Post - kidney Transplantation Thrombotic Microangiopathy : A Diagnostic Dilemma

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TMA

- TMA is associated with poor patient & graft outcomes.
- Incidence of post TX TMA : 5.6/1000 renal transplant /year.
- Mortality rate 50% three years after diagnosis

- TMA after TX : De novo TMA

- Recurrent TMA

Reynolds JC, Agodoa LY, Yuan CM, Abbott KC.

Thrombotic microangiopathy after renal transplantation in the United States. Am J Kidney Dis 2003 ;42

Which is more prevalent , de novo or recurrent TMA?

- **Reynolds et al** , in a United States Renal Data System –based study , declared : 112 de novo TMA , 12 recurrent TMA.
- TMA recurrence was 36.5 times higher in kidney Tx recipients due to HUS as compared to other etiologies (29.2% vs 0.8%)

- **Langer et al** reported the incidence of de novo TMA to be 1.5% .
- The incidence of de novo TMA is as high as 3 – 14%.

- Graft loss rate of 40% is reported in de novo TMA within a couple of years of diagnosis. Abbas F et al .

TMA after renal transplantation*World J Transplant* 2018 September 10; 8(5): 1

DE NOVO TMA

- A number of precipitating factors trigger the development of ***de novo*** TMA :

- AMR

- Immunosuppressive –associated TMA: CNIs , mTOR inhibitor
- Viral infections : HCV, CMV, BK, parvovirus

- Other medications ; e.g., anti VGFI
- Genetic abnormalities in the complement cascade

- Phenotypical shift of C3 glomerulopathy to an aHUS post TX
- Missed diagnosis of TMA in the native kidney.(i.e recurrent TMA)

Calcineurin –induced TMA

- Three underlying mechanisms :
- Loss of normal balance between the vasodilator & vasoconstrictors.
- Platelet activation , pro-coagulant & anti-fibrinolytic activity.
- Microparticle production from endothelial cells(activation of AP)

- **Garg N**, . De novo thrombotic microangiopathy after kidney transplantation
- . *Transplant Rev* (Orlando) 2018; **32**: 58-68

- Nava *et al*, studied 396 KTR, 36 (7.3%) developedTMA and 17 of them were drug-related.

- Not only were the drug levels of CNI and mTORi higher in the TMA group, but the sum of both drug levels in the TMA group was also higher.

- **Nava F**, et al. Everolimus, cyclosporine, and thrombotic microangiopathy:
- clinical role and preventive tools inrenal transplantation. *Transplant Proc* 2014; **46**

- Three points apposed the role of CNI:

- > 95% of kidney transplant recipients utilizing CNI & a small percentage can develop TMA.

- CNI withdrawal in de novo TMA does not always gaurantee a favorable outcome.

- A USRDS based study demonstrates a significantly higher incidence of TMA in KTR was not under CNI as compared to those on CNI (11.9 /1000/year vs 5/1000/year)

m TOR inhibitor –associated TMA:

- m-TORi has antiangiogenic properties & can decrease renal expression of VEGF with death of endothelial progenitor cells.
- The VEGF inhibition is associated with reduced renal levels of CFH.
- Repair of endothelial injury could be hampered by mTORi use.
- The procoagulant & antifibrinolytic activity of mTORi might play additional roles.

Keller K, et al. . *Nephrol Dial Transplant* 2006; **21**

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Effect of Immunosuppressive Therapy on the Occurrence of Atypical Hemolytic Uremic Syndrome in Renal Transplant Recipients

Our study is a retrospective analysis using data from the United States Renal Data System from 2004 to 2012

Table 1. Demographics and clinical characteristics of patients.

	aHUS patients		Other diagnoses		P
n	14		179126		
Donor age in years (median [IQR])	46.00 [35.50, 54.00]		40.00 [27.00, 51.00]		0.199
Donor sex n (%)					
Unknown	N≤10	(57.1)	64983	(36.3)	
Female	N≤10	(35.7)	45190	(25.2)	
Male	N≤10	(7.1)	68953	(38.5)	
Donor race n (%)					
Native American	N≤10	(0)	887	(0.5)	
Asian	N≤10	(0)	4977	(2.8)	
Black	N≤10	(0)	24026	(13.4)	
White	14	(100)	148225	(82.7)	
Unknown	N≤10	(0)	1011	(0.6)	
Living donor n (%)	N≤10	(57.1)	64983	(36.3)	0.178
Recipient age in years (median [IQR])	35.00 [27.00, 49.00]		52.00 [39.00, 61.00]		0.002

Maintenance immunosuppression (n (%))					
Cyclosporin	N≤10	(21.4)	27478	(15.3)	
Tacrolimus	12	(85.7)	145677	(81.3)	0.938
Sirolimus	N≤10	(35.7)	20593	(11.5)	0.015
Everolimus	N≤10	(0)	1501	(0.8)	
Azathioprine	N≤10	(28.6)	13079	(7.3)	
Mycophenolate mofetil	13	(92.9)	151767	(84.7)	0.635
Corticosteroids	14	(100)	125087	(69.8)	0.030
Cyclophosphamide	N≤10	(0)	204	(0.1)	
Methotrexate	N≤10	(0)	133	(0.1)	
Antilymphocyte globulin	N≤10	(0)	318	(0.2)	
Antithymocyte globulin	N≤10	(0)	5650	(3.2)	
IL-1R agents	N≤10	(0)	25	(0.0)	
Nucleotide synthesis inhibitors	N≤10	(0)	3421	(1.9)	
Anti-CD3 antibody	N≤10	(0)	2136	(1.2)	
Anti-IL2 antibody	N≤10	(0)	540	(0.3)	
Rituximab	N≤10	(7.1)	1458	(0.8)	
Alemtuzumab	N≤10	(0)	259	(0.1)	
Other antibody	N≤10	(0)	65	(0.0)	
Other IL2	N≤10	(0)	51	(0.0)	
Other	N≤10	(35.7)	7452	(4.2)	<0.001

AMR associated de novo TMA:

- Endothelial cells are a well-known target of allo-immune response.

- The PTC C4d staining has been reported to be present in 16.2% of recipients with TMA.

- Satoskar et al reported an incidence of 55% of de novoTMA patients express diffuse PTC C4d positivity.

- **Satoskar AA**, et al. De novo thrombotic microangiopathy in renal allograft
- biopsies-role of antibody-mediated rejection. *Am J Transplant* 2010

- Viral infection : CMV infection
- BK virus
- Parvovirus
- chronic Hepatitis C
- Antiviral medications eg: ribavirin
- interferon
- Disseminated histoplasmosis
- Ischemia –reperfusion injury
- C3 glomerulopathy disease in a native kidney can undergo phenotypical shift.

Original Article

Thrombotic microangiopathy in renal allografts

S. Radha[1], Afroz Tameem[1], G. Sridhar[2], A. Aiyangar[2], K. G. Rajaram[3], R. Prasad[4], K. Kiran[5]

Consultants, [1]Department of Pathology, and [2]Nephrology, Aware Global Hospitals, Consultant [3]Nephrologist, Hyderabad Kidney and Laparoscopic Centre, [4]Professor of Nephrology, Andhra Medical College and King George Hospital, Visakhapatnam, [5]Consultant Nephrologist, Kamineni Hospitals, Hyderabad

131 kidney TX biopsy were evaluated.

Out of 12 cases of TMA ,5 were associated with CNI ,

3 with AMR,2 with recurrent HUS,1 with sirolimus , 1 with ganciclovir.

Indian Journal of Nephrology, January 2014 / Vol 24 / Issue 1

Table 1: Case details of the 12 cases with thrombotic microangiopathy

Age/sex	Donor	Time of presentation	Etiology	Prognosis	Native disease
28/m	Live related	7 days	Tacrolimus	Recovered	Unknown
31/m	Live related	3 months	AHR	Recovered	FSGS
45/m	Live related	3 months	Tacrolimus	Expired	Chronic glomerulonephritis
30/m	Live related	2.5 months	Tacrolimus	Recovered	Unknown
28/m	Live related	2.8 months	Ganciclovir	Graft loss	Chronic IgA
38/f	Live related	6 days	Recurrence	Graft loss	HUS
48/m	Live related	1 month	Sirolimus	Recovered	Unknown
52/m	Cadaver	5 days	AHR	Graft loss	Unknown
10/m	Cadaver	2 days	AHR	Graft loss	Vesico-ureteral reflux
48/m	Live related	10 days	Recurrence	Graft loss	HUS
30/m	Live related	10 months	Cyclosporin	Recovered	Chronic IgA
48/m	Cadaver	4 months	Cyclosporin	Recovered	Chronic diabetic glomerulo-sclerosis

FSGS: Focal and segmental glomeruloscerosis, HUS: Hemolytic uremic syndrome

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Complement Factor C4d Is a Common Denominator in Thrombotic Microangiopathy

Jamie S. Chua,* Hans J. Baelde,* Malu Zandbergen,* Suzanne Wilhelmus,* Leendert A. van Es,* Johan W. de Fijter,† Jan A. Bruijn,* Ingeborg M. Bajema,* and Danielle Cohen*

*Department of Pathology and †Department of Nephrology, Leiden University Medical Center, Leiden, The Netherlands

Complement gene mutation

- *Chua et al* reported C4d deposits in more than 88% and C4d with localized C5b-9 in about 60% of 42 biopsy samples from patients with histologically confirmed diagnosis of TMA.

- *Le Quintrec et al reported the presence of genetic mutations in CFH,CFI or both in 29% of de novo TMA.*

- *25% showed low CFB and/or low C3 .*

.

Clinical manifestations

- . TMA could develop at any time
- .
- TMA mostly encountered in the first 3 – 6 mo post transplantation.
- The systemic form of TMA consists of the classic triad.
- TMA can vary from a limited formed confined to the kidney.

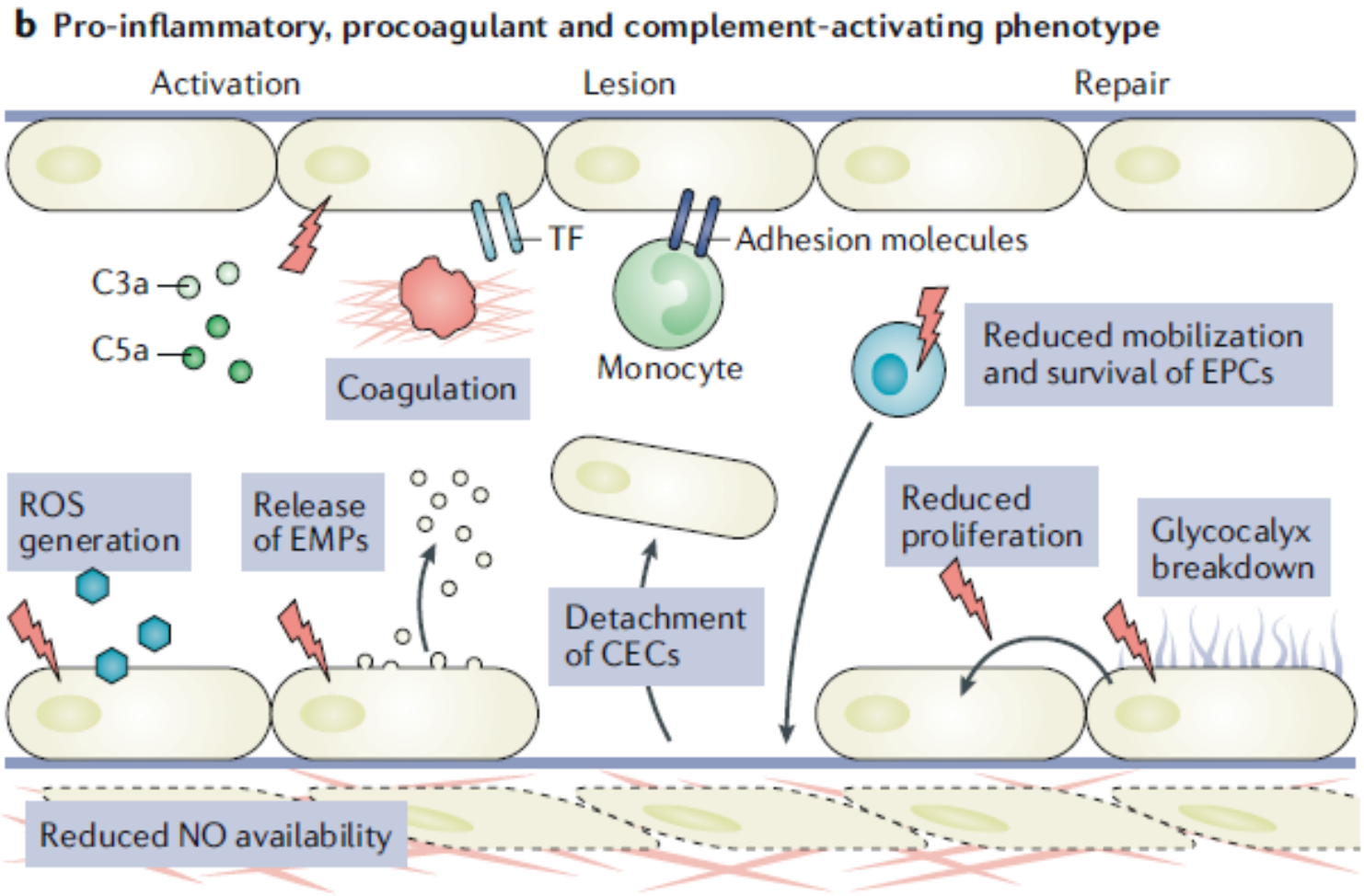
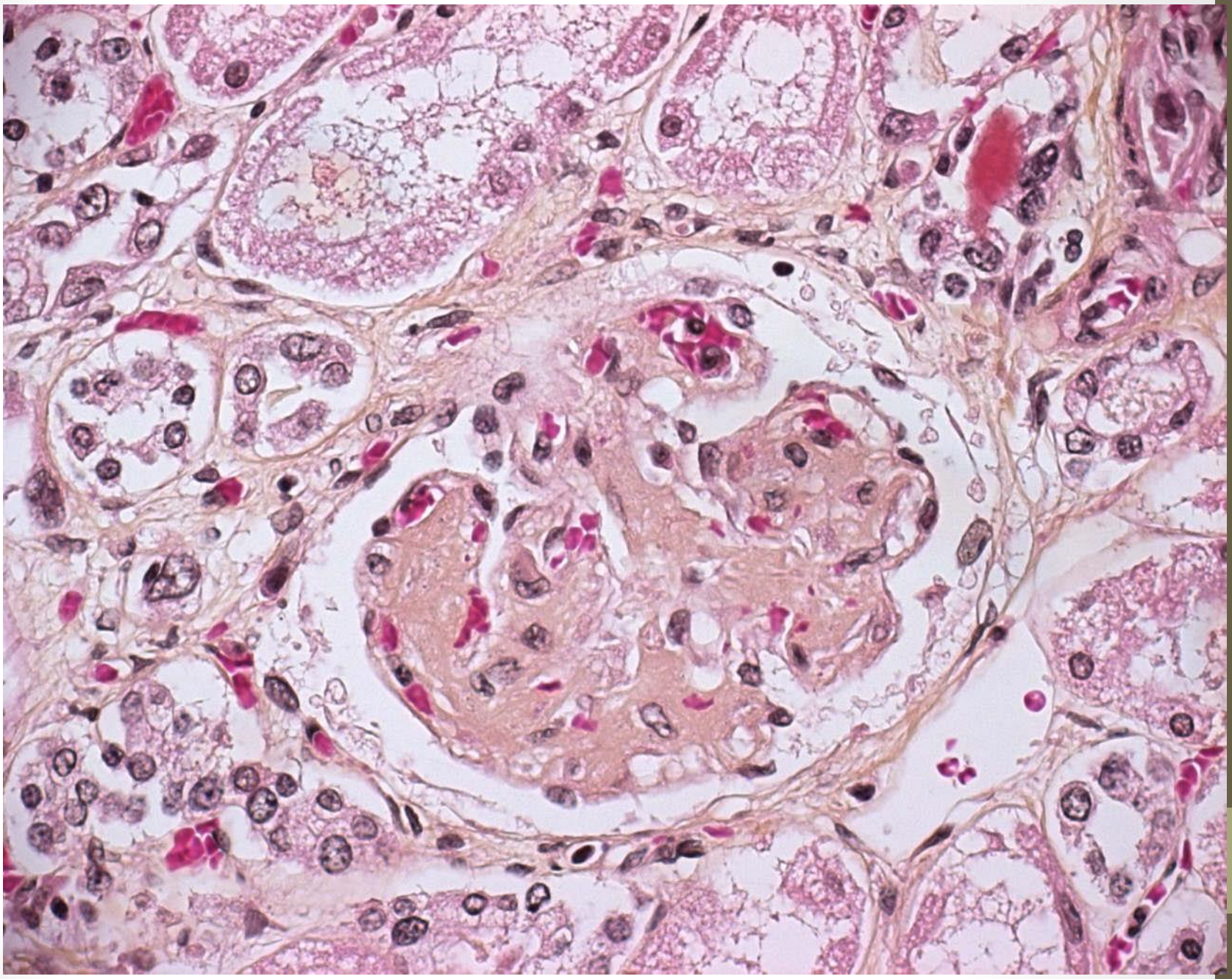


Fig. 2 | **Endothelium dynamics in health and disease. a** | Under physiological



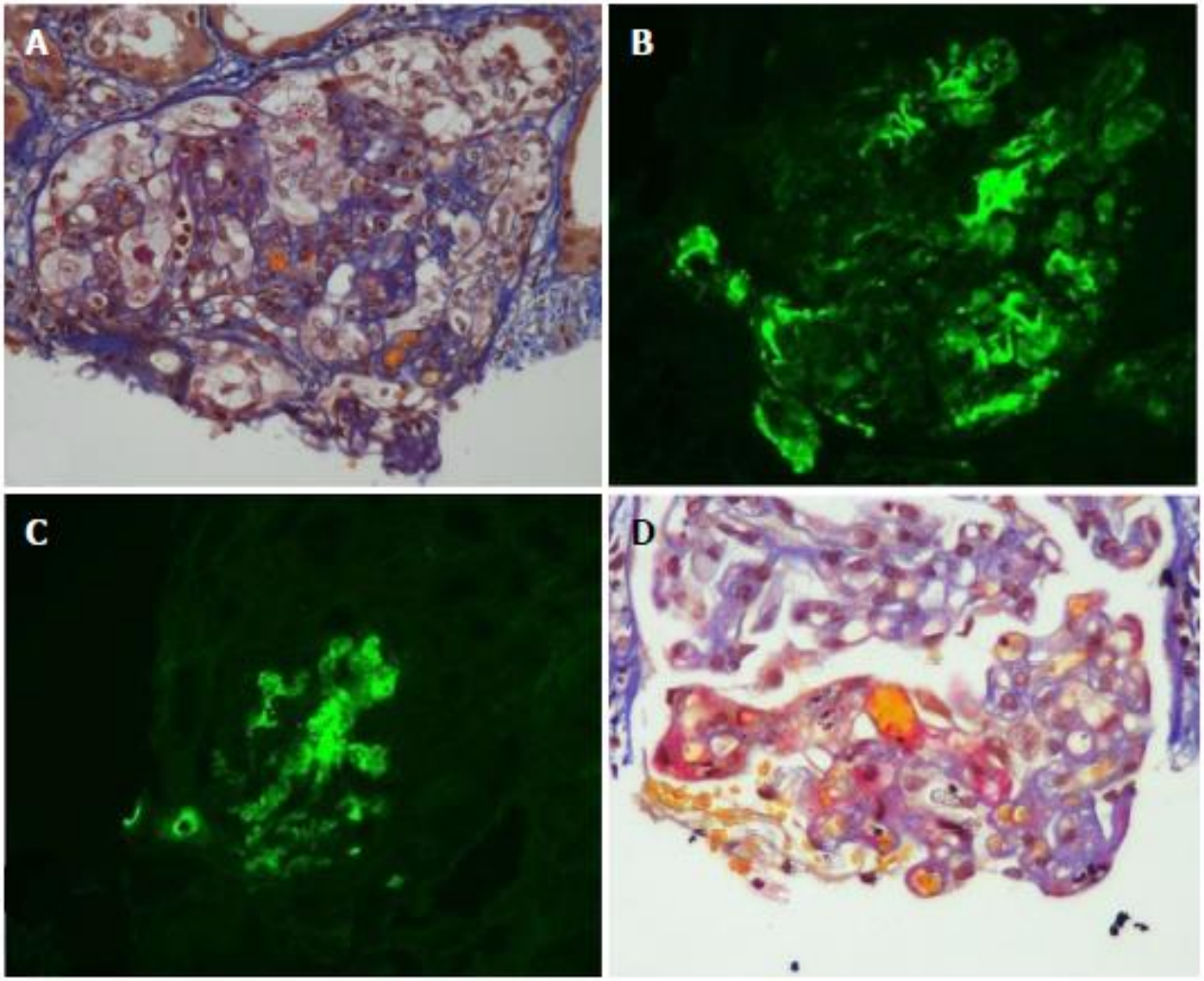


Figure 1 Acute and chronic thrombotic microangiopathy and calcineurin inhibitors-associated arteriolopathy with severe acute ischemic tubular lesions. A: Advanced interstitial inflammatory fibrosis (Masson trichrome stain); B: Immunofluorescence, diffuse and segmental C3; C: C1q deposits within glomerular capillary walls; D: Diffuse acute and chronic arteriolar and glomerular thrombotic microangiopathy lesions on light microscopy (LM). (Adapted from: Yassine *et al*[45]).

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Table 1 Morphological features in microangiopathy

Active lesions	Chronic lesions
Glomeruli: Thrombi - Endothelial swelling or denudation - Fragmented RBCs - Subendothelial flocculent material. EM: Mesangiolysis - Microaneurysms Arterioles: Thrombi - Endothelial swelling or denudation-Intramural fibrin-Fragmented red blood cells-Intimal swelling-Myocyte necrosis Arteries: Thrombi - Myxoid intimal swelling -Intramural fibrin- Fragmented red blood cells	Glomeruli: LM: Double contours of peripheral capillary walls, with variable mesangial interposition - EM: New subendothelial basement membrane - Widening of the subendothelial zone Arterioles: Hyaline deposits Arteries: Fibrous intimal thickening with concentric lamination (onion skin)

Adapted from: Goodship *et al*[58]. EM: Electron microscopy; LM: Light microscopy.

- Once the diagnosis of TMA has been established, a prompt ***revision of the etiology*** of the native kidney ESRD should be instituted.
- In a HUS who do not show systemic manifestations, the diagnosis could be obscure.
- In the absence of renal biopsy ,many cases can be misdiagnosed as hypertensive nephrosclerosis.
- A prompt ***testing for genetic mutations*** should be accomplished.
- Since *de novo* TMA has limited therapeutic options, in contrast to recurrent aHUS after transplantation, which has a better chance of C-5 blockade.

.

Prognosis of de novo TMA

- The prognosis of post Tx de novo TMA is quite ***poor.***
- A bout ½ of the patients loses their graft within the first two years after diagnosis.

- Reynolds reported 50% mortality rate after 3 years of diagosis.
- Schwimmer et al reported 54% of systemic TMA dialysis – requiring AKI & 38% lost their grafts.

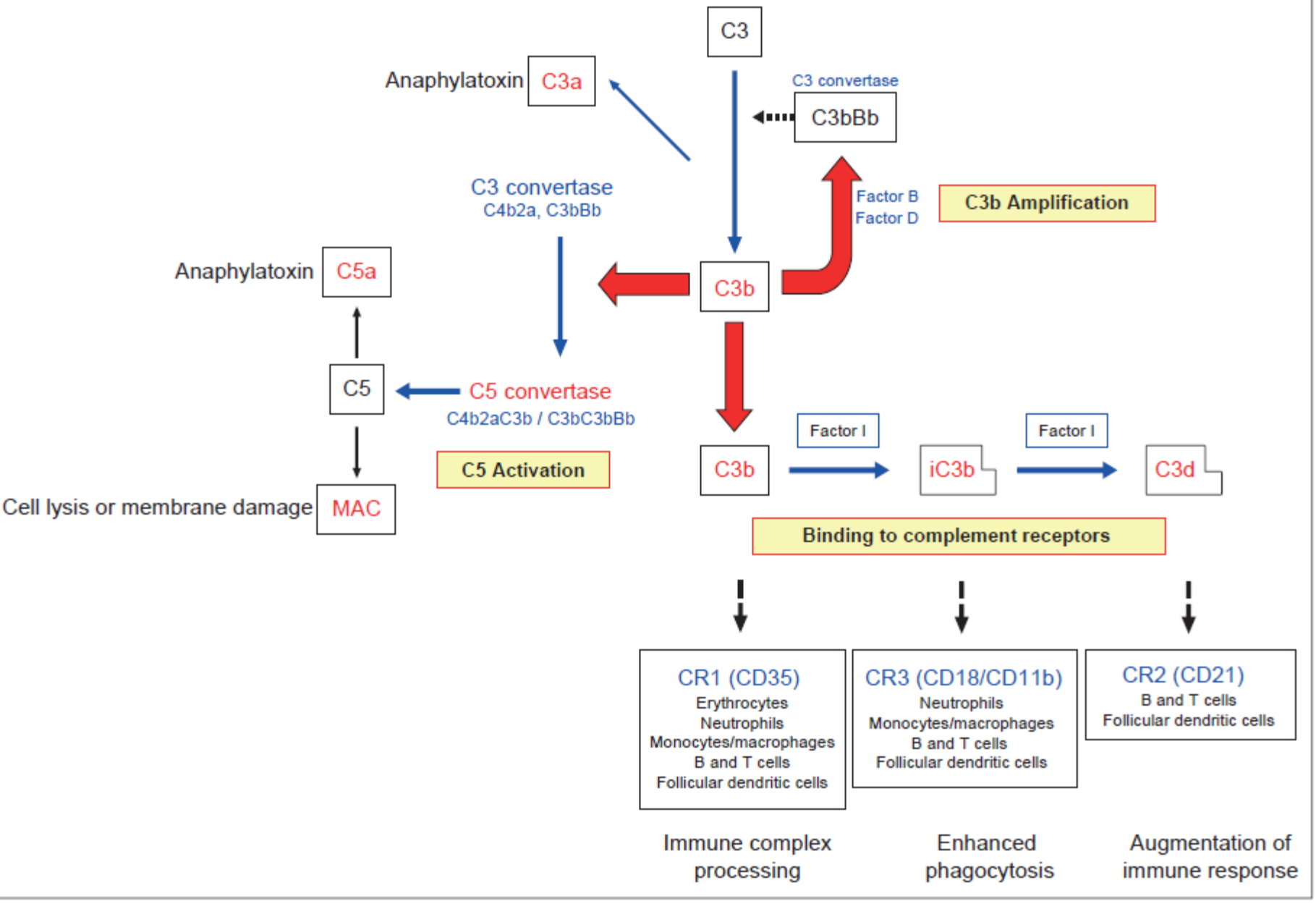
- None of the localized TMA developed TMA related early graft loss or required dialysis.

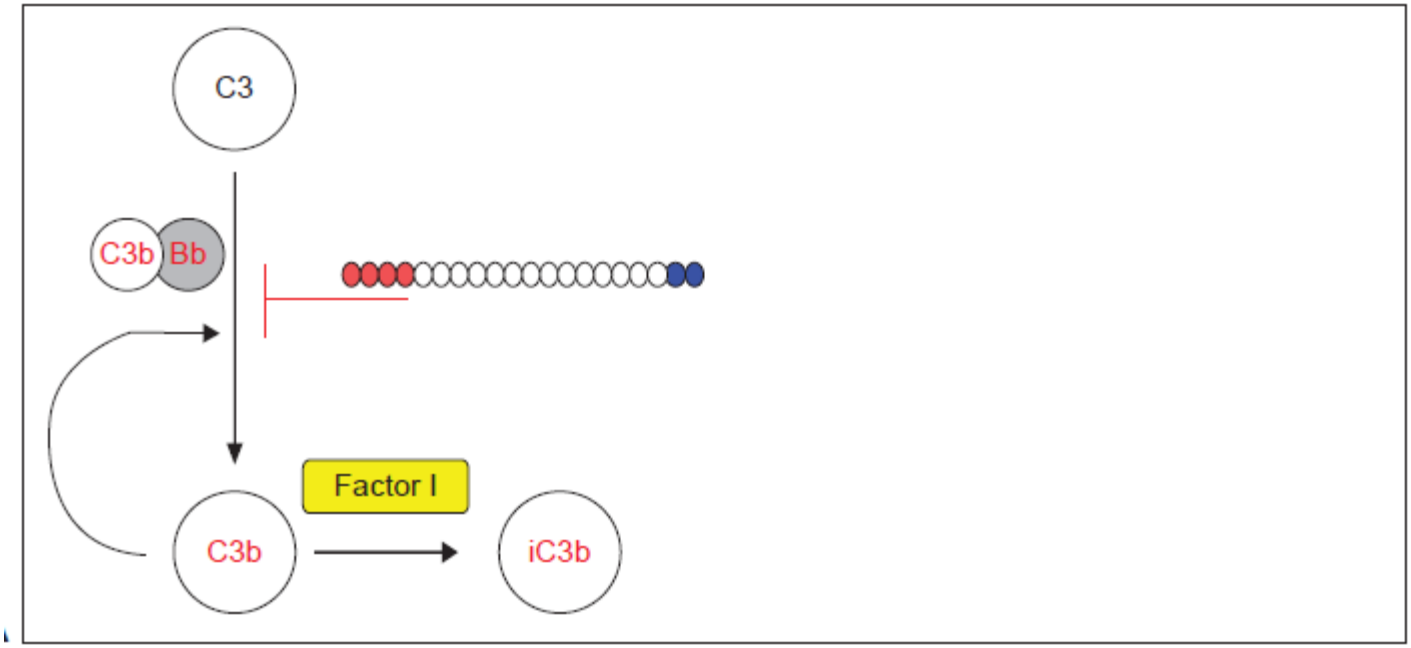
Recurrent TMA After Renal Transplantation

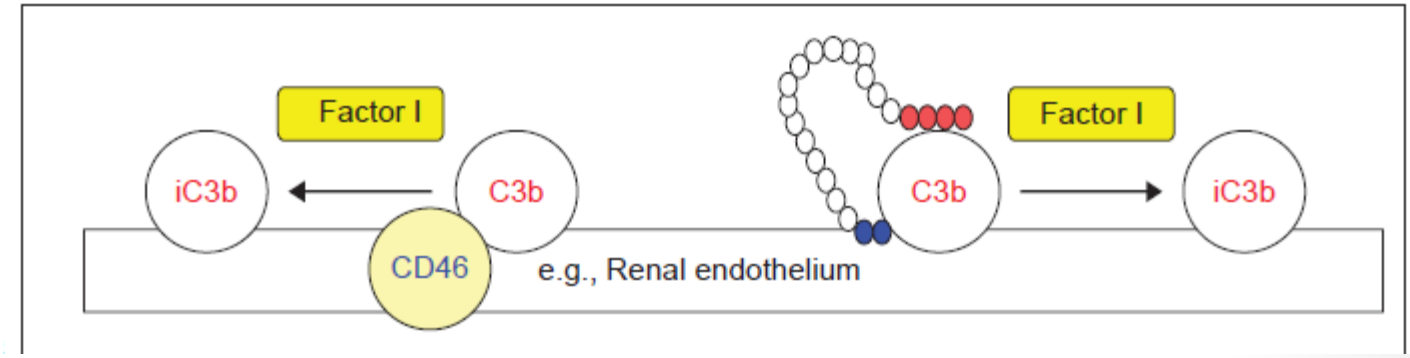
- aHUS
- TTP
- Autoimmune diseases: scleroderma, SLE
- (with or without antiphospholipid syndrome.

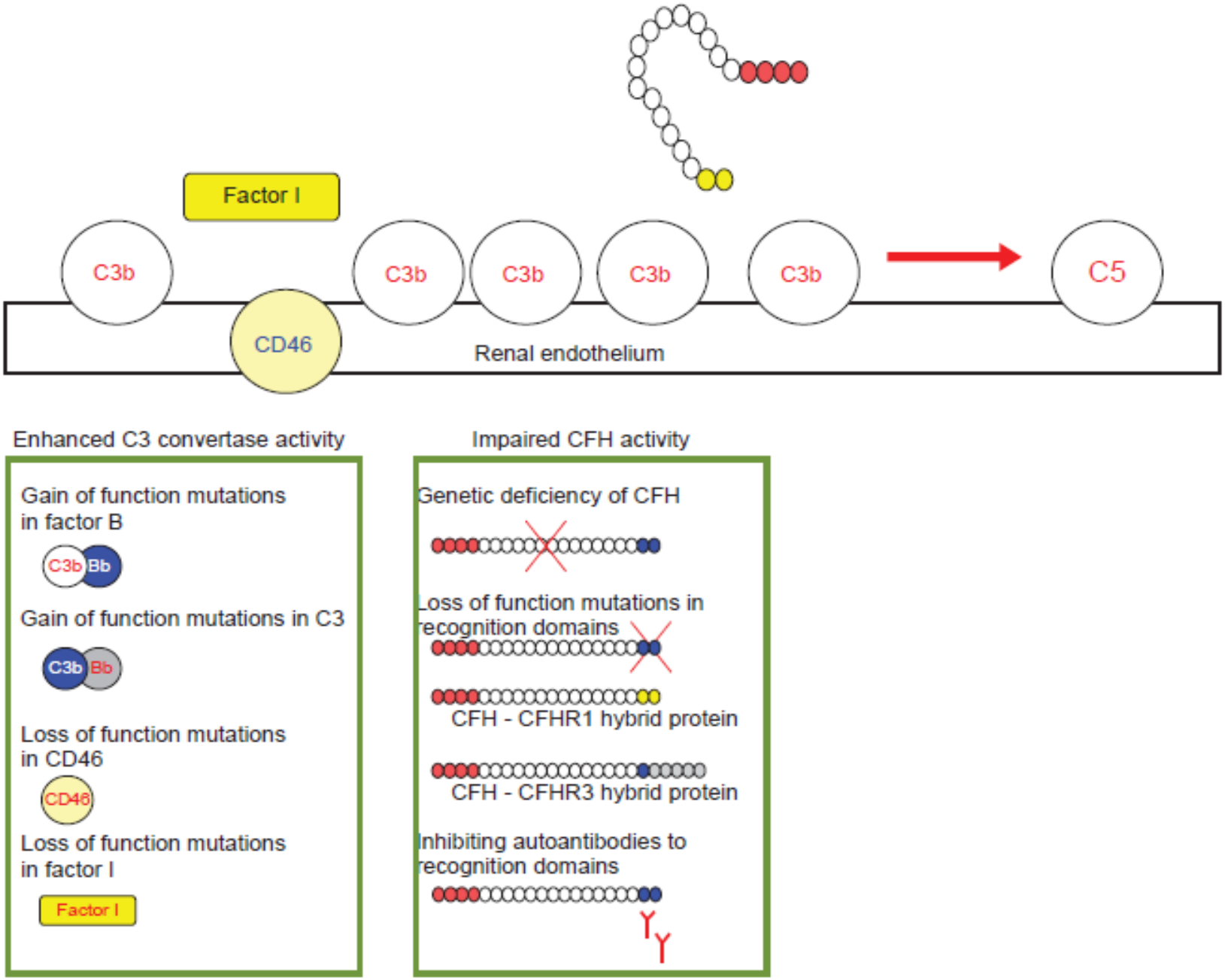
a HUS

- a HUS is the most common diagnosis in TMA associated with recurrence.
- CFH and CFI mutation have a robust impact in the evolution of a HUS recurrence.
- The reported recurrence rate :70-90% .


C3
Anaphylatoxin
C3a
C3 convertase
C3bBb
C3 convertase
C4b2a, C3bBb
Factor B
Factor D
C3b Amplification
Anaphylatoxin
C5a
C3b
C5
C5 convertase
C4b2aC3b / C3bC3bBb
C5 Activation
Factor I
Factor I
C3b
iC3b
C3d
Cell lysis or membrane damage
MAC
Binding to complement receptors
CR1 (CD35)
Erythrocytes
Neutrophils
Monocytes/macrophages
B and T cells
Follicular dendritic cells
CR3 (CD18/CD11b)
Neutrophils
Monocytes/macrophages
B and T cells
Follicular dendritic cells
CR2 (CD21)
B and T cells
Follicular dendritic cells
Immune complex processing
Enhanced phagocytosis
Augmentation of immune response


C3
C3b
Bb
Factor I
C3b
iC3b


Factor I
iC3b
C3b
CD46
e.g., Renal endothelium
Factor I
C3b
iC3b


Factor I
C3b
C3b
C3b
C3b
C3b
C5
CD46
Renal endothelium
Enhanced C3 convertase activity
Gain of function mutations in factor B
C3b Bb
Gain of function mutations in C3
C3b Bb
Loss of function mutations in CD46
CD46
Loss of function mutations in factor I
Factor I
Impaired CFH activity
Genetic deficiency of CFH
Loss of function mutations in recognition domains
CFH - CFHR1 hybrid protein
CFH - CFHR3 hybrid protein
Inhibiting autoantibodies to recognition domains

B

a HUS

- MCP produced by kidney endothelial cells ,keeps a HUS recurrence lower.

- In a study by Bresin et al., 22.6% of patients with MCP mutations carried additional mutations in other complement genes.
- One-third (4/12) of the allografts were lost to recurrence in presence of other concomitant pathogenic mutations, as opposed to only one of 13 with isolated MCP mutations.
- The global recurrence rate is as high as 60%.

- Untreated patients ,ultimately develop graft loss at a rate of 90%.

TTP

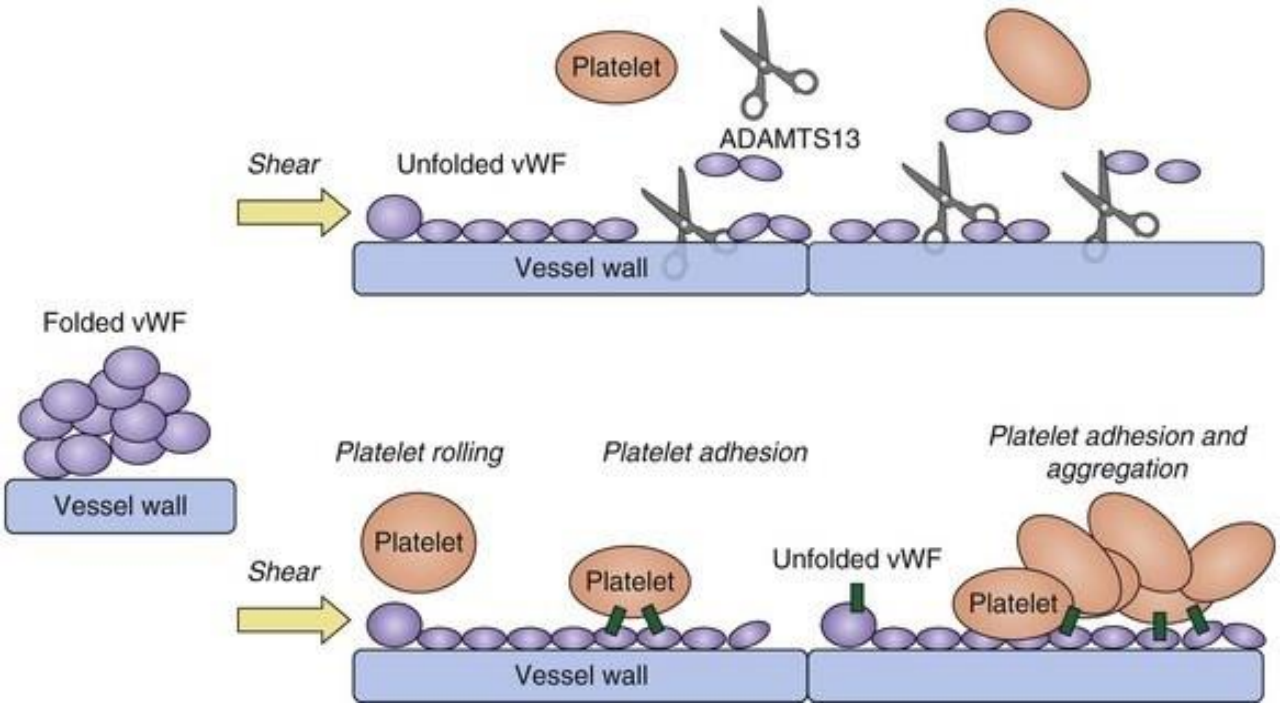
- Genetic or acquired lack of ADAMTS13 has been recognized….

- In a recent analysis of 92 patients diagnosed with TTP based on low ADAMTS13 activity, ***acute kidney*** injury was present in ***more than half*** the patients , of which ***50 % developed chronic kidney disease (CKD) or ESRD***.

- It is reasonable to expect TTP recurrence aslong as the underlying defect is present after Transplantation..

L. Zafrani , et al .Acute renal failure is prevalent in patients with thrombotic thrombocytopenic purpura associated with low plasma ADAMTS13 activity , J Thromb Haemost , 13 (2015) 380-389.

Pathophysiology of Platelet Aggregation in Thrombotic Thrombocytopenic Purpura



- lupus nephritis (with or without documented anti-phospholipid antibodies) is associated with TMA

in 5-10% of the cases and has been documented to recur in the allograft in case report and small case series.

T.D.Barbour,et al , Antiphospholipid syndrome in renal transplantation, Nephrology (Carlton), 19 (2014) 177-185.

Pathophysiology Of TMA Recurrence

- The AP is constitutively active.
- The regulatory components exist either in the serum (fluid phase) or attached onto cell membranes.
- CFH is the main inhibitor of the AP.
- CFH can act as a co-factor to CFI.
- "***Membrane regulators***" include the following:
- Membrane cofactor protein (MCP/CD46)
- Complement receptor 1 (CR1/CD35)
- Decay accelerating factor (DAF/CD55)
- Protectin (CD59), which prohibits MAC formation

- Complement dysregulation is the fundamental etiology involved in TMA evolution.

- Both genetic aberrations as well as autoantibodies can be involved in this process.

- Usually, there is (are) an inciting ***environmental trigger*** factor.

Current classification of TMA :

- *Primary hereditary TMA*
- *Primary acquired TMA*
- *Infection-associated TMA*

World Journal of Transplantation

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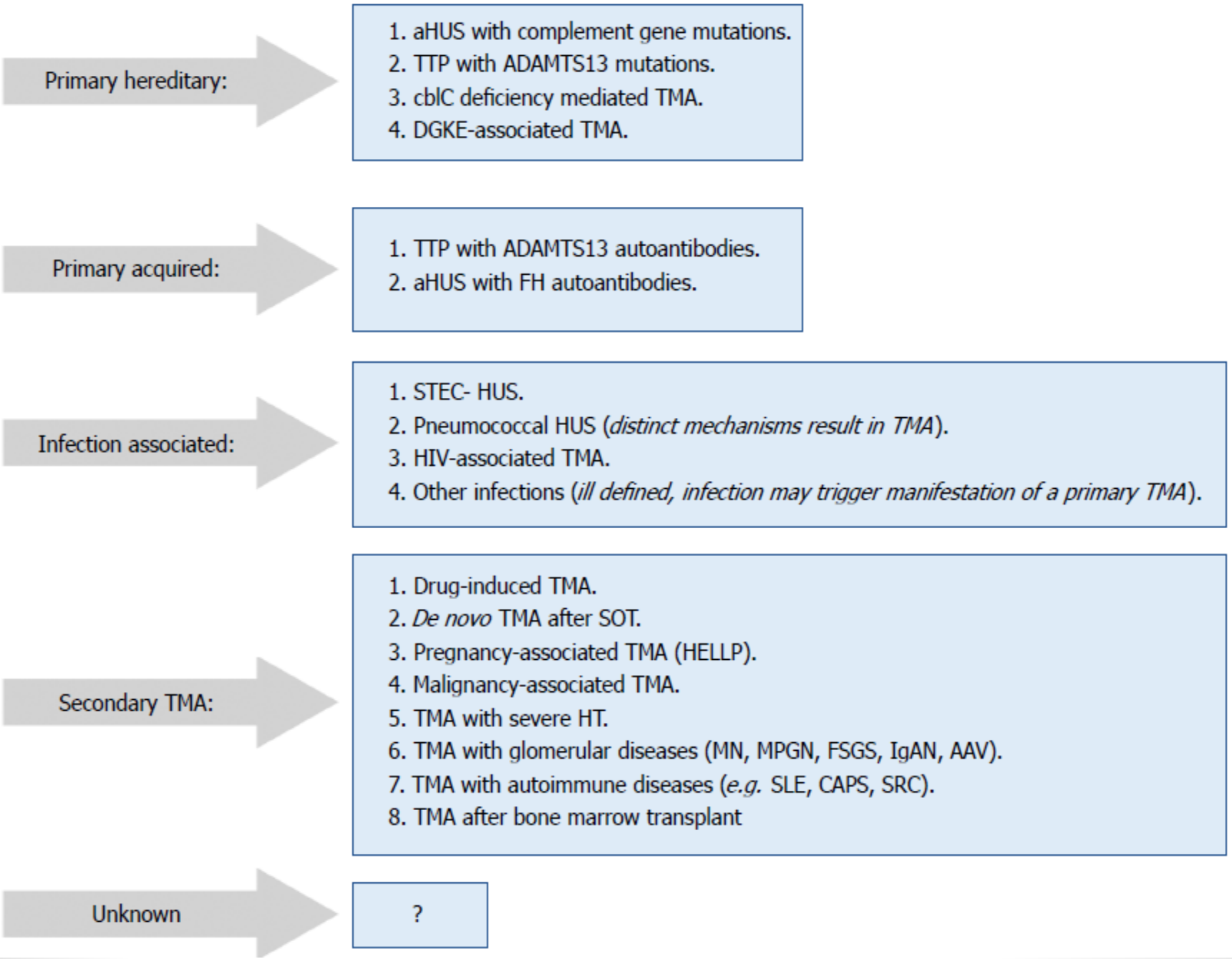
REVIEW

Thrombotic microangiopathy after renal transplantation: Current insights in *de novo* and recurrent disease

Fedaey Abbas, Mohsen El Kossi, Jon Jin Kim, Ajay Sharma, Ahmed Halawa


Primary hereditary:
1. aHUS with complement gene mutations.
2. TTP with ADAMTS13 mutations.
3. cblC deficiency mediated TMA.
4. DGKE-associated TMA.
Primary acquired:
1. TTP with ADAMTS13 autoantibodies.
2. aHUS with FH autoantibodies.
Infection associated:
1. STEC- HUS.
2. Pneumococcal HUS (distinct mechanisms result in TMA).
3. HIV-associated TMA.
4. Other infections (ill defined, infection may trigger manifestation of a primary TMA).
Secondary TMA:
1. Drug-induced TMA.
2. De novo TMA after SOT.
3. Pregnancy-associated TMA (HELLP).
4. Malignancy-associated TMA.
5. TMA with severe HT.
6. TMA with glomerular diseases (MN, MPGN, FSGS, IgAN, AAV).
7. TMA with autoimmune diseases (e.g. SLE, CAPS, SRC).
8. TMA after bone marrow transplant
Unknown
?

Abbas F *et al*. TMA after renal transplantation

Table 2 Risk of atypical hemolytic uremic syndrome recurrence according to the implicated genetic abnormality

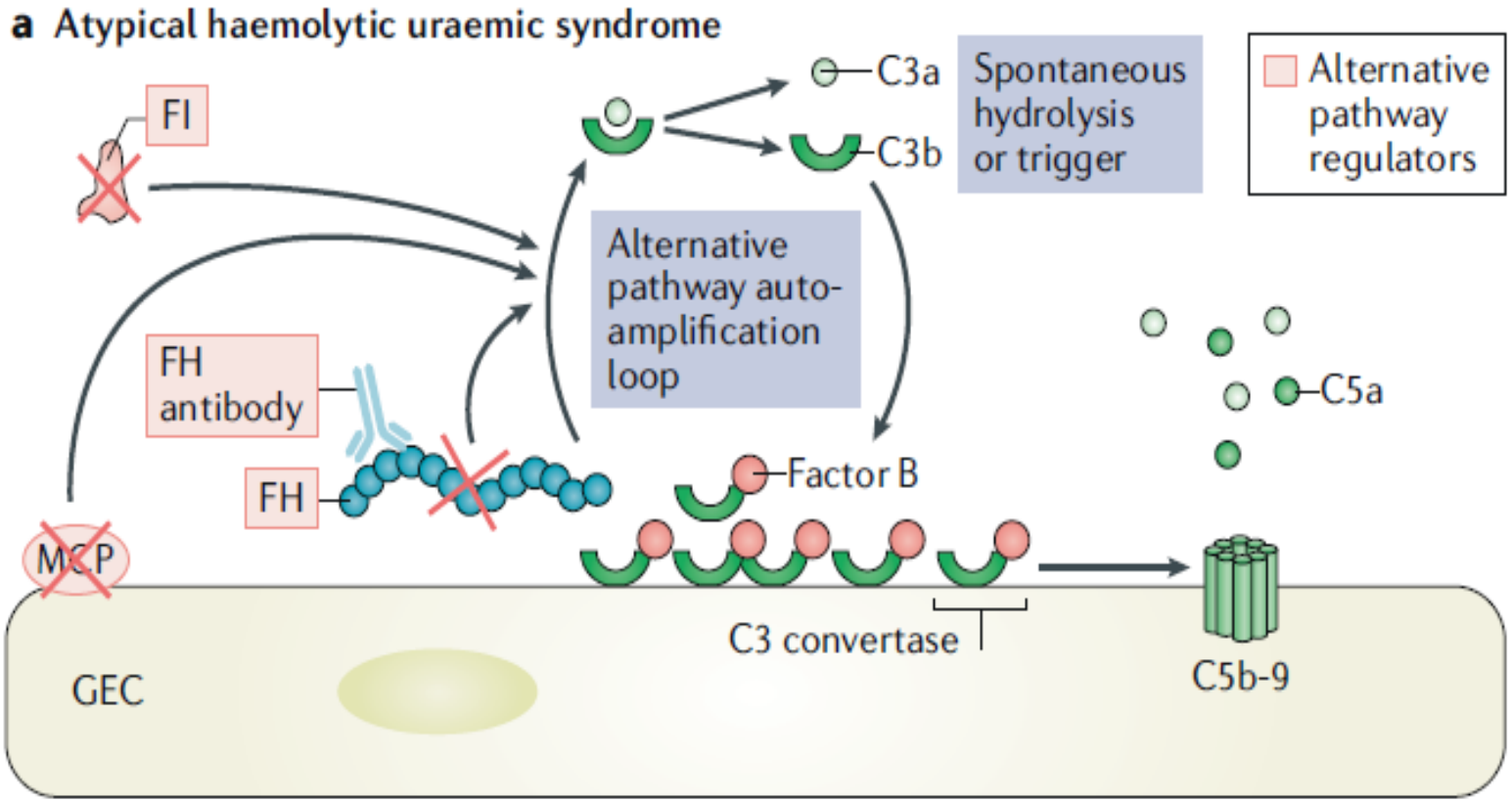
Gene mutation	Location	Functional impact	Mutation frequency in aHUS (%)	Recurrence after transplantation (%)
CFH	Plasma	Loss	20-30	75-90
CFI	Plasma	Loss	2-12	45-80
CFB	Plasma	Gain	1-2	100
C3	Plasma	Gain	5-10	40-70
MCP	Membrane	Loss	10-15	15-20
THBD	Membrane	Loss	5	One case
Homozygous CFHR1 del (3%-8%)	Circulating	Undetermined	14-23 (> 90% with anti-CHF AB)	NA

Abbas F *et al*. TMA after renal transplantation

Table 4 Genotype-phenotype correlations in atypical hemolytic uremic syndrome (data refer to the period before introduction of eculizumab)

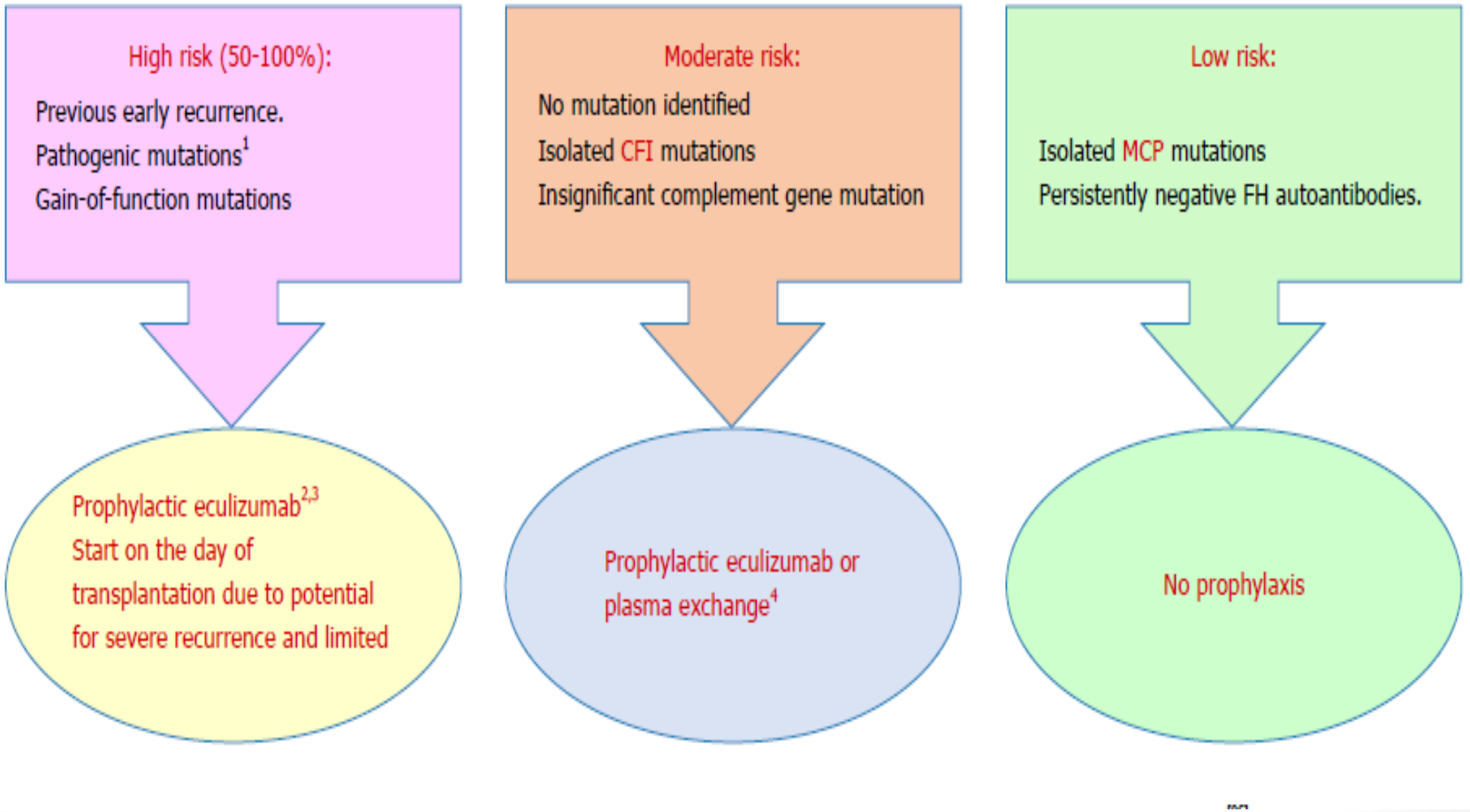
Gene	Risk of death or ESRD at onset or first yr	Risk of recurrence	Risk of death or ESRD after 3-5 yr	Risk of recurrence in allograft
CFH or *CFH-CFHR1/3* hybrid genes	50%-70%	50%	75%	75%-90%
CFI	50%	10%-30%	50%-60%	45%-80%
MCP single	0%-6%	70%-90%	6%-38%	< 20%
MCP combined[1]	30%-40%	50%	50%	50%-60%
C3	60%	50%	75%	40%-70%
CFB	50%	100%	75%	100%
THBD	50%	30%	54%	?
Anti-FH	30%-40%	40%-60%	35%-60%	Depends on antibody titers

[1]Combined with *CFH* or *CFI* or *C3* mutations. Adapted from: Goodship *et al*[58]. *CFB*: Complement factor B gene; *CFH*: Complement factor H gene; *CFHR*: Complement factor H-related genes; *CFI*: Complement factor I gene; FH: Factor H protein; *THBD*: Thrombomodulin gene.



Noemie Jourde- Chiche,et al. Endothelium structure and function in kidney health and disease, Nature, volume 15 | FEBRUARY 2019 | 87

Genes associated only with aHUS	Thrombomodulin (THBD)
Genes associated with aHUS & C3G	*Complement genes:* Complement Factor H (CFH) Complement Factor H-related genes 1 to 5 (CFHR1-5) Membrane cofactor protein (MCP) Complement Factor I (CFI) Complement Factor B (CFB) Complement Component 3 (C3) *Non-complement genes:* • Diacylglycerol kinase-ε (DGKE)
aHUS prototypical genetic variants	1) CFH C-terminal variants associated with normal FH expression levels 2) Gene conversion events and genomic rearrangements between CFH & CFHR1 or CFHR3 resulting in FH-FHR & FHR-FH hybrid proteins 3) C3 pathogenic variants (*i.e.*, p.R161W and p.I1157T) 4) CFH- H3 and MCP ggaac aHUS risk haplotypes 5) Absence of FHR-1 usually associated with homozygous deletion of the CFHR3- CFHR1 genes, which is a common CNV and is strongly associated with development of FH autoantibodies


High risk (50-100%):
Previous early recurrence.
Pathogenic mutations[1]
Gain-of-function mutations
Moderate risk:
No mutation identified
Isolated CFI mutations
Insignificant complement gene mutation
Low risk:
Isolated MCP mutations
Persistently negative FH autoantibodies.
Prophylactic eculizumab[2,3]
Start on the day of
transplantation due to potential
for severe recurrence and limited
Prophylactic eculizumab or
plasma exchange[4]
No prophylaxis

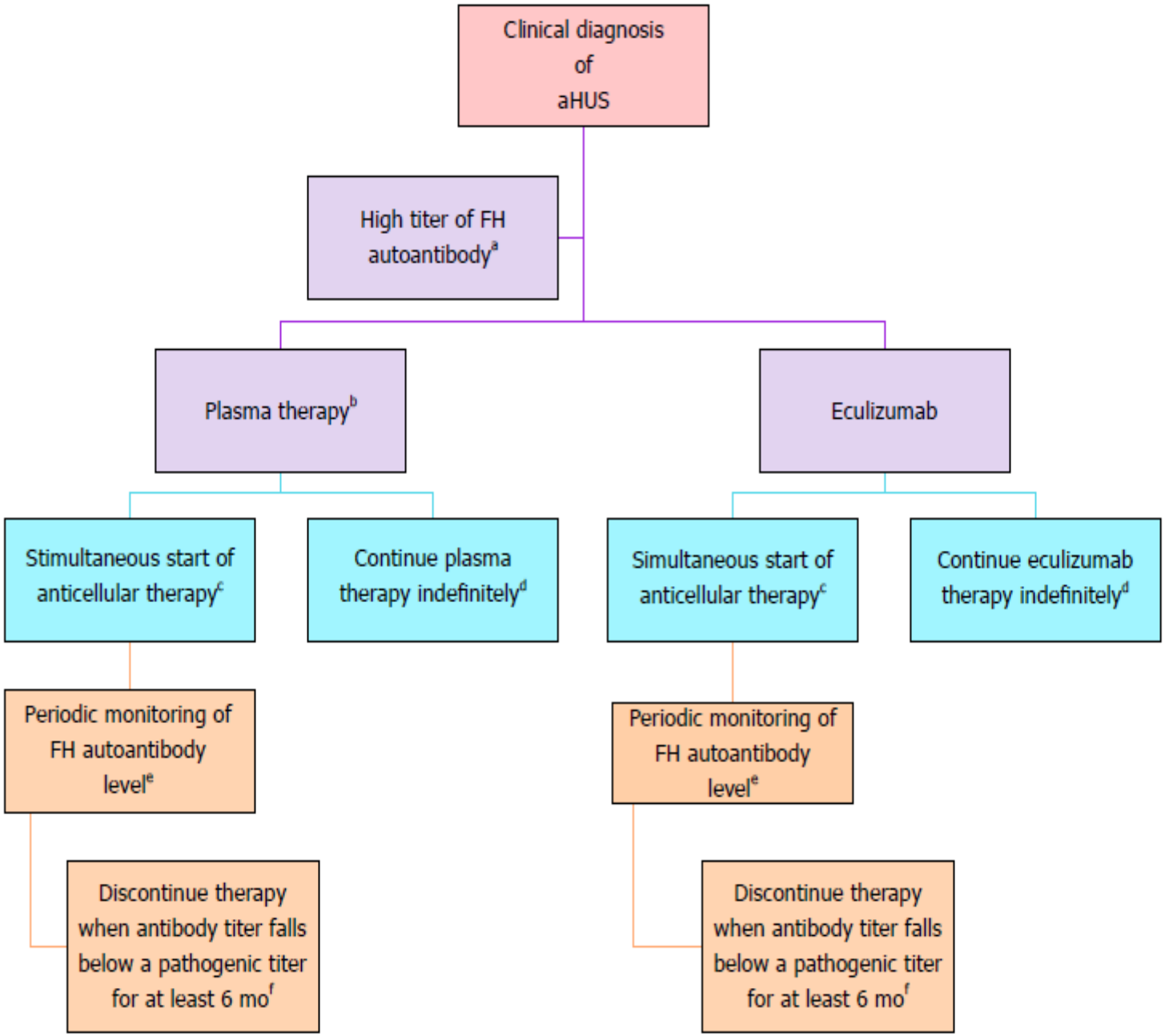

Clinical diagnosis of aHUS
High titer of FH autoantibody[a]
Plasma therapy[b]
Eculizumab
Stimultaneous start of anticellular therapy[c]
Continue plasma therapy indefinitely[d]
Simultaneous start of anticellular therapy[c]
Continue eculizumab therapy indefinitely[d]
Periodic monitoring of FH autoantibody level[e]
Periodic monitoring of FH autoantibody level[e]
Discontinue therapy when antibody titer falls below a pathogenic titer for at least 6 mo[f]
Discontinue therapy when antibody titer falls below a pathogenic titer for at least 6 mo[f]

Table 6 Monitoring eculizumab therapy

Description	
CH50 (total complement activity)	Measures the combined activity of all of the complement pathways Tests the functional capability of serum complement components to lyse 50% of sheep erythrocytes in a reaction mixture Low in congenital complement deficiency (C1-8) or during complement blockade Normal range is assay dependent Recommended goal during therapeutic complement blockade: < 10% of normal
AH50 (alternative pathway hemolytic activity)	Measures combined activity of alternative and terminal complement pathways Tests the functional capability of alternate or terminal pathway complement components to lyse 50% of rabbit erythrocytes in a Mg^{2+}-EGTA buffer Will be low in congenital C3, FI, FB, properdin, FH, and FD deficiencies or during terminal complement blockade Normal range is assay dependent Recommended goal during complement blockade: < 10% of normal
Eculizumab trough	May be a free or bound level ELISA: Using C5 coated plates, patient sera, and an anti-human IgG detection system Not affected by complement deficiencies Recommended trough level during complement blockade: 50-100 μg/mL
Alternative assays	The following assays are under investigation (or awaiting to be replicated in different laboratories)[83] as a means to monitor therapeutic complement blockade Free C5 *In vitro* human microvascular endothelial cell test sC5b -9 (also referred to as sMAC and TCC) may remain detectable in aHUS patients in remission and therefore is not recommended as a monitoring tool

Adapted from: Goodship *et al*[58]. aHUS: Atypical hemolytic uremic syndrome; C3: Complement component 3; C5: Complement component 5; EGTA: Ethyleneglycol tetraacetic acid; ELISA: Enzyme-linked immunosorbent assay; FB: Complement factor B; FD: Complement factor D; FH: Complement factor H; FI: Complement factor I; sC5b-9: Soluble C5b-9; sMAC: Soluble membrane attack complex; TCC: Terminal complement complex

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Case report

Successful kidney transplant with eculizumab, thymoglobulin and belatacept therapy in a highly sensitised patient with atypical haemolytic uraemic syndrome due to factor H mutation☆

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Induction	Maintenance
Thymoglobulin 75 mg IV per day for three days	Mycophenolate sodium 720 mg po every 12 h from day 0 of the transplant
Methylprednisolone 500 mg IV per day for three days	Prednisolone 50 mg po starting from the fourth day after transplant with progressive decrease to 10 mg per day
Adjustment of the eculizumab dose at the time of the transplant to 900 mg IV weekly for four weeks, 1200 mg at week 5, and later 1200 mg fortnightly	Trimethoprim-sulfamethoxazole 960 mg every other day
Belatacept: 500 mg day 0, 4, 14, 28, 56, 84, and starting in the fourth month 250 mg monthly	Valganciclovir 900 mg per day for 100 days
IV: intravenous; PO: orally.	

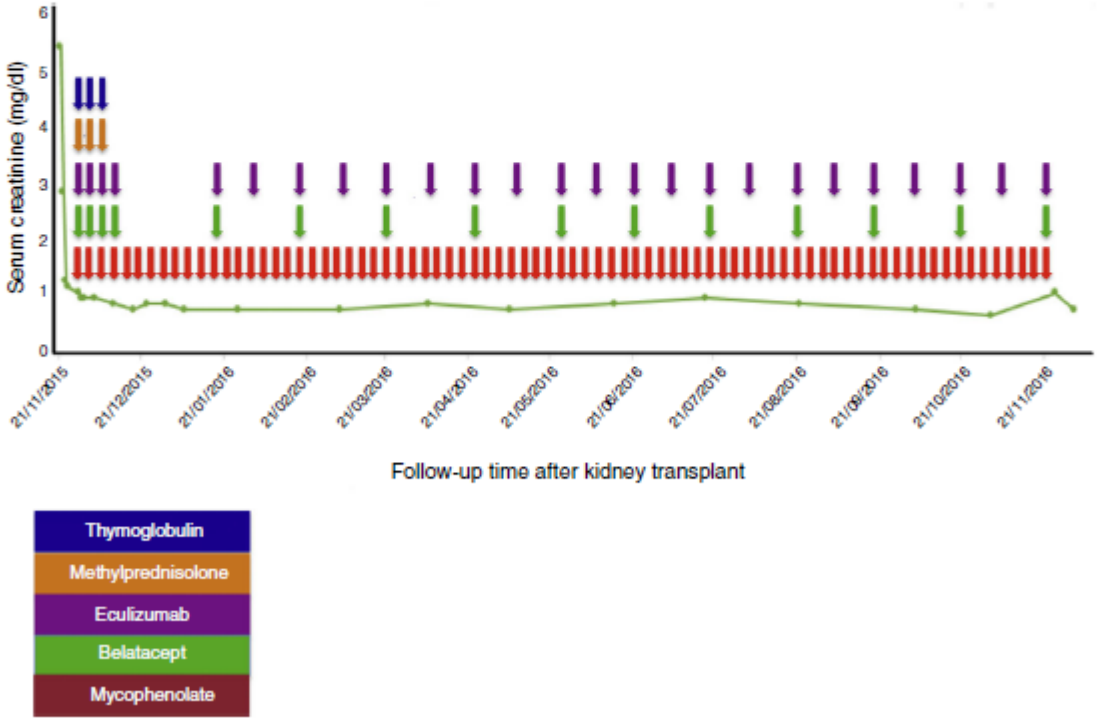

Fig. 1 – Evolution of the kidney graft function and immunosuppressant therapy received.