Spectrum of complement-mediated thrombotic microangiopathies after kidney transplantation

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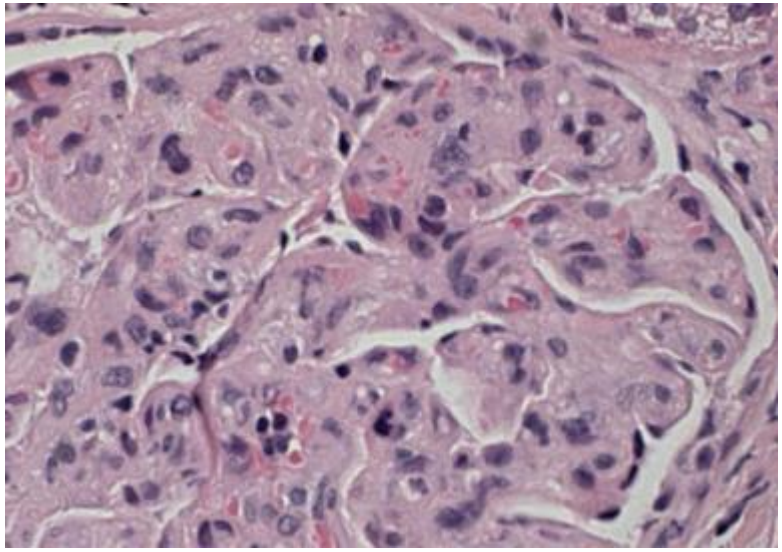
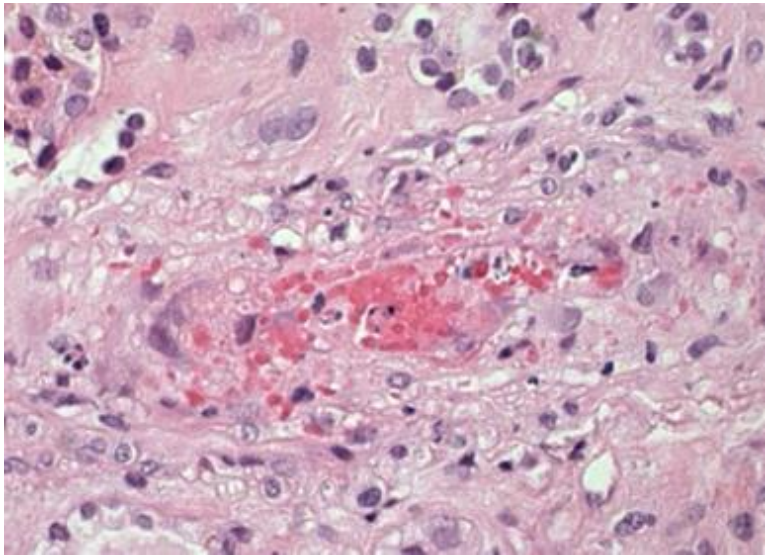
European Reference Network
for rare or low prevalence complex diseases

Network Kidney Diseases (ERKNet)

Thrombotic microangiopathy (TMA)

Thrombotic microangiopathy, a pathologic description, is characterized by a clinical presentation with thrombocytopenia, microangiopathic hemolytic anemia, and organ injury (acute renal injury, extra-renal injuries are rare)

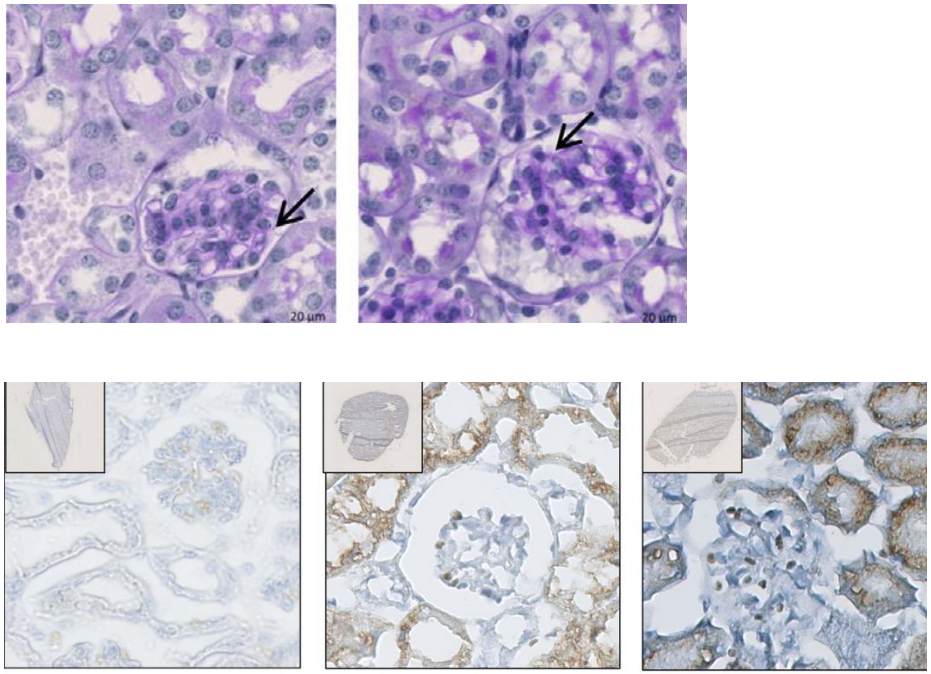




Q 1. Renal tropism (glomerular endothelial injury) for TMA is explained by:

1) Complement dysregulation
2) Impaired hemolysis
3) Complement clearance

Renal injury in intravascular hemolysis model



- Heme oxygenase 1 (HO-1) expression induced in tubular kidneys in response to hemolysis
- Glomerular endotelial cells fail to upregulate HO-1 – a major cytoprotective heme-degrading enzyme
- Heme triggers rapid P selectin, C3aR, and C5aR expression and downregulates CD46 on endothelial cells

Merle NS, et al. Frontiers in immunology, 2018,9:179
May O, et al. ERA-EDTA, Copenhagen, 2018

Classification of thrombotic microangiopathies (1)

Primary TMA: hereditary

- aHUS with complement gene mutation
  (*CFH*; *CFI*; *CFB*; *C3*; *CD46*; *CFHR1* hybrid)
- TTP with *ADAMTS13* mutation — **ADAMTS13 deficit**
- MMACHC TMA
- DGKE TMA

— **non-complement genes**

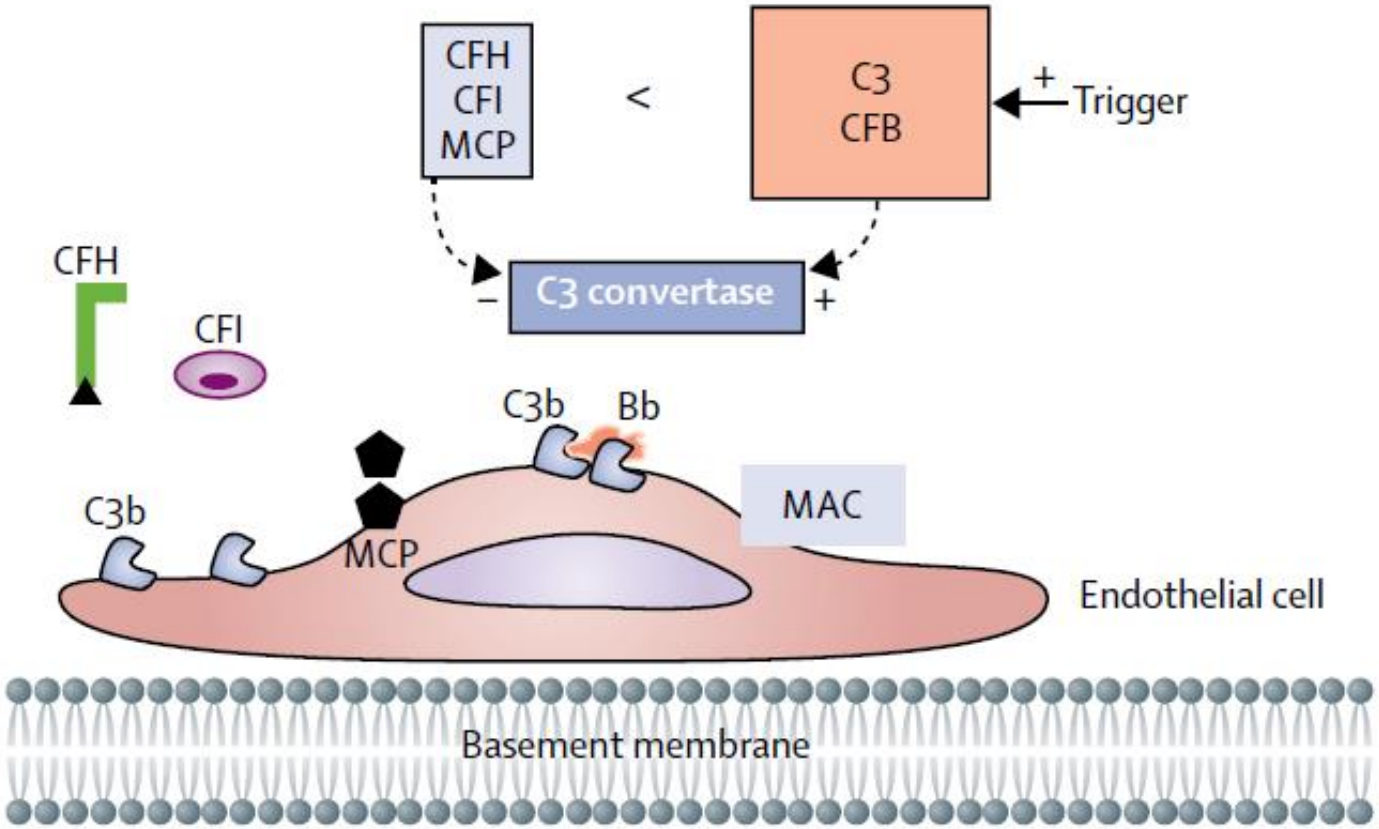
Primary TMA: hereditary

- aHUS with complement autoantibodies
  (anti-FH; anti-FI)
- TTP with ADAMTS13 autoantibody — **ADAMTS13 deficit**

Wong EKS, Kavanagh D. Seminars in Immunopathology 2018;40:49–64

- **A complement-mediated TMA due to to dysregulation of the alternative complement pathway is classically called atypical haemolytic and uremic syndrome (a-HUS)**

Sustained endothelial cell damage due to dysregulation of the complement alternative pathway in atypical HUS



Fakhouri F et al., Lancet 2017;390:681–96

Classification of thrombotic microangiopathies (2)

- Secondary TMAs
  - TMA with glomerular disease
    (FSGS; IgAN, C3G/MPGN, MN, AAV)
  - Malignancy associated TMA
  - Drug induced TMA
    - Direct toxicity (interferon B; bevacizumab)
    - Immune mediated damage (e.g., quinine)
  - TMA with autoimmune conditions
    (SLE, SRC, CAPS)
    - TMA after solid organ transplant
  - HELLP
- Infection associated TMA
  - STEC-HUS
  - Pneumococcal HUS
  - HIV associated aHUS
  - Other

Wong EKS, Kavanagh D. Seminars in Immunopathology 2018;40:49–64

Q 2. Finding the cause for secondary HUS fully excludes the primary aHUS :

1) I agree
2) I disagree
3) I am not sure

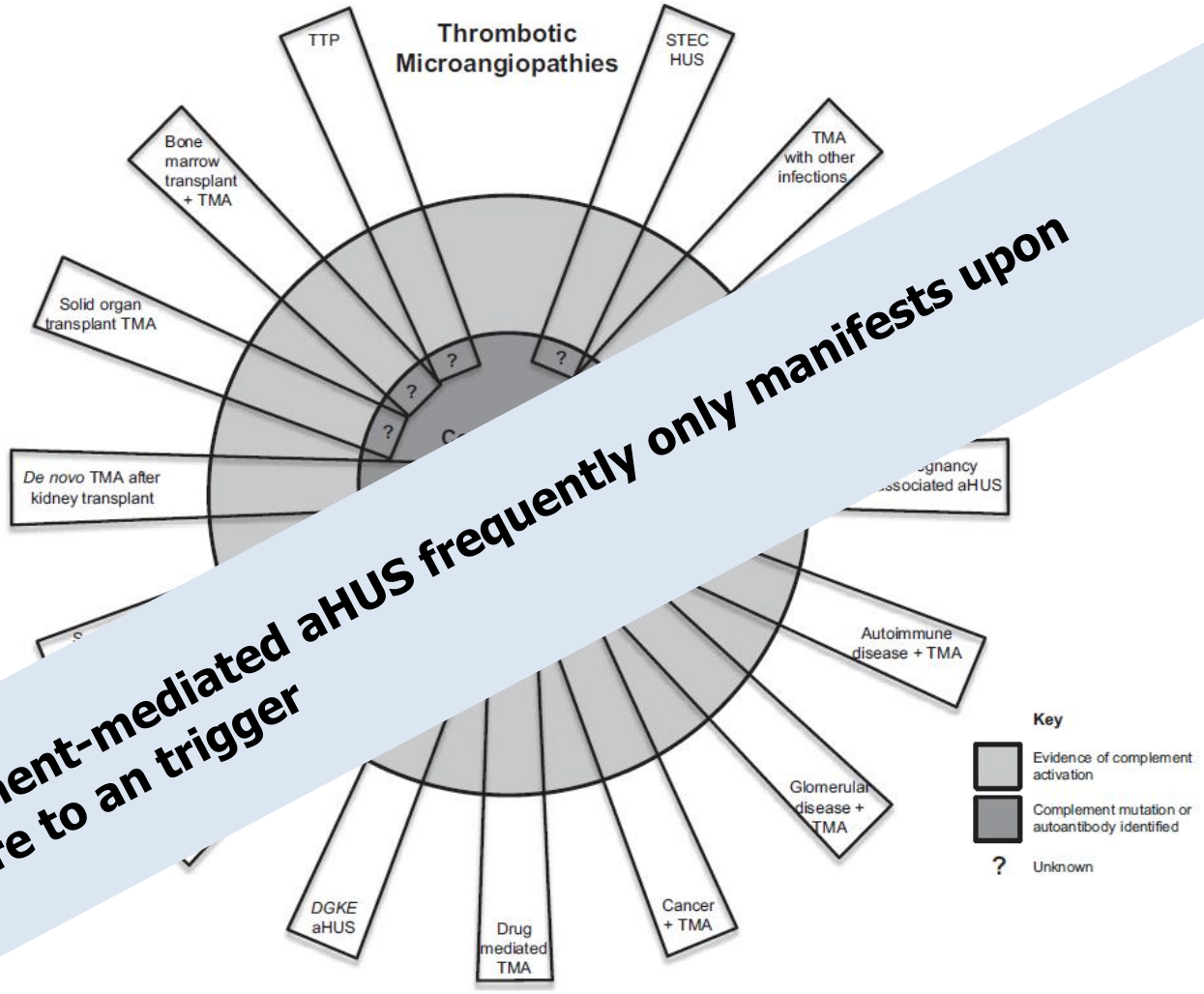
~1/3 of presumed "secondary" HUS are primary aHUS with trigger

	Patients (n=189)	With ations (%)
Pregnancy-associated HUS: mutations: CHF (n=7), CFI (n=2) or combined mutations (n=2)		1%
Malignant hypertension: mutations: CHF (n=3), C3 (n=2), CFB (n=1)		18%
Systemic diseases: mutations: CHF (n=5), CFI (n=3), C3 (n=1), MCP (combined mutations (n=1)	49	24%
***De-novo* post-transplant T** mutations: CFH (n=3), CFI (n=	23	17%
With other overlap s (MPGN, FSGS, IgA) mutations: CHF (1) or combined mutations (n=1)	22	23%
Severe (neurological signs, dialysis) mutatio (n=1), C3 (n=3), MCP (n=1), combined =1)	18	44%

Current hypothesis: the development of aHUS requires 'two hits'

Updated from Noris et al., CJASN, 2010

The role of complement in thrombotic microangiopathies



Complement-mediated aHUS frequently only manifests upon exposure to an trigger

Clinical Kidney Journal, 2017, vol. 10, no. 5, 600–624

The largest study evaluating the epidemiology and outcomes in post-transplant TMA

- A United States Renal Data System (USRDS)-based study of 15,870 renal transplant recipients reported a total incidence density of 5.6 episodes per 1000 persons-years
- Patient mortality was reported at approximately 50% at three years after the diagnosis

Reynolds JC, Agodoa LY, Yuan CM, Abbott KC. Thrombotic microangiopathy afterrenal transplantation in the United States. Am J Kidney Dis 2003;42:1058–68

Post-transplant TMA

Acute kidney injury (25% increase in serum creatinine) or slow & progressive increase in serum creatinine*

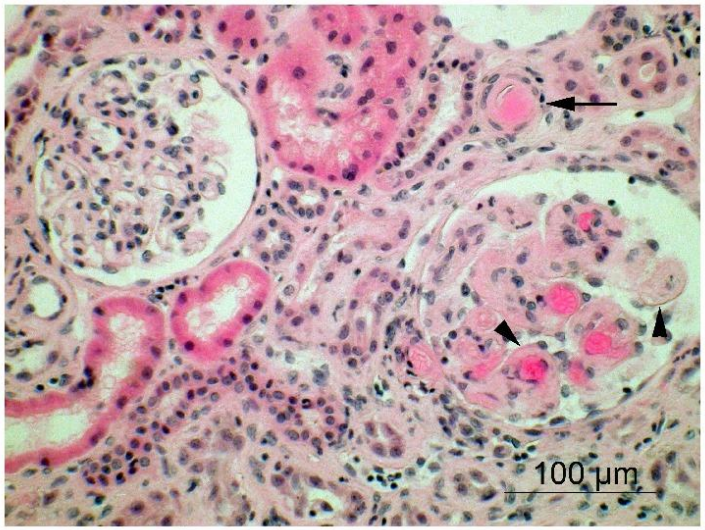
+/-

Microangiopathic hemolytic anemia
(Dropping Hematocrit
+
2-fold or more increase in LDH or low haptoglobin or schistocytes on peripheral smear)

+/-

Absolute or relative (25% or more drop from baseline) thrombocytppenia

Renal allograft biopsy



Garg N. et al. Transplantation Reviews 2018;32:58–68
Devresse A et al. Case Rep Nephrol. 2018:1727986

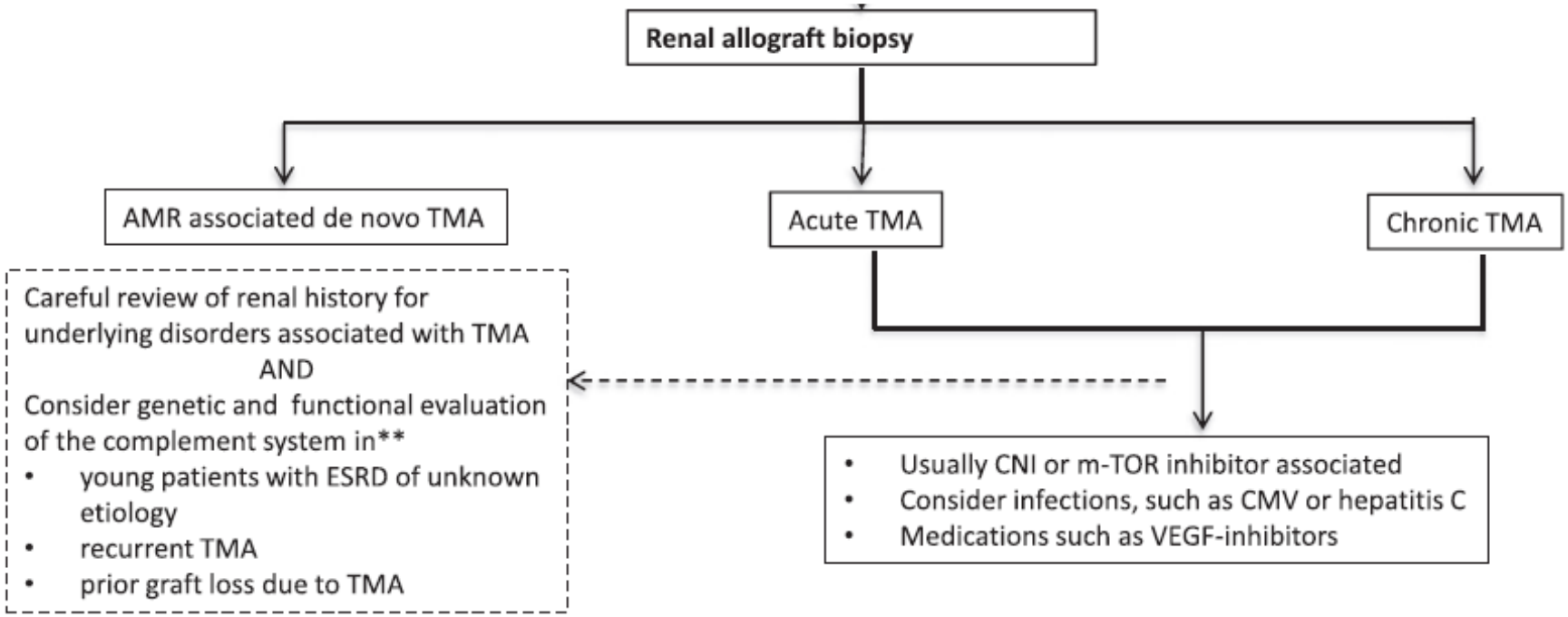
Post-transplant TMA

1) **recurrent disease**, where the same disease process that manifests as TMA in the native kidney re-develops in the allograft
2) **de novo TMA** after transplantation, where TMA develops for the first time in patients who have never had any evidence of the disease prior to transplantation

The diagnosis of aHUS may be missed in the native kidneys, and subsequently a recurrence in the allograft may be misclassified as de novo TMA

N. Garg et al. / Transplantation Reviews 32 (2018) 58–68

Systemic signs? Renal limited?



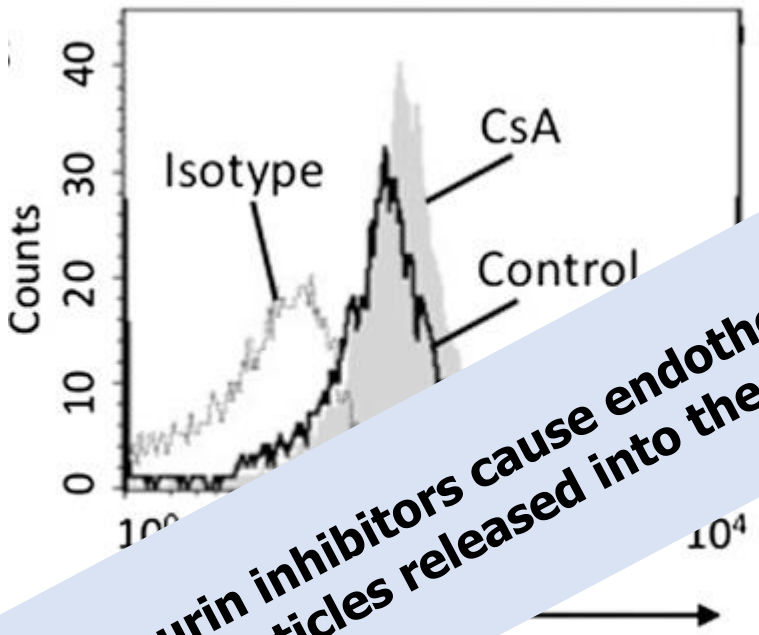
Garg N. et al. Transplantation Reviews 2018;32:58–68

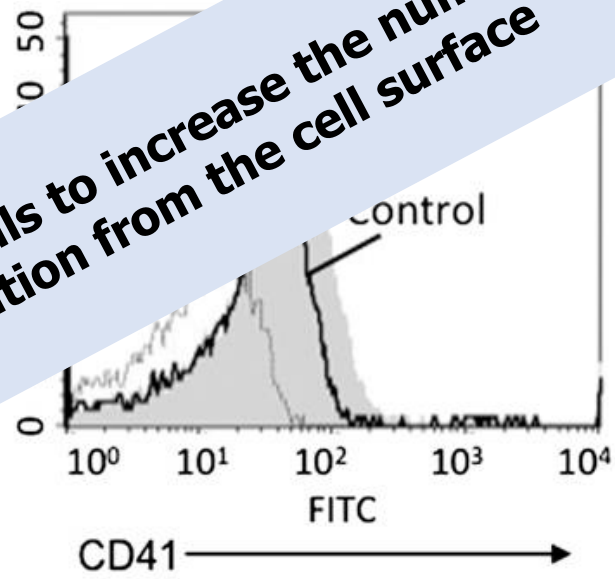
Kidney transplantation may lead to the endothelial damage

- Brain death
- Ischaemia–reperfusion injury
- Infections
- Immunosuppressive drugs
- Rejection

Okumi M, Tanabe K. Nephrology 2016;21(1):9–13

Cyclosporine induces endothelial cell release of complement-activating microparticles



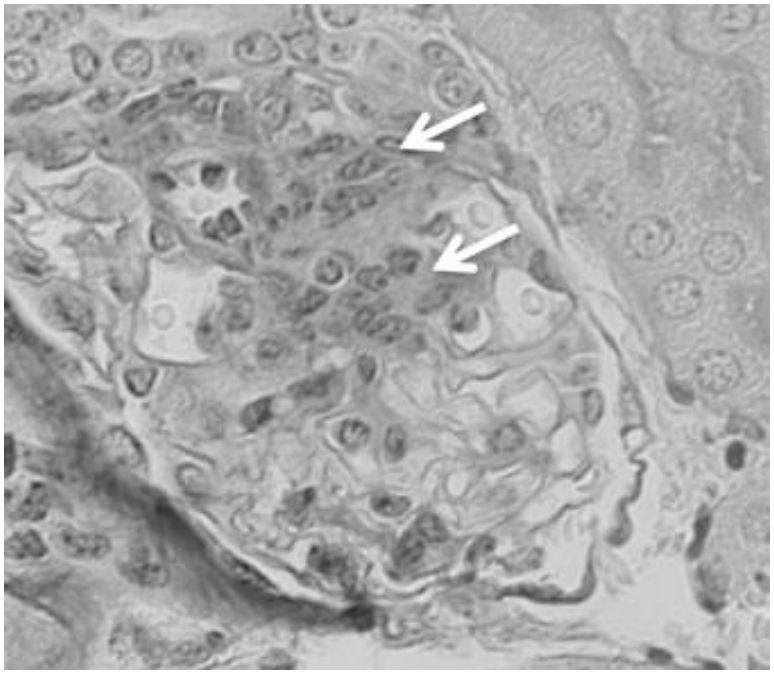


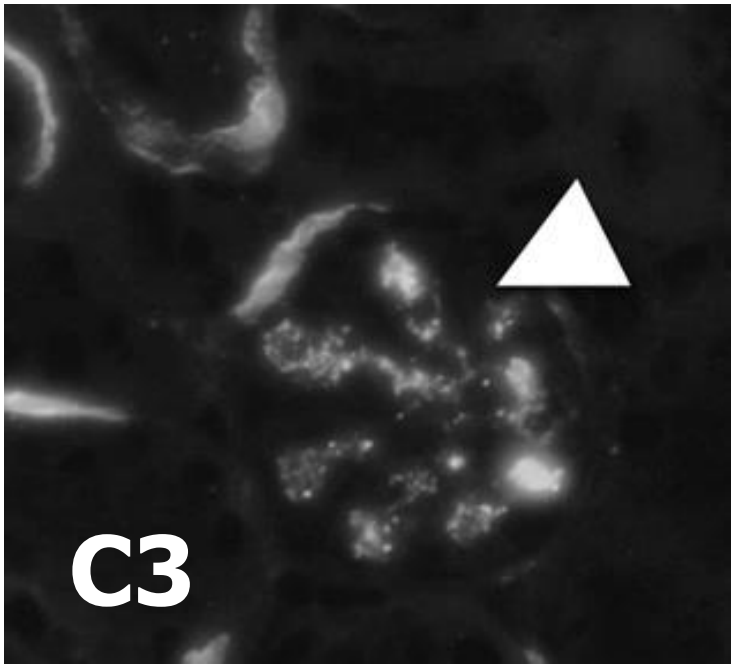
Calcineurin inhibitors cause endothelial cells to increase the number of microparticles released into the circulation from the cell surface

(CD31+) and platelet (CD41+) microparticles in the circulation

Renner B. J Am Soc Nephrol 2013;24:1849–1862

Cyclosporine-induced endothelial microparticles cause mesangial expansion and complement activation





Renner B. J Am Soc Nephrol 2013;24:1849–1862

CNI-induced TMA

- More than 95% of renal transplant recipients receive cyclosporine or tacrolimus
- Only a small minority of them develops TMA
- Temporary (or permanent) discontinuation of CNI after development of de novo TMA in the allograft has not been consistently shown to improve long term graft outcomes
- The endothelium is already injured as a result of ischemia-reperfusion injury, antibody mediated rejection, CNI overdose?

Garg N. et al. Transplantation Reviews 2018;32:58–68

Antibody-mediated rejection associated TMA

De novo Thrombotic Microangiopathy in Renal Allograft Biopsies—Role of Antibody-Mediated Rejection

During a 6-year period 55% of the patients with de novo TMA in the renal allograft had evidence of AMR

American Journal of Transplantation 2010

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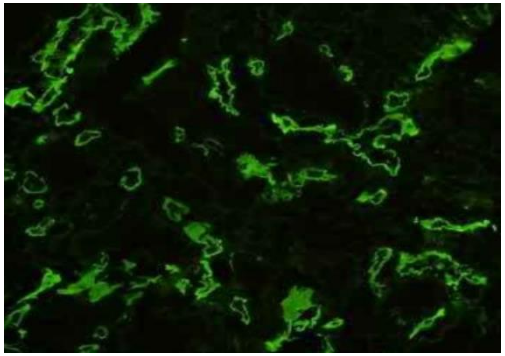


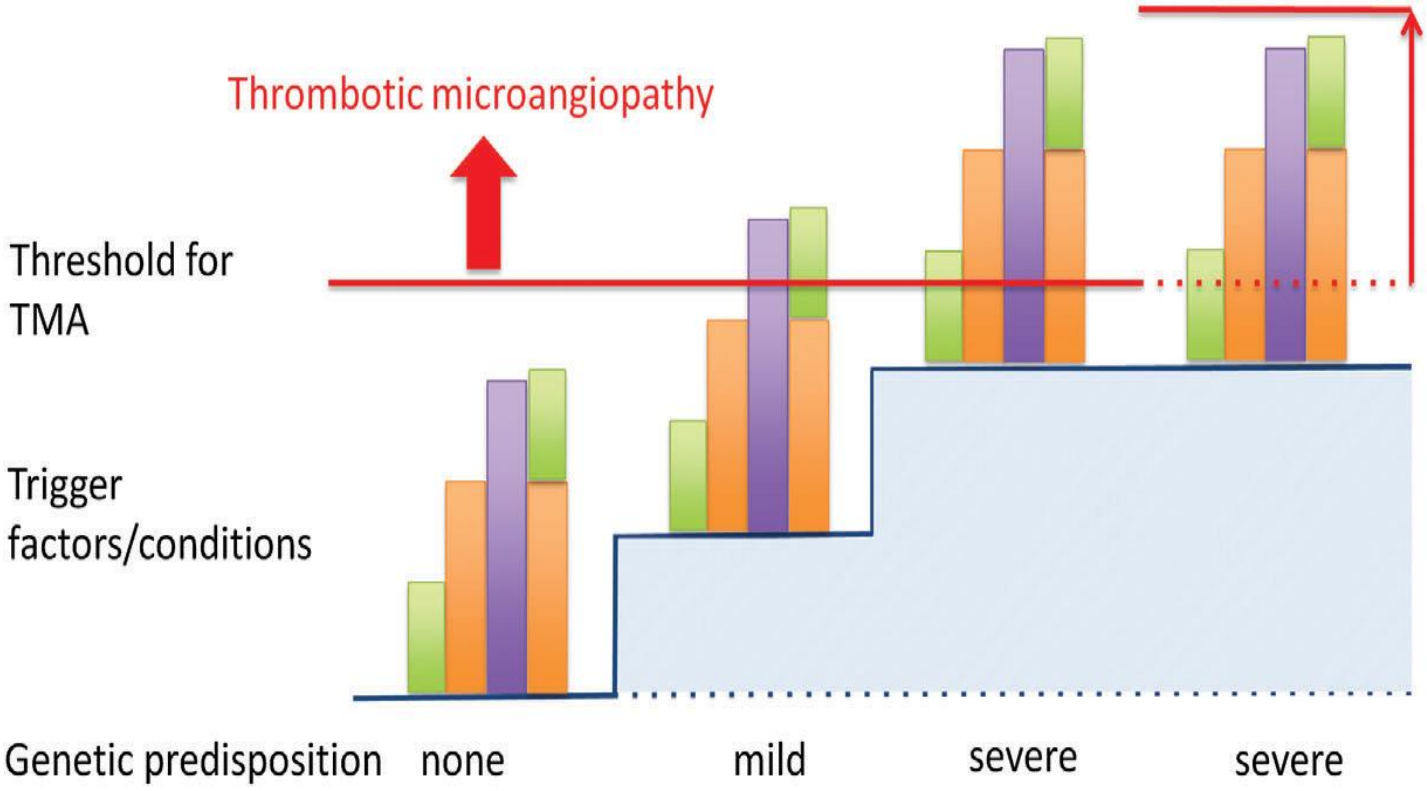
TMA in C4d positive biopsies was four times higher relative to C4d negative biopsies

American Journal of Transplantation 2010

Complement genetic testing

- Most a-HUS associated genetic variants predispose to rather than cause the disease
- Penetrance of disease is age related (64% by the age of 70) for individuals carrying a single genetic mutation
- A small proportion of aHUS patients (~ 3%) will have more than one mutation with increased penetrance per additional mutation
- Risk haplotypes have also been shown to increase disease penetrance
- **Even with multiple genetic risk factors, triggers are necessary to develop symptoms**

Interplay between genetic predisposition to TMA and triggering events



Semin Thromb Hemost 2014; 40:444–464

Q 3. Genetic testing is mandatory to confirm the diagnosis of aHUS

1) I agree
2) I disagree
3) I am not sure

Complement genetic testing

- The finding of no mutations in complement proteins does not rule out aHUS
- Approximately 30–48% of individuals with aHUS do not have complement mutations

Jokiranta TS. HUS and atypical HUS. Blood 2017;129:2847–2856

Complement serology

- Decrease in C3 and AH50, CFB, concentrations
- Increase in C5a, C3a, C5b-9, C3 convertase C3bBbP, complement activation product C3d and in C3d/C3 ratio
- Complement pathway assessment is a useful tool to aid in diagnosis of aHUS
- Normal results do not exclude a diagnosis of aHUS
- The lack of standardization in complement testing across laboratories

Sridharan M, Go RS, Willrich MAV. Journal of Immunological Methods 2018;46:115–22

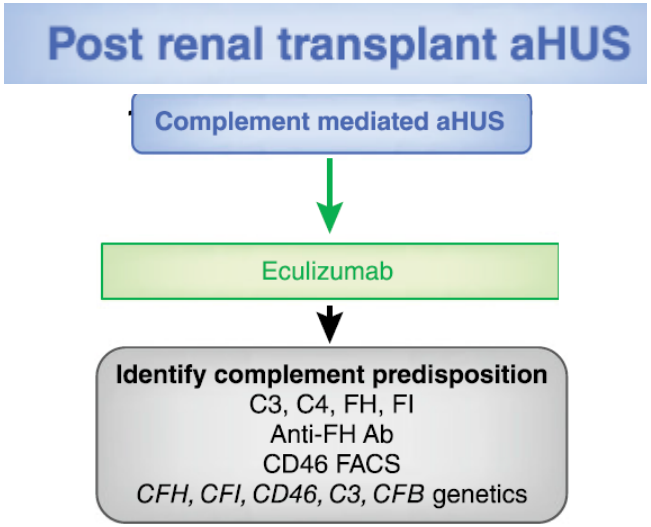
Treatment

Q 4. In my center I start eculizumab for patients with post-transplant aHUS:

1) As a first line therapy
2) As a second line therapy for aHUS refractory to plasmapheresis
3) No access to eculizumab in my center

aHUS treatment

- No biomarker currently will confirm the diagnosis of a primary complement-mediated aHUS in the acute setting
- The diagnosis is "of exclusion"
- To start treatment once a diagnosis of TMA is established and before a formal diagnosis of aHUS is confirmed
- Importance of prompt treatment with eculizumab



Sridharan M, Go RS, Willrich MAV. Journal of Immunological Methods 2018;46:115–22
Brocklebank V, Wood KM, Kavanagh D. Clin J Am Soc Nephrol 2018;13:300–317

TMA - Indications for PEX

	Category	Grade
TTP	**I**	**1A**
HUS -associated with Streptococcus pneumonia	III	2C
aHUS - **factor H antibodies** - complement gene mutations	**I** II	**2C** 2C
Drug-assiciated TMA - **ticlopidine** - clopidogrel - cyclosporine/tacrolimus	**I** III III	**2B** 1B 2C
Transplantation associated TMA	III	2C

Schwartz J, et al. J Clin Apher 2016; 31:149-162

How?

Eculizumab for aHUS after kidney transplantation

- The recommended doses:

  900 mg/week for 1 month and then

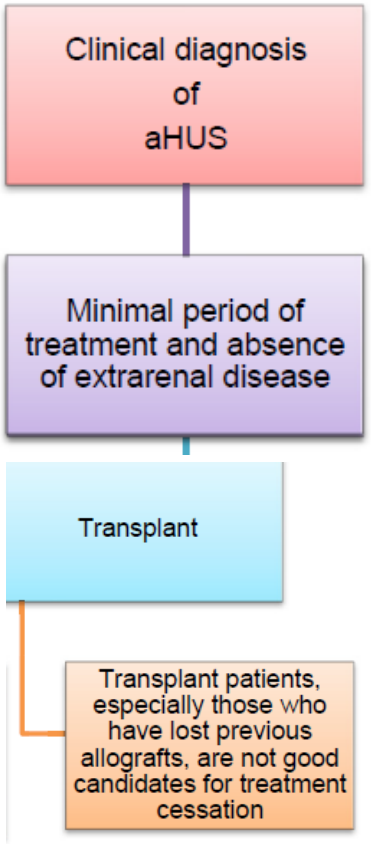
  1200 mg/2 weeks

  - Could be discontinued if an alternative etiology is subsequently identified *or*
  - have genetic variants in the non-complement genes DGKE, INF2, and MMACHC

How long?

Eculizumab for aHUS after kidney transplantation

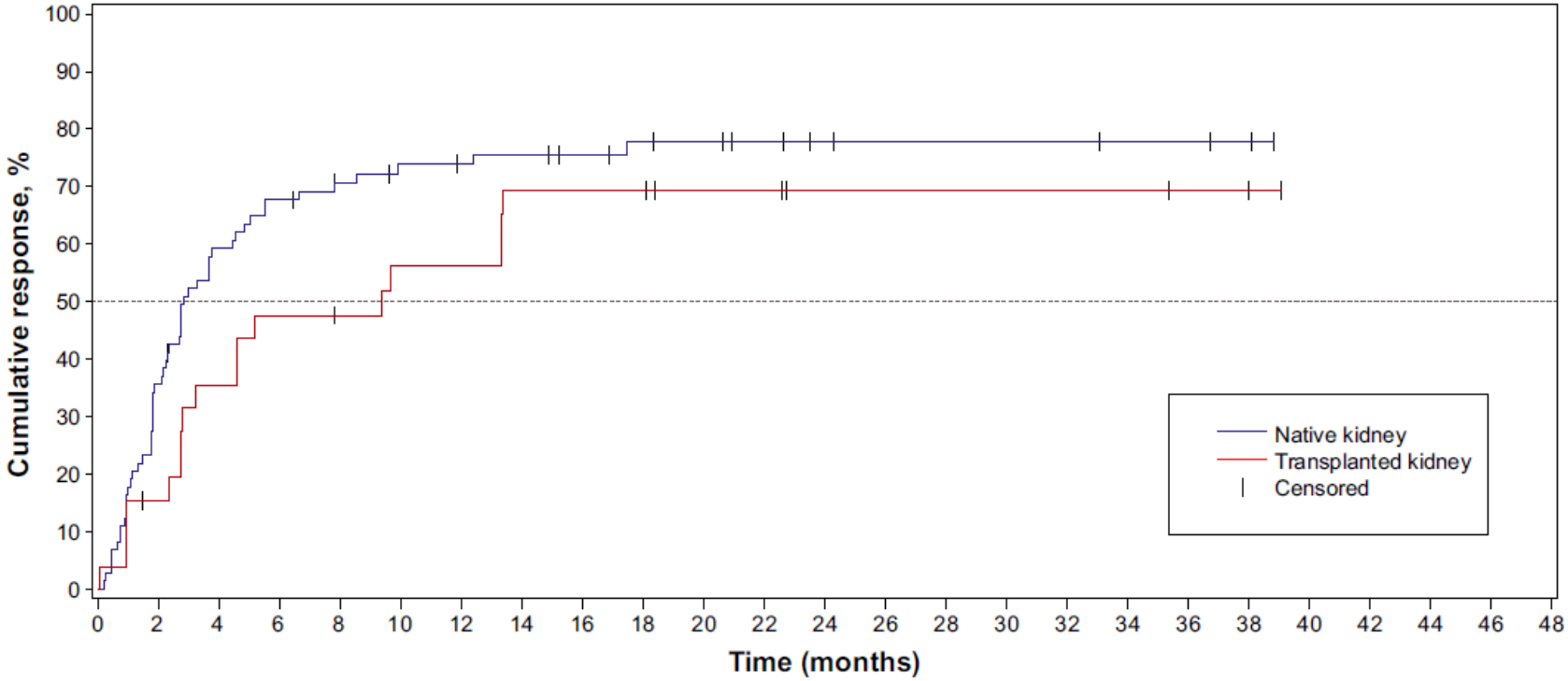
- The optimal duration of eculizumab therapy is unclear
- Time-limited (e.g., up to 6 or 10 months)
- Time-unlimited protocols
- How to define the patients suitable for safe termination of the treatment?



Modified from Grenda R, Durlik M. Ann Transplant 2017;22:550-554
Goodship THJ *et a*l. Kidney Intl 2017;91:539–551

Outcomes of patients with atypical haemolytic uraemic syndrome with native and transplanted kidneys treated with eculizumab: a pooled *post hoc* analysis

Christophe M. Legendre[1], Josep M. Campistol[2], Thorsten Feldkamp[3], Giuseppe Remuzzi[4,5], John F. Kincaid[6], Åsa Lommelé[7], Jimmy Wang[8], Laurent E. Weekers[9] & Neil S. Sheerin[10]



Transplant International, 2017, 30.12: 1275-1283

How to monitor?

Complement activity for assessing eculizumab therapy efficacy

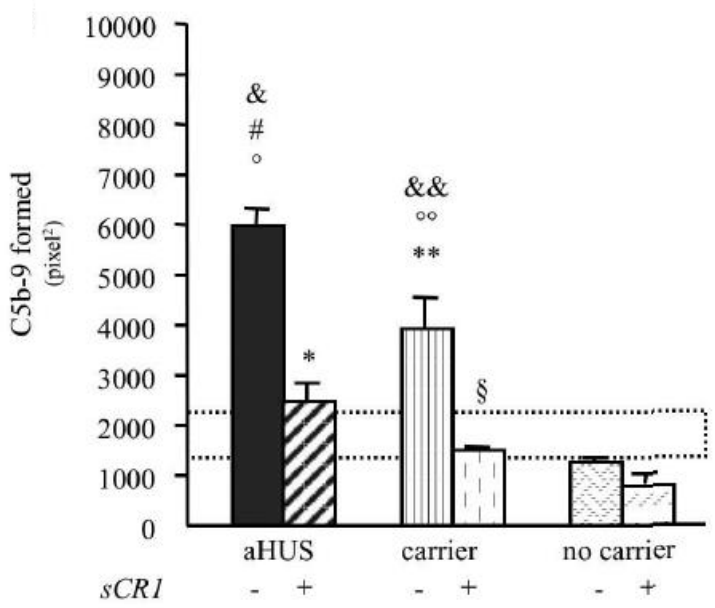
CH50 (Total complement activity)

AH50 (Alternative pathway hemolytic activity)

Eculizumab trough

Alternative assays

In vitro human microvascular endothelial cell test



Goodship THJ *et al*. Kidney Int 2017;91:539–55

Noris M, Galbusera M, Gastoldi S, et al. Dynamics of complement activation in aHUS and how to monitor eculizumab therapy. Blood 2014;124:1715–1726.

Risk of post-transplant aHUS recurrence

- Historically recurrence was reported in 60% to 80% of aHUS transplant recipients
- It was strongly associated with transplant failure (poor response to treatment with plasma exchange)

Zuber J, Le Quintrec M, Morris H et al. Targeted strategies in the prevention and management of atypical HUS recurrence after kidney transplantation. Transplant. Rev. (Orlando) 2013;27:117–25

Prevention

aHUS: kidney transplantation

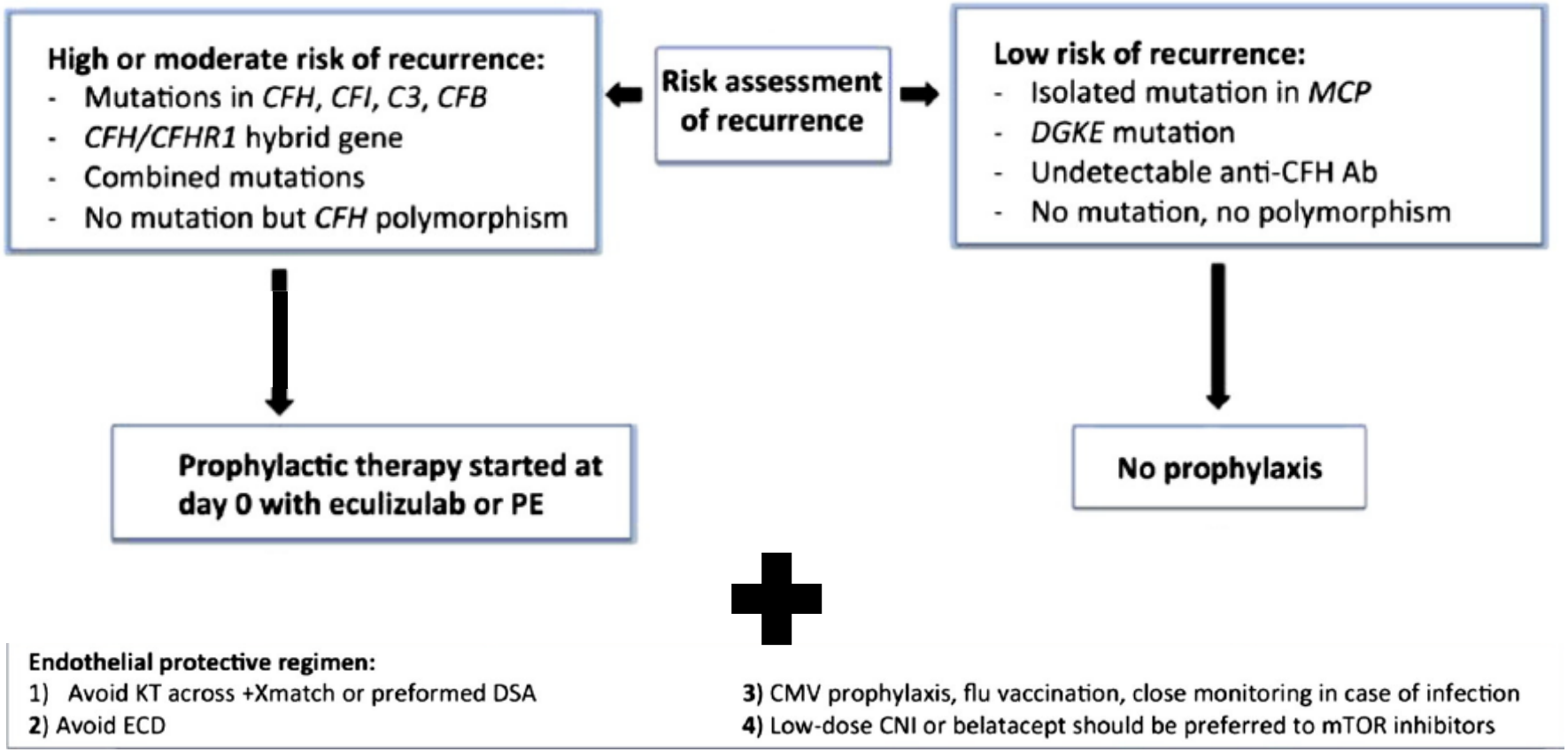
- Kidney transplantation should be **delayed** until at least 6 months after the start of dialysis
- The **resolution of hematological TMA features and extrarenal manifestations**
- Bilateral **native nephrectomy**?
- Combined **liver-kidney** or isolated **liver** transplantation:
  on a case-by-case basis – CFH, CFB, C3 mutations, availability of eculizumab
- **Prophylactic eculizumab** based on recurrence risk

Kidney Int 2017:91:539–551
Pediatr Nephrol 2016:

The genetic diagnosis of a-HUS (before kidney transplantation)

- The risk of recurrence after kidney transplantation depends on whether the mutant complement factor is **membrane-bound** (*low risk*) or **circulating** (*high risk*)

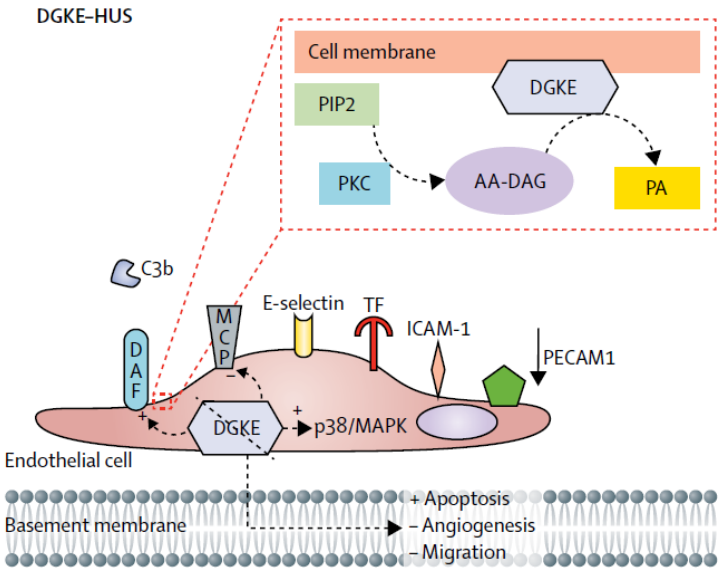
Diagnostic algorithm for aHUS candidates to renal transplantation



Modified from Zuber J *et al*. Transplantation Reviews 2013;27:117–125

The Phenotypic Spectrum of Nephropathies Associated with Mutations in Diacylglycerol Kinase ε

Karolis Azukaitis,* Eva Simkova,† Mohammad Abdul Majid,† Matthias Galiano,‡ Kerstin Benz,‡ Kerstin Amann,§ Clemens Bockmeyer,§ Radha Gajjar,| Kevin E. Meyers,| Hae Il Cheong,¶** Bärbel Lange-Sperandio,†† Therese Jungraithmayr,‡‡ Véronique Frémeaux-Bacchi,§§|||| Carsten Bergmann,¶¶ Csaba Bereczki,*** Monika Miklaszewska,††† Dorottya Csuka,‡‡‡ Zoltán Prohászka,‡‡‡ Patrick Gipson,§§§ Matthew G. Sampson,§§§ Mathieu Lemaire,||||¶¶¶**** and Franz Schaefer††††



Loss of DGKE function results in enhanced signaling through
arachidonic acid-containing DAGs and enhanced activation of PKC:
upregulation of prothrombotic factors

44 patients analyzed
Five patients received renal allografts, with no post-transplant recurrence reported

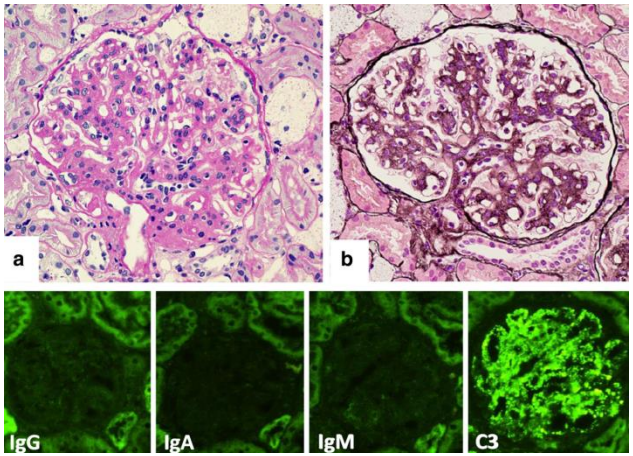
J Am Soc Nephrol 2017
Lancet 2017
Seminars in Immunopathology 2018

C3 Glomerulopathy (C3G)

Orphan Disease with No Approved Therapy

US: 700 - 1000 new cases/year In Europe: 1000 – 1500 new cases / year

- No approved effective treatment
- Problem: Uncontrolled activation of the complement system leading to complement protein deposition in the kidney
  - Characterized by C3 but also C5/C5a deposition in glomeruli
  - Complement deposition in glomeruli disrupts kidney function, leading to kidney failure
  - Can be life-threatening
  - Half of all people with C3G have kidney failure
  - Kidney transplant does not cure the disease; relapsing disease is common



Which donor?

Q 5. In my center kidney transplantation from living donors is contraindicated for recipients with ESRD due to aHUS:

1) I agree
2) I disagree
3) I am not involved in the transplant care

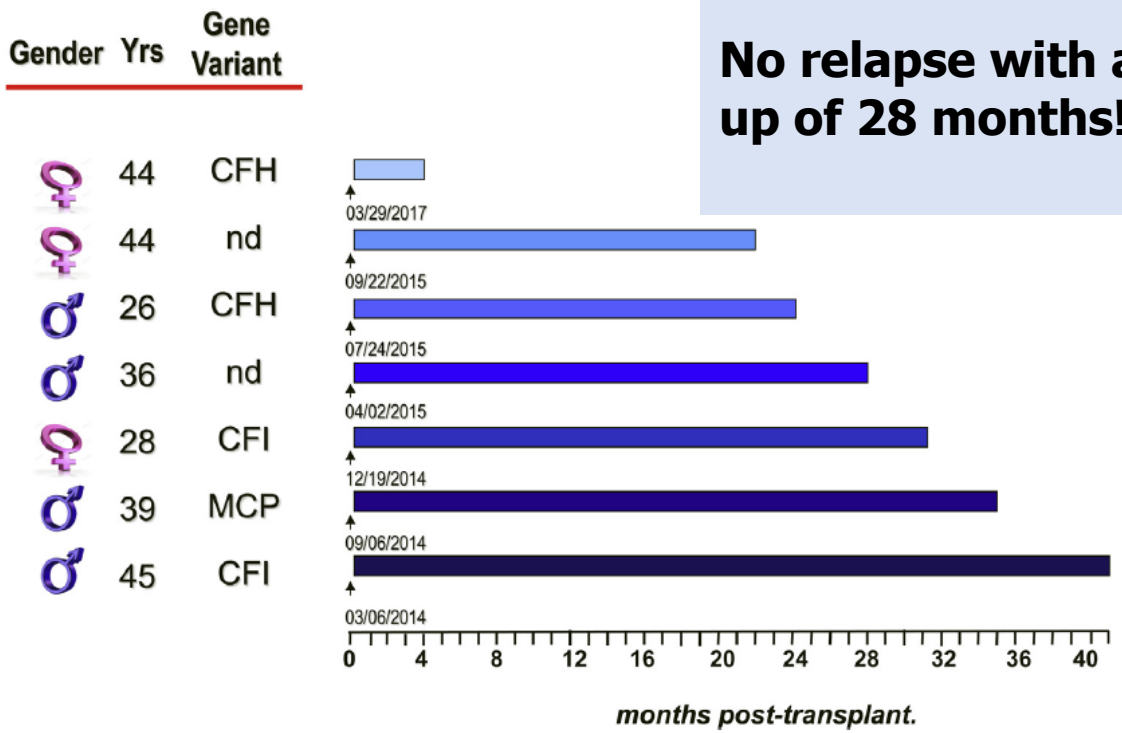
A case series including 17 patients with a-HUS who underwent living kidney transplantation without prophylactic eculizumab

Duineveld *et al*. Am J Kidney Dis 2017;70(6):770–777

- ✓ Median follow-up after transplantation was 25 (range, 7-68) months
- ✓ One patient had aHUS recurrence 68 days after transplantation, which was successfully treated with eculizumab
- ✓ At the end of follow-up, median serum creatinine concentration was 106 (range, 67-175) µmol/L and proteinuria was negligible

1) all living donors were genotyped
2) cold ischemia time was short
3) low targets of tacrolimus were used

Posttransplantation outcome in patients with aHUS who received a deceased donor kidney transplant at the Renal Transplant Unit, Bergamo, Italy (2014 – 2017)



No relapse with a median follow-up of 28 months!

Patients received the following treatment:

pretransplantation **plasma exchange** (1 volume fresh frozen plasma)

induction therapy: basiliximab and antithymocyte globulin

cyclosporine (tapering), mycophenolate mofetil or azathioprine, steroids (1 week)

No eculizumab prophylaxis was given

Noris M, Ruggenenti P, Remuzzi G.

Changing paradigm?

- Should posttransplantation eculizumab therapy change from a prophylaxis strategy to a rescue approach?

Noris M, Ruggenenti P, Remuzzi G. Am J Kidney Dis 2017;70(6):754-757

Conclusions

1) a genetic screening in TMA before (after) kidney transplantation

2) identifying the underlying mutation allowing treatment that can reverse the fate of renal function

3) the sooner the treatment the better the results

4) preventive measures!

5) familial screening (for asymptomatic carrier status) and counselling in the context of living donation

Devresse A *et al*. 2018
Legendre C 2018