al, AJKD 2016

# Improvement in eGFR in the 3 prospective trials of eculizumab in adults



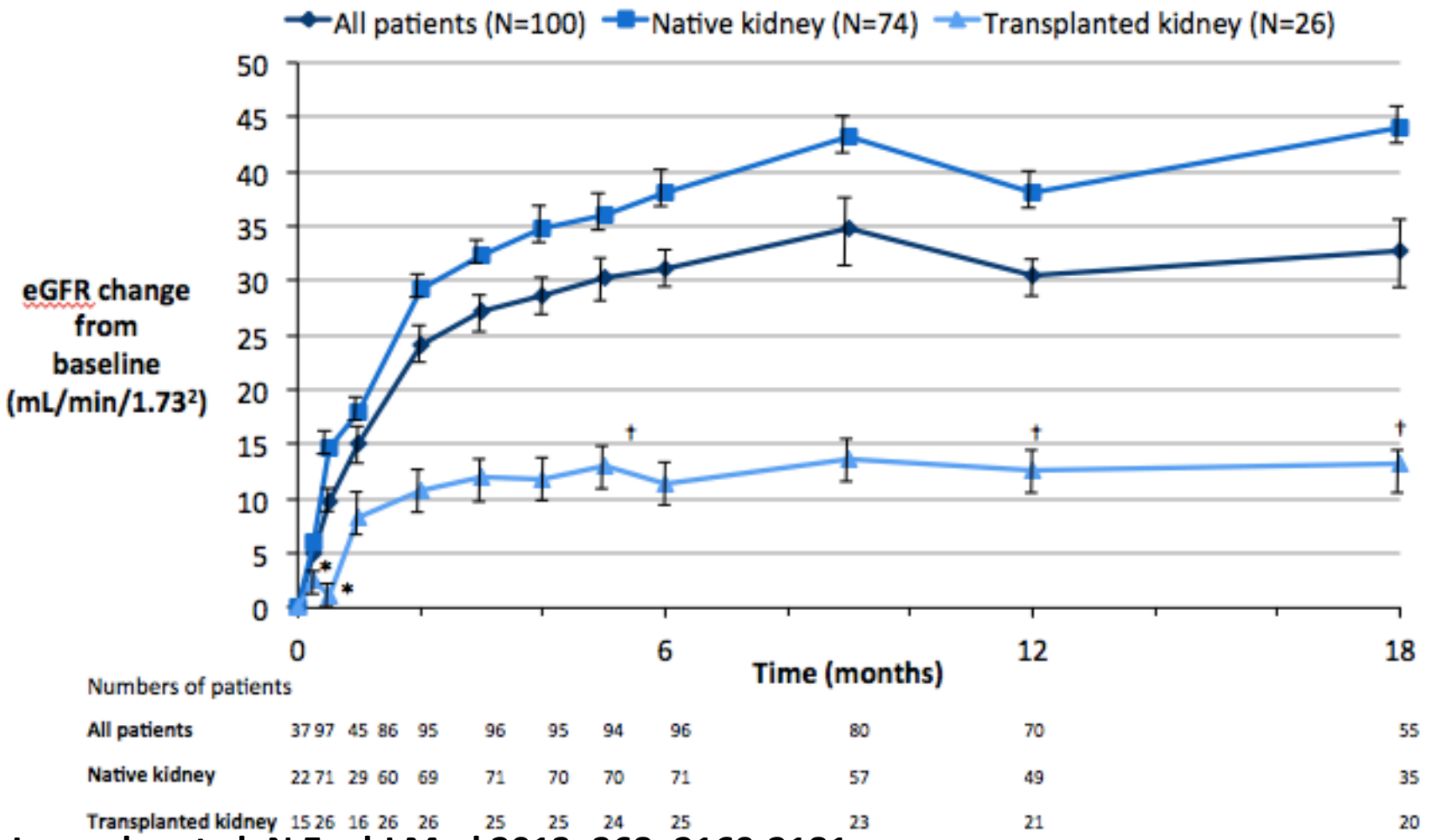

Fakhouri *et al*, JASN 2014,25:751A and AJKD 2016

Shorter time from clinical manifestation predicted greater eGFR gain (p=0.009 and < 0.0001 in trial 1 and 2 respectively)

| Mean increase in eGFR (ml/min/1.73m²) | | | |
|---|---|---|---|
| | Trial 1 | Trial 2 | Trial 4 |
| At 6 m | 33±33 | 6±6 | 29±24 |
| At 1 yr | 25±30 | 7±10 | 30±27 |
| At 2 yrs | 37±30 | 8±17 | |

Ch Legendre et al, NEJM 2013; C Licht et al, KI 2015

# Atypical Hemolytic Uremic Syndrome: renal function



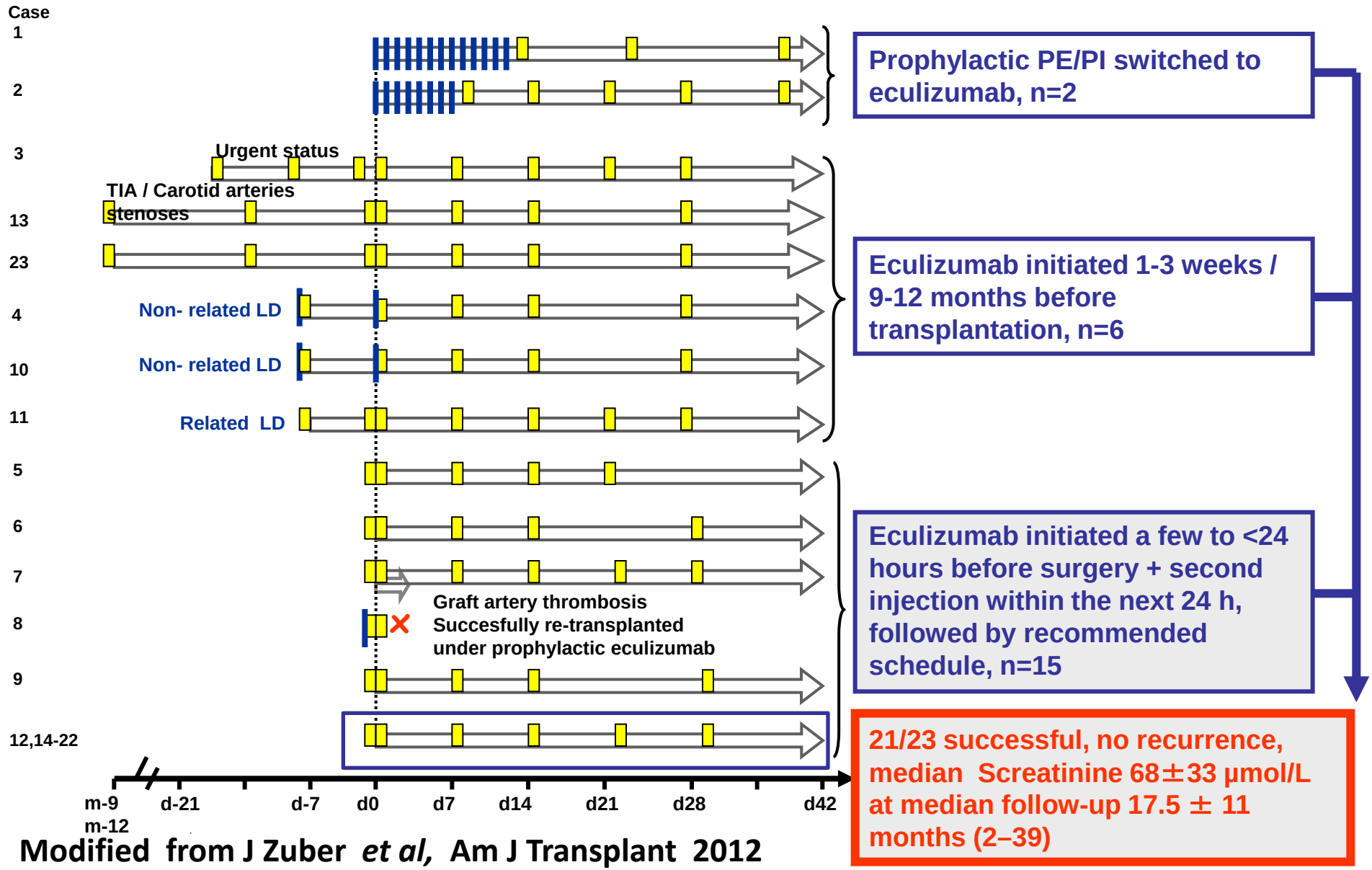

Ch Legendre et al, N Engl J Med 2013, 368: 2169-2181.

F Fakhouri et al, AJKD 2016, 68: 84-93.

# Prophylactic eculizumab therapy

PE

Eculizumab dose according to weight




Prophylactic PE/PI switched to eculizumab, n=2

Eculizumab initiated 1-3 weeks / 9-12 months before transplantation, n=6

Eculizumab initiated a few to <24 hours before surgery + second injection within the next 24 h, followed by recommended schedule, n=15

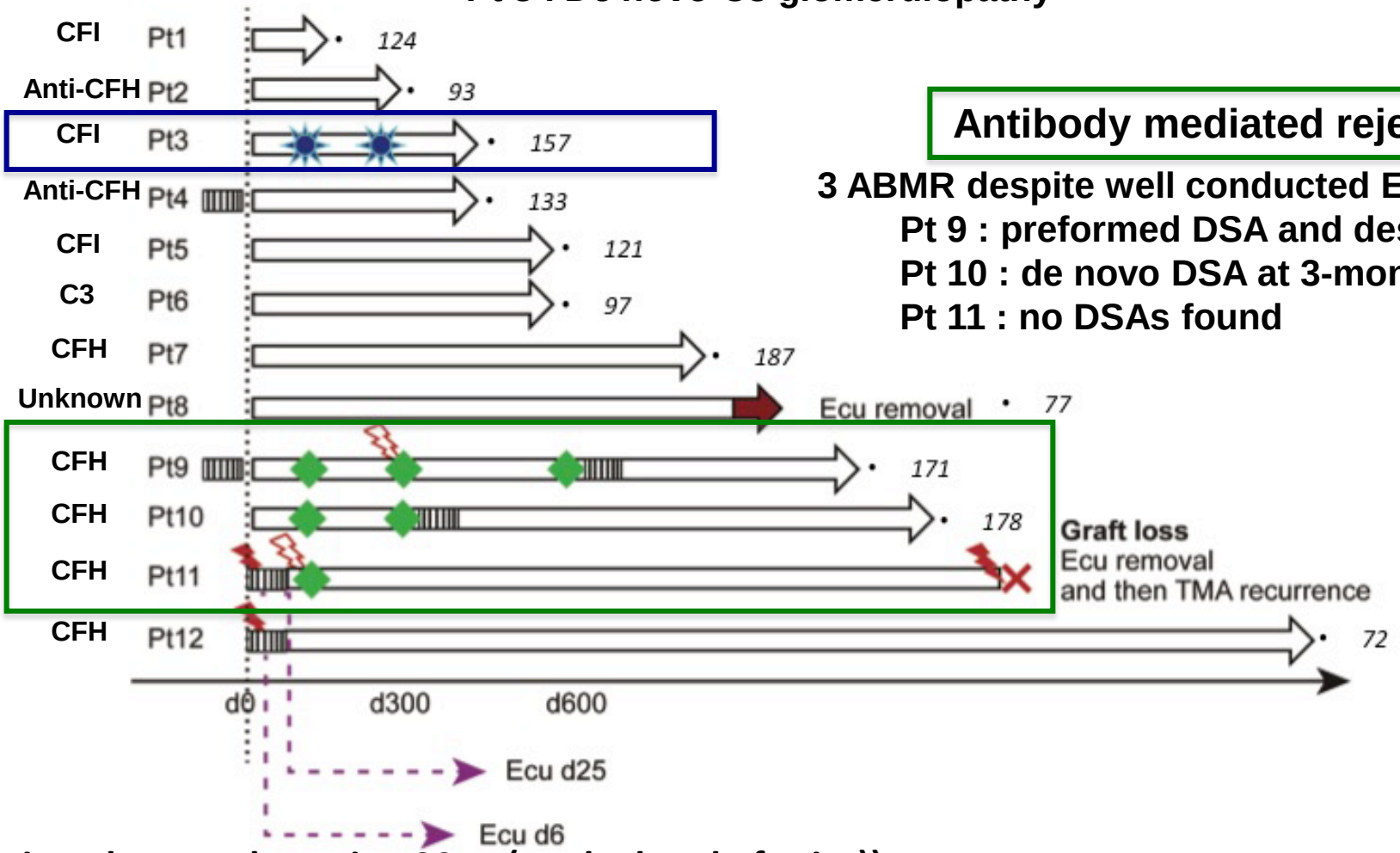
21/23 successful, no recurrence, median Screatinine 68±33 µmol/L at median follow-up 17.5 ± 11 months (2–39)

Modified from J Zuber *et al*, Am J Transplant 2012

# Necker's experience

**De novo C3 glomerulonephritis**

**Pt 3 : *De novo* C3 glomerulopathy**




**Antibody mediated rejection**

**3 ABMR despite well conducted Eculizumab**

**Pt 9 : preformed DSA and desensitizati**

**Pt 10 : de novo DSA at 3-months**

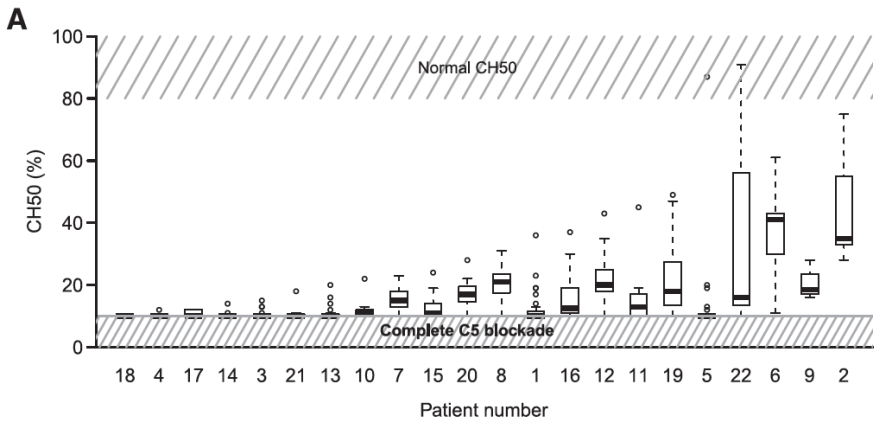
**Pt 11 : no DSAs found**

**C Levi et al, Transplantation 2017 (Epub ahead of print))**

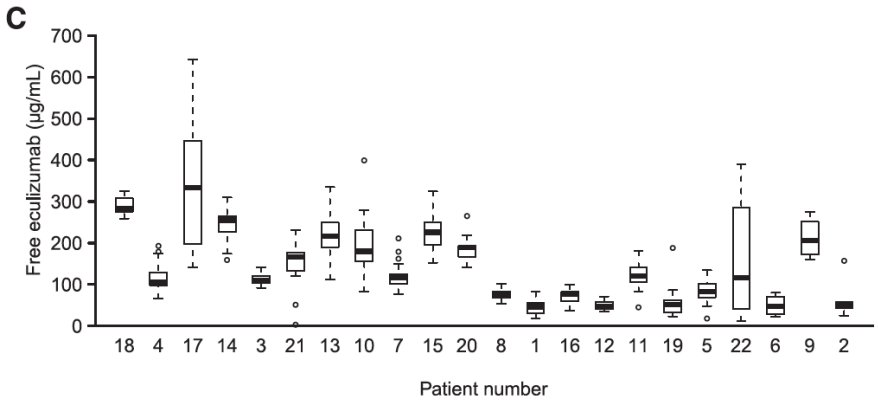
# Which eculizumab therapeutic monitoring?

*R Peffault de latour et al. Blood 2015,125:775-783; M Noris et al. Blood 2014, 124:1715-1726; P Gatault et al. Mabs 2015,7:1205-1211.*

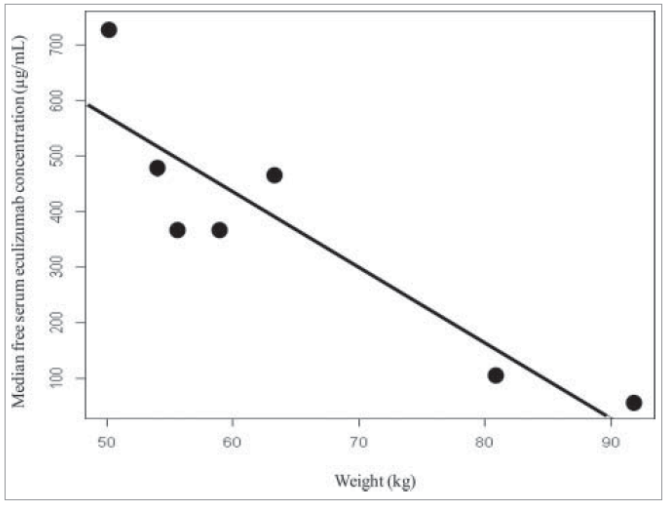
## CH50



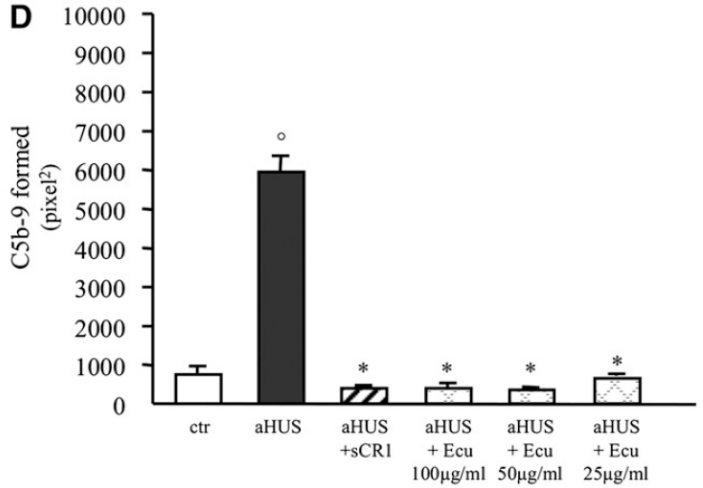

## free EC




## weight




## C5b-9 deposition



# Eculizumab discontinuation in aHUS patients with native kidneys

| | Literature[a] N=40 | | French retrospective experience[b] N=37 | |
|---|---|---|---|---|
| **Mutations** | **Patients who discontinued** | **Patients who relapsed after discontinuation** | **Patients who discontinued** | **Patients who relapsed after discontinuation** |
| **CFH** | 11 | **6 (54%)** | 11 | **8 (72%)** |
| **MCP** | 6 | **1 (16%)** | 8 | **4 (50%)** |
| **CFI** | 3 | 0 | / | / |
| **C3** | 2 | 1 | 1 | 0 |
| **No mutation identified** | 18 | **1 (5%)** | 17 | **0** |

**Treatment was reinitiated in all patients who relapsed but one, and outcome was favourable in all re-treated patients**

a. 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; Habbig *et al*, 2015; De Sousa Amorin et al, 2015; Toyada *et al*, 2016; Sahutoglu *et al*, 2016

b. Fakhouri F, Fila M et al, 2016, CJASN 2016, in press

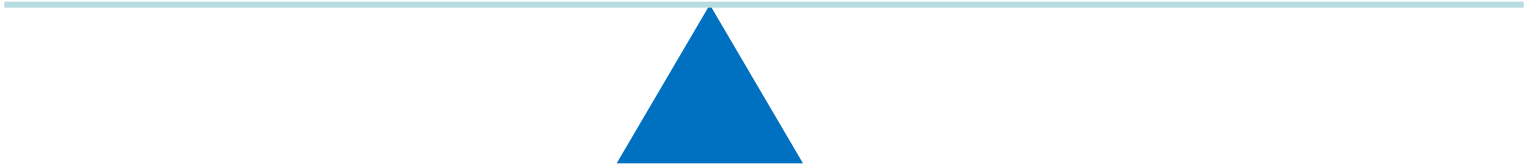
# Eculizumab discontinuation after kidney transplantation

**« Pros »**

**Risk of meningococcal meningitis (x5000;
2/100 in trials (1/74 with native kidneys;1/26 transplanted)
Infusion every 2 weeks
Cost**

**« Cons »**

**Risks in case of recurrence:
Acute kidney graft injury
Subsequent graft loss
Extra-renal manifestations**



# In which patients can eculizumab discontinuation be considered? Proposals from the French Study Group for HUS and C3G

- aHUS children, treated for at least 6 months (3 months in children with MCP mutations)
- Hematological remission and normalisation of renal function (eGFR, proteinuria) and no or mild HT for > 3 months

**Patients with no identified complement genes mutations** → **Consider eculizumab discontinuation**

**Patients with MCP mutation** → **Consider eculizumab discontinuation**

**Patients with CFH mutation** → **Decision to discontinue or not eculizumab should take into account the high risk of relapse after discontinuation**

**Patients with anti-CFH antibodies** → **Consider eculizumab discontinuation if anti-FH Ab titer < 1000 AU/ml following immunosuppressive trt***

- Close monitoring of renal function and hematological parameters, for early detection and treatment of relapse (twice weelkly urine dipstix, frequent blood samples (weekly for M1, every 2 wks for M2-M6…), intensified in case of infection, vaccination, surgery
- Education of patient/family

**Patients who experience aHUS relapse after eculizumab discontinuation** → **« On-demand » treatment ? Extended treatment ?**

F Fakhouri, et al, Clin J Am Soc Nephrol 2017, 12: 50-59.

# No prevention with eculizumab?

**Table 3.** Follow-up After Kidney Transplantation

| Pt No. | F/U, mo | Kidney Function at End of F/U: Scr, µmol/L | eGFR, mL/min/1.73 m$^2$ | Proteinuria, mg/10 mmol Scr | aHUS Recurrence | Rejection | No. of Antihypertensives | Current immunosuppressive Therapy | Complications and/or Adjustment of Immunosuppressive Therapy |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 68 | 132[a] | 39 | 0 | No | No | 2 | Tac/MMF | Pred discontinued because of psychological problems |
| 2 | 66 | 80 | 71 | 0.06 | No | No | 1 | Tac/MMF/Pred | |
| 3 | 66 | 106 | 46 | 0 | No | No | 2 | Tac/Aza/Pred | MMF discontinued because of diarrhea |
| 4 | 63 | 104 | 65 | 0.1 | No | No | 2 | Tac/MMF/Pred | |
| 5 | 45 | 76 | 72 | 0.07 | No | No | 2 | Tac/Aza | MMF discontinued because of diarrhea; Pred discontinued because of weight gain and mood disturbances |
| 6 | 43 | 158[a] | 39 | 0.27 | No | No | 3 | Tac/Pred | BK nephropathy; MMF discontinued |
| 7 | 32 | 84 | 59 | 0 | No | No | 2 | Tac/MMF/Pred | |
| 8 | 32 | 91[a] | 64 | 0.05 | No | Yes (biopsy proven) | 2 | Tac/MMF/Pred | Rejection treated with methylprednisolone/ATG |
| 9 | 25 | 166[a] | 36 | 0.12 | No | Yes (no biopsy) | 3 | Tac/Pred | Rejection treated with methylprednisolone; lymphocele with compression of transplant; MMF discontinued because of HSV infection |
| 10 | 14 | 143 | 35 | 0.05 | Yes | No | 2 | Tac/Pred | aHUS recurrence treated with eculizumab; MMF and Aza discontinued due to gastrointestinal symptoms |
| 11 | 9 | 151[a] | 30 | 0.14 | No | Yes (biopsy proven) | 3 | Tac/Pred | Rejection treated with methylprednisolone/ alemtuzumab; BK nephropathy; MMF discontinued because of diarrhea; Aza discontinued because of BK nephropathy |
| 12 | 7 | 140[a] | 51 | 0.09 | No | No | 3 | Tac/MMF/Pred | Hypercalcemia due to tertiary hyperparathyroidism |
| 13 | 7 | 67 | 86 | 0.06 | No | No | 2 | Tac/MMF/Pred | |
| 14 | 13 | 77 | 76 | 0.31 | No | No | 2 | Tac/MMF/Pred | |
| 15 | 22 | 145 | 50 | 0.10 | No | No | 2 | Tac/MMF/Pred | |
| 16 | 10 | 79 | 72 | 0.17 | No | No | 2 | Tac/MMF/Pred | |
| 17 | 7 | 175[a] | 28 | 0.44 | No | No | 2 | Tac/Pred | Chronic norovirus infection, MMF discontinued |

Abbreviations: aHUS, atypical hemolytic uremic syndrome; ATG, antithymocyte globulin; Aza, azathioprine; eGFR, estimated glomerular filtration rate; F/U, follow-up; HSV, herpes simplex virus; MMF, mycophenolate mofetil; Pred, prednisolone; pt, patient; Scr, serum creatinine; Tac, tacrolimus.

[a]These patients had complications other than aHUS and/or lower kidney function than expected (eGFR < 45 mL/min/1.73 m$^2$) and are described in Item S2.

**C Duineveld, et al, Am J Kidney Dis 2017 (In press).**

# Take-Home Message #6

**Eculizumab has revolutionized the treatment of aHUS both in native kidney diseases and in kidney transplants. Duration of treatment and safe discontinuation of this drug are still debated.**

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27. C Taylor et al, BJH Guideline 2009
28. Ch Legendre et al, N Engl J Med. 2013 Oct 3;369(14):1379-80.

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