Atypical Hemolytic Uremic Syndrome

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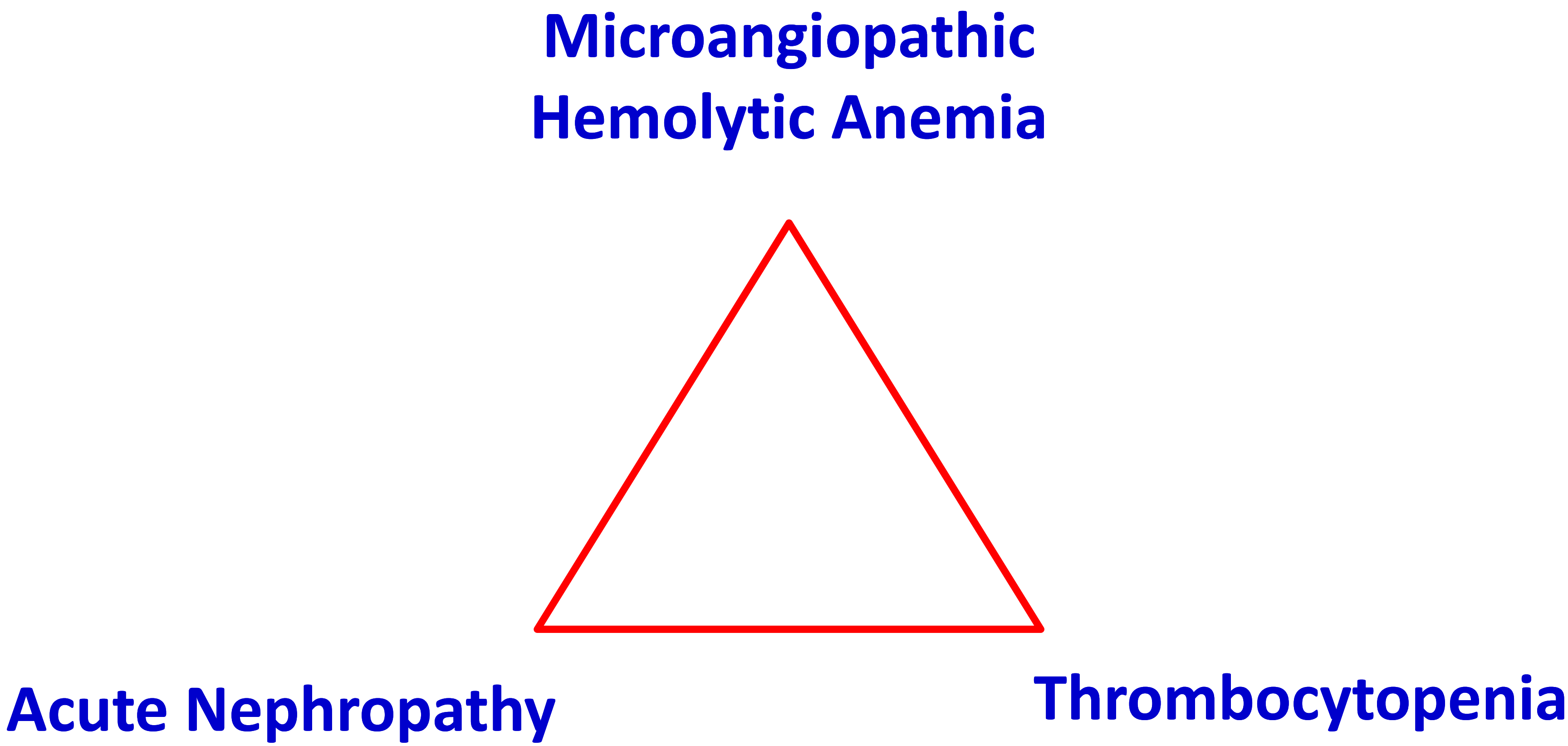
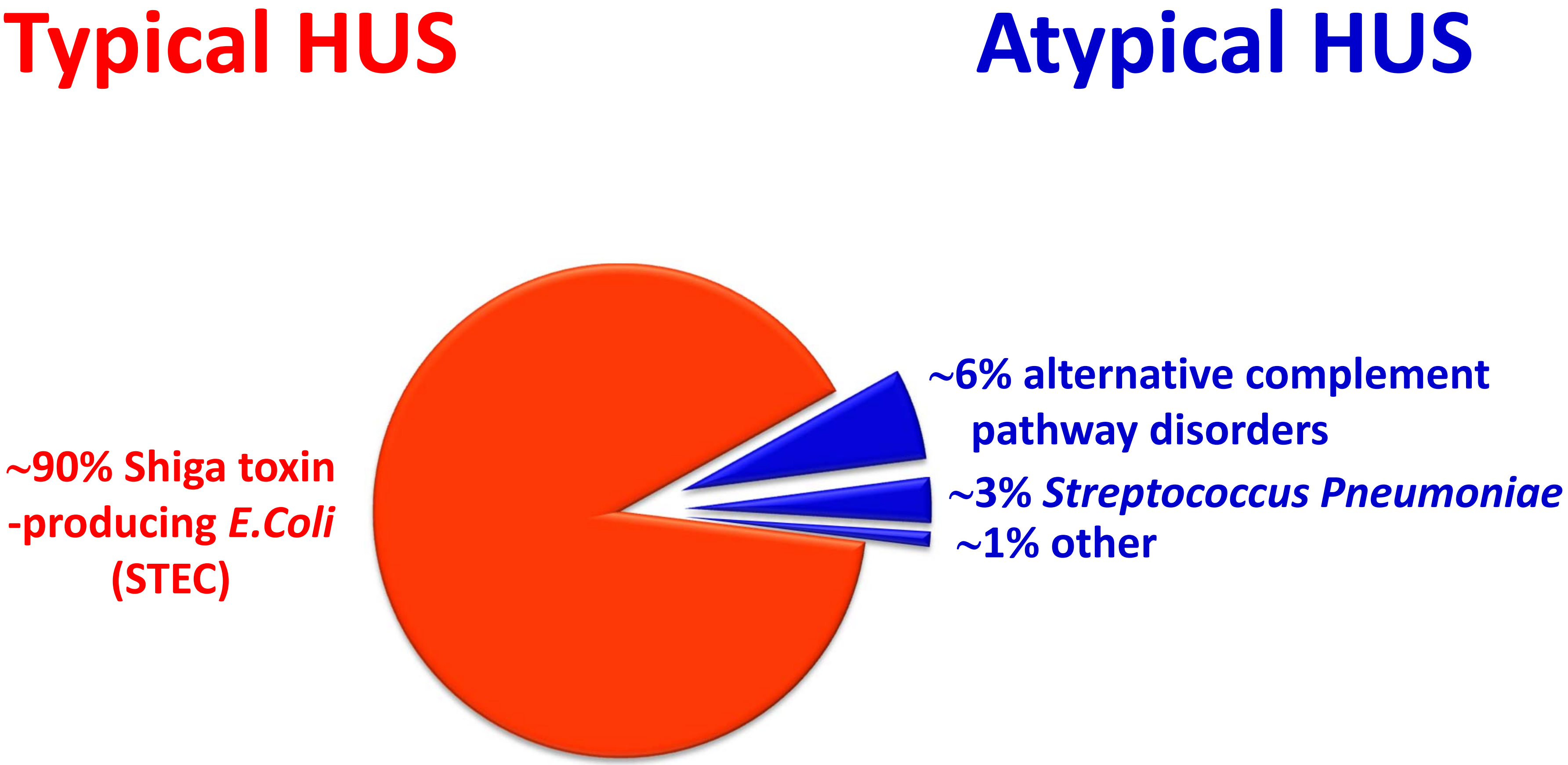
OSPEDALE PEDIATRICO

Hemolytic Uremic Syndrome (HUS)



Hemolytic Uremic Syndrome (HUS)



Atypical and secondary HUS

- **Other pathogens**
  Streptococcus Pneumoniae, Influenza A, **H1N1*,***
  HIV, Q fever, CMV, *Staphylococcus*, Hantavirus

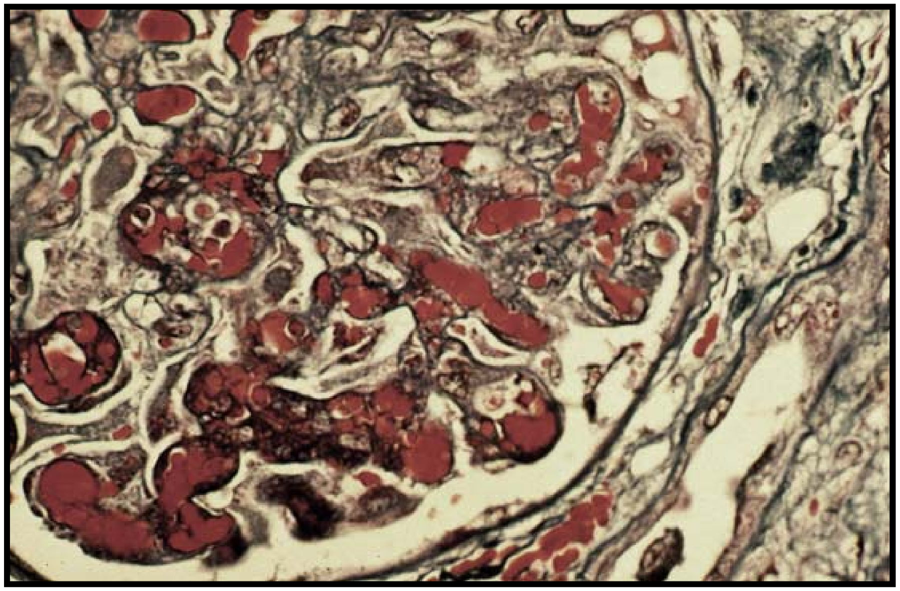
- **Drugs**
  cyclosporine, tacrolimus
  bleomycin, cisplatin, mitomycin

- **Autoimmune**
  anti-factor H antibodies

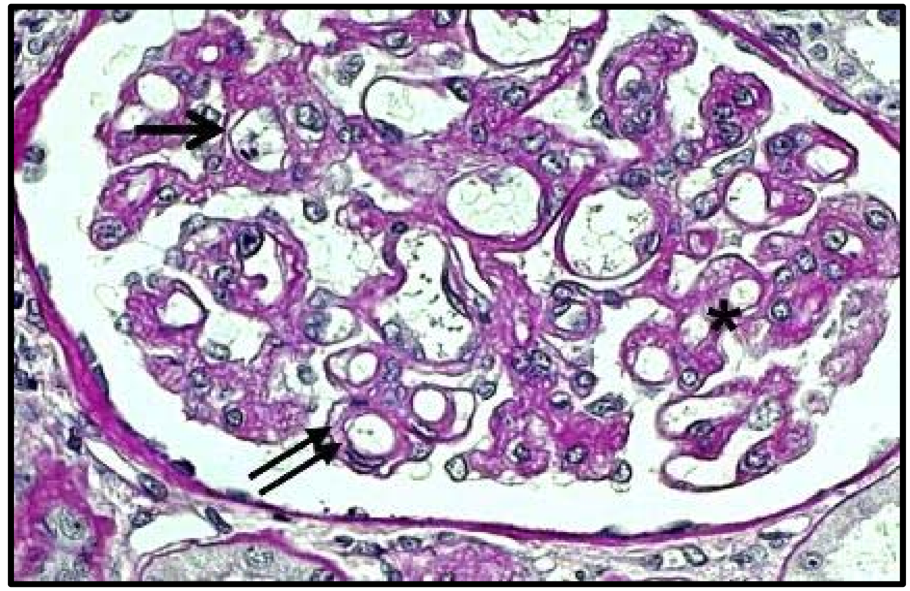
- **Underlying genetic defects**
  complement factors deficiency
  DGKE mutations
  cobalamin-C defect (methylmalonic aciduria and homocystinuria)

Renal pathology

Acute



Chronic



Clinical characteristics at onset of children with HUS

	S pneumoniae	STEC-HUS	CblC defect-HUS	aHUS
Age (years)	<2	<0.5: ~5% 0.5-3: ~ 65% >3: ~30%	<0.1: ~50% 1.5-14: ~40% ≥20: ~10%	Birth-0.5: 28% 0.5 to 2: 28% 2-15: 44%
Diarrhea (%)	No	95% Bloody ≥60%	Possible in neonatal forms + vomiting, poor sucking, failure to thrive	39%
Progressive onset (%)	No, sudden, severe infection pneumonia ~70% meningitis ~30% bacteremia ~80%	No	Common	Possible
Hematological characteristics	Positive direct Coombs ~90% Elevated WBC count	Platelets often >30G/L Elevated WBC count frequent	Megaloblastosis Leukocytopenia Pancytopenia	Platelets generally >30G/L, >150G/L in 15%; Hemoglobin >10 g/dl in 6%

Loirat et al, Ped Nephrol, 2015

Clinical characteristics at onset of children with HUS

	S pneumoniae	STEC-HUS	CblC defect-HUS	aHUS
Acute renal failure (%)	100%, dialysis required in 40 to 80%	95%, dialysis required in ~50%	ProtU/hematU/HT Progression to CKD ± acute episodes in ~50%	85%, dialysis required in 60%
Neurological symptoms (%)	Meningitis ~30%	~20%	100% in neonatal forms + retinopathy Psychiatric symt., cognitive impair. frequent in late forms	16%
Family history	No	Epidemic cases	AR	27% (NB: delay!) AR or AD with variable penetrance

Loirat et al, Ped Nephrol, 2015

Streptococcus Pneumoniae-associated HUS

- Nearly always invasive disease
  ± 60% empyema
  ± 30% meningitis

- Overall mortality: 13% (30% if meningitis)

- Acute phase more severe than D+HUS
  more dialysis (84%)
  more transfusions (98%)

- Long term renal sequelae similar to D+HUS
  protU and/or CRF 20-25%

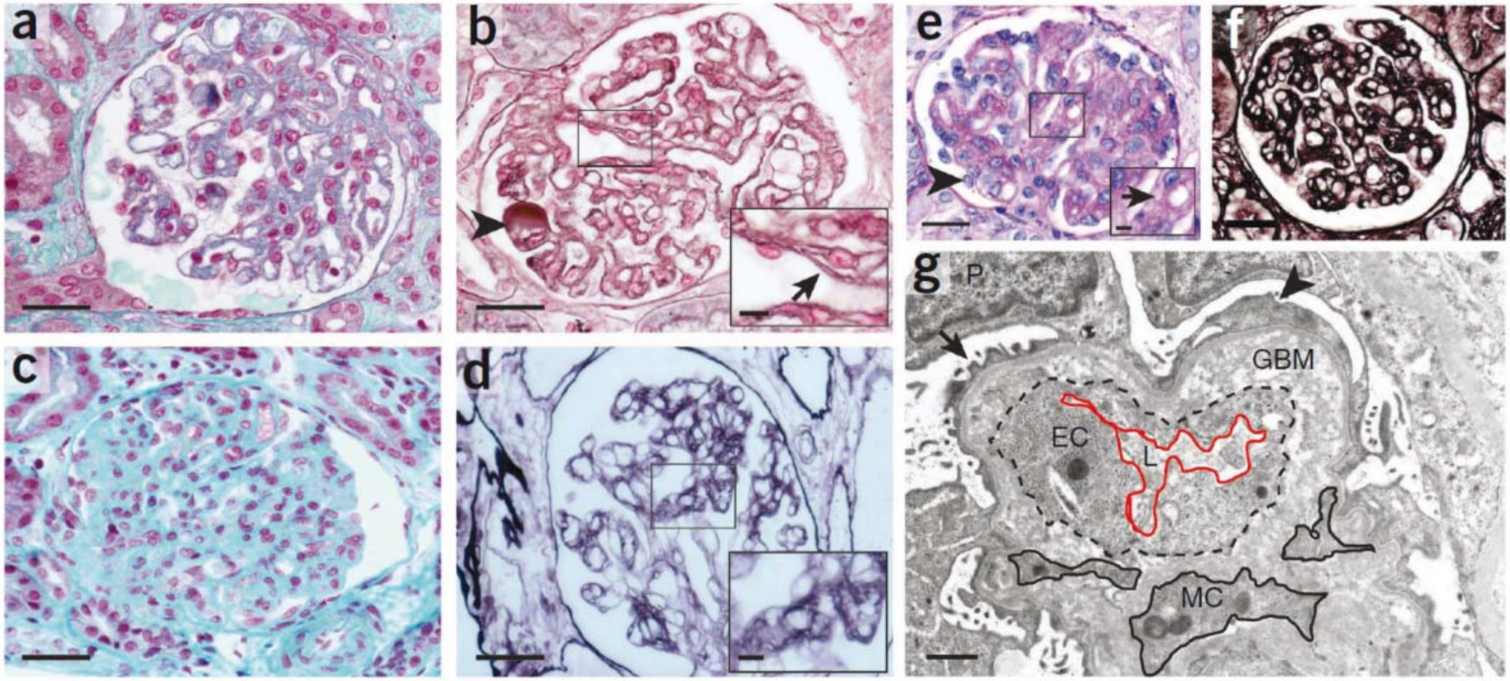
Novak 1983, Martinot 1889, Mc Graw 1989, Eber 1993, Pan 1995, Sajjannar 1996, Mizuwa 1996, Cabrera 1998, Nathanson 2001, Brandt 2002, Waters 2007, Waters 2007

DGKE (diacylglycerol kinase ε) mutations

Recessive mutations in *DGKE* cause atypical hemolytic-uremic syndrome

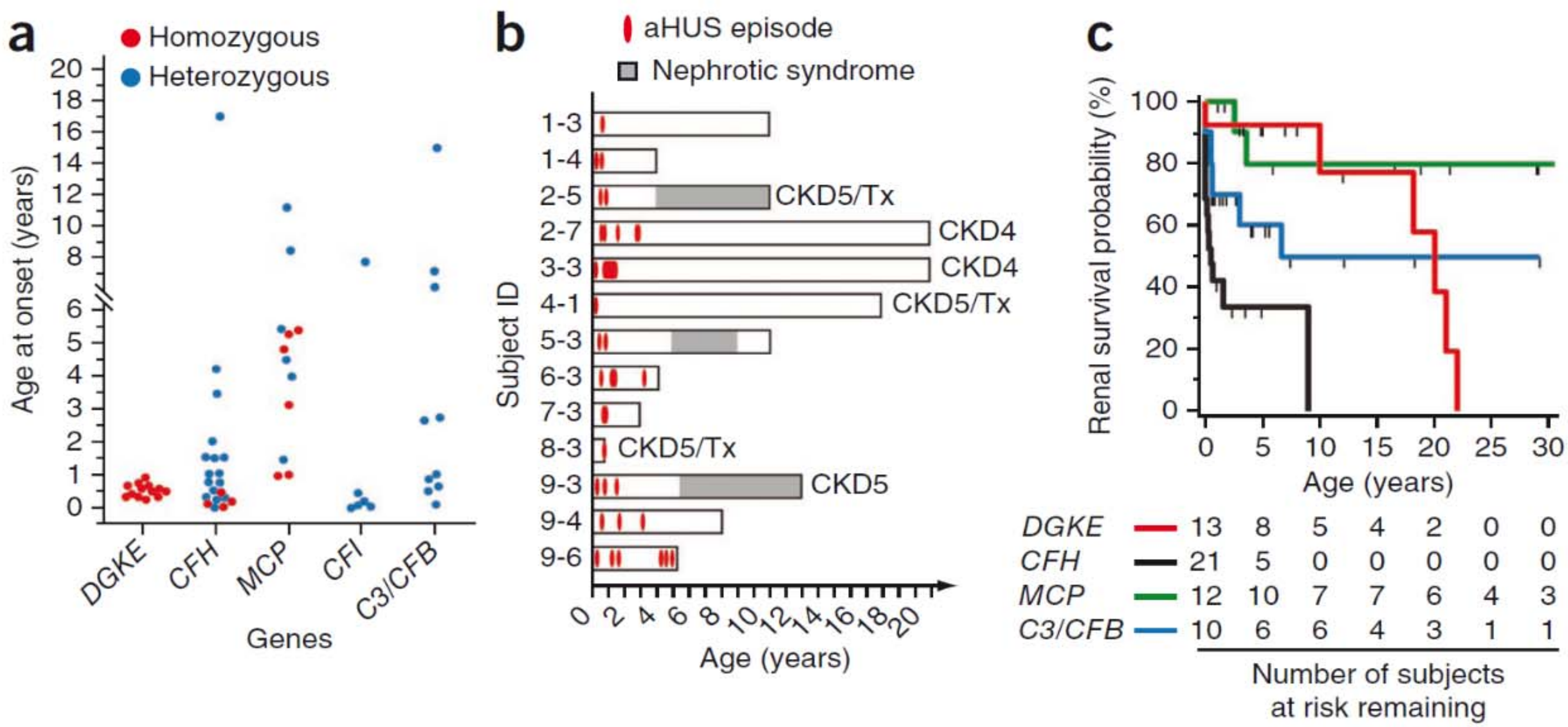
nature genetics

Mathieu Lemaire[1,2,24], Véronique Frémeaux-Bacchi[3,4,24], Franz Schaefer[5,6], Murim Choi[1,2,7], Wai Ho Tang[8], Moglie Le Quintrec[4], Fadi Fakhouri[9], Sophie Taque[10], François Nobili[11], Frank Martinez[12], Weizhen Ji[1,2], John D Overton[1,7], Shrikant M Mane[1,7], Gudrun Nürnberg[13], Janine Altmüller[13], Holger Thiele[13], Denis Morin[14], Georges Deschenes[15], Véronique Baudouin[15], Brigitte Llanas[16], Laure Collard[17], Mohammed A Majid[18], Eva Simkova[18], Peter Nürnberg[13,19,20], Nathalie Rioux-Leclerc[21], Gilbert W Moeckel[22], Marie Claire Gubler[23], John Hwa[8], Chantal Loirat[15] & Richard P Lifton[1,2,7]



Lemaire et al, Nature Genetics 2013

DGKE (diacylglycerol kinase ε) mutations



Lemaire et al, Nature Genetics 2013

DGKE (diacylglycerol kinase ε) mutations

- DGKE is expressed in endothelium, platelets and podocytes
- DGKE inactivates arachidonic acid signaling through diacylglycerols (DAG) (activates thrombosis)
- First gene implicated in aHUS that is not an integral component of the complement cascade
- Symptoms: hypertension, microhematuria and proteinuria and unique finding of nephrotic syndrome
- Relapse of aHUS in subjects while receiving anti-C5
- Renal transplantation could be efficacious and safe

Lemaire et al, Nature Genetics 2013

Defects of intracellular MMA and Cbl metabolism

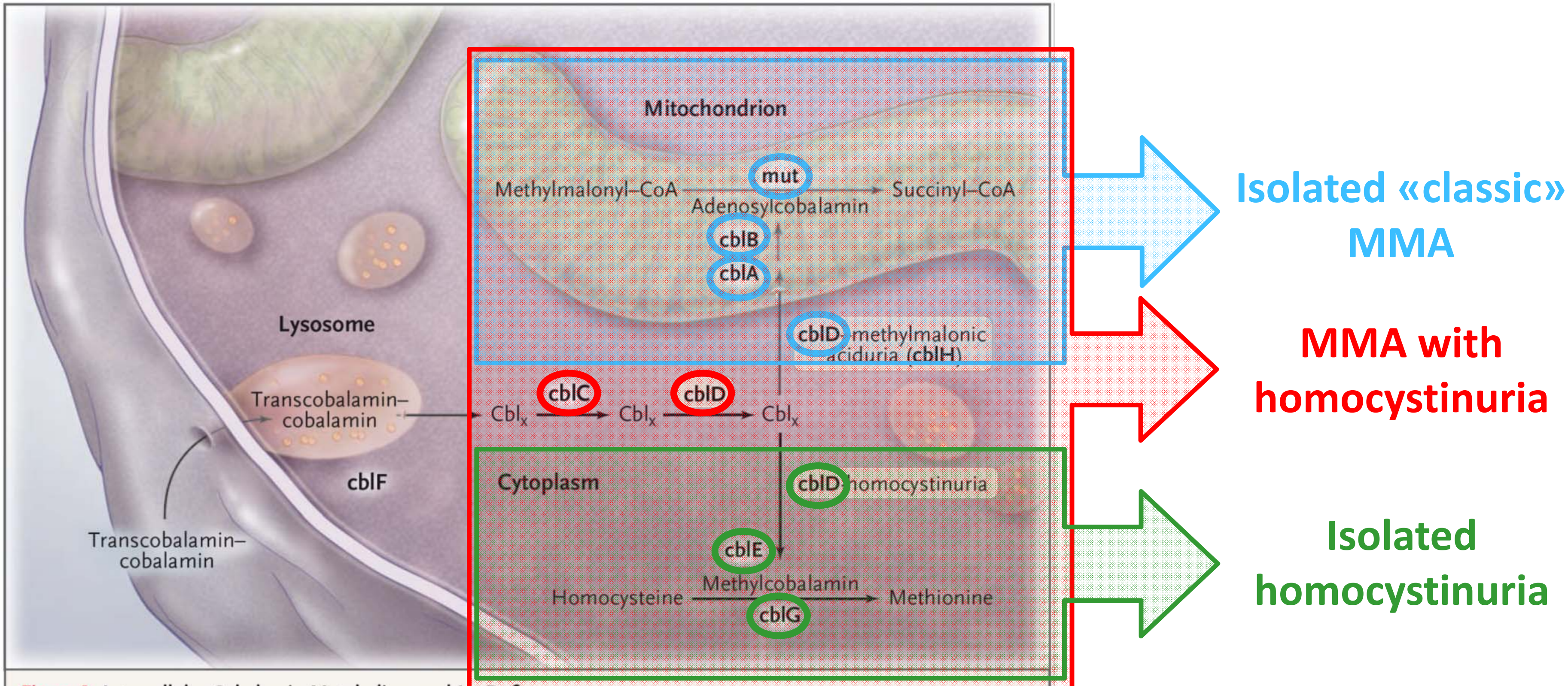


Figure 1. Intracellular Cobalamin Metabolism and Its Defects.

To date, nine complementation-group defects of the cobalamin pathway have been described. Cobalamin bound to transcobalamin enters the cell by means of lysosome-mediated endocytosis and is released through proteolysis. Export from the lysosome into the cytoplasm is defective in patients with the cblF defect. The steps in the cytosol after lysosomal release are still unclear but are defined by the complementation groups cblC and cblD. In addition, the exact form of cobalamin at this stage is unclear (as indicated by "Cbl_x"). In the cytoplasm, cobalamin is reductively methylated by methionine synthase reductase (cblE) to methylcobalamin, the cofactor for methionine synthase (cblG). After its transport into the mitochondrion, cobalamin is converted to adenosylcobalamin, the cofactor for methylmalonyl–coenzyme A (CoA) mutase (mut), by cobalamin adenosyltransferase (cblB). The exact role of the protein associated with the cblA complementation group is unclear. Our studies show that the cblD protein constitutes a branch point between the cytosolic and mitochondrial pathways, controlled by the cblD–methylmalonic aciduria variant and the cblD-homocystinuria variant, respectively. We also show that the cblH complementation group is identical to the cblD–methylmalonic aciduria group.

Coelho et al., *N Engl J Med*, 2008

CblC defects

Mild facial dysmorphisms

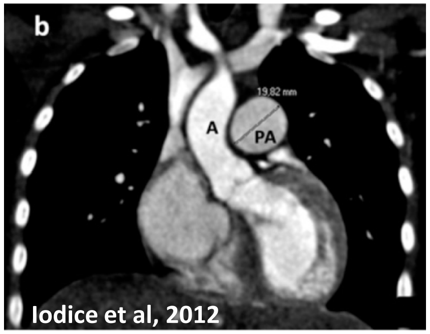
in utero toxicity?

Cardiomyopathy

vascular toxicity

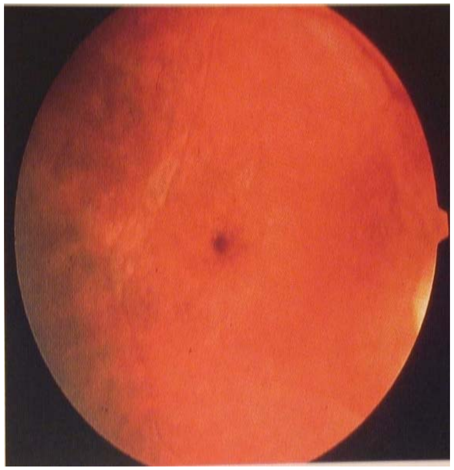
Pulmonary hypertension

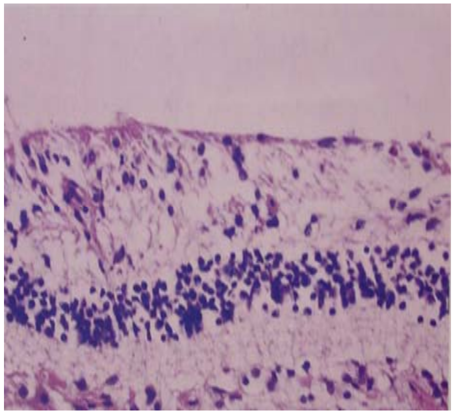
vascular toxicity



CblC defects

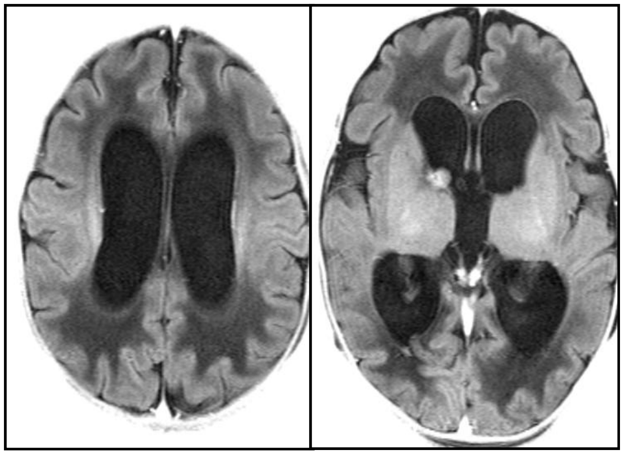
Retinopathy – optic nerve atrophy
vascular toxicity? - congenital?



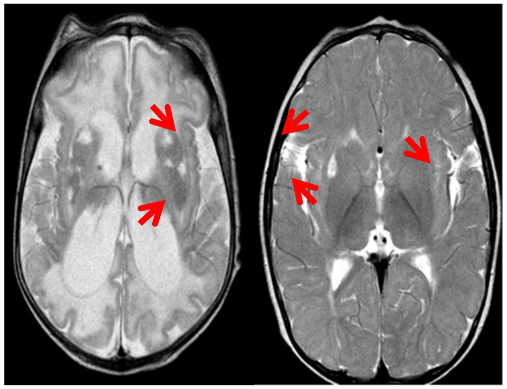


Ricci 2005

Hydrocephalus
vascular lesions? (impaired CSF reabsorption)



Basal ganglia lesions
vascular lesions? / mitochondrial toxicity?

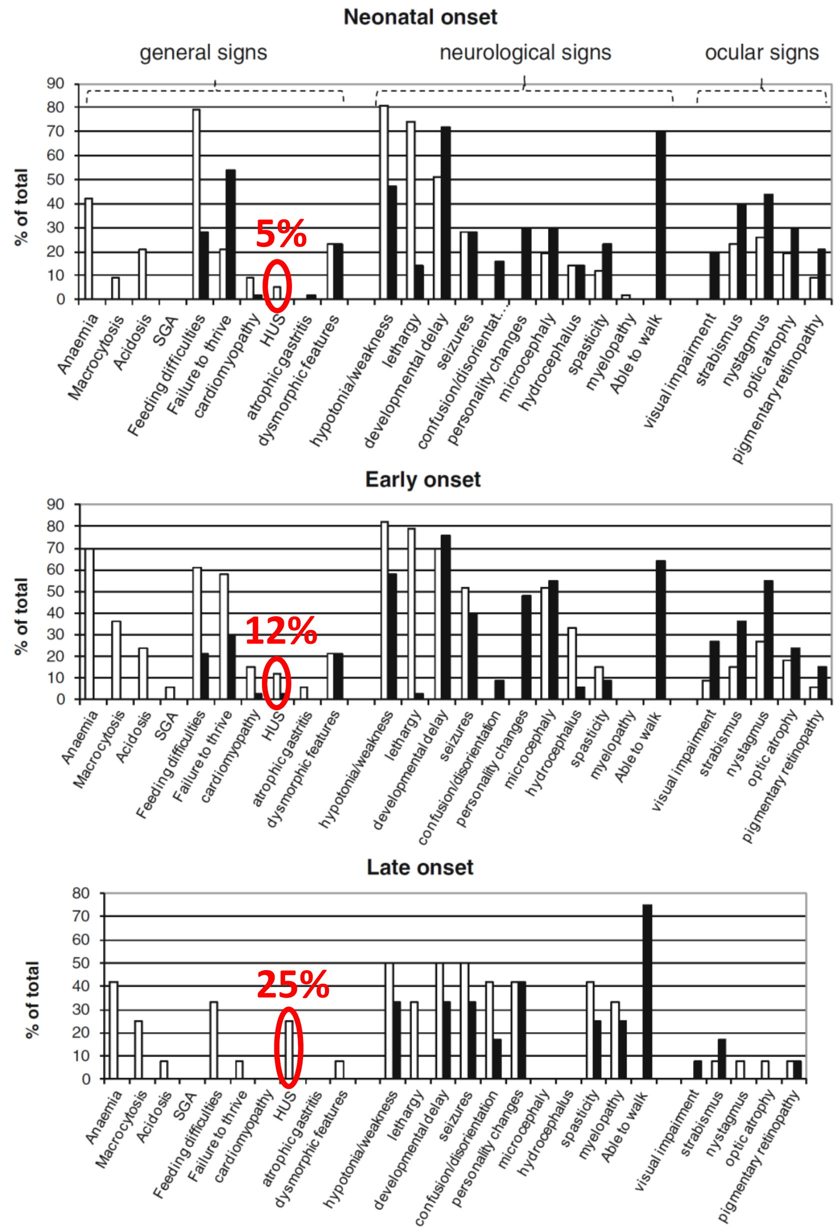


Hemolytic uremic syndrome in CblC defects

< 1 mo (n = 43)

1-12 mo (n = 33)

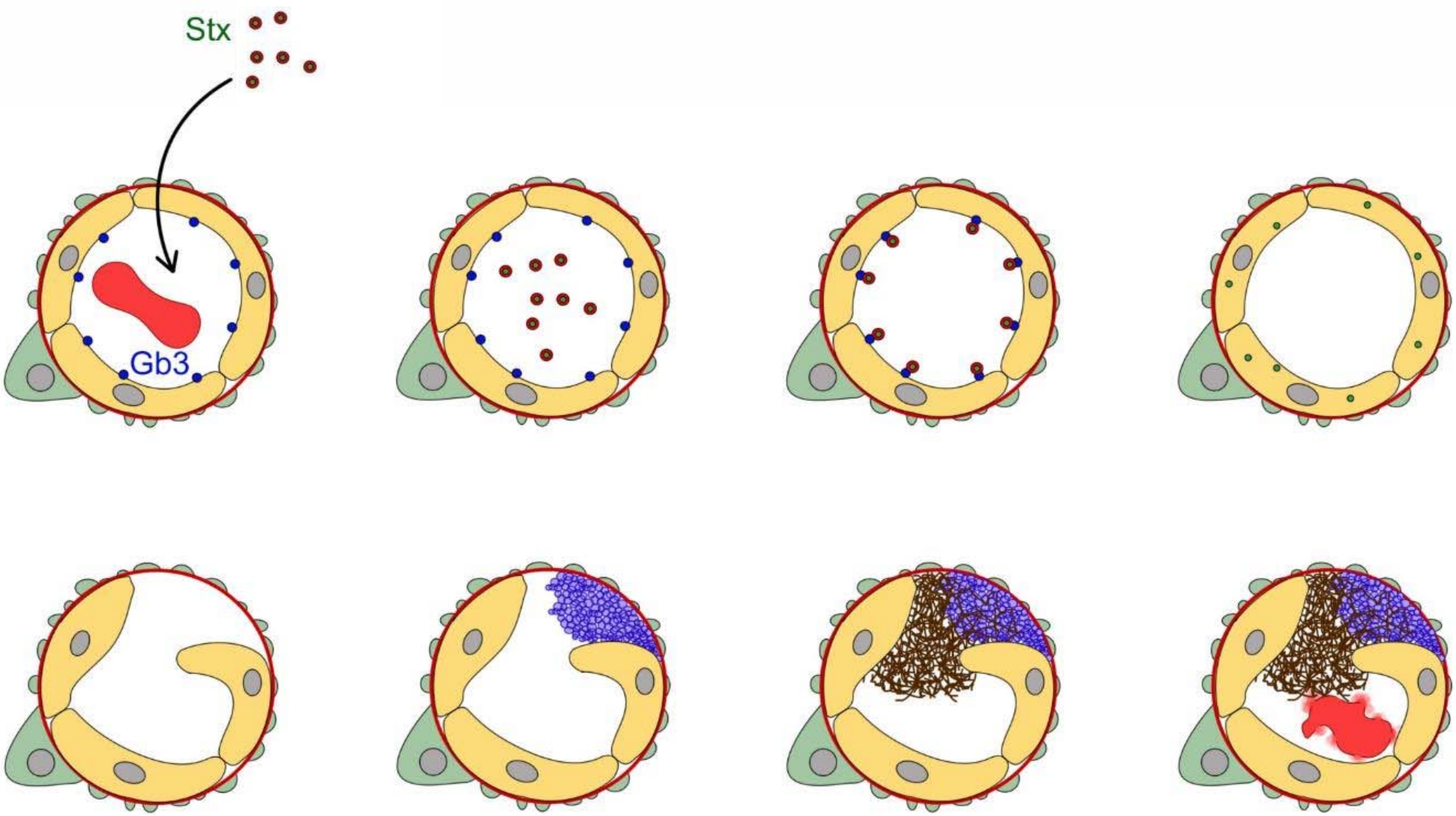
> 12 mo (n = 10)



☐ at diagnosis
■ follow-up

Fisher et al, 2014

STEC-HUS



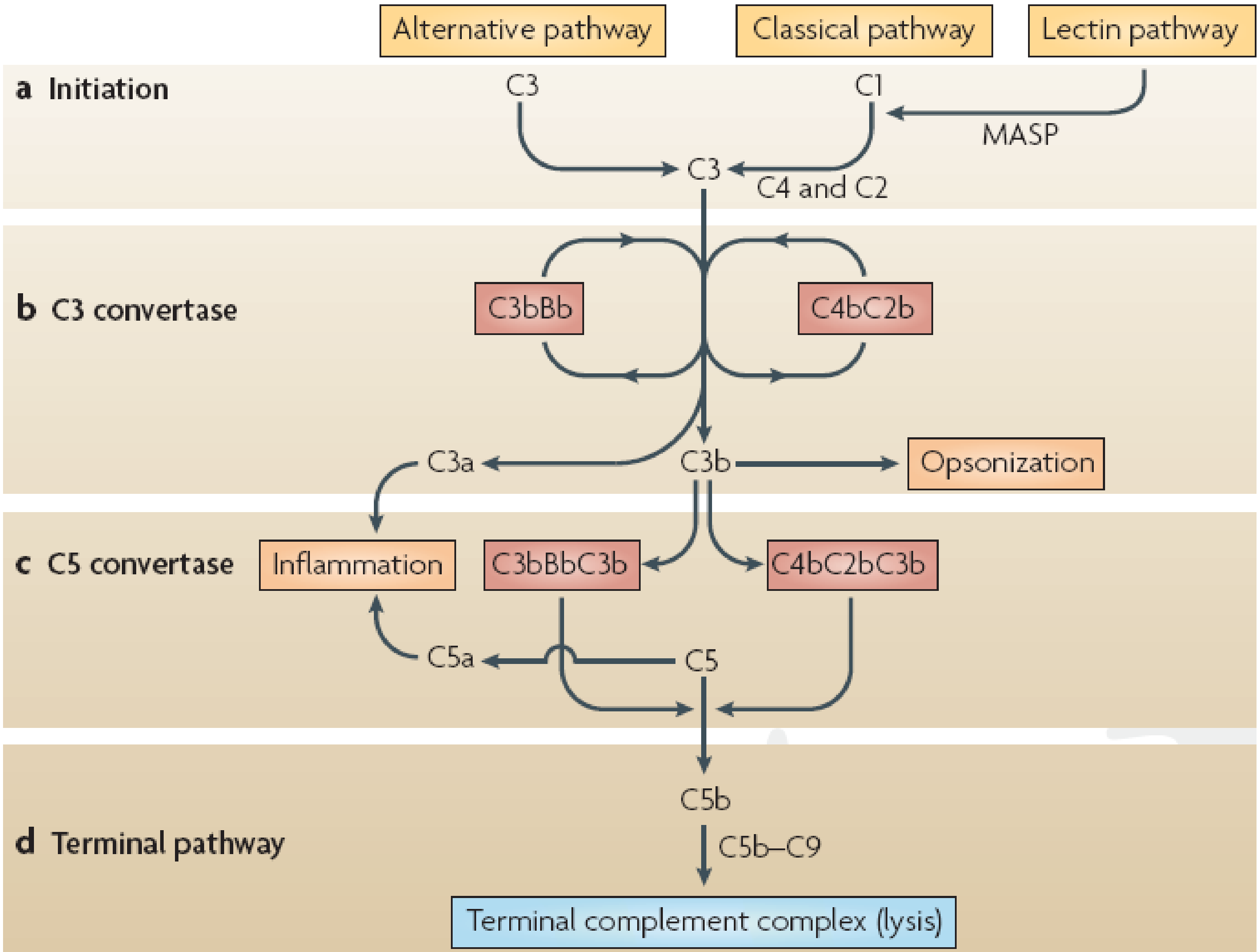
cell swelling and death
endothelial cell detachment
basement membrane exposure

platelet activation

fibrin deposition

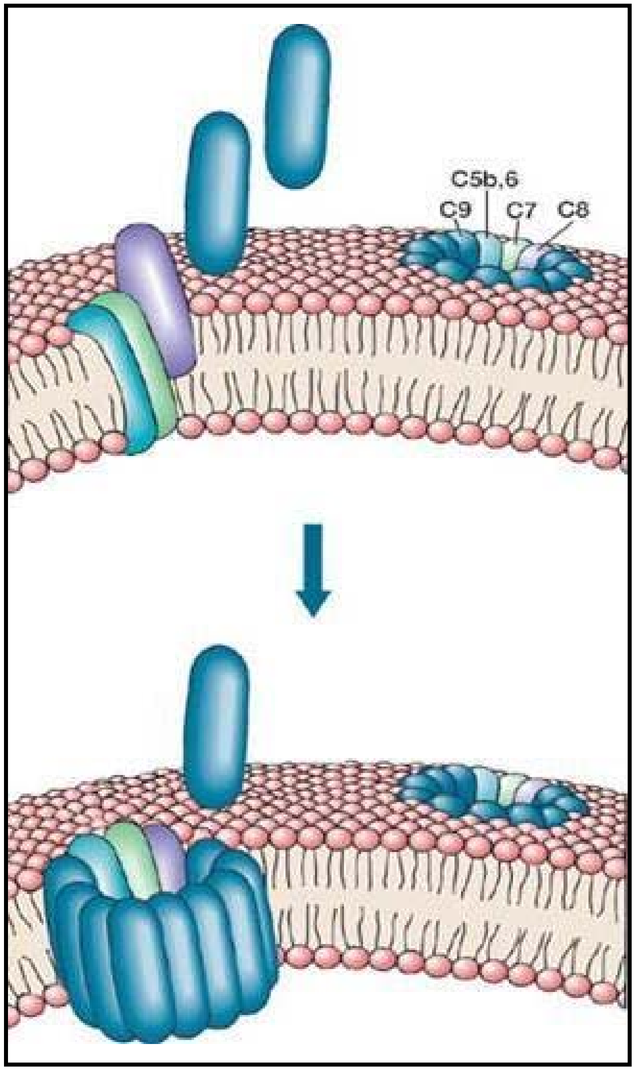
RBC destruction

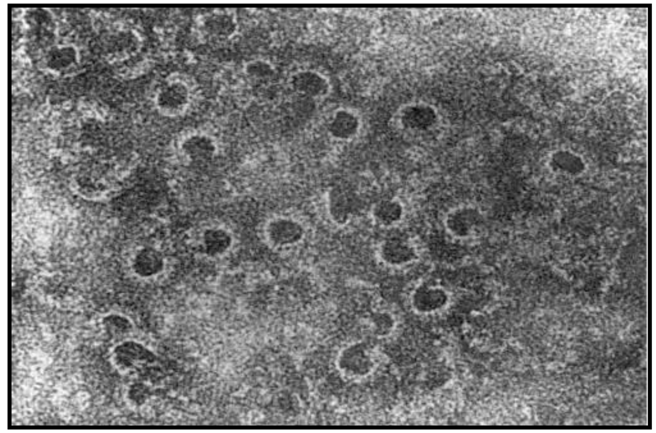
A (very) simplified view of the complement system

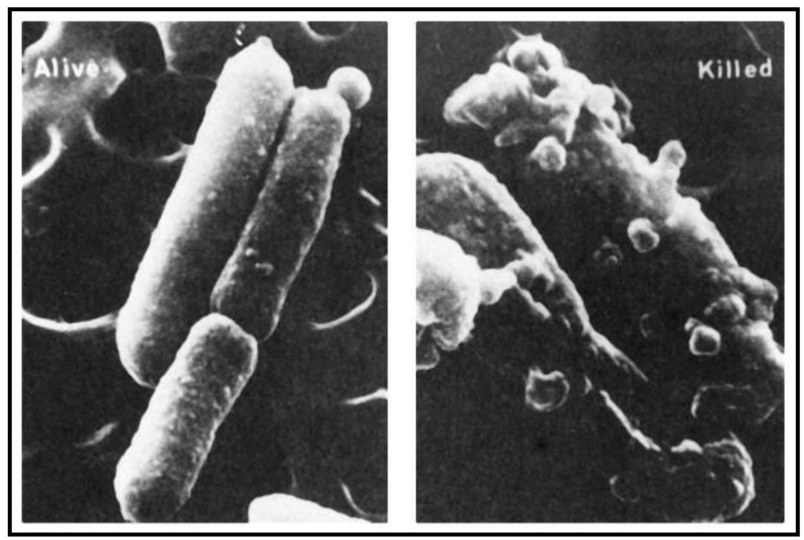


Zipfel and Skerka, Nat Rev Immunol 2009

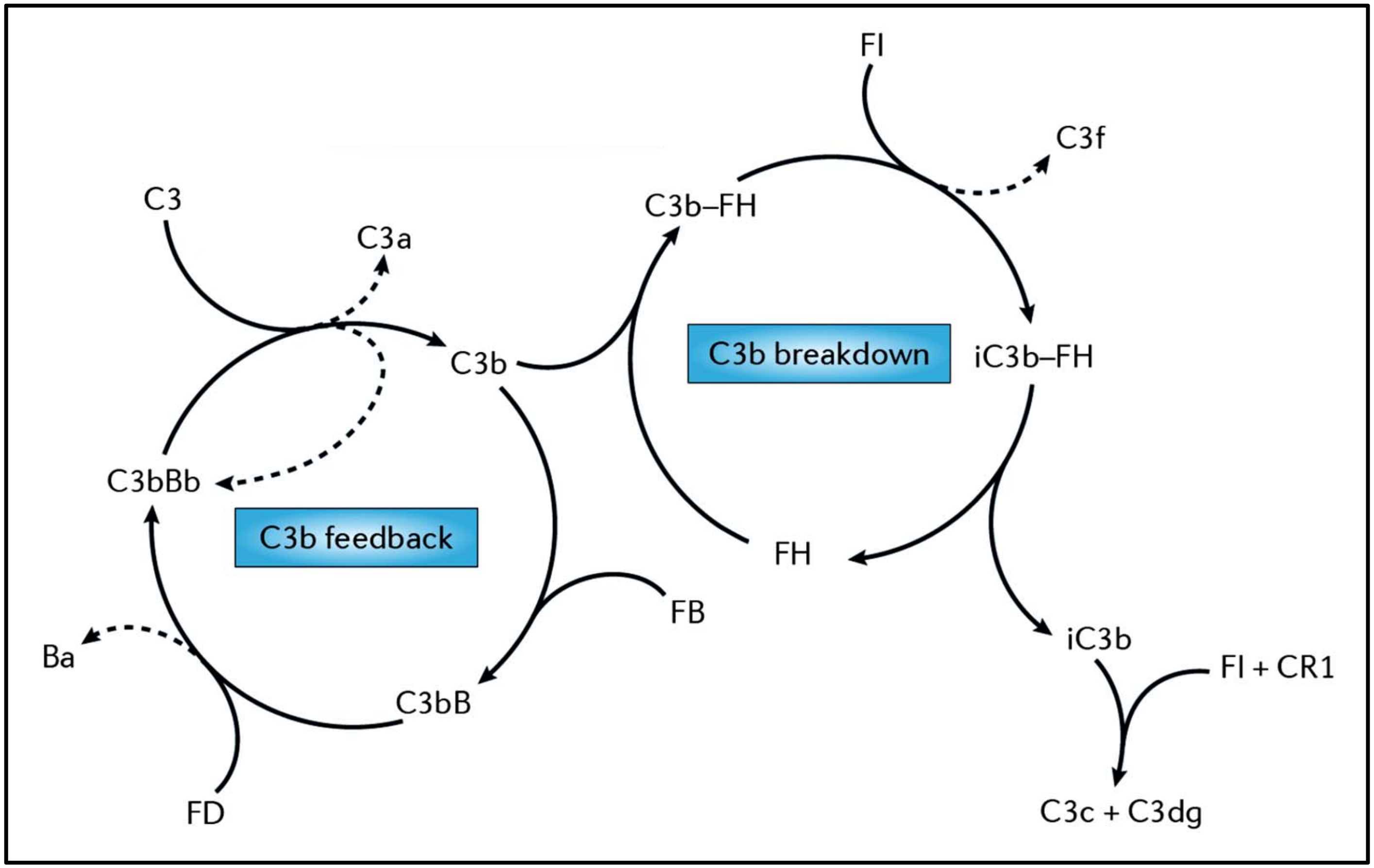
Membrane Attack Complex (MAC)





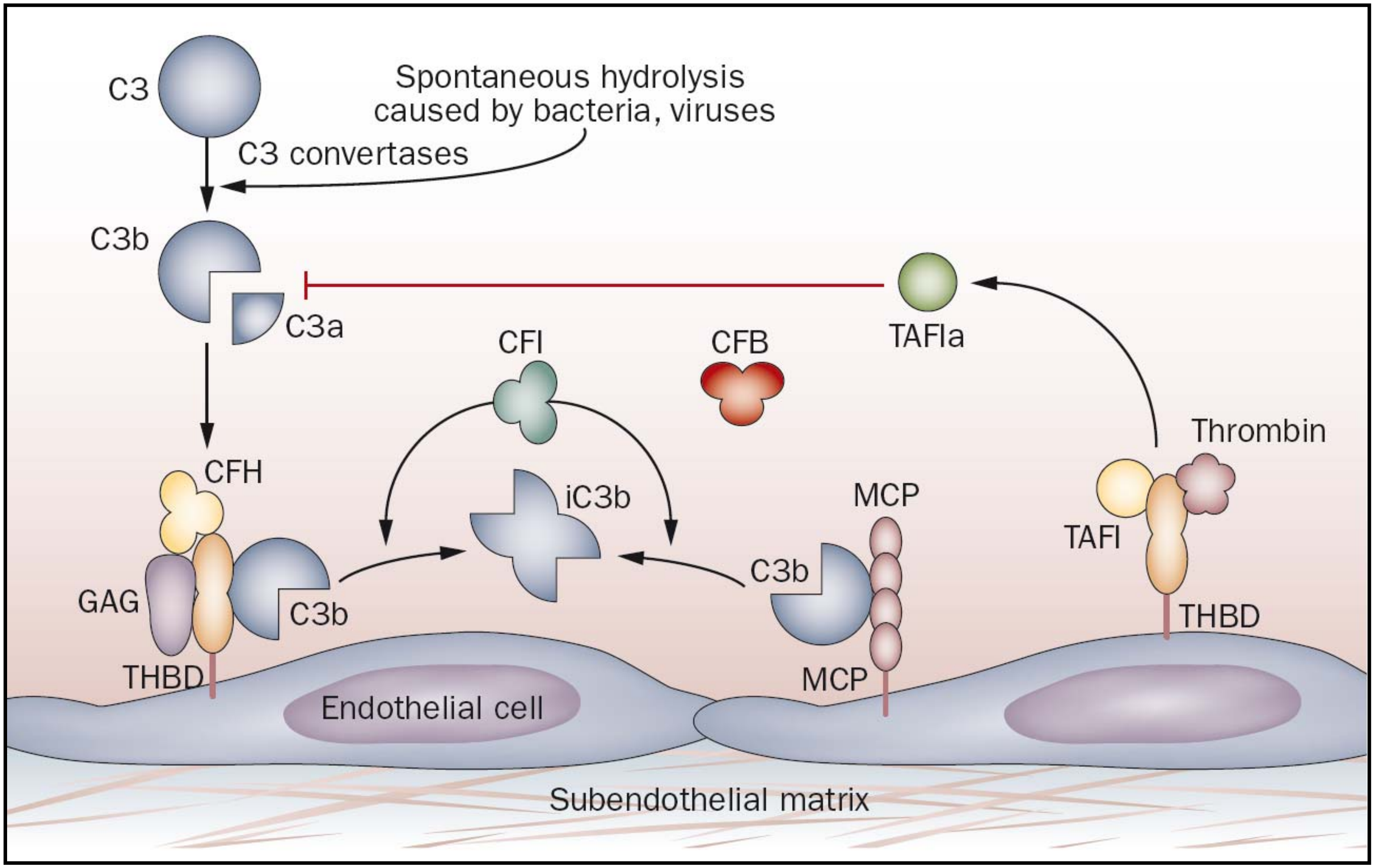


Controlling the alternative-pathway amplification loop



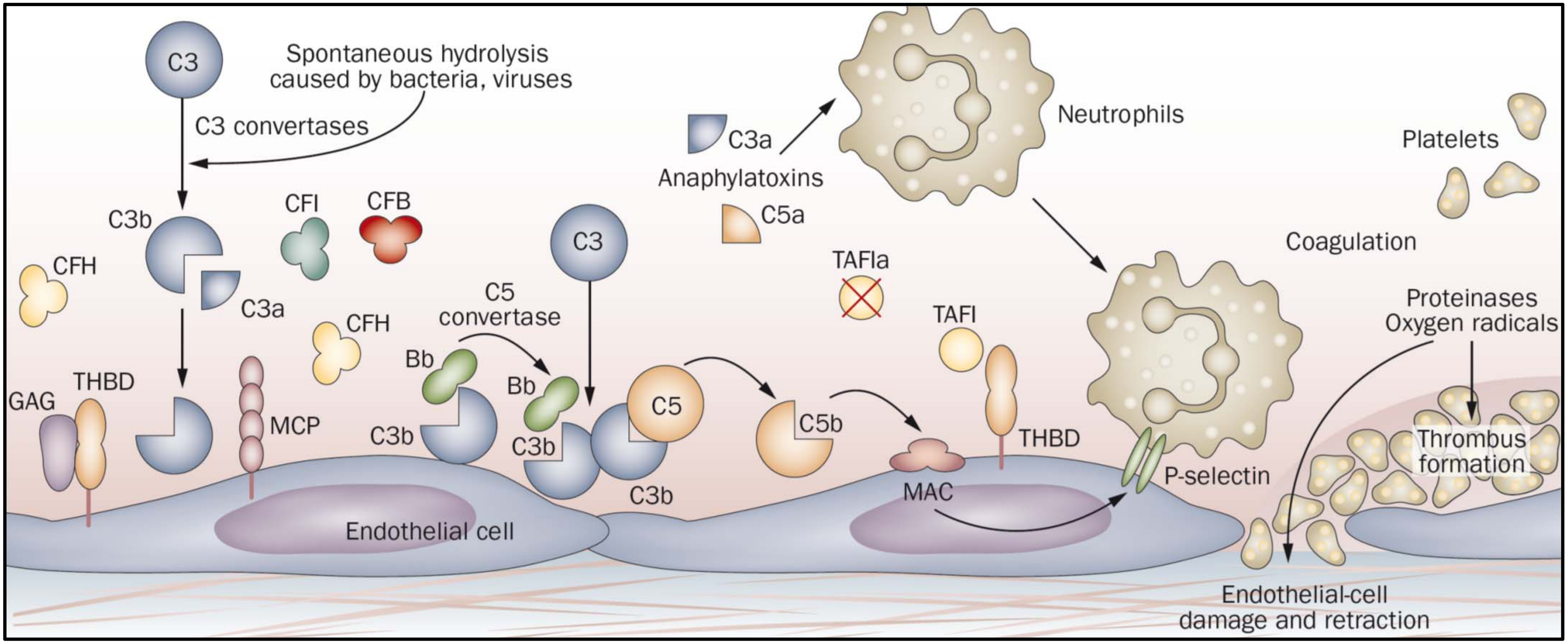
Morgan and Harris, Nat Rev Drug Discovery, 2015

Endothelial cells with functional complement regulation



Chiang and Inagi, Nat Rev Nephrol, 2010

Endothelial cell with dysfunctional complement regulation



Chiang and Inagi, Nat Rev Nephrol, 2010

aHUS related complement mutations

- **Loss of function mutations:**

  - Factor H (CFH)

  - Factor I (CFI)

  - Membrane cofactor protein (MCP; CD46)

  - Thrombomodulin (THBD; CD141)

- **Gain of function mutations:**

  - Factor B (CFB)

  - C3

- **Autoantibodies:**

  - CFH autoantibodies ± CFHR3-CFHR1 deletion (DEAP-HUS)

Courtesy of Christoph Licth

Frequency complement/DGKE abnormalities in aHUS

	[3]			[1]		
	Total	Children	Adults	Total[a]	Children[a]	Adults[a]
No. of patients	214	89	125	256	152	104
CFH (%)	27.5	21.3	32	25.3	25.6	25
Homozygous	1.8	4.4	0	4.2		
Heterozygous	25.7	16.8	32	21.1		
MCP (%)	9.3	13.5	6.4	7	9.2	3.8
Homozygous	2.8	5.6	0.8			
Heterozygous	6.5	7.8	5.6			
CFI (%)	8.4	6.7	9.6	3.9	2.6	5.7
C3 (%)	8.4	7.8	8.8	4.6	3.9	5.7
CFB (%)	1.4	1	2.4	0.4		
Anti-CFH antibodies (%)	6.5	11	3.2	3.1	3.9	1.9
THBD (%)	0	0	0	5	7.8	0.9
Combined (%)	4.2	3.4	4.8	3		
Complement-mediated (%)	65.7	64.7	67.2	52.3	53	43
DGKE (%)	3.2	7.9	0			
No identified abnormality (%)	31.1	27.4	32.8	47.7	47	57

CFB: complement factor B; CFH: complement factor H; CFI: complement factor I; DGKE: diacylglycerol kinase ε;

MCP: membrane cofactor protein (CD46); THBD: thrombomodulin

[a] Calculated from Table 2 in [1]

[%] percentage of patients

Empty line: not documented

Number in brackets: reference number

Loirat et al, Ped Nephrol, 2015

Source and location of complement-related proteins

Protein	Source	Location
Factor H	Liver	circulates
Factor I	Liver	circulates
C3	Liver, ?	circulates
Factor B	Liver, ?	circulates
MCP	Widespread	Membrane bound
Thrombomodulin	Liver, ?	Membrane bound - 5% circulates
Anti-FH-Ab	Lymphocyte	circulate

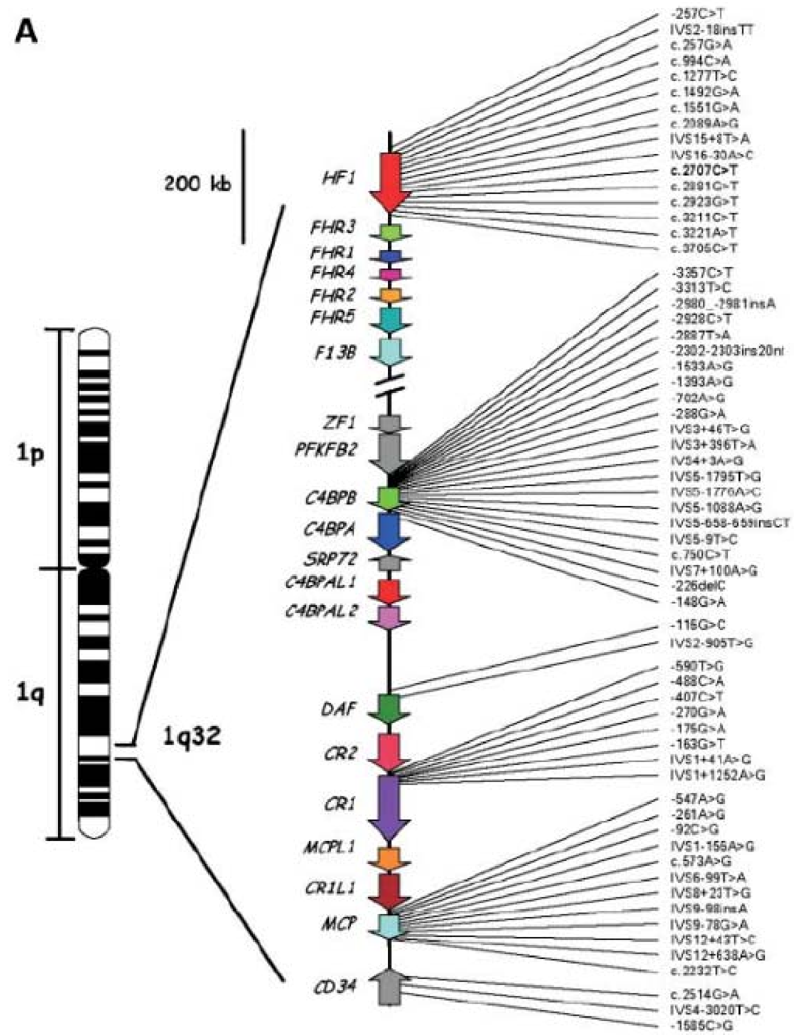
Jozsi et al. Blood 2008, Frémeaux-Bacchi V et al. Blood 2008, Goicoechea de Jorge 2007, Caprioli, et al Blood 2006,
Kavanagh Curr Opin Nephrol Hypertens, 2007, Noris, NEJM 2009

Genotype – phenotype correlation

Protein	%	Response to PE (*Remission*)	Long-term outcome (*Death or ESRD*)	Outcome after kidney tx (*Recurrence*)
Factor H	20-30%	60%	70-80%	80-90%
Factor I	4-10%	30-40%	60-70%	70-80%
C3	5-10%	40-50%	60%	40-50%
Factor B	1-2%	30%	70%	Recurrence in 1 case
MCP	10-15%	Not indicated	<20%	15-20%
Thrombomodulin	5%	60%	60%	Recurrence in 1 case
Anti-FH-Ab	6-10%	70-80% (PE + IS)	30-40% ESRD	20%

Noris and Remuzzi, N Engl J Med 2009

Risk aplotypes in aHUS



Esparza-Gordillo et al, Hum Mol Genet 2005

“Old” criteria for plasma infusions or exchange in aHUS

Table 1. Criteria for empiric plasma therapy treatment of aHUS

Presence of any of the Following	*or*	Absence of the Following
Patient age <6 mo		Prodromal diarrhea
Slow or insidious onset of HUS		Invasive *Streptococcus pneumoniae* infection
Multiple HUS episodes or relapses		
Associated family history of HUS		
Previous unexplained anemia		
HUS after any type of organ transplantation		

- **Plasma <u>infusion</u>: repletes but does not remove mutant protein**
- **Plasma <u>exchange</u>: removes mutant protein + repletes**

Post-transplant aHUS recurrence

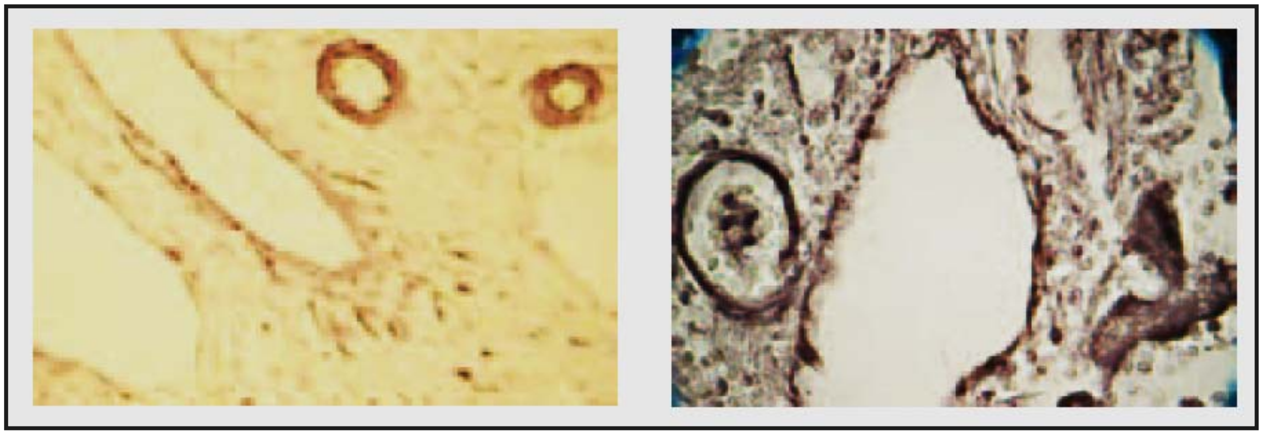
- **Most recurrences occur within 1 month**
- **If untreated, usually graft loss**

Combined liver kidney transplant for aHUS (CFH mutations)

First experiences not encouraging

Native liver **Transplanted liver**

C5-b9



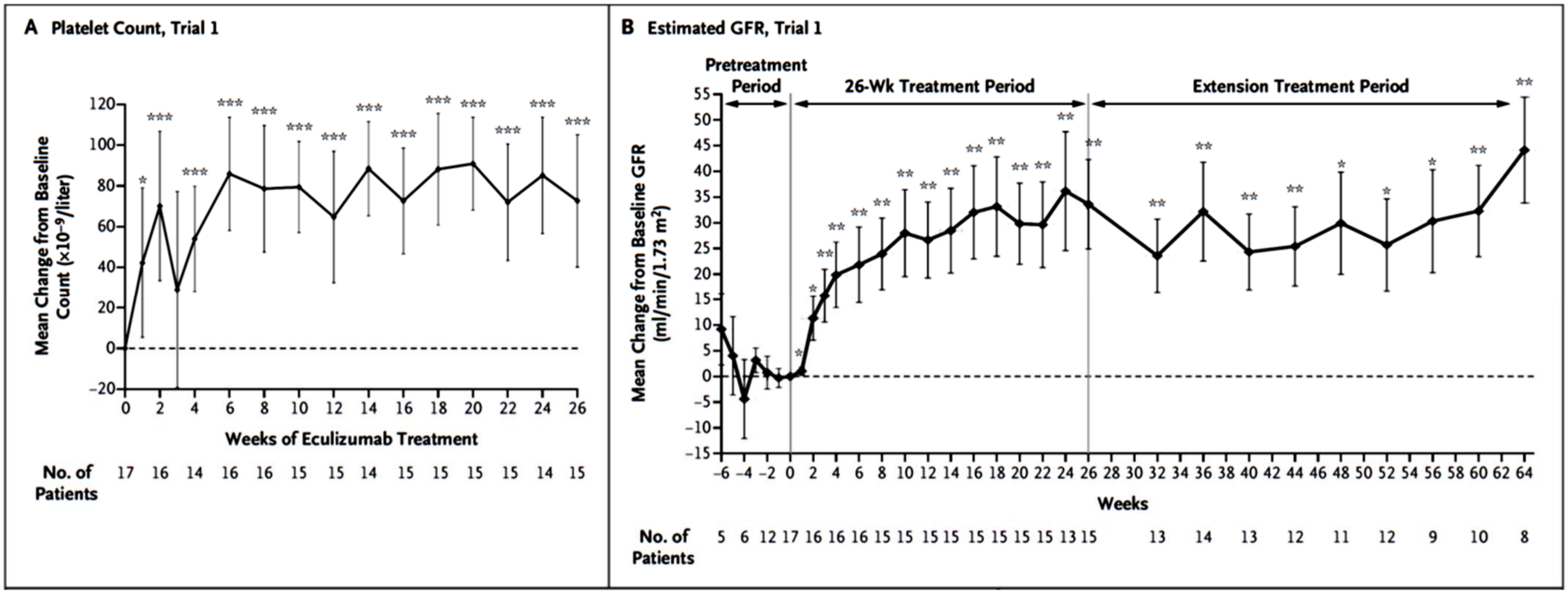
Remuzzi G, Lancet 2002, Remuzzi AJT 2005

Subsequent experiences more favorable with intensive PE

Favorable Long-Term Outcome after Liver-Kidney Transplant for Recurrent Hemolytic Uremic Syndrome Associated with a Factor H Mutation

Saland et al, AJT 2006

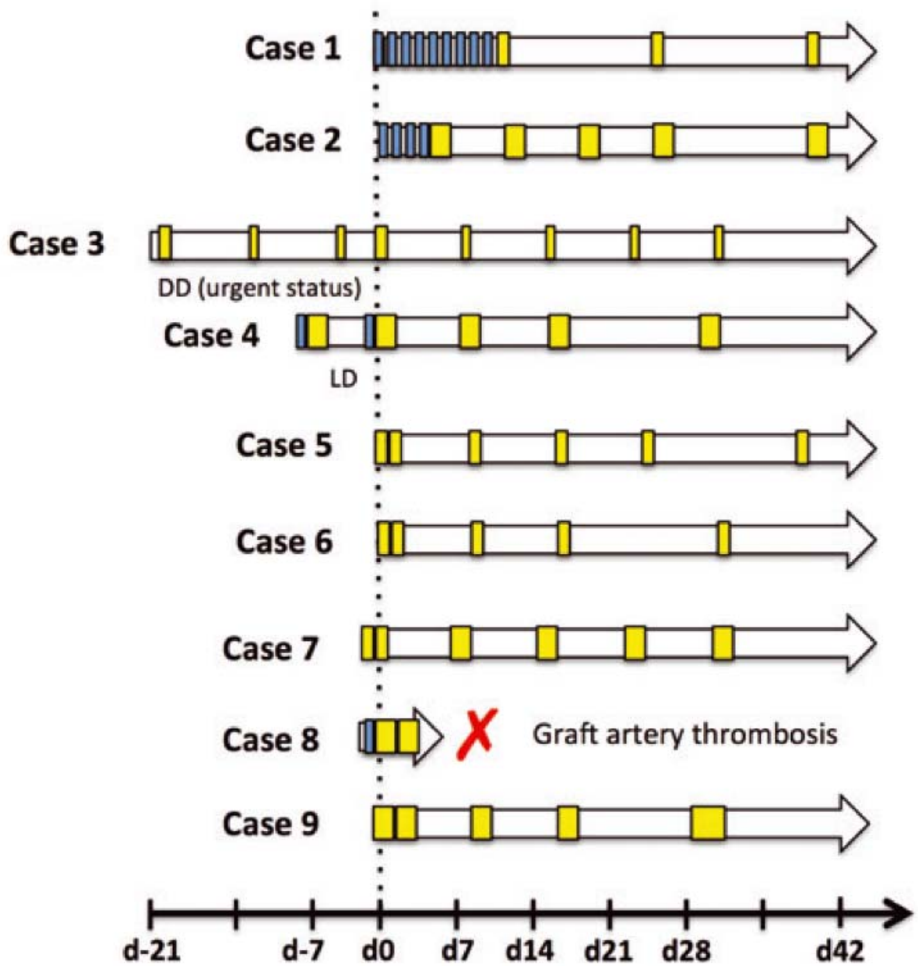
Eculizumab for aHUS



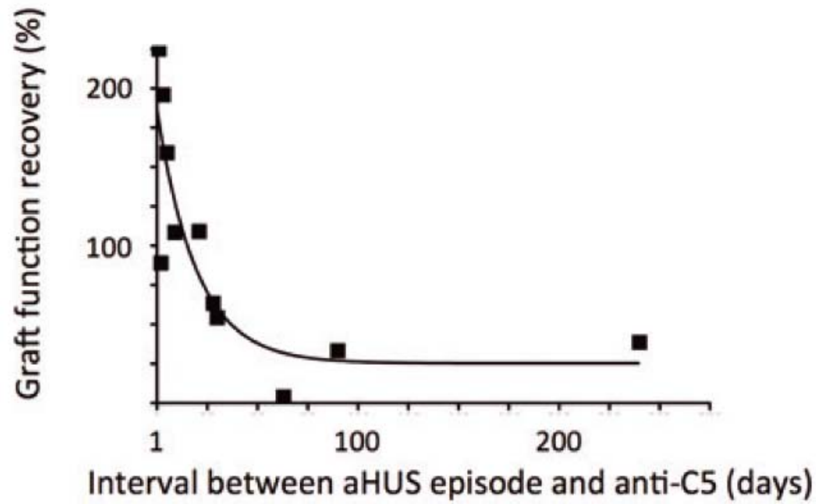
Legendre et al, NEJM 2013

anti-C5 therapy for renal transplantation

Prophylactic



After recurrence



Zuber et al, Am J Transplant, 2012

Eculizumab to prevent post-transplant recurrence: what we have learned in the past years

- **Post-transplant aHUS recurrence is a strong predictor of early graft failure**
- **Anti-C5 efficiently prevents aHUS post-transplant recurrences**
- **If eculizumab is not used preemptively, early initiation of anti-C5 therapy is associated with better recovery of renal function**
- **Prophylactic plasma therapy may fail to prevent aHUS recurrences and may mask subclinical, yet progressive, aHUS recurrences**
- **In principle, with the advent of anti-C5 therapy, combined kidney-liver transplantation is no longer a first line treatment for aHUS**

If treated with eculizumab, patients should not require a renal transplantation….

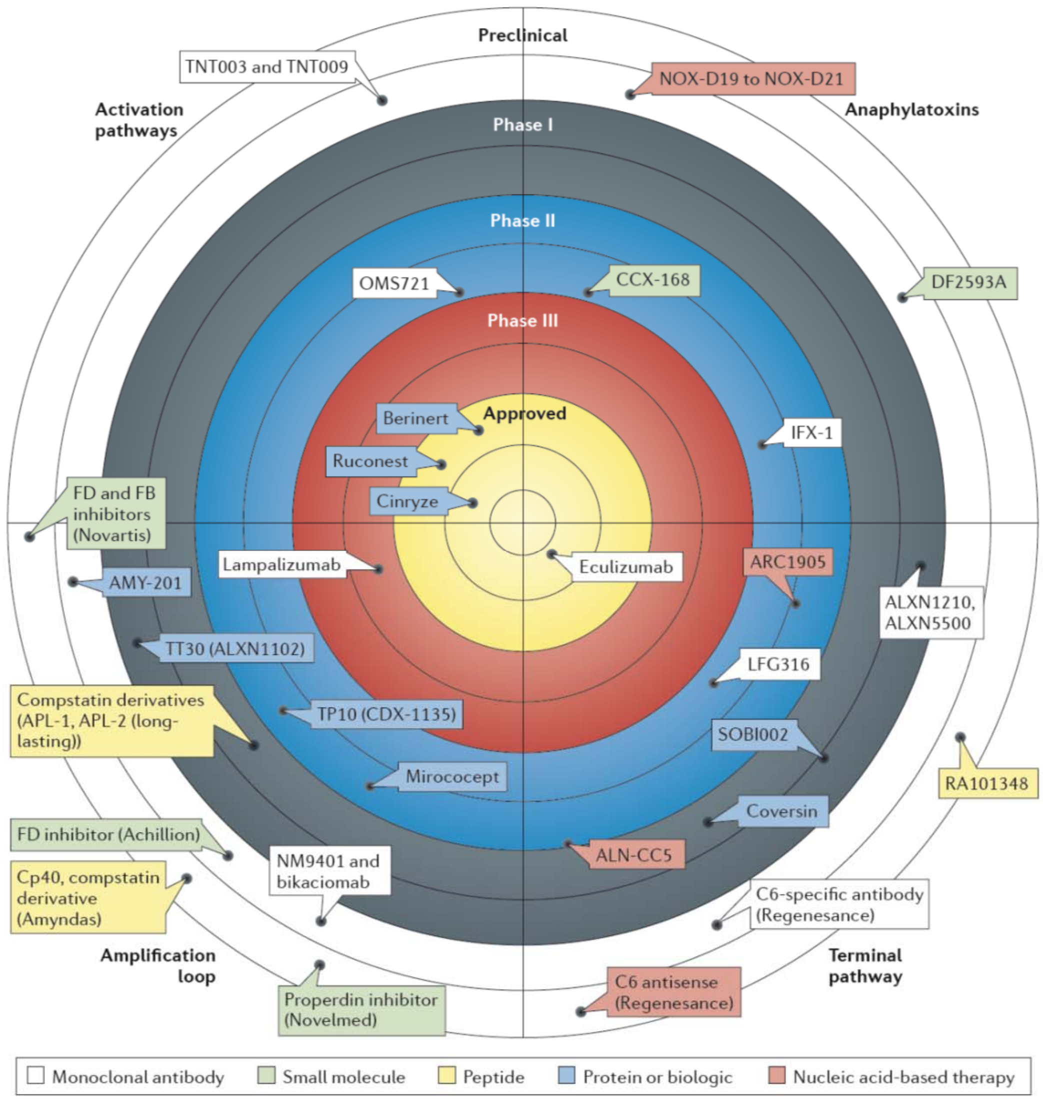
aHUS in patients with STEC infections

Two Patients With History of STEC-HUS, Posttransplant Recurrence and Complement Gene Mutations

Alberti et al, Am J Transplant 2013

- **Patient # 1: heterozygous CFI mutation**
  Patient #2: heterozygous MCP mutation + LR kidney tx from the mother
- **aHUS was triggered by a STEC infection on a genetic background of impaired complement regulation**
- **Complement gene sequencing should be performed before kidney transplantation in patients who developed ESRD following STEC-HUS**
- **Genetic analysis of donors is mandatory before living-related transplantation to exclude carriers of HUS-predisposing mutations**

Progress of complement therapeutics towards clinical use.



Morgan and Harris, Nat Rev Drug Discovery, 2015

Eculizumab for patients with STEC-HUS