Management of TMAs in Kidney Transplantation

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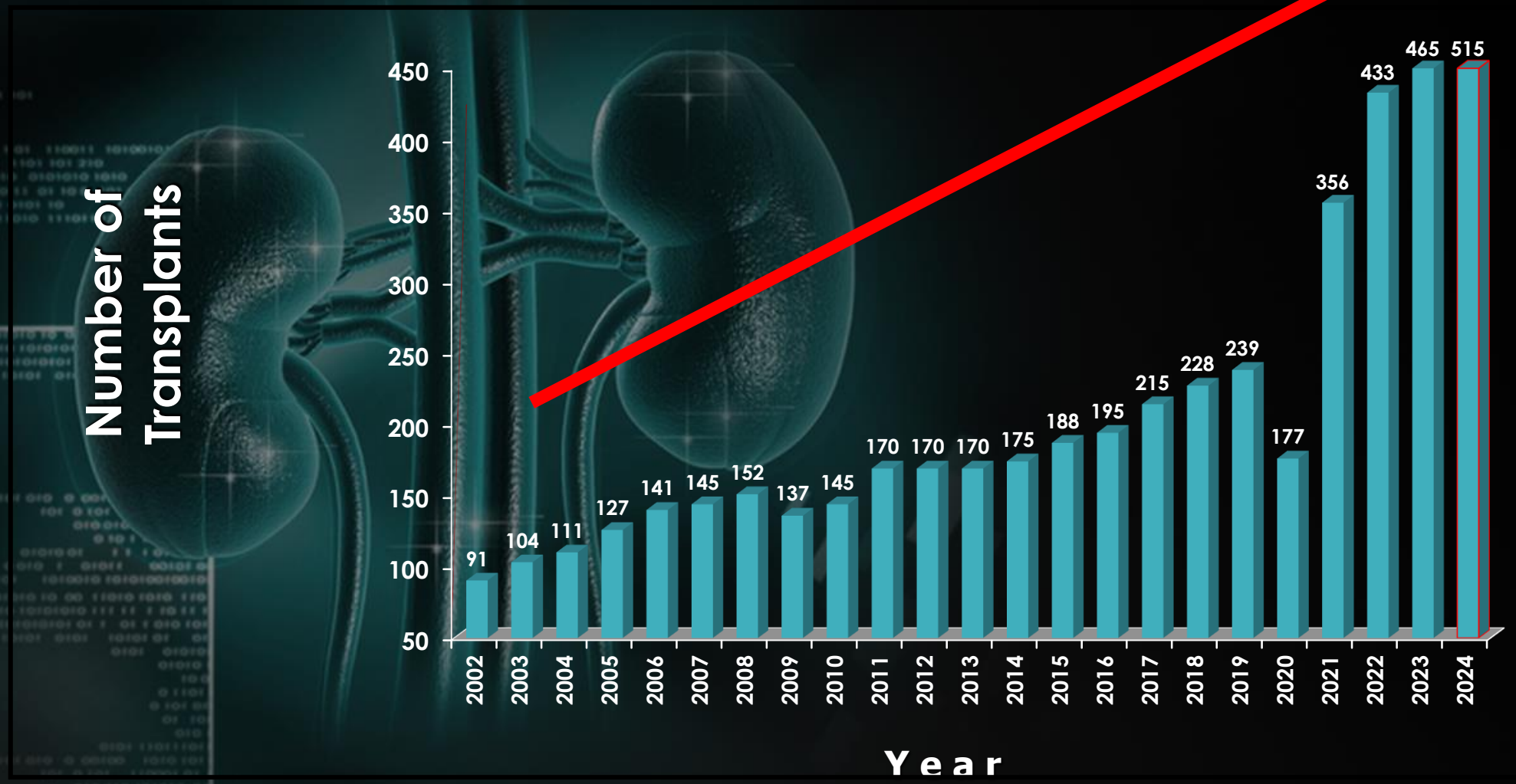
Renal Transplants at KFSH&RC

2000 to 2024



What is thrombotic microangiopathy (TMA)?

Systemic Endothelial damage

Thrombotic

Thrombotic comes from the word thrombosis, meaning likely to develop a clot comprising various blood cells and proteins within the vasculature[1]

Micro

Clots form in the small blood vessels, such as the capillaries and arterioles[2]

Angiopathy

Angiopathy is a disease of the blood vessels, evident if vessel lesions are in histologic sections[2]

Transplant associated

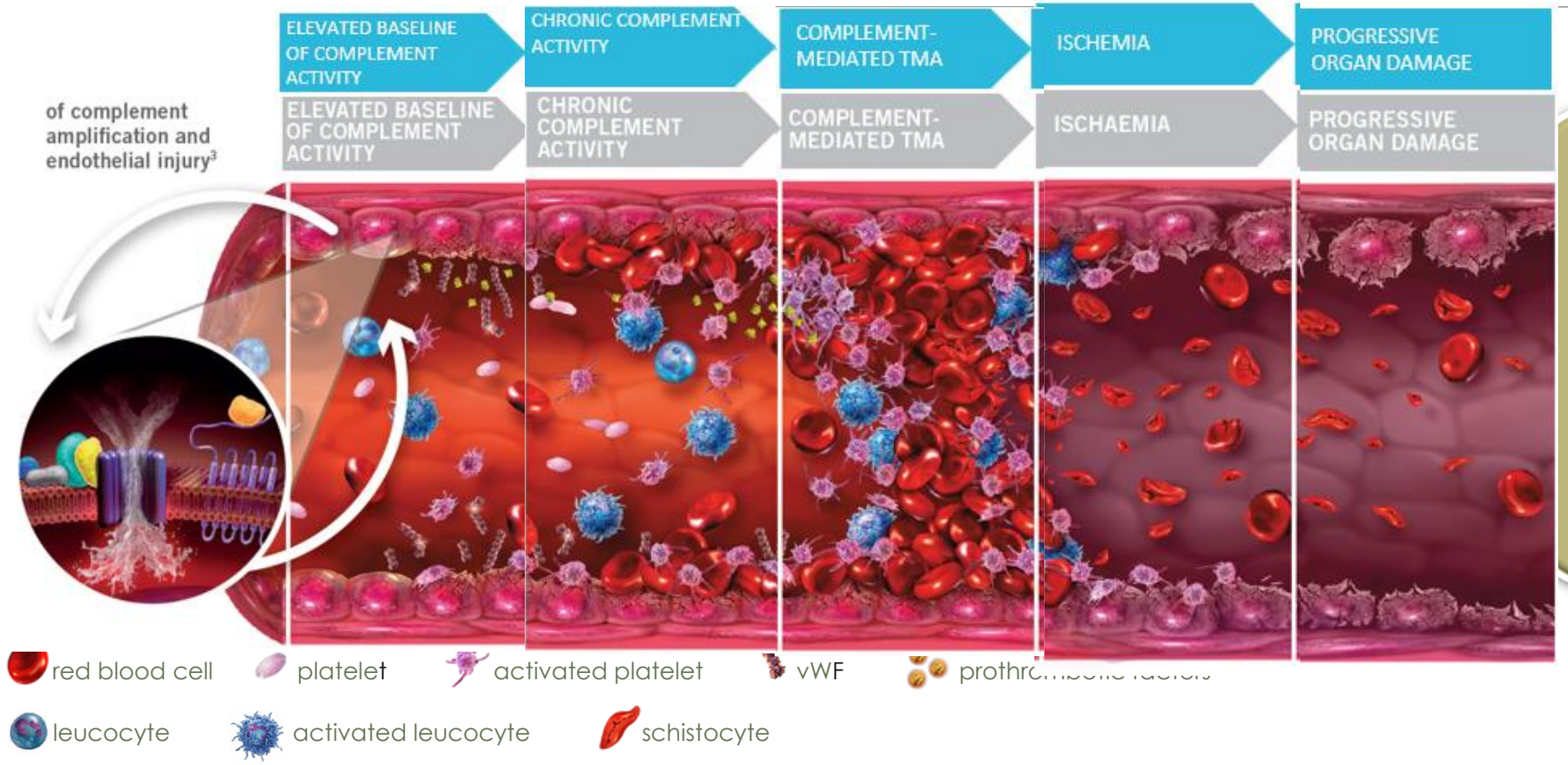
1. **Bone marrow**
2. **Solid organ**

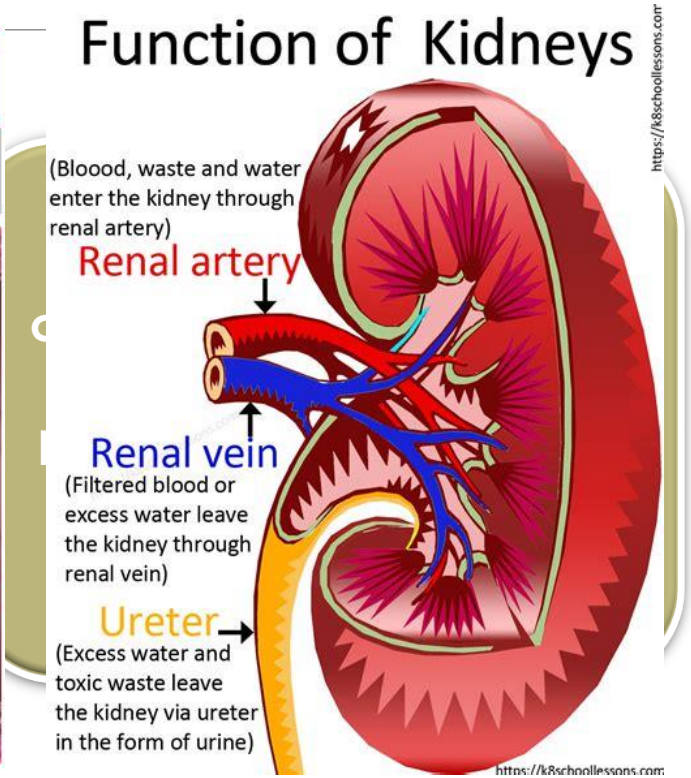
- **Kidney**

1. Pendleton RC, Rodgers GM. Thrombosis and antithrombotic therapy. In: Greer JP *et al.*, eds. *Wintrobe's Clinical Hematology*. 13th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2014;pp 1218–57. **2.** Campistol JM *et al. Nefrologia* 2015;35:421–47.

TMA lesions and tissue damage[1]

Vicious cycle of complement amplification and endothelial injury[2]

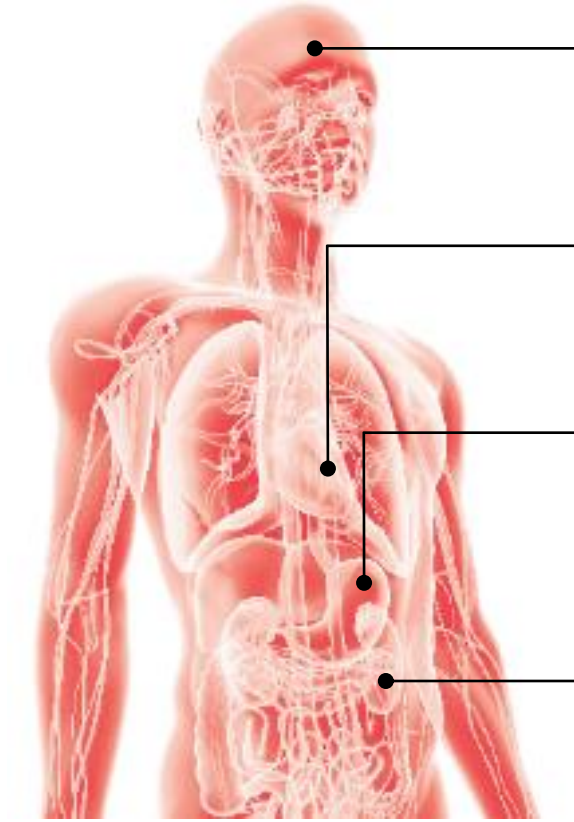




AHUS, ATYPICAL HEMOLYTIC UREMIC SYNDROME; TMA, THROMBOTIC MICROANGIOPATHY.

1. GOODSHIP THJ *ET AL. KIDNEY INT* 2017;91:539–51. **2.** NORIS M *ET AL. NAT REV NEPHROL* 2012;8:622–33. **3.** LE QUINTREC M *ET AL. AM J TRANSPLANT* 2013;13:663–75.
4. MACIA M *ET AL. CLIN KIDNEY J* 2017;10:310–19.

Patients with sever TMA complications



Up to 25% **experience neurological symptoms, including[5]:**

- Confusion[3]
- Encephalopathy[4,5]
- Stroke[5]
- Seizure[3]

Up to 33% **experience CV symptoms, including[8]:**

- Arterial thrombosis[5]
- Vascular stenosis[4]
- Cardiomyopathy[3]
- Hypertension[3]
- Myocardial infarction[4,5]

Up to 47% **experience GI symptoms, including[5]:**

- Colitis[5]
- Abdominal pain[3]
- Pancreatitis[5]
- Nausea/vomiting[5]
- Gastroenteritis[2,7]
- Diarrhea[3]

More than 49% **progress to ESRD[4,5]:**

- Elevated creatinine[3]
- Decreased eGFR[1]
- Proteinuria[6]

Other macrovascular complications[8]:

Peripheral arterial disease
Phalangeal gangrene

AHUS, ATYPICAL HEMOLYTIC UREMIC SYNDROME; CV, CARDIOVASCULAR; EGFR, ESTIMATED GLOMERULAR FILTRATION RATE; ESRD, END-STAGE RENAL DISEASE; GI, GASTROINTESTINAL.
[A]THE ORGAN-SPECIFIC SYMPTOMS ASSOCIATED WITH AHUS ARE REPORTED FROM THE PUBLISHED LITERATURE AND ARE NOT LIMITED TO ONLY THOSE LISTED IN THIS SLIDE.

1. LEGENDRE CM *ET AL. N ENGL J MED* 2013;368:2169–81. **2.** GOODSHIP THJ *ET AL. KIDNEY INT* 2017;91:539–51. **3.** JAMME M *ET AL. PLOS ONE* 2017;12:E0177894. **4.** HOFER J *ET AL. FRONT PEDIATR* 2014;2:97. **5.** CAMPISTOL JM *ET AL. NEFROLOGIA* 2015;35:421–47. **6.** KRISHNAPPA V *ET AL. THER APHER DIAL* 2018;22:178–88. **7.** SCHONERMARCK U, RIES W *ET AL. CLIN KIDNEY J* 2020;13:208-16. **8.** NORIS M, REMUZZI G. *NAT REV NEPHROL* 2014;10:174–80.

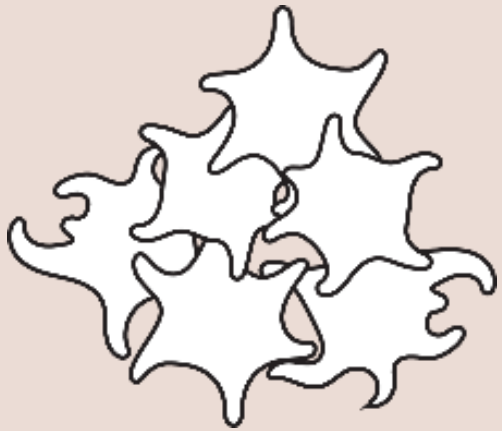
TMAs: Underlying cause

Incidence[b,7]

Underlying cause

TTP
13%

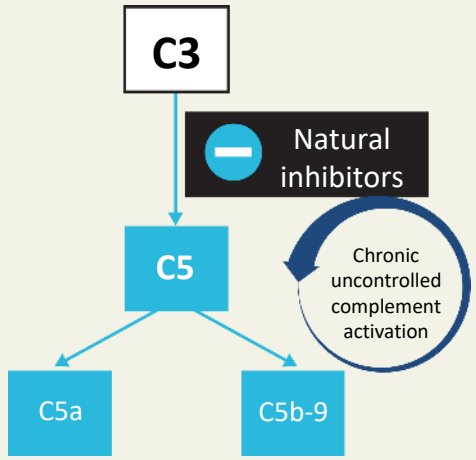
Severe deficiency (≤5%) of ADAMTS13 activity



Insufficient ADAMTS13 activity (≤5%)[a] leaves von Willebrand factor uncleaved, causing excessive platelet aggregation[1,2]

aHUS
61%

Complement-mediated



Genetic defects in natural inhibitors lead to chronic, uncontrolled activation of the complement system, causing continuous endothelial cell damage and platelet aggregation[3–5]

STEC-HUS
6%

Shiga-toxin induced

Certain bacteria, notably *Escherichia coli*, produce toxins that cause uncontrolled complement activation, direct cell damage, and apoptosis[1,6]

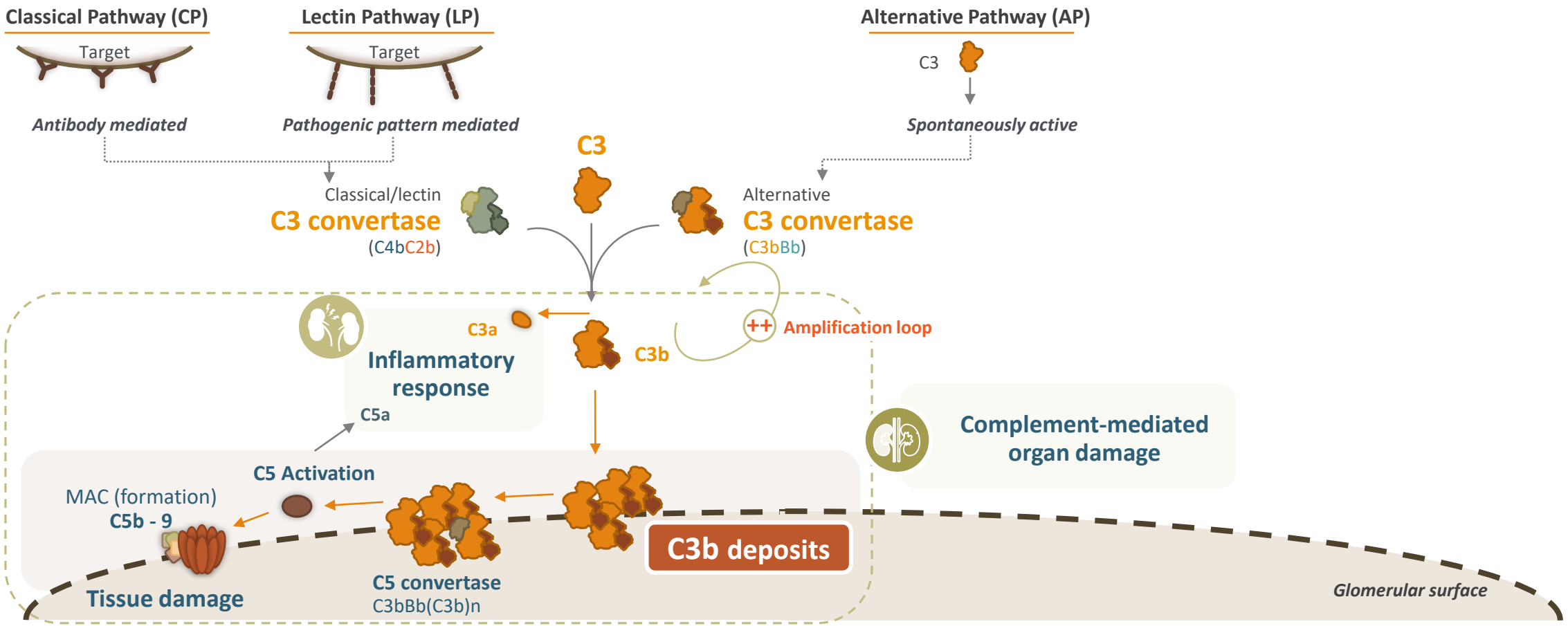
ADAMTS13, A DISINTEGRIN AND METALLOPROTEINASE WITH A THROMBOSPONDIN TYPE 1 MOTIF MEMBER 13; AHUS, ATYPICAL HEMOLYTIC UREMIC SYNDROME; STEC-HUS, SHIGA TOXIN–PRODUCING *ESCHERICHIA COLI* HEMOLYTIC UREMIC SYNDROME; TMA, THROMBOTIC MICROANGIOPATHY; TTP, THROMBOTIC THROMBOCYTOPENIC PURPURA.

[A]SOME ASSAYS REPORT ADAMTS13 <10% AS INDICATIVE OF TTP. [B]DERIVED FROM A PROSPECTIVE CROSS-SECTIONAL MULTICENTRE NON-INTERVENTIONAL EPIDEMIOLOGICAL STUDY IN GERMANY; TMAS OTHER THAN AHUS, TTP AND STEC-HUS HAD AN INCIDENCE OF 20%.[7]

1. LAURENCE J *ET AL. CLIN ADV HEMATOL ONCOL* 2016;14(11 SUPPL 11):2–15. **2.** AZOULAY E *ET AL. CHEST* 2017;152:424–34. **3.** GOODSHIP THJ *ET AL. KIDNEY INT* 2017;91:539–51. **4.** KATO H *ET AL. PEDIATR INT* 2016;58:549–55. **5.** LOIRAT C *ET AL. PEDIATR NEPHROL* 2016;31:15–39. **6.** CAMPISTOL JM *ET AL. NEFROLOGIA* 2015;35:421–47. **7.** SCHONERMARCK U, RIES W *ET AL. CLIN KIDNEY J* 2020;13:208–16.

Dysregulation of the complement

Complement pathways[1–4]



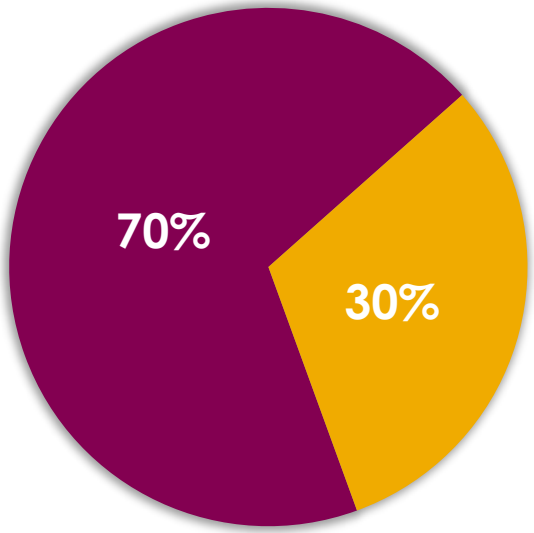
C3/3a/3b/3d/5, complement 3/3a/3b/3d/5; C3G, C3 glomerulopathy; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; MAC, membrane attack complex.

1. Smith RJH, *et al. Nat Rev Nephrol* 2019;15:129–43; 2. Zipfel PF, *et al. Front Immunol* 2019;10:2166; 3. Meuleman MS, *et al. Semin Immunol* 2022;60:101634; 4. Merle NS, *et al. Front Immunol* 2015;6:262.

Trigger of aHUS

- In some cases, genetic mutations alone are not enough to cause aHUS[1]
- aHUS is often unmasked by a new or preexisting condition that promotes complement activation and endothelial damage (trigger)[1,2]

aHUS unmasked by a trigger[2,a]

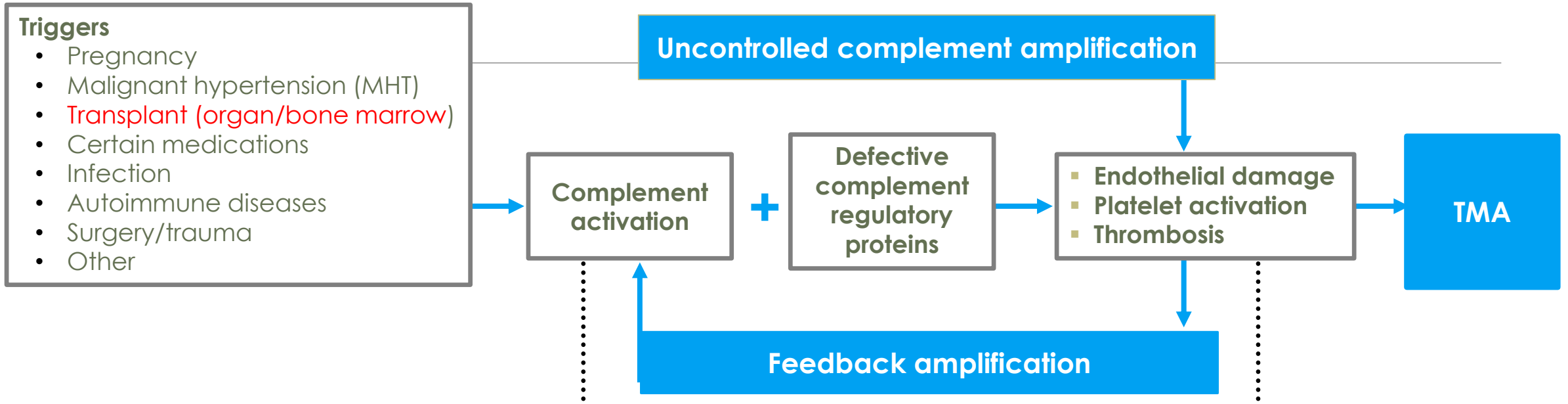


aHUS with no identifiable trigger [2,a]

70% (191/273) of patients with aHUS presented their first clinical manifestations while experiencing a trigger[2,a]

aHUS, atypical hemolytic uremic syndrome.
[a]From a study of 273 patients with aHUS enrolled in the International Registry of Recurrent and Familial HUS/TTP between 1996 and 2007.[2]
1. Riedl M *et al. Semin Thromb Hemost* 2014;40:444–64. **2.** Noris M *et al. Clin J Am Soc Nephrol* 2010;5:1844–59.

Triggers in aHUS and TMA manifestations



If the signs and symptoms of TMA do not rapidly resolve in response to trigger management, continue to evaluate following the differential diagnostic pathway of TMAs[2]

USED WITH PERMISSION FROM LAURENCE J *ET AL. CLIN ADV HEMATOL ONCOL* 2016;14(11 SUPPL 11):2–15.
AHUS, ATYPICAL HEMOLYTIC UREMIC SYNDROME; TMA, THROMBOTIC MICROANGIOPATHY.
1. LAURENCE J *ET AL. CLIN ADV HEMATOL ONCOL* 2016;14(11 SUPPL 11):2–15. **2.** RIEDL M *ET AL. SEMIN THROMB HEMOST* 2014;40:444–64. **3.** ASIF A *ET AL. J NEPHROL* 2017;30:347–62.

De Novo TMA triggers

Immune suppressive associated TMA(CNI/MTOR)

Antibody Mediated Rejection (AMR)

Viral infection

HCV, CMV, BK and parvovirus

Genetic abnormalities in the complement cascade

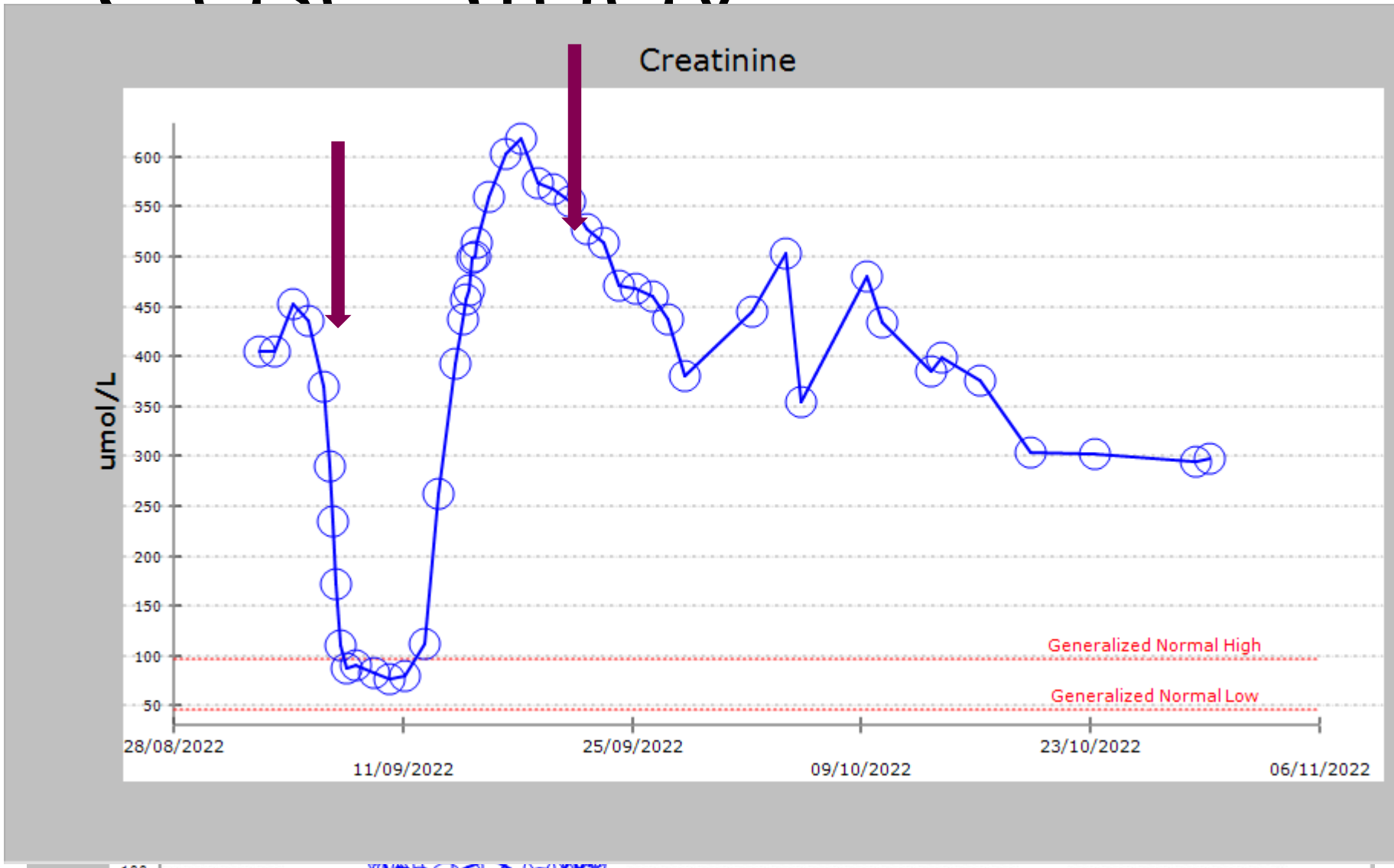
Phenotypical shift of c3 glomerulopathy with ESRD to aHUS post transplant

Missed diagnosis of TMA in the native kidney as a cause of ESRD

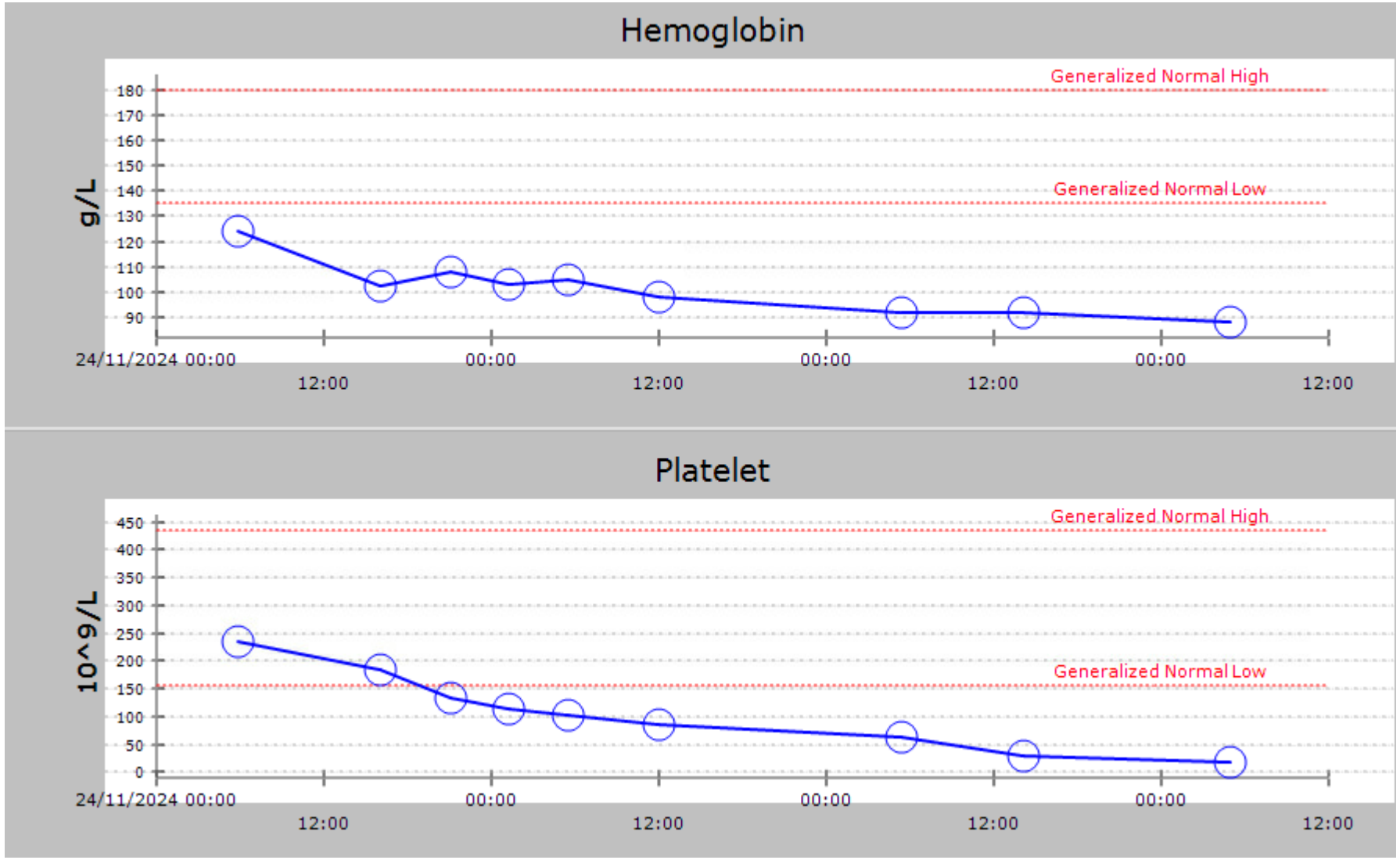
Garg N, Rennke HG, Pavlakis M, Zandi-Nejad K. De novo thrombotic microangiopathy after kidney transplantation. *Transplant Rev* (Orlando) 2018; **32**: 58-68 [PMID: 29157988 DOI: 10.1016/j.trre.2017.10.001]

Case Study

- 60 Years old lady underwent kidney transplantation from her son.
- Developed thrombocytopenia and drop in hemoglobin requiring transfusion.
- Biopsy showed TMA
- Tacrolimus was stopped and treated with Eculizumab and belatacept.



Case Presentation developed by the speaker



Case Presentation developed by the speaker

Patients at high risk (solid organ)

1. patient with previous TMA
   - Atypical HUS
   - Recurrent after kidney transplantation
2. genetic compliment disorder
   - Factor H
3. Preeclampsia associated kidney failure
4. Hypertensive young patients with ESRD

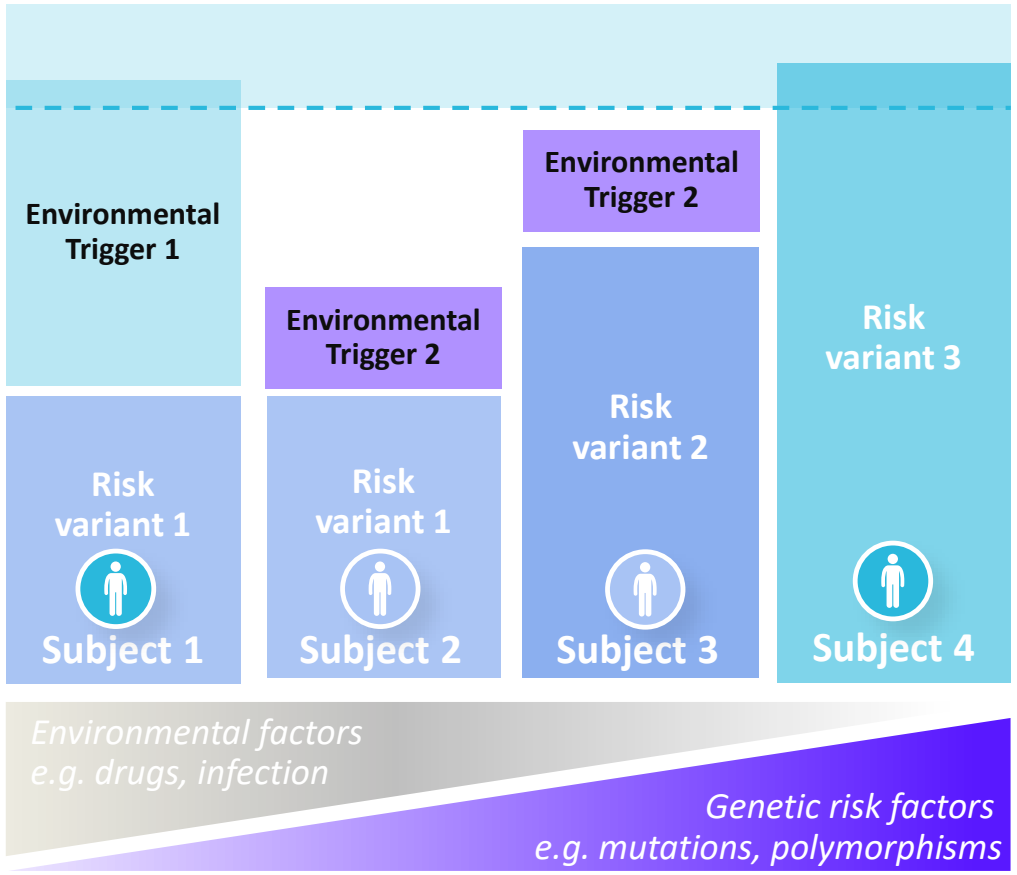
Need for proper diagnosis pre transplantation including genetic testing

High prevalence of ESRD of unknown etiology in our population (failure to diagnose)

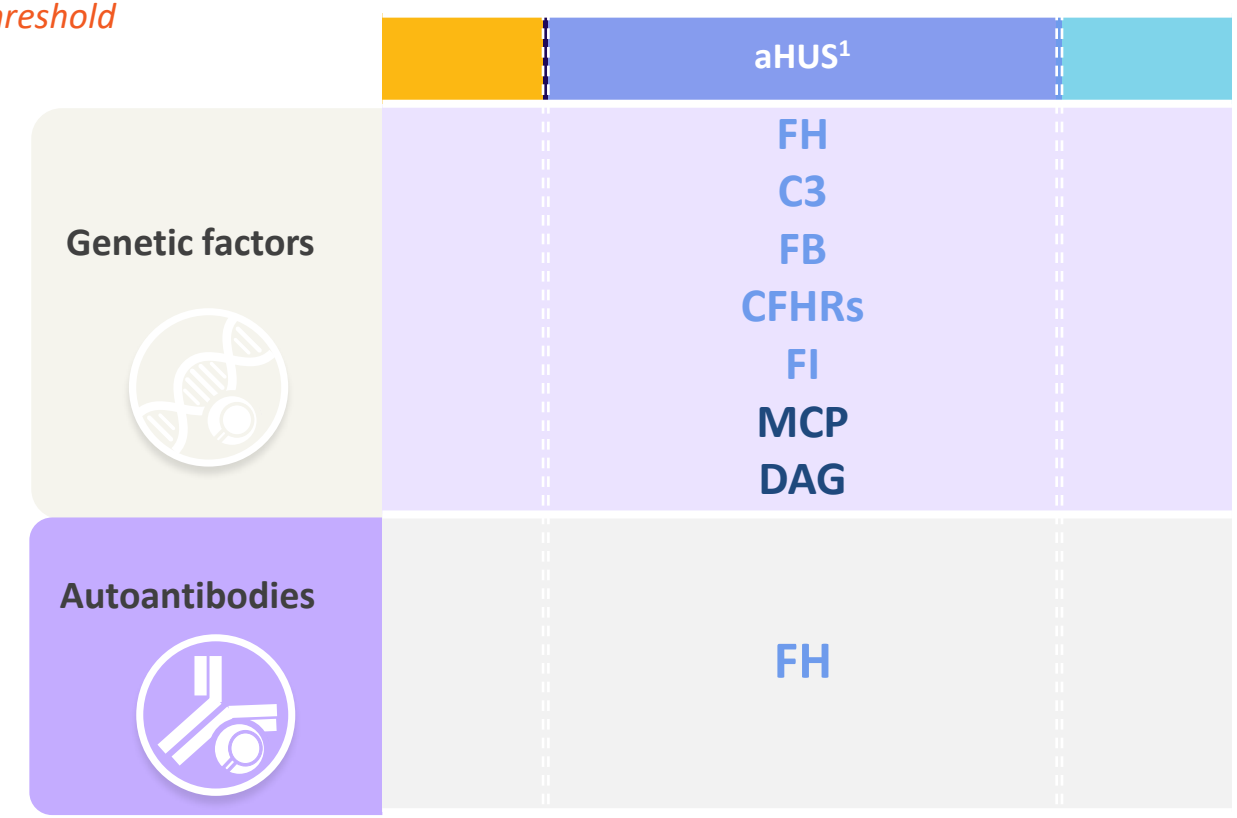
*BASED ON MY CLINICAL EXPERIENCE AND OPINION.
AHUS, ATYPICAL HAEMOLYTIC URAEMIC SYNDROME; TMA, THROMBOTIC MICROANGIOPATHY.
1. GOODSHIP TH ET AL. *KIDNEY INT* 2017;91:539–551.

TMA disease development : multifactorial diseases

Genetic and environmental factors can increase or decrease the risk for disease development*[1,2]



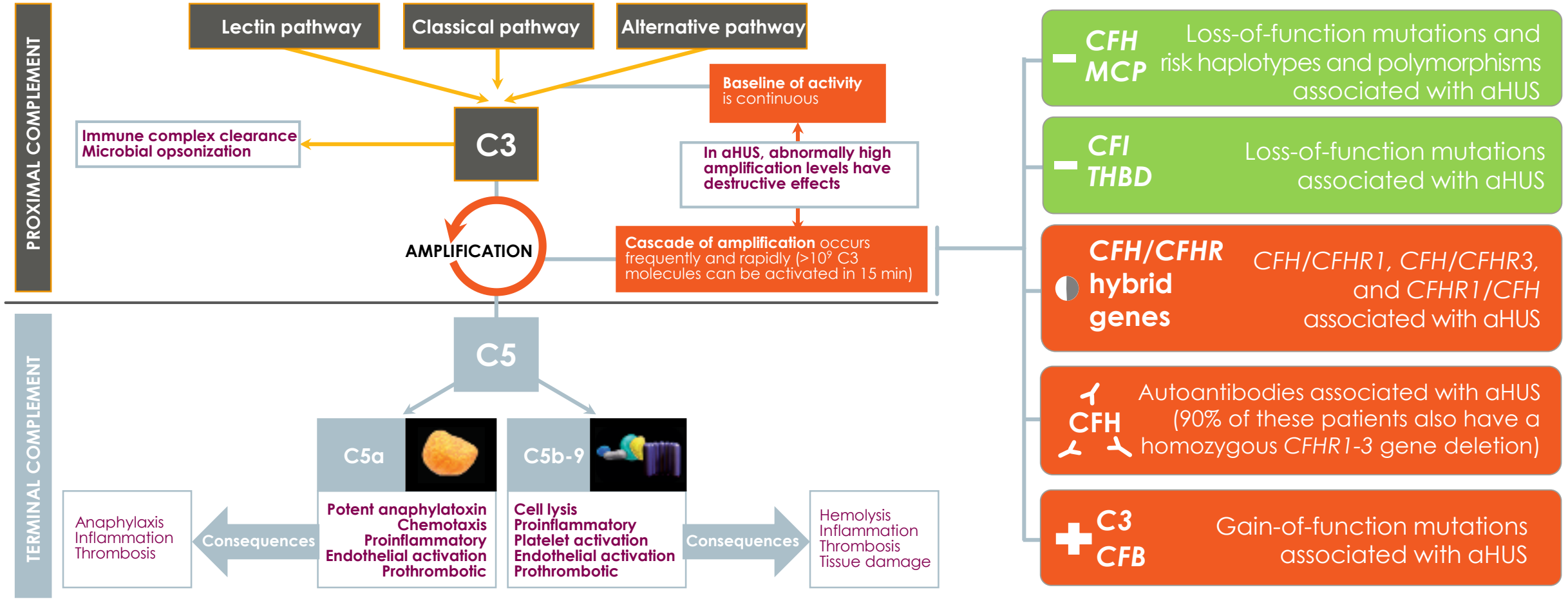
Affected genes and self antigens are common to other glomerular diseases, but disease mechanisms differ[1]



*The figure shown on the left is illustrative, showing how risk variants and environmental triggers can contribute to disease.
aHUS, atypical haemolytic uraemic syndrome; C3/4/5, complement 3/4/5; C3G, C3 glomerulopathy; DAG, diacylglycerol; FB, factor B; FH, factor H; CFHR, complement factor H-related protein; FI, factor I; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; IgA, immunoglobulin A; IgAN, IgA nephropathy; MCP, membrane cofactor protein; MN, membranous nephropathy; NeF, nephritic factor; PLA2R, phospholipase A2 receptor; THSD7A, thrombospondin type-1 domain-containing 7A.

1. Zipfel PF, *et al. Cell Tissue Res* 2021;385:355–70; 2. Asano M, *et al. CEN Case Rep* 2022;11:259–64; 3. Iatropoulos P, *et al. J Am Soc Nephrol* 2018;29:283–94.

Genetic mutations, polymorphisms, autoantibodies and uncontrolled complement activity[1–6]



aHUS, atypical hemolytic uremic syndrome; *C3*, complement component 3 gene; *CFB*, complement factor B gene; *CFH*, complement factor H gene; *CFHR1*, complement factor H-related protein 1; *CFI*, complement factor I gene; *MCP*, membrane cofactor protein gene; *THBD*, thrombomodulin gene.

1. Noris M *et al. Nat Rev Nephrol* 2012;8:622–33. **2.** Campistol JM *et al. Nefrologia* 2015;35:421–47. **3.** Jokiranta TS. *Blood* 2017;129:2847–56. **4.** Maga TK *et al. Hum Mutat* 2010;31:E1445–60. **5.** Noris M *et al. Clin J Am Soc Nephrol* 2010;5:1844–59. **6.** Noris M, Remuzzi G. *N Engl J Med* 2009;361:1676–87.

Importance of diagnosing aHUS in patients with malignant hypertension and TMA

The role of complement was evaluated in 9 consecutive patients with biopsy-proven renal TMA who presented with severe hypertension[1,a]

- 7/9 of these patients had a history of hypertension
- Profound signs and symptoms of TMA were only evident in 1 patient[b]
- None of the patients had a family history consistent with familial aHUS

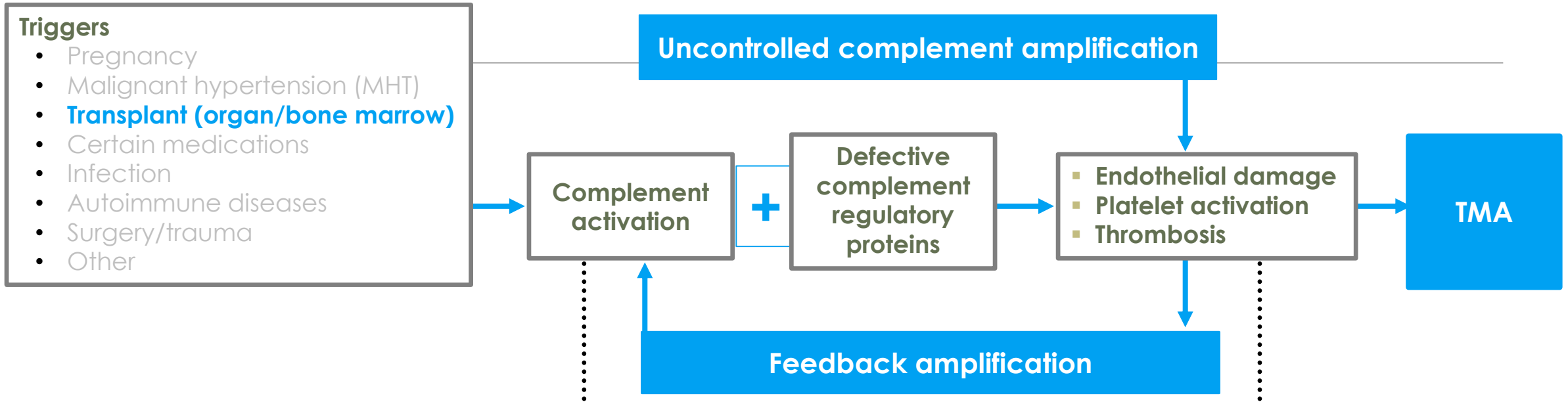
Patient	TMA progression			Clinical characteristics	
	Progression to ESRD	Renal transplant	TMA recurrence following renal transplant	Complement abnormality	Profound hematologic signs of TMA
1	✓	✓	✓	✓	
2	✓	✓	✓	✓	
3	✓	✓	✓	✓	✓
4	✓	✓		✓	
5					
6	✓			✓	
7	✓			✓	
8	✓				
9	✓				
TOTAL	8/9 (89%)	4/9 (44%)	3/9 (33%)	6/9 (67%)	1/9 (11%)

[A]PATIENTS 1 AND 2 EACH HAD 2 TRANSPLANTED ALLOGRAFTS, AND PATIENTS 3 AND 4 EACH HAD 1 TRANSPLANTED ALLOGRAFT. PATIENT 1 EXPERIENCED 2 TMA RECURRENCE EVENTS, AND PATIENTS 2 AND 3 EACH EXPERIENCED 1 TMA RECURRENCE EVENT. . [B]HEMATOLOGIC SIGNS OF TMA INCLUDE A HIGH LACTATE DEHYDROGENASE LEVEL, THROMBOCYTOPENIA, AND MICROANGIOPATHIC HEMOLYTIC ANEMIA.

AHUS, ATYPICAL HEMOLYTIC UREMIC SYNDROME; ESRD, END-STAGE RENAL DISEASE ; TMA, THROMBOTIC MICROANGIOPATHY.

1. TIMMERMANS S *ET AL. KIDNEY INT* 2017;91:1420–5.

Transplant-associated complement amplification and aHUS[1]



Endothelial damage and complement activation occur during transplantation due to multiple factors that may include alloimmune responses, ischemia-reperfusion events, viral infections and the use of immunosuppressive therapies[2,3]

TMA may persist despite management of factors causing endothelial injury and complement activation[2]

Patients with *CFH* mutations have a ~75% to 90% risk of subsequent post-transplant TMA manifestations and graft loss vs patients with other genetic abnormalities[4,a]

USED WITH PERMISSION FROM LAURENCE J *ET AL. CLIN ADV HEMATOL ONCOL* 2016;14(11 SUPPL 11):2–15.

[A]REPORTED RISKS FOR PATIENTS WITH CFI ABNORMALITY: 45–80%; C3: 40–70%; MCP: <20%.[4]

AHUS, ATYPICAL HEMOLYTIC UREMIC SYNDROME; *CFH*, COMPLEMENT FACTOR H GENE; TMA, THROMBOTIC MICROANGIOPATHY.

1. LAURENCE J *ET AL. CLIN ADV HEMATOL ONCOL* 2016;14(11 SUPPL 11):2–15. **2.** ZUBER J *ET AL. NAT REV NEPHROL* 2011;7:23–35. **3.** NORIS M *ET AL. NAT REV NEPHROL* 2012;8:622–33. **4.** LOIRAT C, FREMEAUX-BACCHI V. *ORPHANET J RARE DIS* 2011;6:60.

Patients with identified complement mutations and risk for post-transplant recurrence[1,2]

Genetic Abnormality	Review of published data, N= 135 transplanted patients[1]		Analysis of international aHUS registry N=273[3*]	
	Subsequent TMA manifestations n/n, (% of grafts)	Graft loss after subsequent TMA manifestations n/n, (% of TMA manifestations)	Graft loss 1 year after renal transplantation n/n, (% of grafts)	ESRD or death after 3 years, n/n, (% of patients)[†]
CFH mutations and CFH/CFHR1 hybrid gene	49/76 (64%)	40/49 (82%)	12/17 (71%)	49/64 (77%)
CFH autoantibodies	5/17 (29%)	4/5 (80%)	1/1 (100%)	5/8 (63%)
CFI mutations	19/26 (73%)	18/19 (95%)	4/6 (67%)	6/10 (60%)
THBD mutations	1/1 (100%)	1/1 (100%)	1/1 (100%)	7/13 (54%)
C3 mutations	16/30 (53%)	12/16 (75%)	3/7 (43%)	8/12 (67%)
CFB mutations	4/4 (100%)	4/4 (100%)	NR	NR
MCP mutations	3/17 (18%)	2/3 (66%)	0/3 (0%)	1/17 (6%)
No identified mutation	NR	NR	17/29 (59%)	60/119 (50%)

[a]Patients 1 and 2 each had 2 transplanted allografts, and patients 3 and 4 each had 1 transplanted allograft. Patient 1 experienced 2 TMA recurrence events, and patients 2 and 3 each experienced 1 TMA recurrence event. . [b]Hematologic signs of TMA include a high lactate dehydrogenase level, thrombocytopenia, and microangiopathic hemolytic anemia.

aHUS, atypical hemolytic uremic syndrome; ESRD, end-stage renal disease ; TMA, thrombotic microangiopathy.

1. Timmermans S *et al. Kidney Int* 2017;91:1420–5.

Objective: Preventing recurrent aHUS

Impact of recurrent aHUS

Without treatment, ESKD is a common outcome in patients with aHUS*

Although aHUS can occur at any age, patients are typically diagnosed at a young age*

High risk of recurrent disease[1]

Poor transplant outcomes[2]

Underlying cause is predictive of risk of recurrence, ESKD and impact on survival[2]

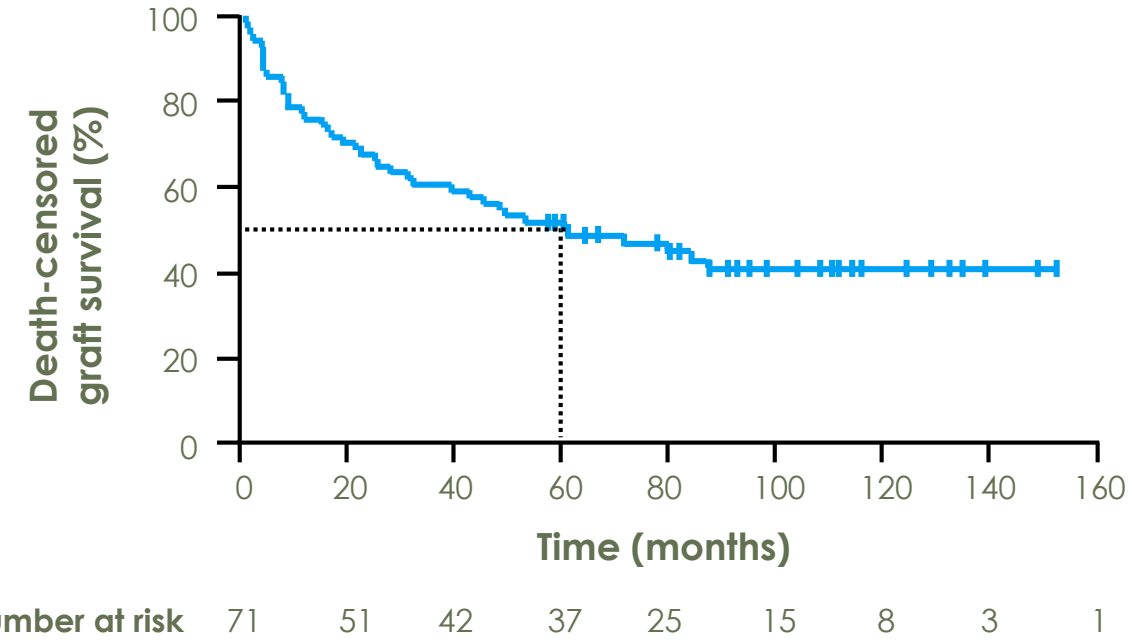
*BASED ON MYEXPERIENCE AND OPINION.

AHUS, ATYPICAL HAEMOLYTIC URAEMIC SYNDROME; ESKD, END-STAGE KIDNEY DISEASE.

1. GOODSHIP TH ET AL. *KIDNEY INT* 2017;91:539–551; 2. GLOVER E ET AL., *TRANSPLANTATION*. 2023 APR 1;107(4):994-1003. DOI: 10.1097/TP.0000000000004355. EPUB 2023 MAR 31.

Renal transplantation in patients with aHUS

Death-censored graft survival in patients with aHUS[1]



From: Le Quintrec M *et al. Am J Transplant* 2013;13:663–75.

In the French aHUS registry, the rate of graft loss was 24% at 1 year and 49% at 5 years following transplantation[a]

AHUS, ATYPICAL HEMOLYTIC UREMIC SYNDROME; ESRD, END-STAGE RENAL DISEASE.
[A]IN RENAL TRANSPLANT RECIPIENTS WITH AHUS-RELATED ESRD, WITH OR WITHOUT MUTATIONS; DEATH-CENSORED DATA. 95% OF GRAFTS WERE FROM DECEASED DONORS;
4% FROM LIVING RELATED DONORS.
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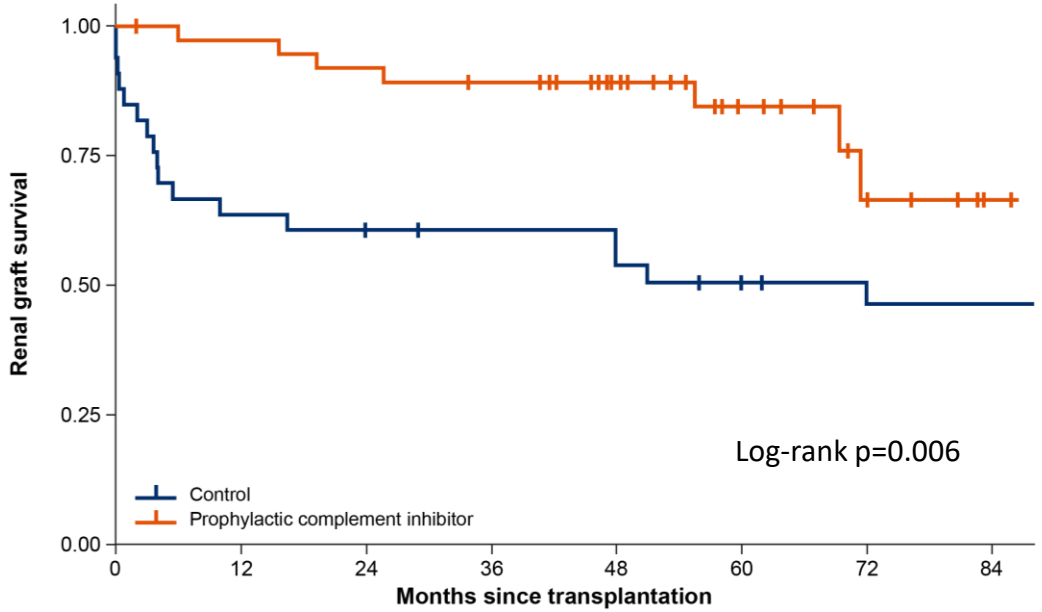
4% FROM LIVING RELATED DONORS.
1. LE QUINTREC M *ET AL. AM J TRANSPLANT* 2013;13:663–75.

Objective: Prevention of recurrent aHUS

KDIGO consensus meeting 2016: prophylaxis against aHUS recurrence during kidney transplant with complement inhibitor treatment is recommended for patients at moderate or high risk of disease recurrence[1]

Death-censored renal graft survival with and without complement inhibitor treatment[2*]



Number at risk								
Control	33	21	20	18	18	14	12	11
Prophylactic complement inhibitor	38	36	34	32	25	14	7	2

*KAPLAN-MEIER ANALYSIS OF RENAL GRAFT SURVIVAL FOR GRAFTS RECEIVED AFTER 2002 IN RECIPIENTS AT MEDIUM OR HIGH RISK OF RECURRENCE OF AHUS. THOSE WHO RECEIVED PROPHYLACTIC COMPLEMENT INHIBITOR TREATMENT FROM THE TIME OF TRANSPLANTATION COMPARED WITH THOSE WHO DID NOT RECEIVE COMPLEMENT INHIBITOR TREATMENT FOR THE DURATION OF THE TRANSPLANT (CONTROL). NUMBERS AT RISK IN EACH GROUP AT 6 MONTHLY TIME POINTS ARE DETAILED BELOW THE GRAPH.[2]

AHUS, ATYPICAL HAEMOLYTIC URAEMIC SYNDROME; KDIGO, KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES.

1. GOODSHIP TH ET AL. *KIDNEY INT* 2017;91:539–551; 2. GLOVER E ET AL., *TRANSPLANTATION*. 2023 APR 1;107(4):994-1003. DOI: 10.1097/TP.0000000000004355. EPUB 2023 MAR 31.

De novo TMA after transplantation

Diagnosing TMA post transplant

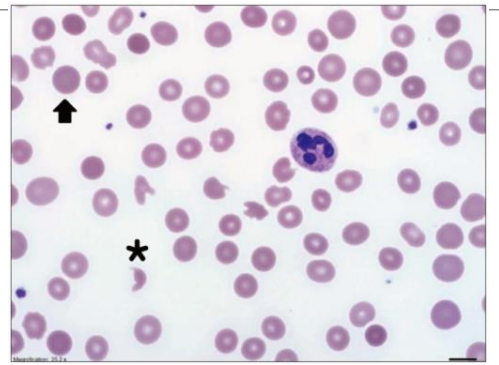
Thrombocytopaenia[1]

MAHA, characteristics of which include:

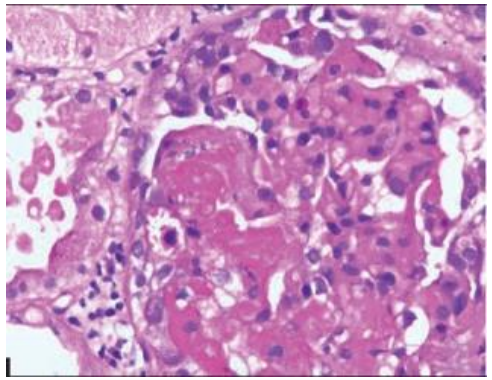
- Anaemia[1]
- Fragments/schistocytes[1]
- Increased LDH[1]
- Decreased haptoglobin levels[1]

End organ damage[1]

*Only present in 25% of patients with post-transplant TMA**



Peripheral blood smear showing RBC fragmentation and schistocytes (asterisk) and polychromasia (arrow)[2]



Glomerulus shows fibrin thrombi and mesangiolysis[3]

*BASED ON MYCLINICAL EXPERIENCE AND OPINION.

IMAGES REPRODUCED FROM PARK YJ ET AL. *J CARDIOVASC ULTRASOUND* 2016 AND RADHA S ET AL. *INDIAN J NEPHROL* 2014.

LDH, LACTATE DEHYDROGENASE; MAHA, MICROANGIOPATHIC HAEMOLYTIC ANAEMIA; TMA, THROMBOTIC MICROANGIOPATHY.

1. YOUNG J ET AL. *BONE MARROW TRANSPLANT* 2021;56:1805–1817; 2. PARK YJ ET AL. *J CARDIOVASC ULTRASOUND* 2016;24:75–78; 3. RADHA S ET AL. *INDIAN J NEPHROL* 2014;24:24–27.

Aetiology of post-transplant TMA

Native kidney disease

- HUS
  - STEC-HUS
  - aHUS
  - Secondary HUS/TMA
- Thrombotic thrombocytopaenic purpura
- Antiphospholipid antibody syndrome

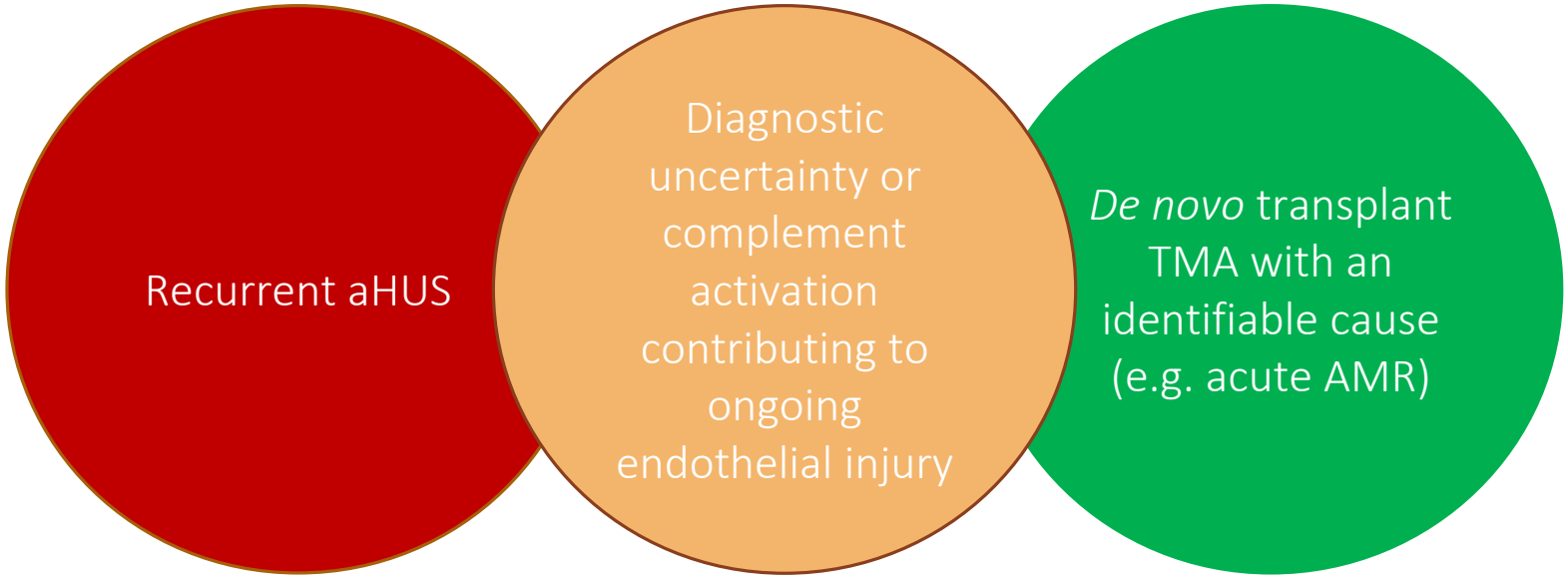
Post transplant (1-2% of transplants)*

- HUS
  - aHUS
  - Secondary HUS/TMA
    - CNIs and mTORis
    - Ischaemia reperfusion
- Acute antibody-mediated rejection

*BASED ON MYCLINICAL EXPERIENCE AND OPINION.

AHUS, ATYPICAL HAEMOLYTIC URAEMIC SYNDROME; CNI, CALCINEURIN INHIBITOR; HUS, HAEMOLYTIC URAEMIC SYNDROME; MTORI, MAMMALIAN TARGET OF RAPAMYCIN INHIBITOR; STEC-HUS, SHIGA TOXIN-PRODUCING *ESCHERICHIA COLI*-ASSOCIATED HAEMOLYTIC URAEMIC SYNDROME; TMA, THROMBOTIC MICROANGIOPATHY.

Identifying the cause of post-transplant TMA*



Complement inhibitor†✓

Complement inhibitor† **?**

Complement inhibitor†✗

*BASED ON MY CLINICAL EXPERIENCE AND OPINION; †COMPLEMENT INHIBITOR TREATMENT SHOULD BE CONSIDERED AND ASSESSED ON AN INDIVIDUAL CASE BY CASE BASIS.
AHUS, ATYPICAL HAEMOLYTIC URAEMIC SYNDROME; AMR, ANTIBODY-MEDIATED REJECTION; TMA, THROMBOTIC MICROANGIOPATHY.

Recurrent or *de novo* aHUS

Complement Mutation-Associated *De Novo* Thrombotic Microangiopathy Following Kidney Transplantation

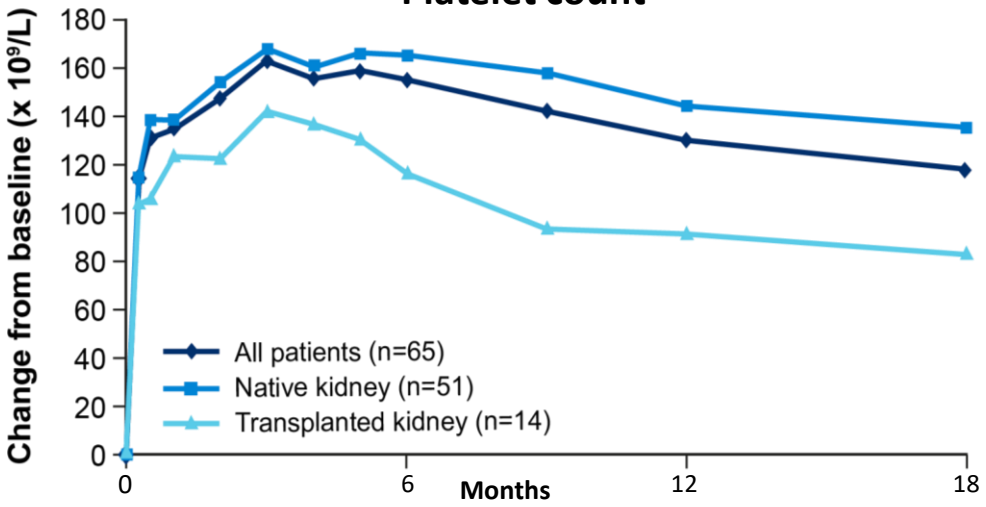
M. Le Quintrec[a], A. Lionet[b], N. Kamar[c], A. Karras[d], S. Barbier[e], M. Buchler[f], F. Fakhouri[g], F. Provost[b], W. H. Fridman[h], E. Thervet[a], C. Legendre[a], J. Zuber[a] and V. Frémeaux-Bacchi[h,*]

genetic abnormalities may represent risk factors for *de novo* TMA after kidney transplantation and raise the question of the best therapeutic strategy.

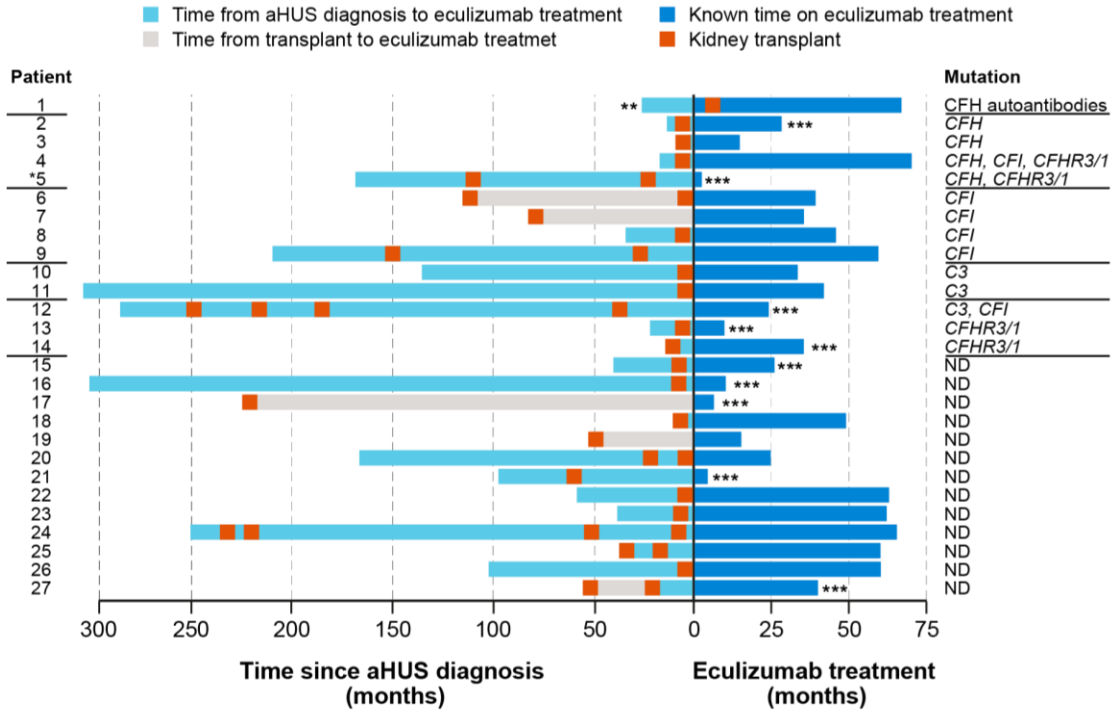
Key words: Complement, complement Factor H, complement Factor I, hemolytic uremic syndrome, kidney transplantation, thrombotic microangiopathy

Of patients (n=26) with post-transplant TMA, 50% have complement mutations/regulatory deficiencies[1]

Platelet count[1]



Timing of kidney transplant in relation to aHUS diagnosis and complement inhibitor treatment†1



FIGURES ADAPTED FROM LEGENDRE ET AL. *TRANSPLANT INT* 2017.

†A *POST HOC* ANALYSIS OF FOUR PROSPECTIVE CLINICAL TRIALS THAT INCLUDED COMPLEMENT INHIBITOR TREATED PATIENTS WITH AHUS THAT HAD NATIVE OR TRANSPLANTED KIDNEYS. STUDY ENDPOINTS INCLUDED COMPLETE TMA RESPONSE, TMA EVENT-FREE STATUS, HAEMATOLOGIC AND RENAL PARAMETERS AND ADVERSE EVENTS[1]; **PATIENT WITHDREW DUE TO AN ADVERSE EVENT; **APPROXIMATE DURATION FROM DIAGNOSIS TO FIRST DOSE OF COMPLEMENT INHIBITOR. AFTER KIDNEY TRANSPLANTATION ON DAY 217, THE PATIENT'S RENAL DATA WERE CENSORED;[1] ***DID NOT ENTER LONG-TERM FOLLOW-UP; NO FURTHER INFORMATION IS AVAILABLE.[1]AHUS, ATYPICAL HAEMOLYTIC URAEMIC SYNDROME; TMA, THROMBOTIC MICROANGIOPATHY.

1. LEGENDRE ET AL. *TRANSPLANT INT* 2017;30:1275–1283; 2. LE QUINTREC ET AL. *AM J TRANSPLANT* 2008;1694–1701.

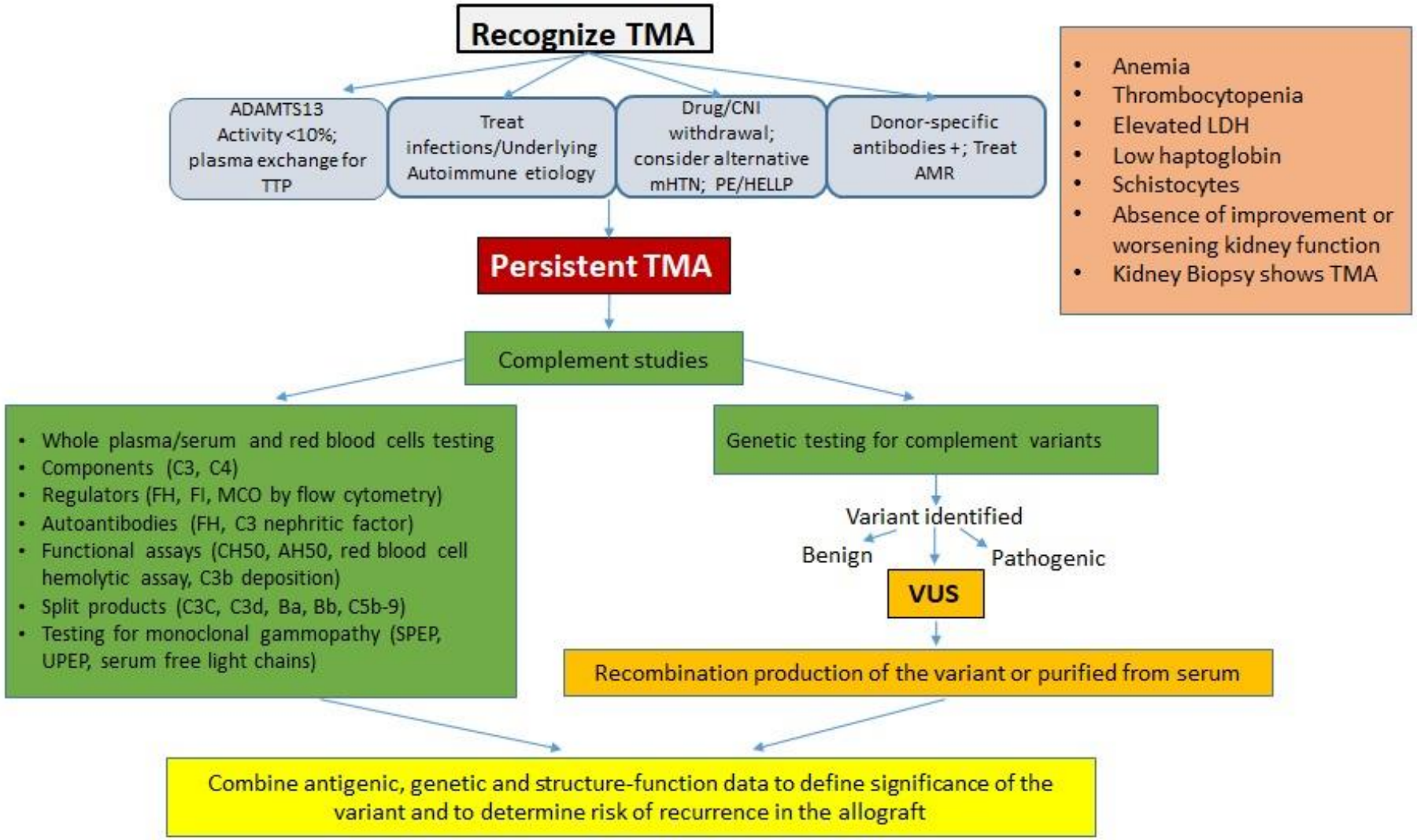
Identifying the cause of post-transplant TMA

	Yes	Possibly	No
Clinical features			
Age		✓	
Sex			✓
Ethnicity			
Cause of ESRD	✓		
Investigations			
Donor-specific antibodies	✓		
Degree of haemolysis/thrombocytopaenia			
Complement biomarkers			
CNI levels			
Renal biopsy	✓		
Complement genetics	✓		

- Should we perform genetic screening?
- If 'yes', in which patients?

- Patients with post-transplant TMA should be assessed for suitability to receive complement inhibitor treatment
- Many will require other management strategies

CNI, CALCINEURIN; ESRD, END-STAGE RENAL DISEASE; TMA, THROMBOTIC MICROANGIOPATHY.
BASED ON MYCLINICAL EXPERIENCE AND OPINION.



CNI, CALCINEURIN; ESRD, END-STAGE RENAL DISEASE; TMA, THROMBOTIC MICROANGIOPATHY.
BASED ON MYCLINICAL EXPERIENCE AND OPINION.

Current therapy

Terminal complement blockers

1. Eculizumab
2. Ravulizumab

3. Other line of therapy

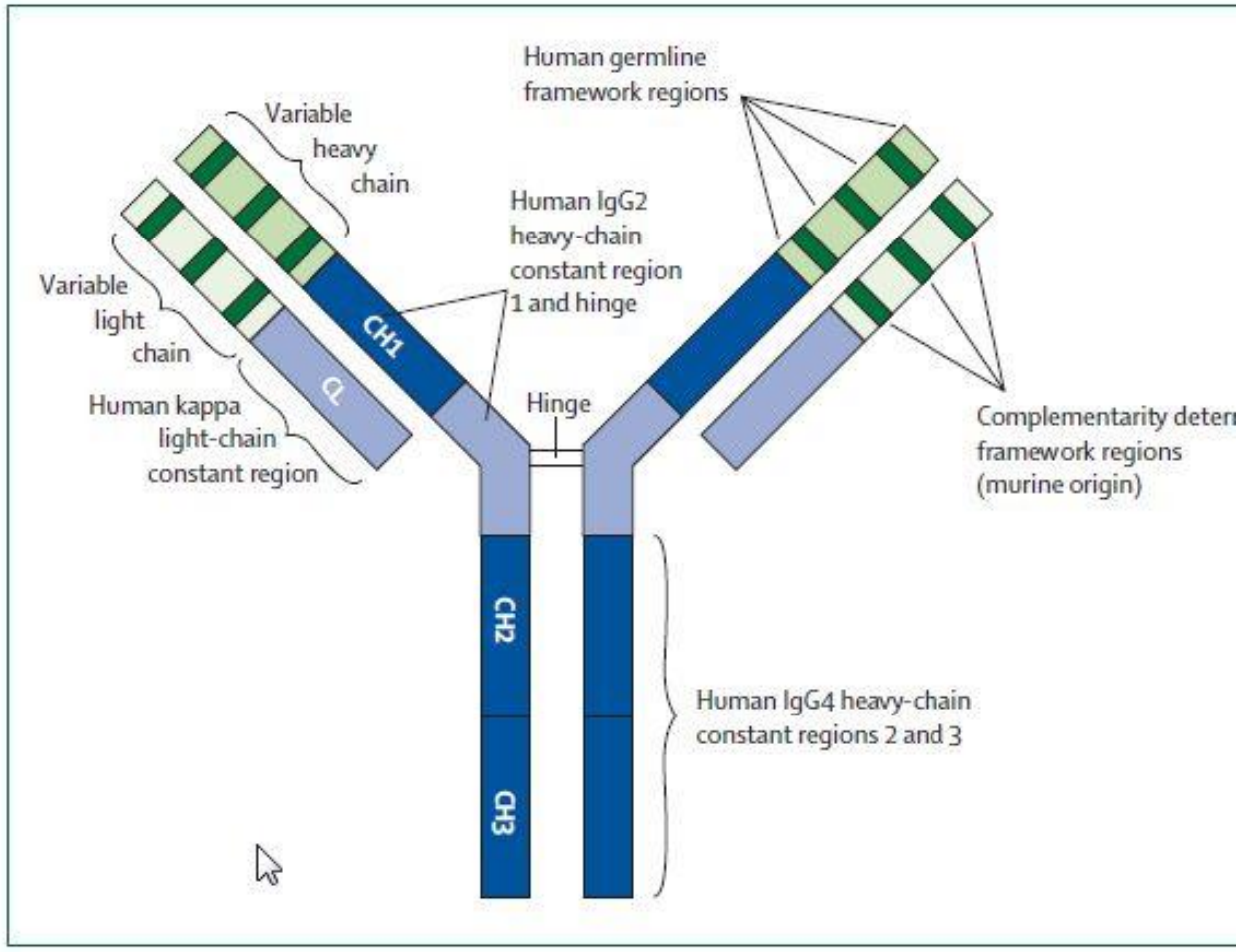
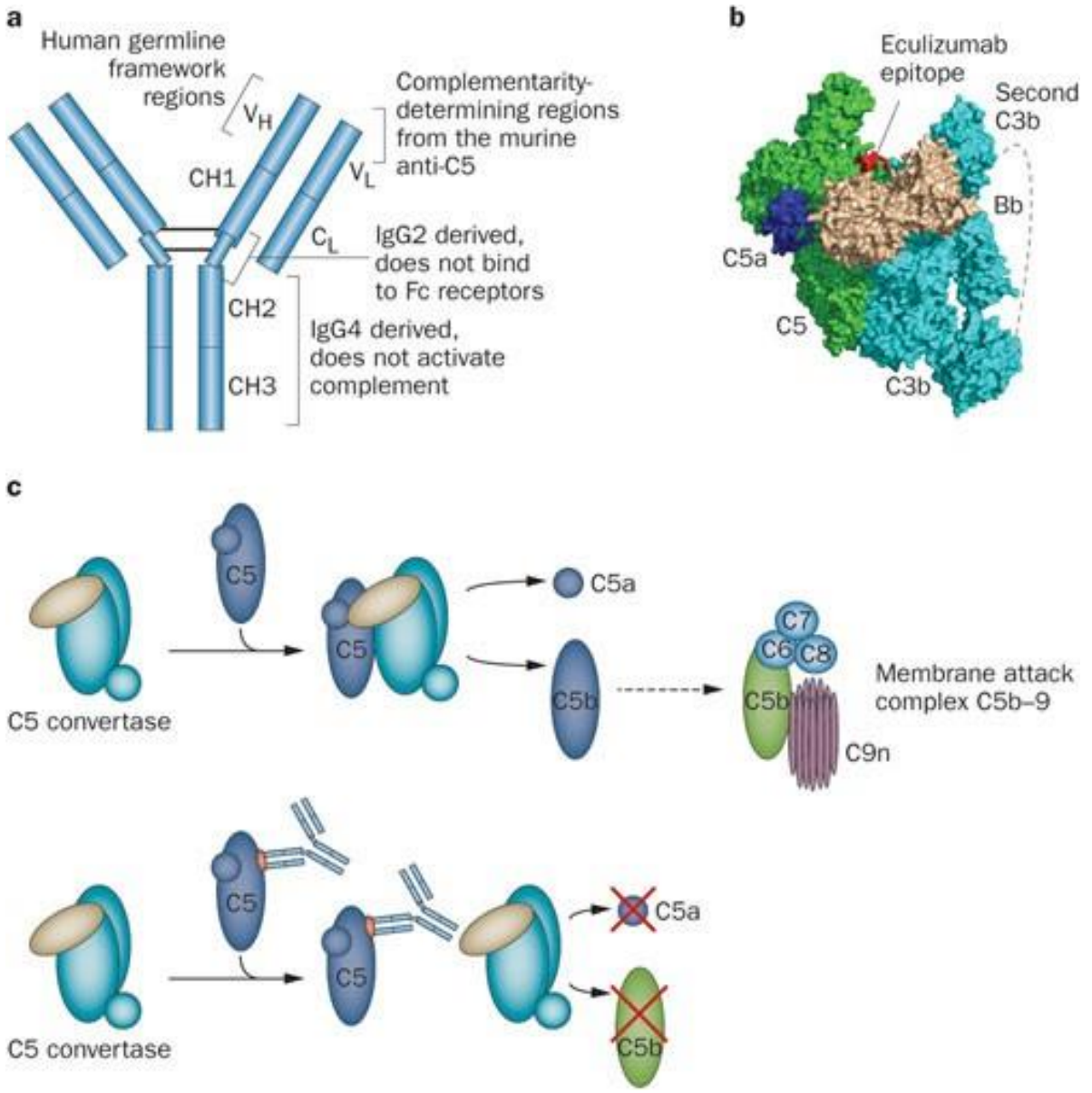


***Figure 3*: Schematic representation of eculizumab**
Reproduced from reference 4 with permission.

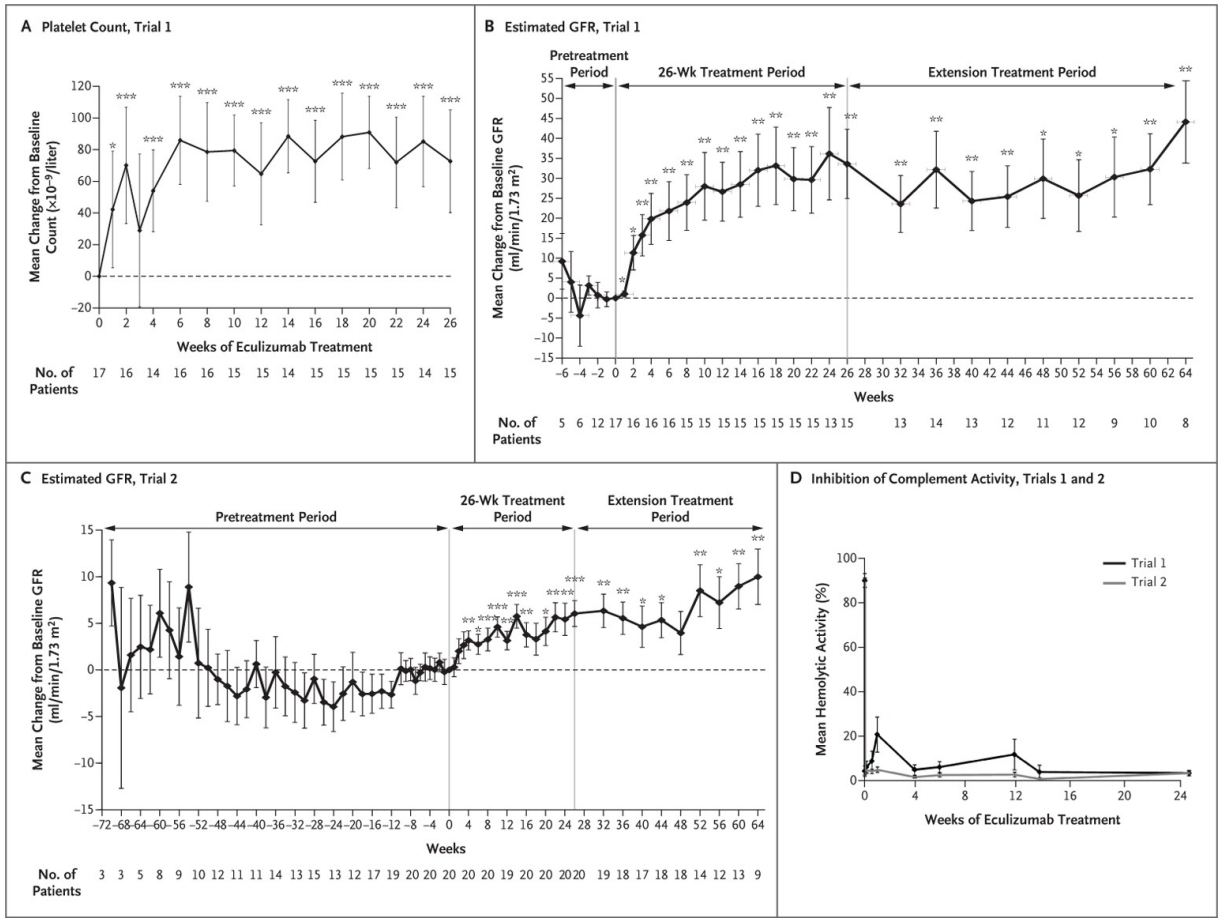
1. Roth A, et al. *Blood Adv.* 2018;2(17):2176-2185 **2.** Andrien BA Jr, Sheridan DL, Tamburini PP, inventors; Alexion Pharmaceutical, Inc, assignee. Anti-C5 antibodies having improved pharmacokinetics. US patent 9,079,949 B1. July 14 2015; **3.** Sheridan D et al. *PLoS One* 2018;13:e0195909.


a
Human germline framework regions
V_H
V_L
CH1
Complementarity-determining regions from the murine anti-C5
C_L
IgG2 derived, does not bind to Fc receptors
CH2
CH3
IgG4 derived, does not activate complement
b
Eculizumab epitope
Second C3b
Bb
C5a
C5
C3b
c
C5
C5a
C5b
C7
C6
C8
C5b
C9n
Membrane attack complex C5b–9
C5 convertase
C5
C5a
C5b
C5 convertase

ORIGINAL ARTICLE

Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

C.M. Legendre, C. Licht, P. Muus, L.A. Greenbaum, S. Babu, C. Bedrosian, C. Bingham, D.J. Cohen, Y. Delmas, K. Douglas, F. Eitner, T. Feldkamp, et al.



June 6, 2013
N Engl J Med 2013; 368:2169-2181
DOI: 10.1056/NEJMoa1208981

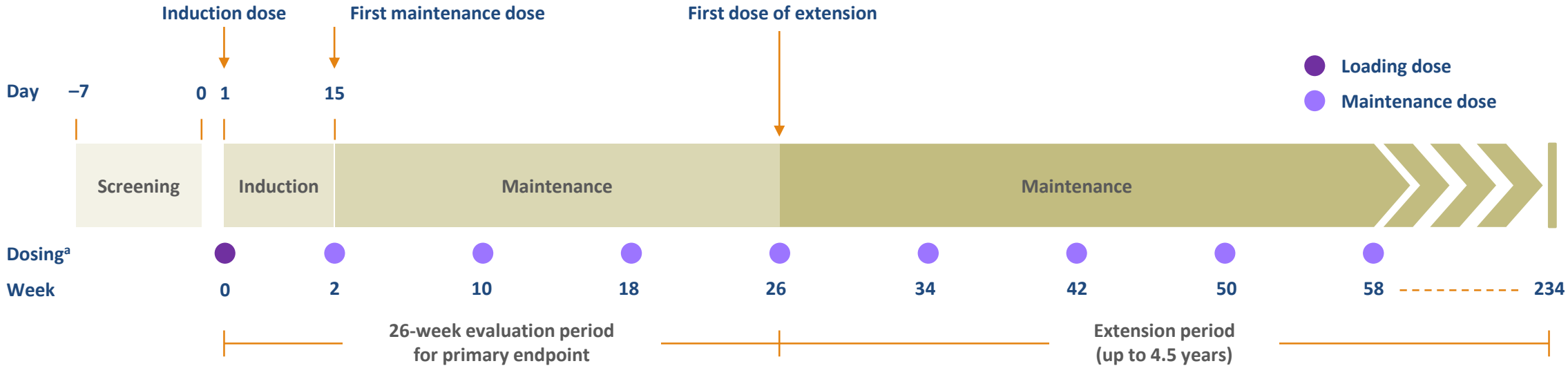
Study design: Ravulizumab-aHUS-311[1,2]

Objective

- To evaluate the safety, efficacy, PK and PD of ravulizumab administered by intravenous infusion for the treatment of complement-mediated TMA in adults with aHUS who are naïve to complement inhibitor treatment

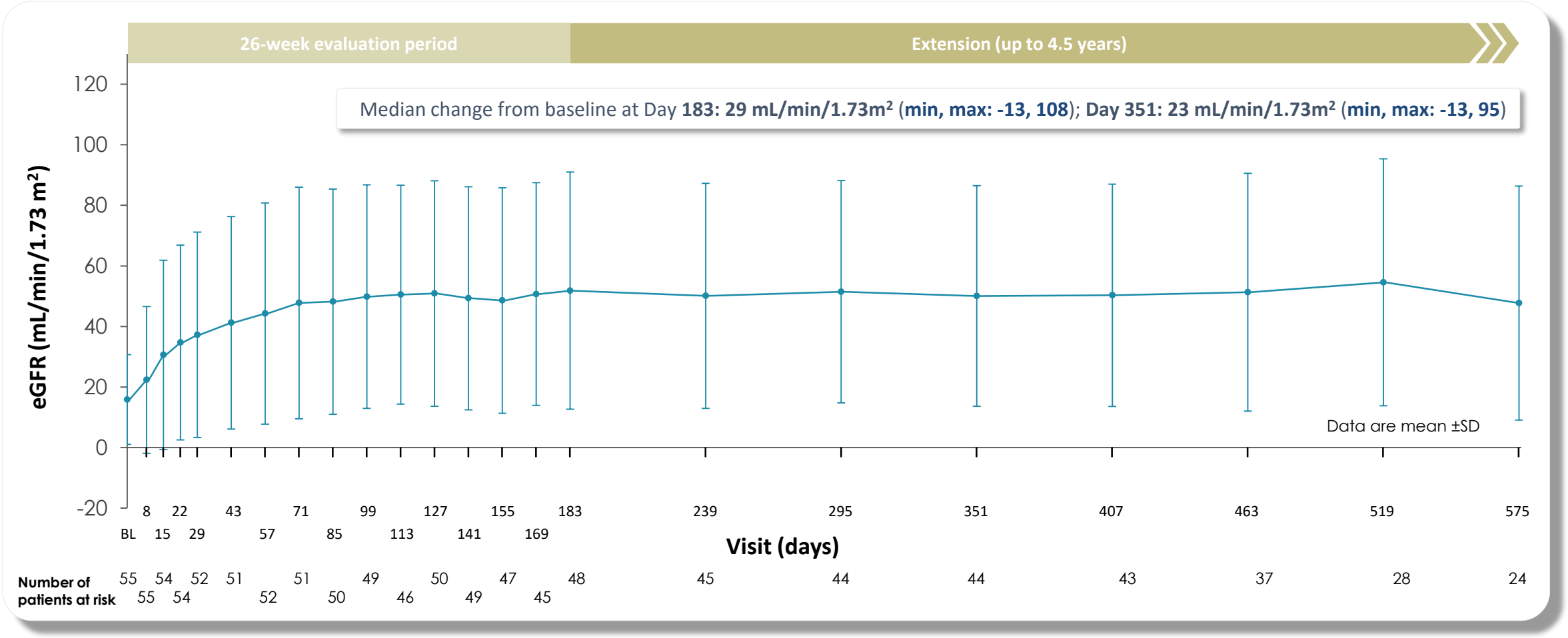
Ravulizumab dosing in 311 Study

Patient body weight (kg)	Induction phase (mg)	Maintenance phase (mg)
≥40 to <60	2400	3000
≥60 to <100	2700	3300
≥100	3000	3600



The criteria for complete TMA response are met when all criteria are concurrently met, and each criterion was met for at least 28 days.
95% confidence intervals (CIs) are represented by the lines at the top of each bar.
LDH, lactate dehydrogenase; **TMA**, thrombotic microangiopathy.
1. Data on file. Alexion Pharmaceuticals, Inc.; 2019. **2.** ULTOMIRIS® (ravulizumab-cwvz) [prescribing information]. Alexion Pharmaceuticals, Inc., Boston, MA; 2022

Renal function - eGFR[1]



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Intervention after TMA suspicion

1. Stop offending medications (Tacrolimus)
   - Start Belatacept if available
   - If belatacept is not available, extend thymoglobulin and restart

2. Do labs testing

3. Start plasma exchange

4. Eculizumab / Ravuluzumab (early enough)

CNI, CALCINEURIN; ESRD, END-STAGE RENAL DISEASE; TMA, THROMBOTIC MICROANGIOPATHY.
BASED ON MYCLINICAL EXPERIENCE AND OPINION.

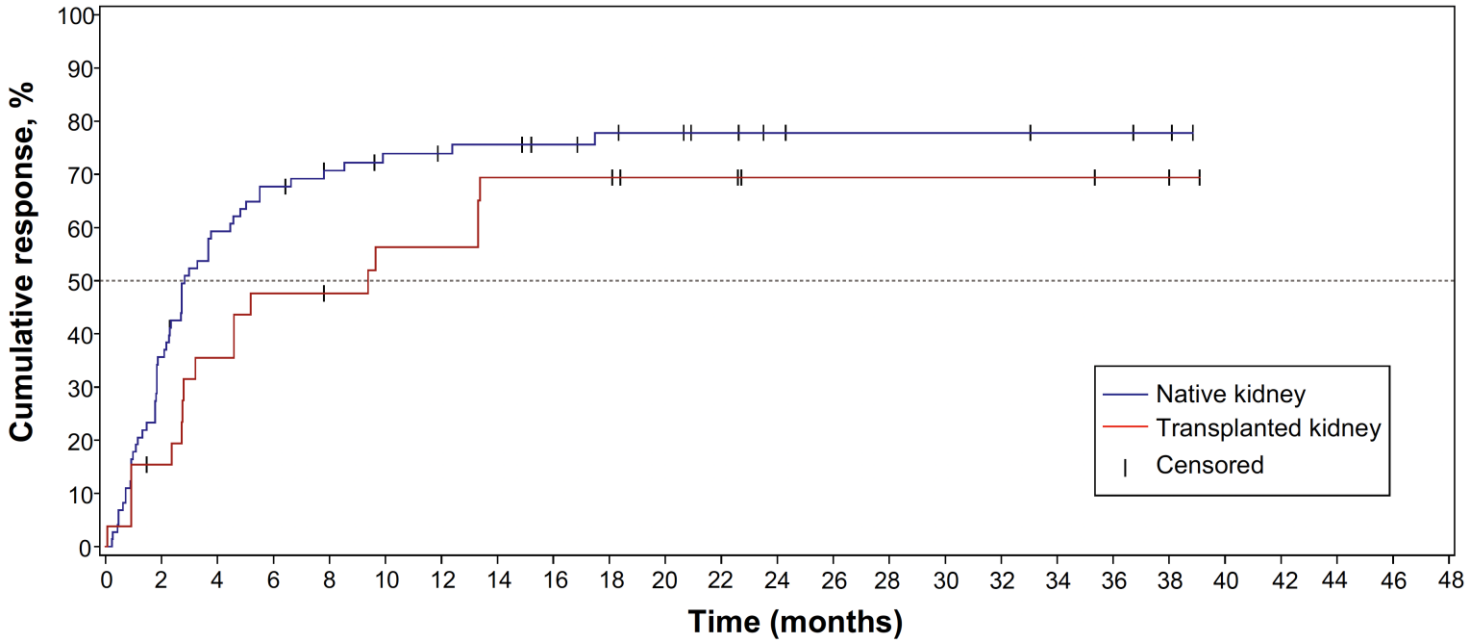
Selected Pooled Baseline Demographics and Clinical Characteristics of Patients Enrolled in the Eculizumab aHUS Clinical trial Program (N=100)

Characteristic	All Patients (n=100)	Native Kidney (n=74)	Transplanted Kidney (n=26)	P value between subgroups*
Age (years), median, range	28.0 (0-80)	24.0 (0-80)	**41.5 (17-69)**	0.0002
Female, n (%)	62 (62)	46 (62)	**16 (62)**	1.0000
Identified complement mutation or autoantibody, n (%)	59 (59)	46 (62)	**13 (50)**	0.3549
Time from aHUS diagnosis to screening (months), median (range)	2.7 (0.03–311.3)	0.85 (0.03–235.9)	**34.8 (0.13–311.3)**	<0.0001
Duration of current TMA manifestation to first eculizumab dose (months), median (range)	0.72 (0.03–47.4)	0.69 (0.03–47.4)	**1.25 (0.03–36.7)**	0.4081
Platelet count (x10^9/L), median (range)	126 (16.9–420.5)	118.5 (18.0–420.5)	**139.8 (16.0–337.5)**	0.1080
Hemoglobin (mg/dL), median (range)	89.5 (41.0–131.0)	85.5 (41.0–131.0)	**96.5 (54.0–131.0)**	0.0075
LDH (U/L), median (range)	369 (131.0–7164)	380.5 (134.0–7164)	**304.5 (131.0–2693)**	0.1313
eGFR (mL/min/1.73 m^2), median (range)	16.0 (5.6–105.5)	12.0 (5.6–105.5)	**22.2 (10.0–72.3)**	0.1386
Dialysis at baseline, n (%)	43 (43)	37 (50)	**6 (23)**	0.0214

**P* values were calculated using Wilcoxon rank sum tests for continuous variables and Fisher exact tests for categorical variables between native kidney and transplant subgroups at baseline.
eGFR, estimated glomerular filtration rate; **LDH,** lactate dehydrogenase; **TMA,** thrombotic microangiopathy; **UL**, upper limit.
Legendre CM, et al. *Transpl Int.* 2017 Dec;30(12):1275-1283.

duration of Eculizumab treatment to Achieve Complete TMA Response in renal transplant recipients

Median time to achieve complete TMA response*‡:
Patients with Native Kidneys: 85 days
Renal Transplant Recipients: 287 days

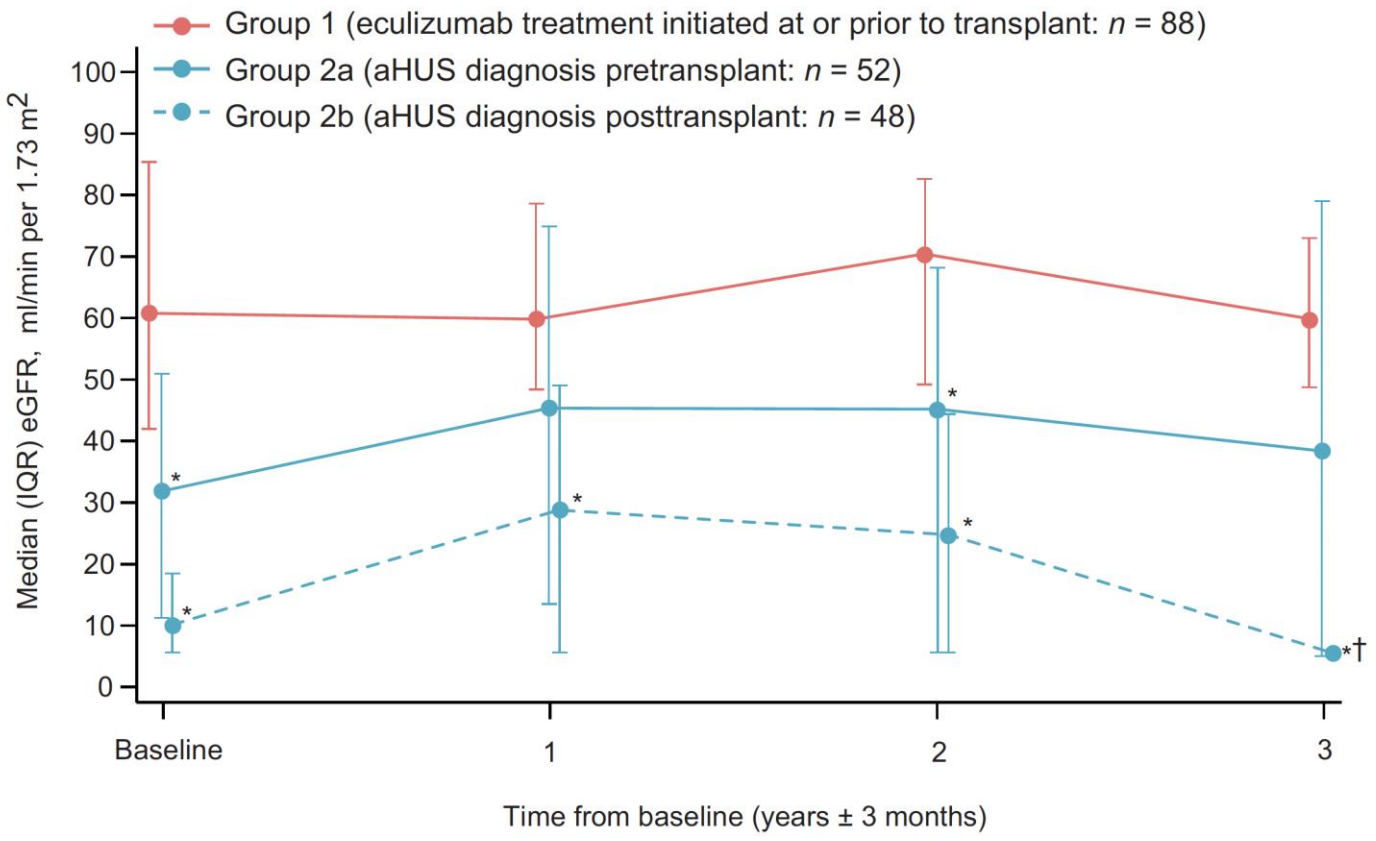


Endpoint	All patients (N=100)	Native Kidney (n=74)	Transplanted kidney (n=26)	P value†
Complete TMA response				
n (%)	72 (72)	55 (74)	17 (65)	0.4486
95% CI	62-81	63-84	44-83	
TMA event-free status				
n (%)	92 (92)	69 (93)	23 (88)	0.6433
95% CI	87-98	87-99	74-99	
Hematologic normalization				
n (%)	93 (93)	71 (96)	22 (85)	0.0727
95% CI	86-97	89-99	65-96	

TMA, thrombotic microangiopathy.

1. Le Quintrec, M. *Am J Transplant.* 2008;13:1694–1701. **2.** Caires, R.A. *Transplantation Proceedings.* 2012;44:2388–2390; **3.** Zarifian, A. *Kidney Int.* 1999;55:2457–2466. **4.** Schwimmer J, et al. *AJKD.* 2003; 41: 471-9.

Renal Outcomes for transplant patients in adult Ravulizumab-cwvz 311 clinical trial (n=8)[1,2,3]



*P < 0.01 vs. group 1; †P < 0.01 vs. group 2a.
Early graft function was denoted by measurements within 6 months post-transplant. Baseline is the first value recorded post-transplant, but within 6 months of transplant. Values for each group are staggered at each timepoint to allow error bars to be clearly discerned and do not indicate differences in the time of measurement. Patients on dialysis had an imputed eGFR of 5 ml/min/1.73 m^2. Data are median (IQR).
IQR, interquartile range.
Siedlecki et al. *Kidney Int Rep* 2019; https://doi.org/10.1016/j.ekir.2018.11.010.

1. Data on file. Alexion Pharmaceuticals, Inc.; 2019. **2.** ULTOMIRIS® (ravulizumab-cwvz) [prescribing information]. Alexion Pharmaceuticals, Inc., Boston, MA; 2022.

Summary

- High risk of recurrence of atypical HUS post-transplant*
- Prophylactic complement inhibitor treatment can be effective in preventing recurrence for patients at moderate or high risk or disease recurrence*[1]
- Optimal post transplant prevention requires an individualised approach*
- Diagnosing and identifying the cause of a post-transplant TMA is challenging*
- Complement inhibition is recommended for treating recurrent atypical HUS but evidence is lacking in other causes of TMA*

*BASED ON MY CLINICAL EXPERIENCE AND OPINION.
AHUS, ATYPICAL HAEMOLYTIC URAEMIC SYNDROME; TMA, THROMBOTIC MICROANGIOPATHY.
1. GOODSHIP TH ET AL. *KIDNEY INT* 2017;91:539–551.

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