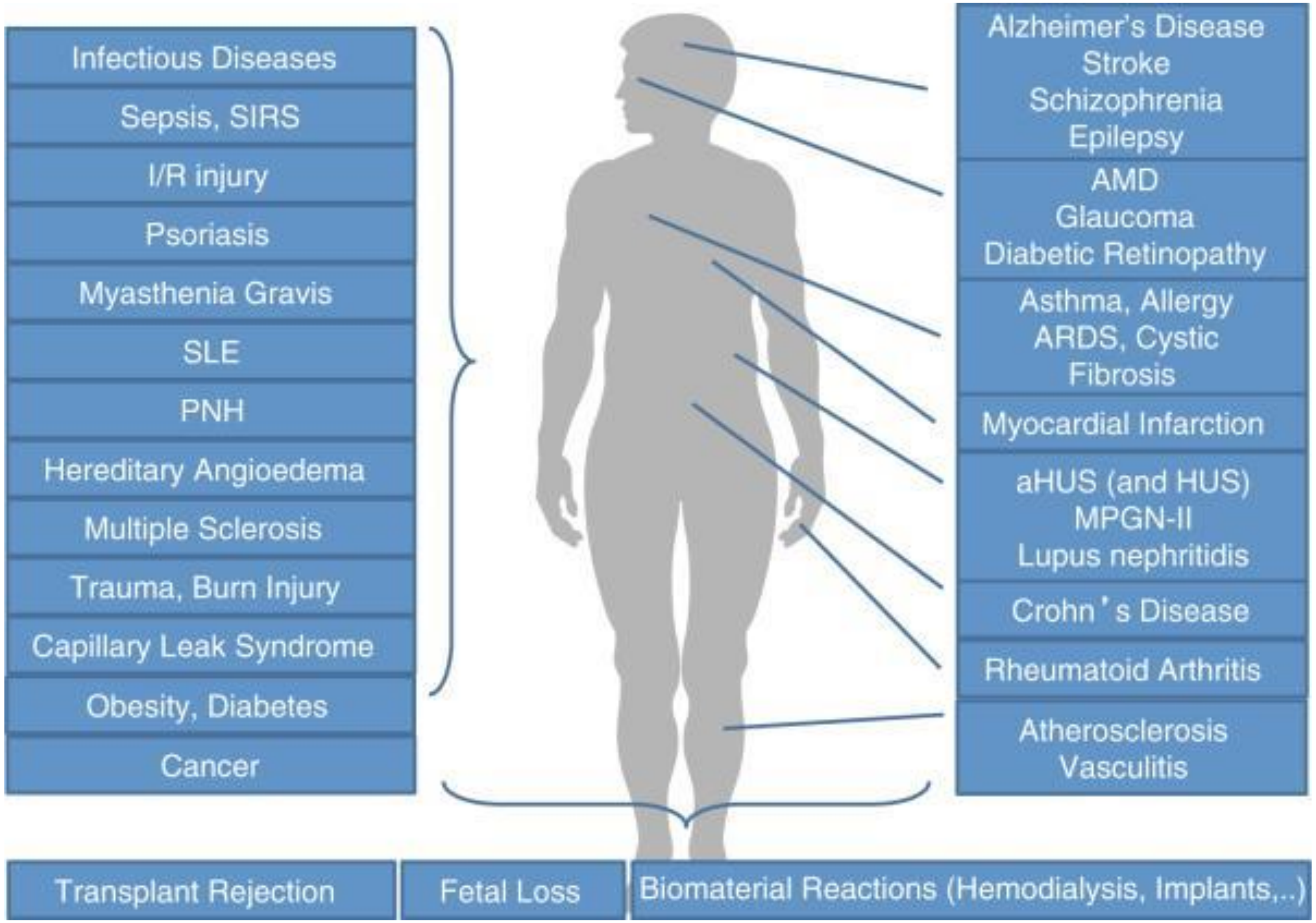
aHUS: recent insights and management

Steven Van Laecke MD, PhD
Renal Division, Ghent University Hospital, Belgium

13 th BANTAO Sarajevo
October 8 2017

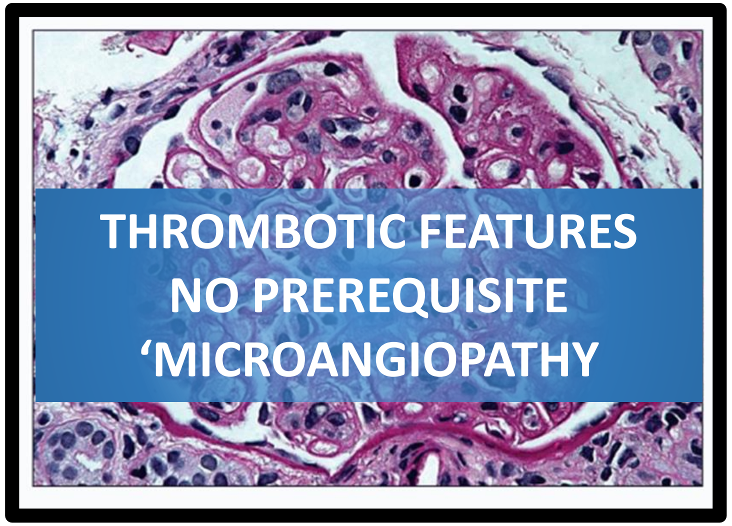
The complement is everywhere…

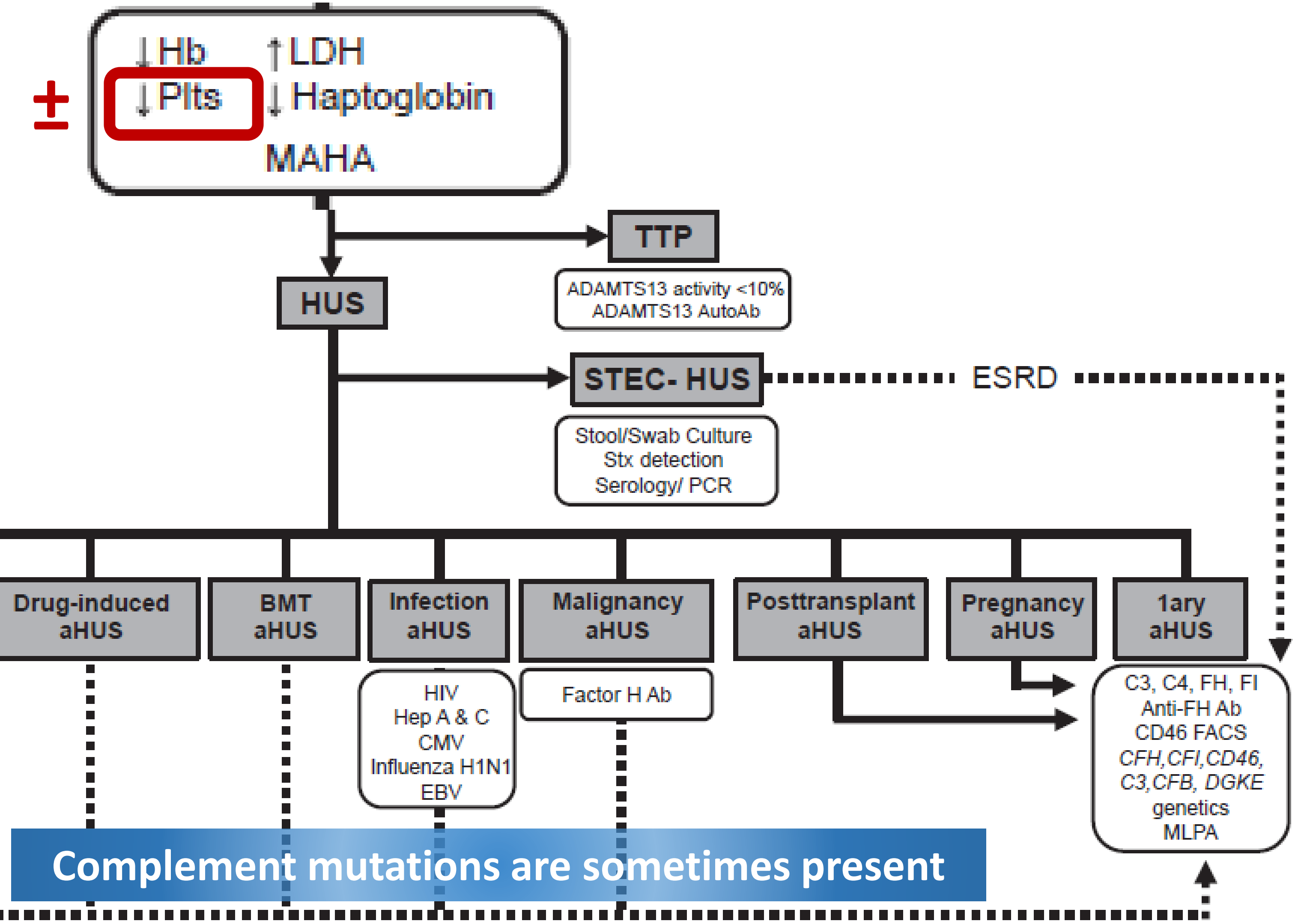


I could benefit from complement inhibitors I guess

Ricklin D et al. Adv Exp Biol Med 2013

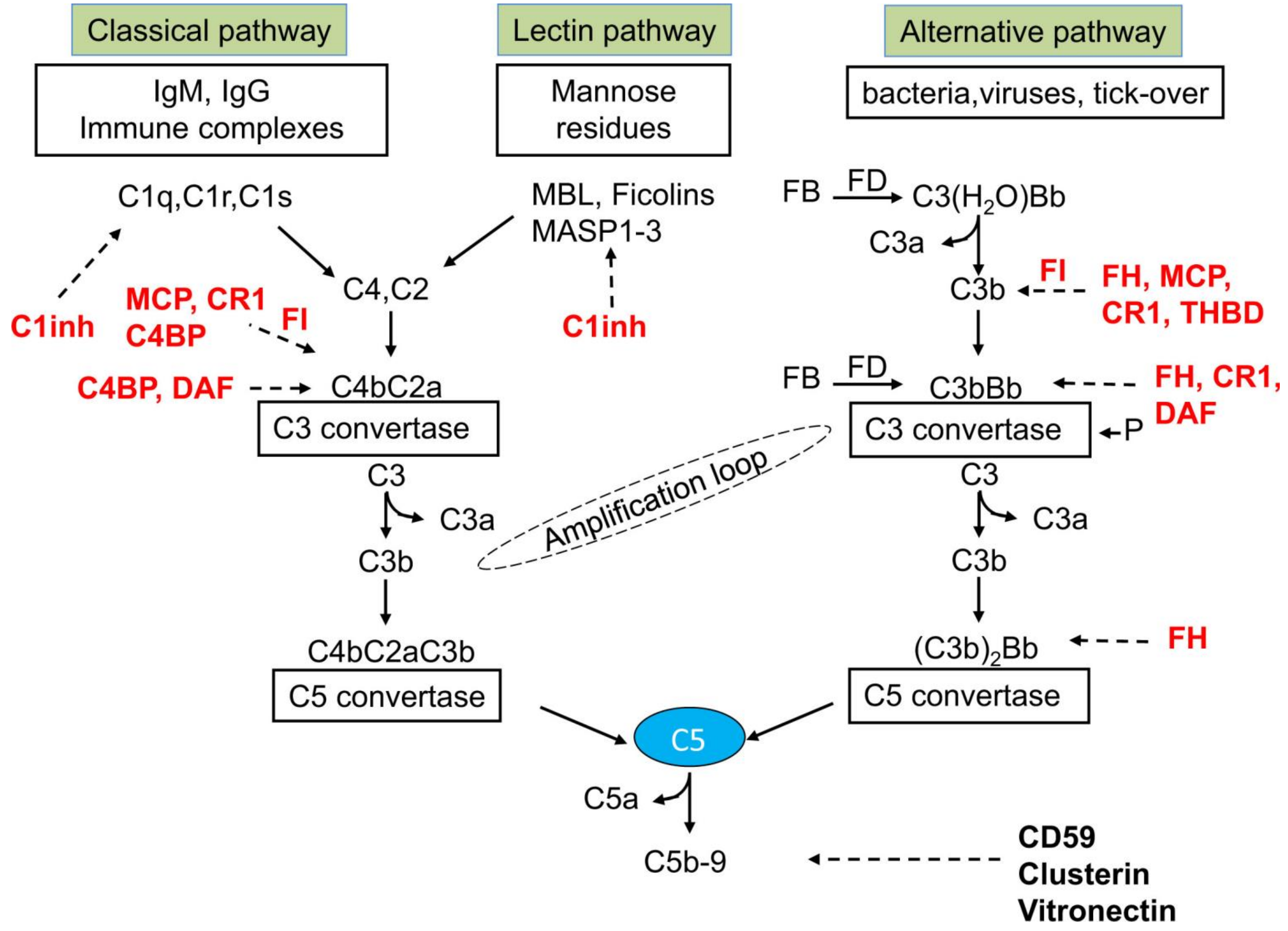
…and definitely in aHUS *(what is aHUS?)*





Goodschip THJ et al. KDIGO Controversies Conference. Kidney Int 2016

The complement cascade (my apologies)

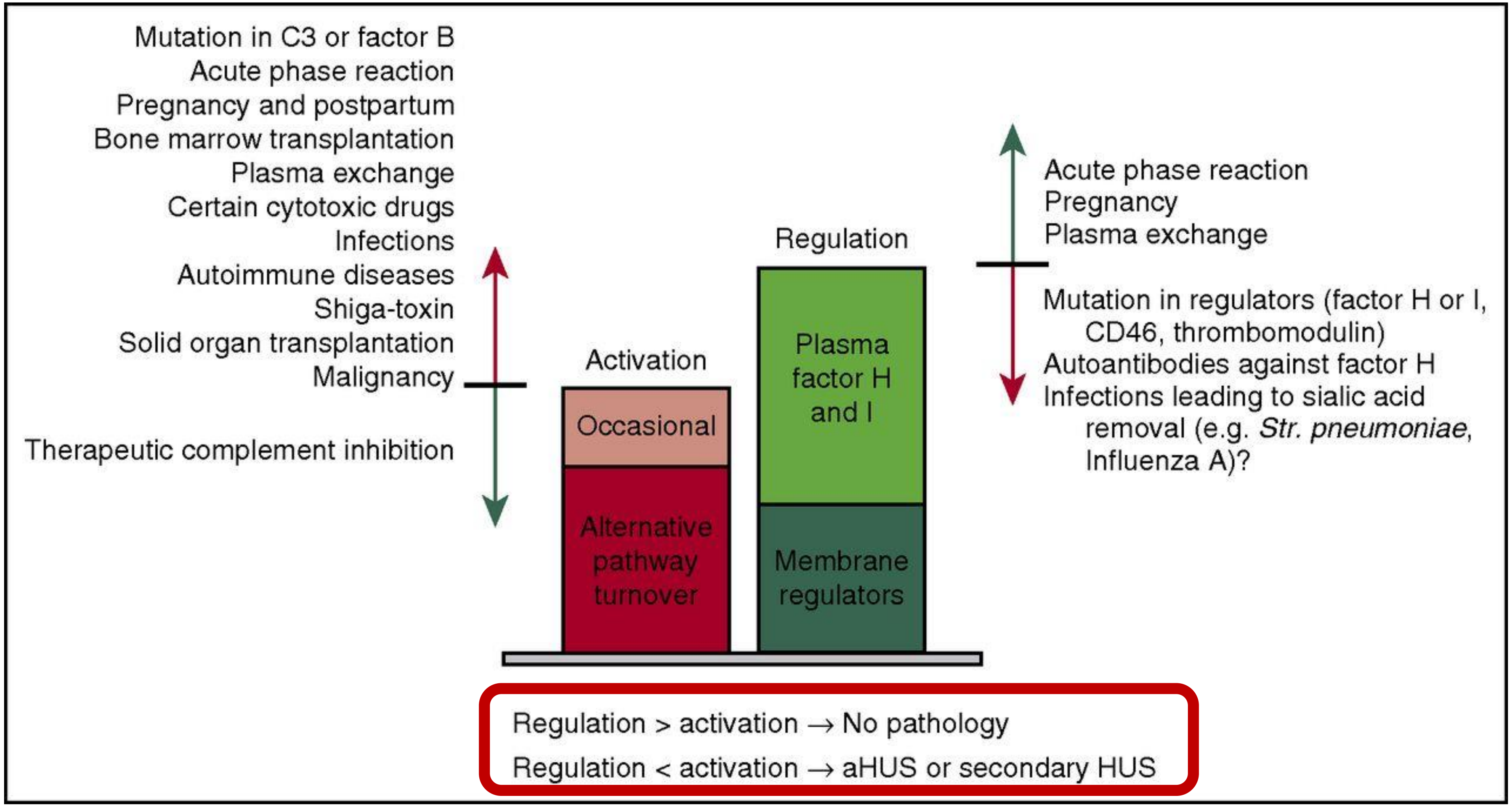


COMPLEMENT ACTIVATION

FINE, BUT WE NEED BRAKES….

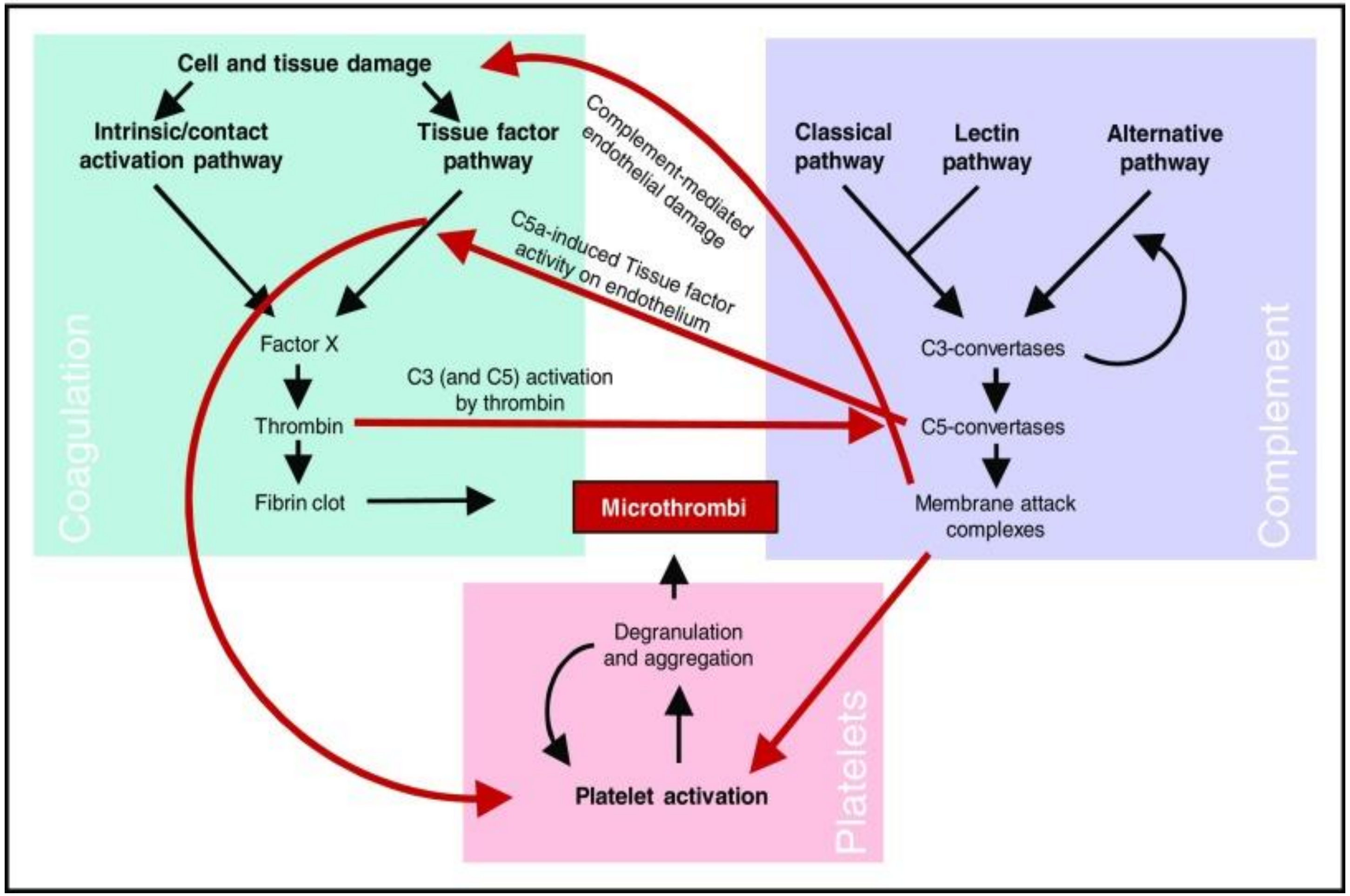
Noris M, Remuzzi G. Seminars in Nephrology 2017

Promotors and triggers of aHUS



Jokiranta TS Blood 2017

Complement activation is procoagulant

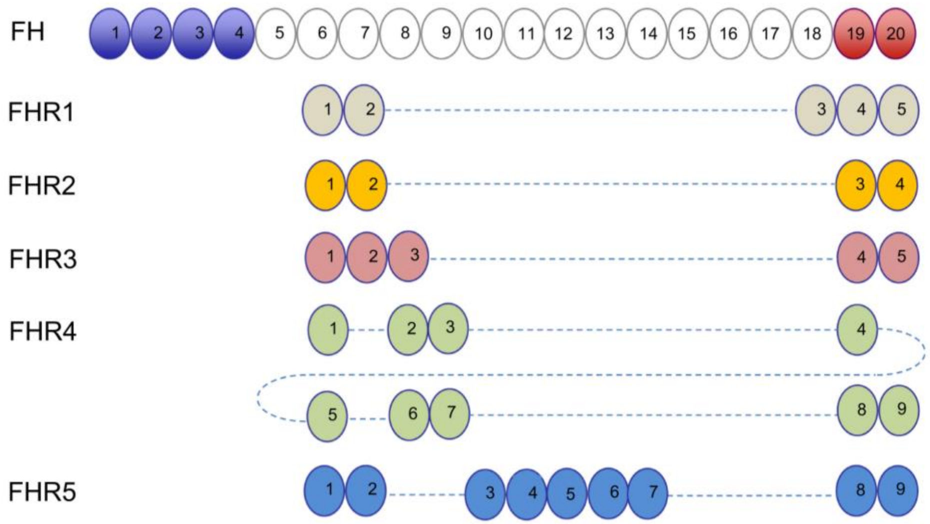


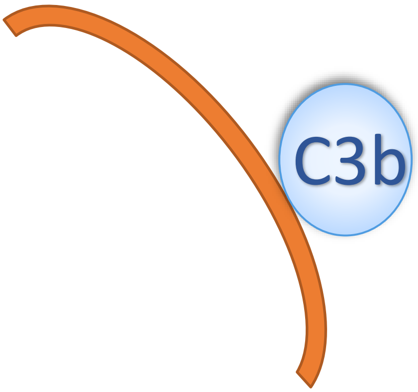
‘A FUTURE FOR COMPLEMENT BLOCKADE IN THROMBOTIC DISEASES?’

Jokiranta TS Blood 2017

aHUS and genetics

The genetics of factor H

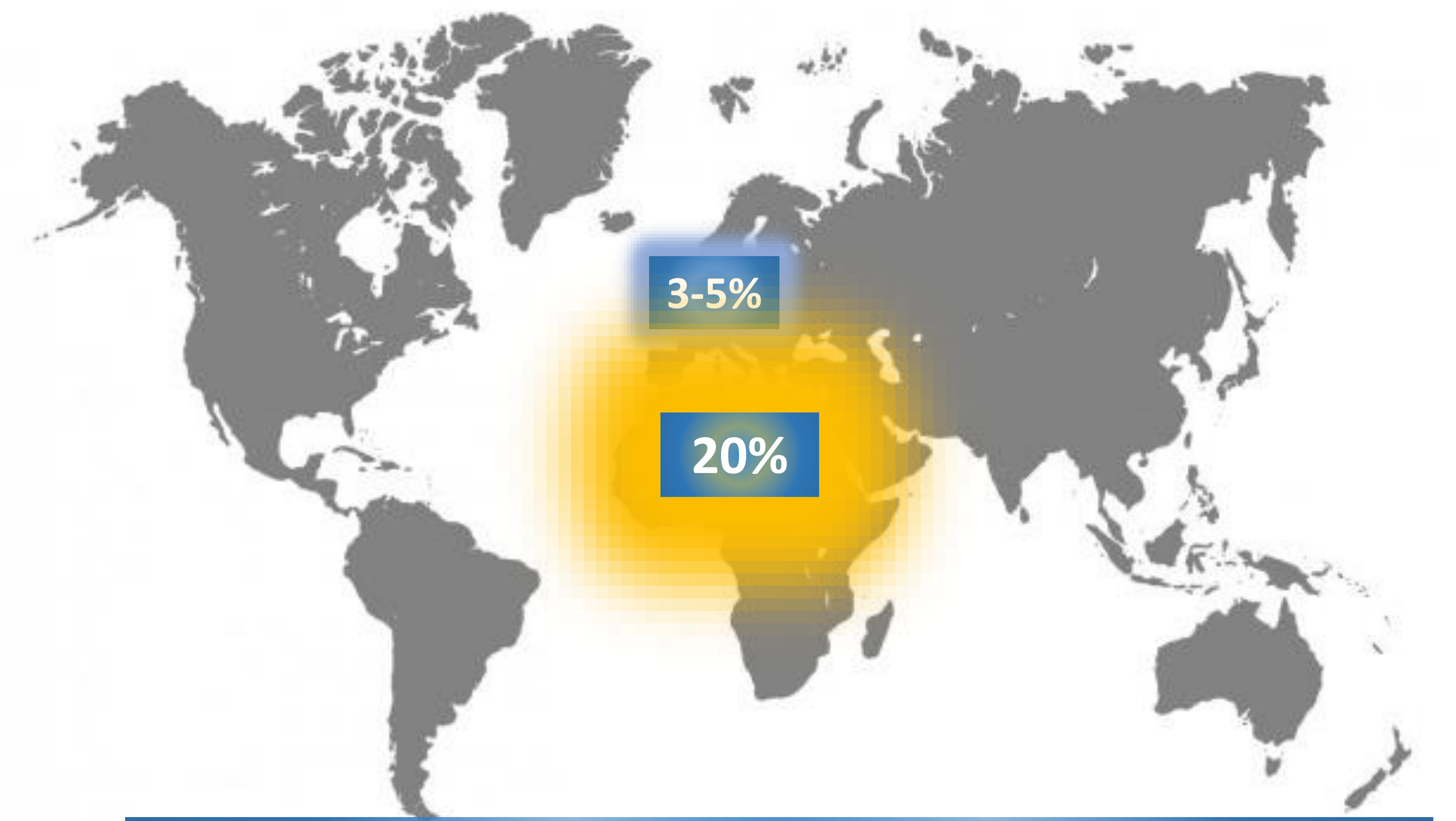




FACTOR H ANTIBODIES

Noris M, Remuzzi G. Seminars in Nephrology 2017

The elusive homozygous CFHR1/CFHR3 deletion

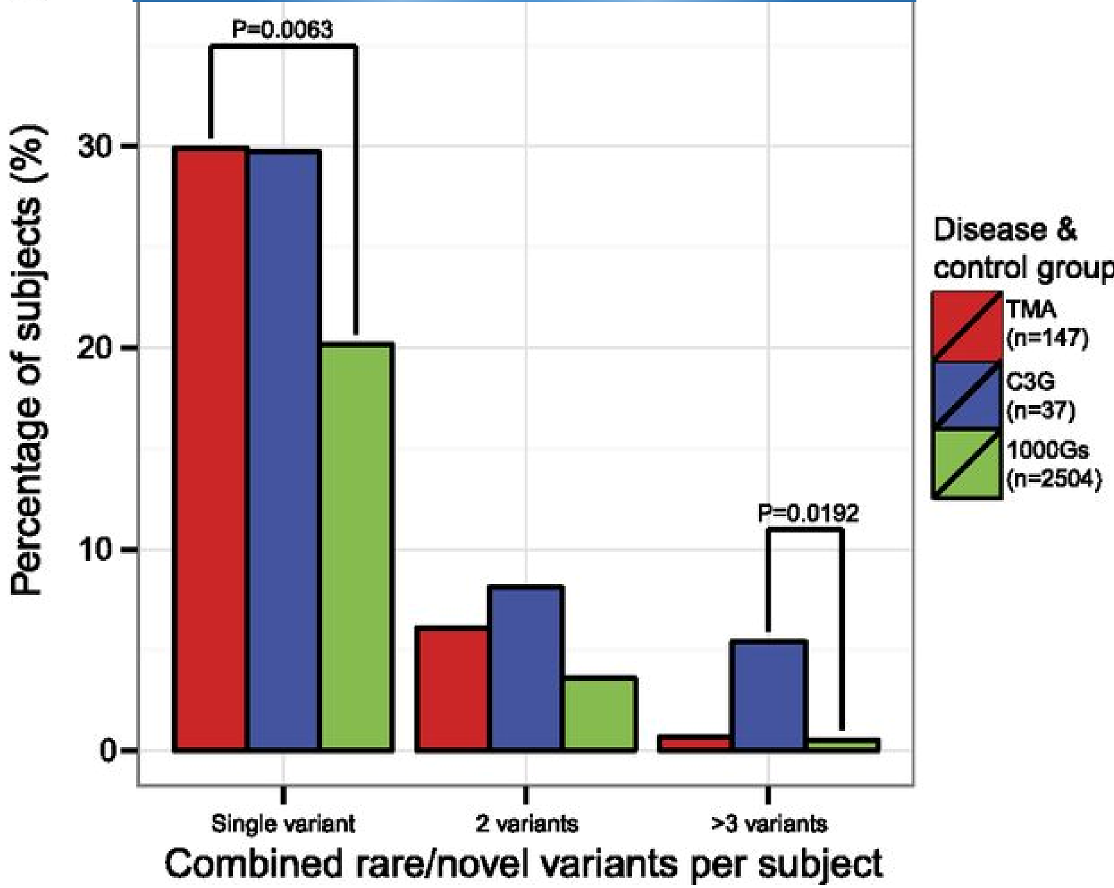


COMBINED GENETIC AND ENVIRONMENTAL FACTORS!

Noris M, Remuzzi G. Seminars in Nephrology 2017

Odds of findings a pathogenic mutation in TMA?

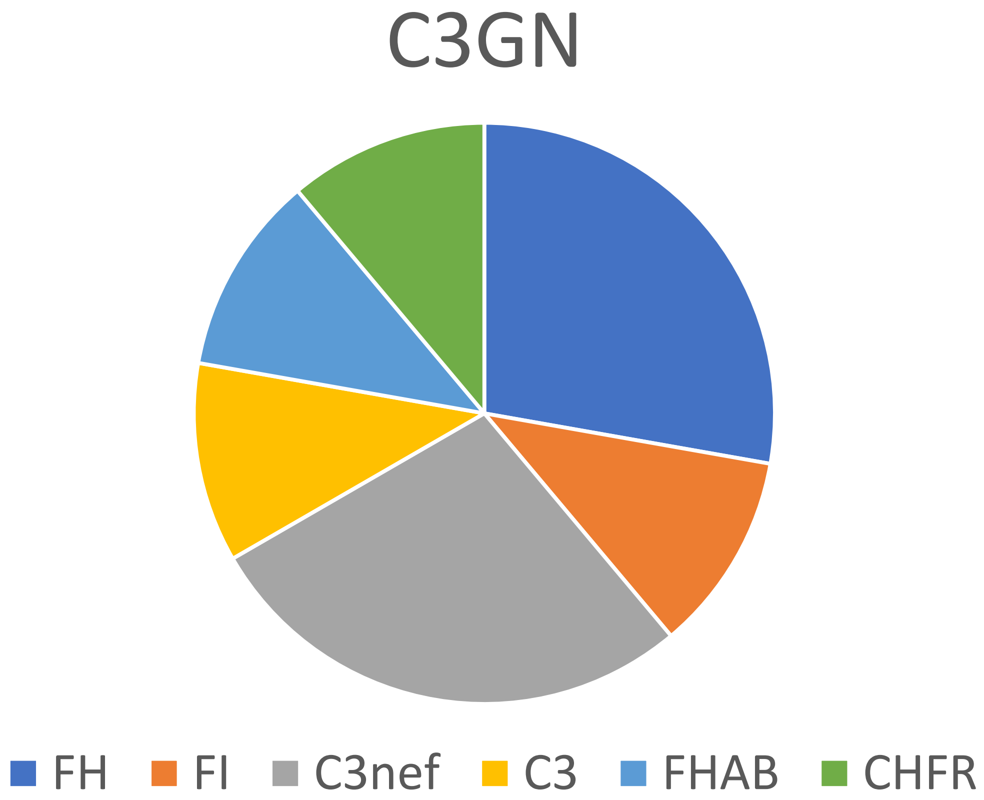
Novel variants vs. ctrls 1000 Genomes Project

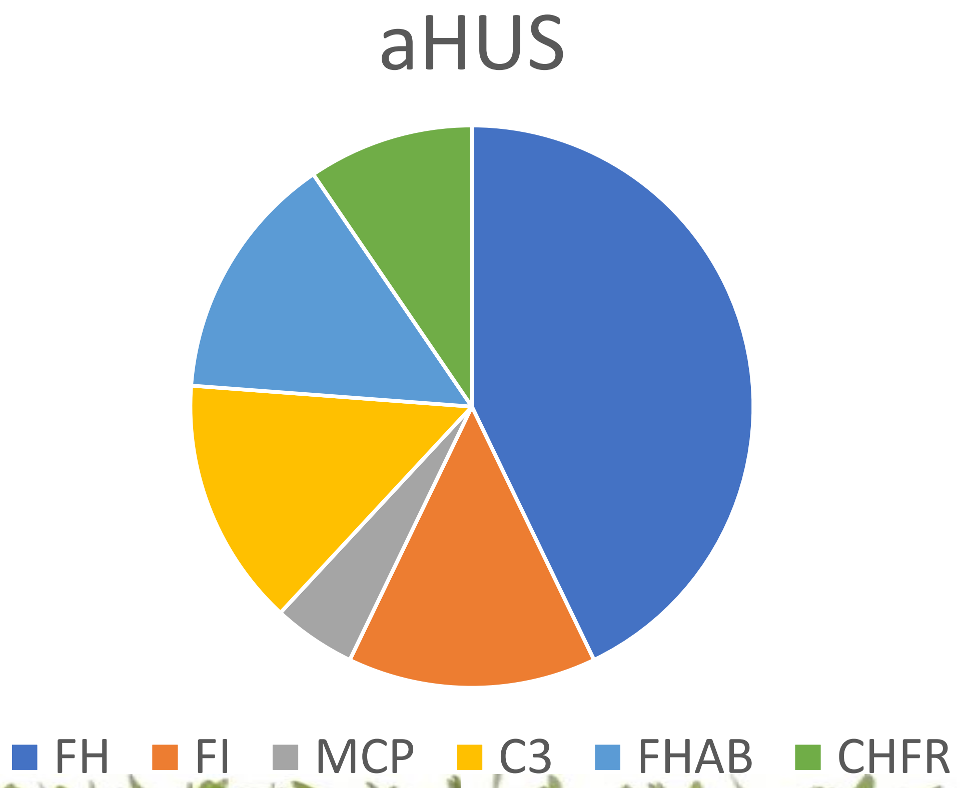


>50% no pathogenic mutation in aHUS

Bu F et al. JASN 2015

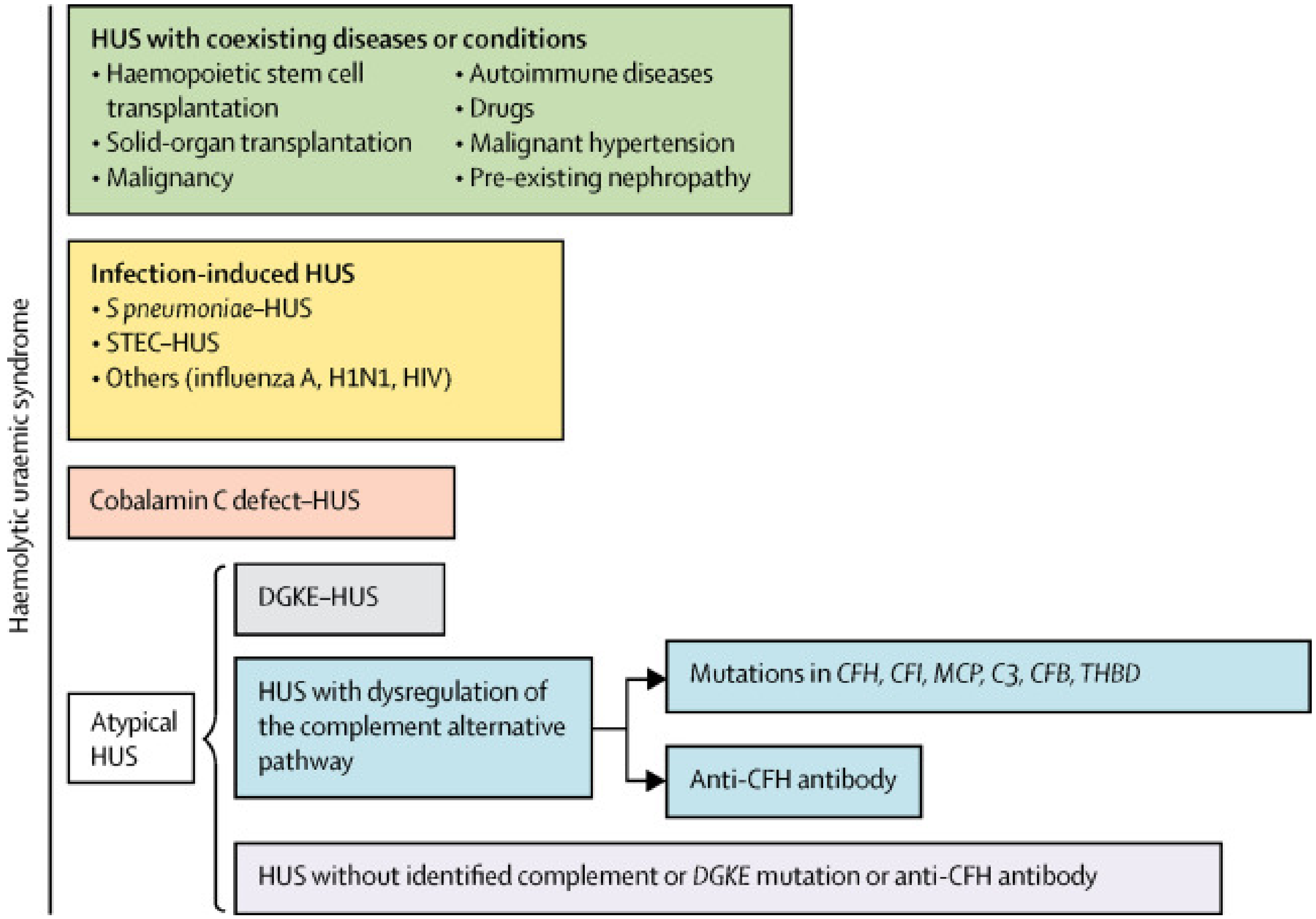
Mutations in aHUS/C3G: a common soil





The approach of secondary HUS

Secondary HUS: does it still exist?



Fakhouri F. et al Lancet 2017

Patients with hypertension-associated thrombotic microangiopathy may present with complement abnormalities

see commentary on page 1271

Sjoerd A.M.E.G. Timmermans[1], Myrurgia A. Abdul-Hamid[2], Joris Vanderlocht[3], Jan G.M.C. Damoiseaux[4], Chris P. Reutelingsperger[5] and Pieter van Paassen[1]; for the Limburg Renal Registry

C5b-9

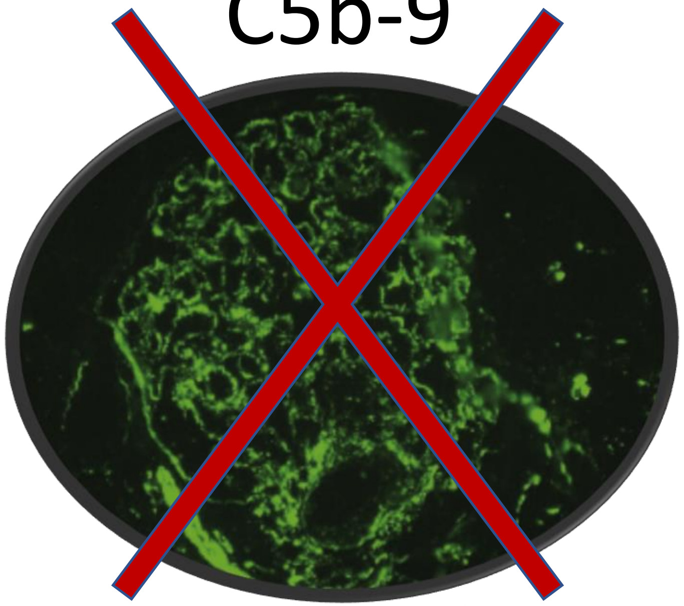
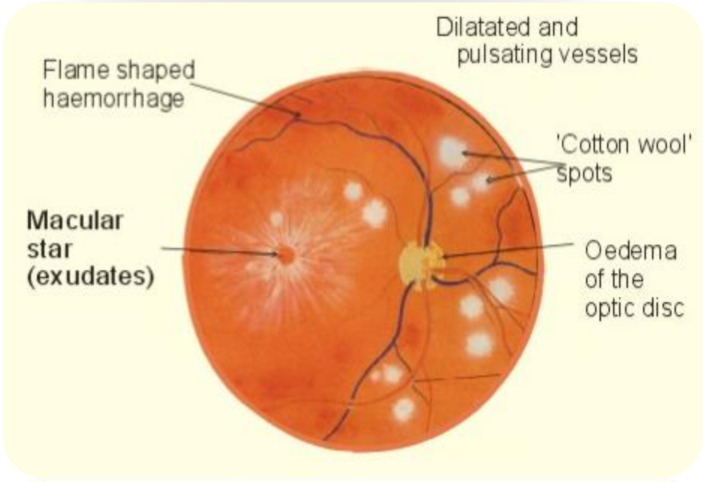


Table 1 | Baseline clinical features and laboratory evaluation

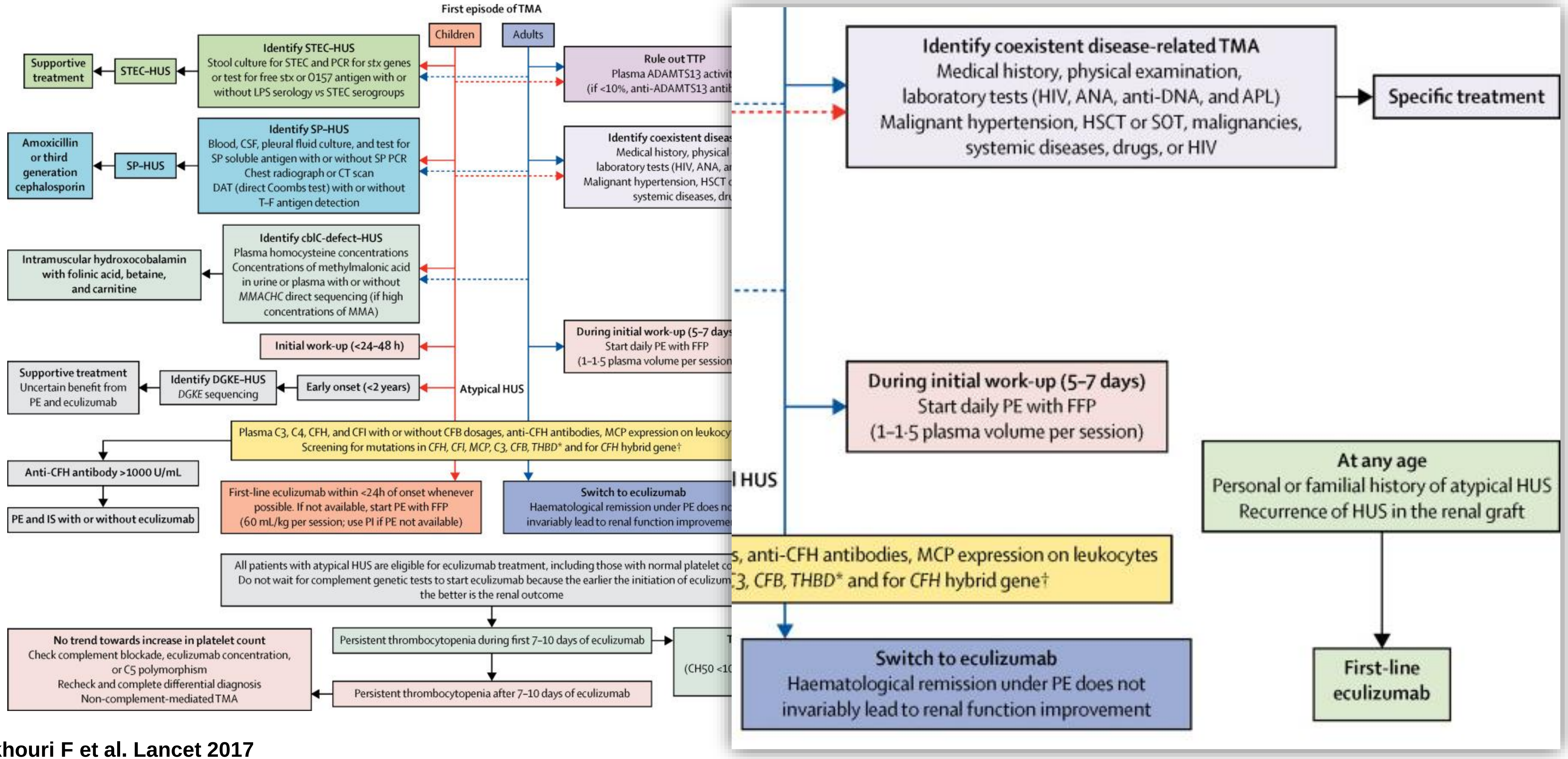
Patient No.	Age (yr)	Sex	BP (mm Hg)	SCr (μmol/l)	uProt (g/d)	uRBC	ESRD	Hb (mmol/l)	LDH (U/l)	MAHA[a]	Platelets ($\times 10^9$/l)[b]
1	38.4	F	184/140	1730	NA	NA	Y	5.1	1800	Y	224
2	40.3	M	205/114	1195	2.3	Y	Y	5.7	1104	Y	158
3	37.7	M	200/120	586	3.9	Y	Y	5.3	2125	Y	100
4	32.0	F	180/120	1138	NA	NA	Y	5.9	1486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

BP, blood pressure; ESRD, end-stage renal disease; F, female; Hb, hemoglobin; LDH, lactate dehydrogenase; M, male; MAHA, microangiopathic hemolytic anemia; N, no; NA, not applicable; SCr, serum creatinine; uProt, proteinuria; uRBC, hematuria; Y, yes.
[a]Cases with hemolytic anemia and schistocytes on peripheral blood smear were defined as MAHA.
[b]Lower limit of normal = 130 $\times 10^9$/l.



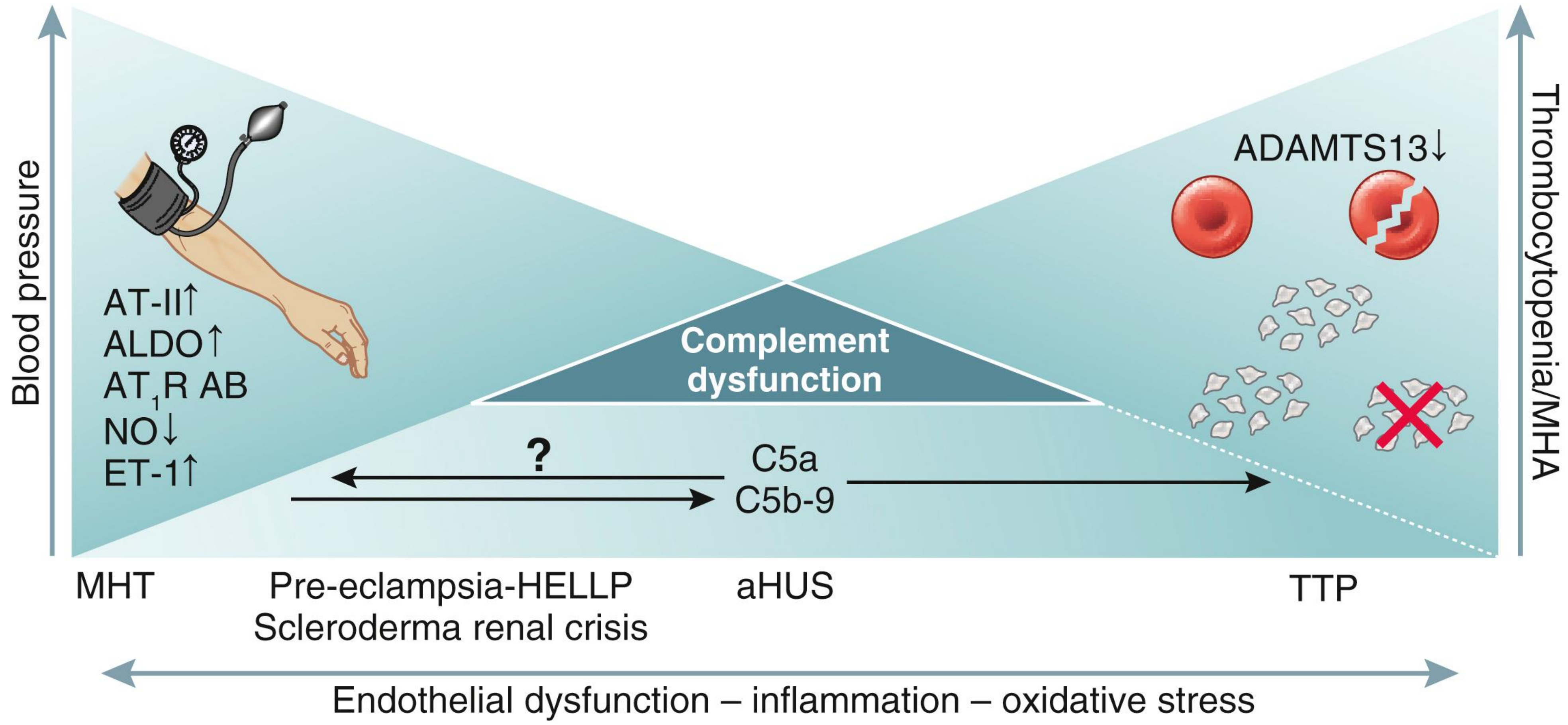
‘Severe’ hypertension might allude to aHUS in absence of TMA

The case of malignant hypertension



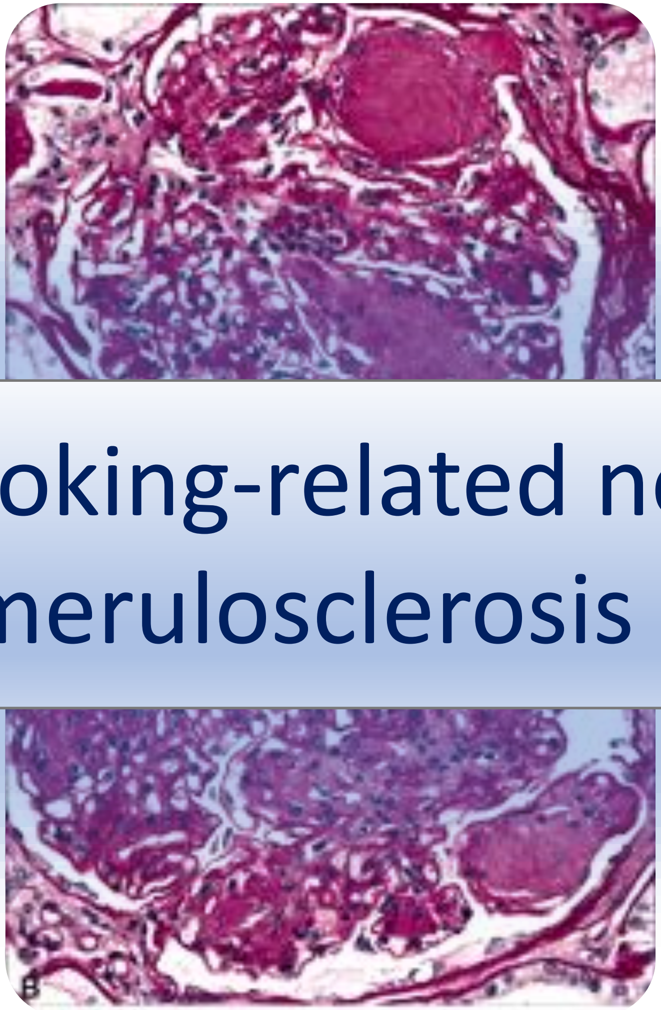
Fakhouri F et al. Lancet 2017

The case of malignant hypertension



Van Laecke S et al. Kidney Int 2017

What is this?



Smoking-related nodular glomerulosclerosis (SNRG)

- Hypertension
- Mostly male
- Thickening GBM/TBM
- Mesangial expansion
- Arteriolar Hyalinosis
- Negative IF

Chronic TMA

Nasr SH et al. JASN 2007/Salvatore SP et al. Am J Nephrol 2015

Pregnancy-associated aHUS: secondary aHUS?

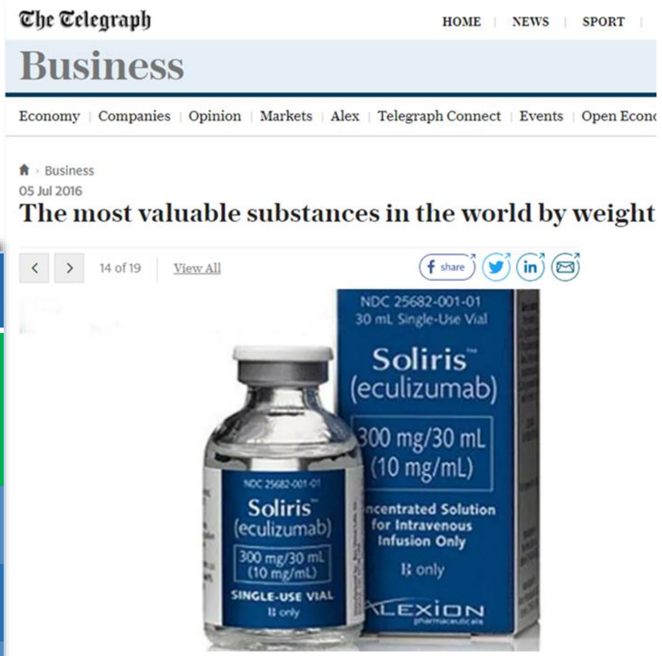
1. **Pregnancy**: Servais et al. NDT 2016
2. **CAPS**: Kazzazz NM et al. Curr Opinion Rheumatol 2016
3. **STEC-HUS**: Fakhouri F et al. Lancet 2017; NCT02205541
4. **SLE**: SciaScia S et al. Rheumatol Int 2017

bjh correspondence

Effective treatment of chemotherapy induced atypical Haemolytic Uraemic Syndrome: a case series of 7 treated patients

14000 EURO per treatment of 1200mg
MEAN 16w: 124,000€

Case	Age	Sex	Drug	Tb count	Tumour	R/ weeks	Outcome
1	27	F	Dasatinib	60	HCC	12	CR; † Ca 6m later
2	42	F	Bevacizumab	50	Ovarian	16	CR; † Ca 9m later
3	66	M	Gemcitabine	161	Pancreas	18	CR
4	61	F	Gemcitabine	56	Unknown	24	CR
5	66	F	Gemcitabine	150	Lung	16	CR
6	57	M	Gemcitabine	150	Urothelial	2	CR
7	22	F	Bleomycin	57	Hodgkin	ongoing	CR



WHAT IS THE NATURAL COURSE?

THEY GOT CHEMOTHERAPY!

Weitz IC et al. BJ Hematol 2017

‘A LIMITED COURSE OF 12-24 WEEKS MAY BE APPROPRIATE’

Potential drawbacks of eculizumab

No benefit with Eculizumab?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

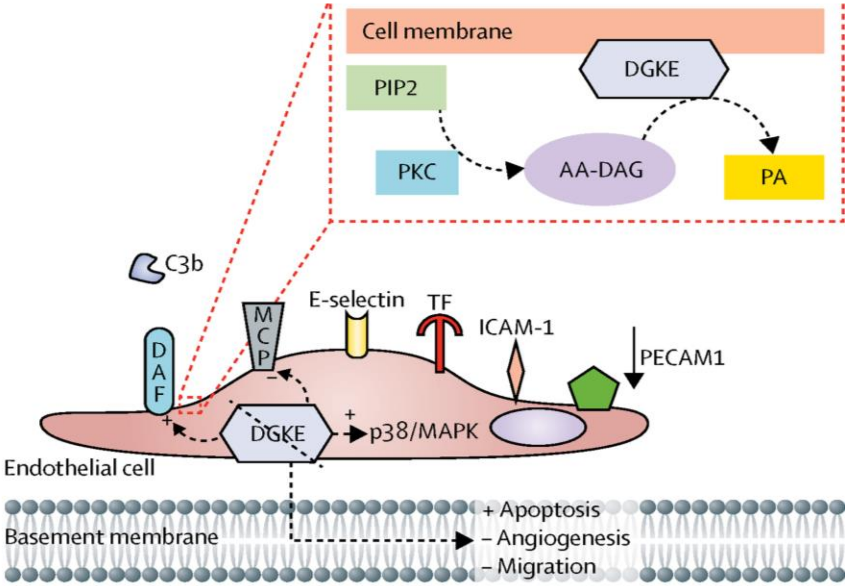
Genetic Variants in C5 and Poor Response to Eculizumab

Nephrol Dial Transplant (2012) 27: 3807–3815
doi: 10.1093/ndt/gfs394

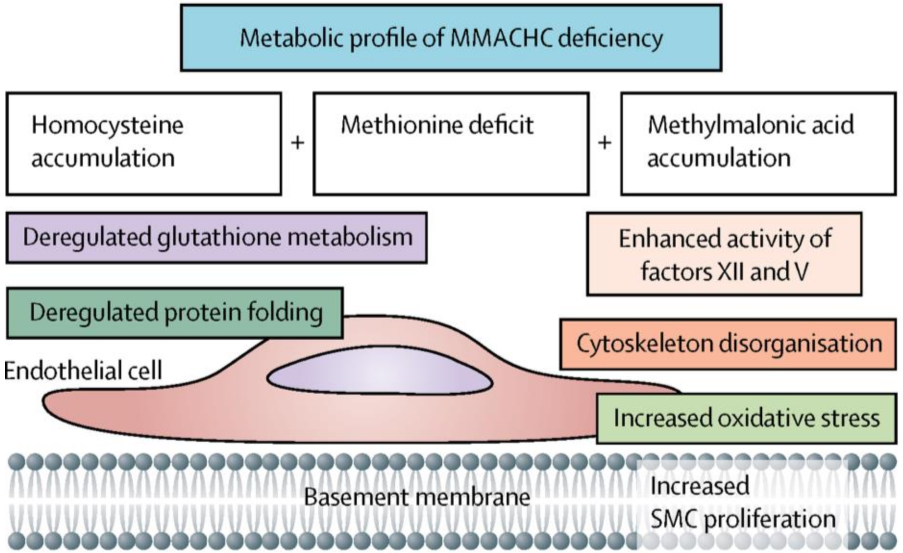
NDT
Nephrology Dialysis Transplantation

Original Article

Best supportive care and therapeutic plasma exchange with or without eculizumab in Shiga-toxin-producing *E. coli* O104:H4 induced haemolytic–uraemic syndrome: an analysis of the German STEC-HUS registry



DGKE mutation

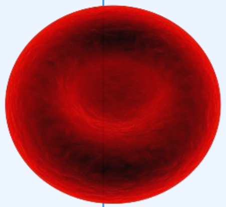


Cobalamin C deficiency

Nishimuri J et al. NEJM 2014 – Fakhouri F et al. Lancet 2017

How to monitor patients on ECULIZUMAB?

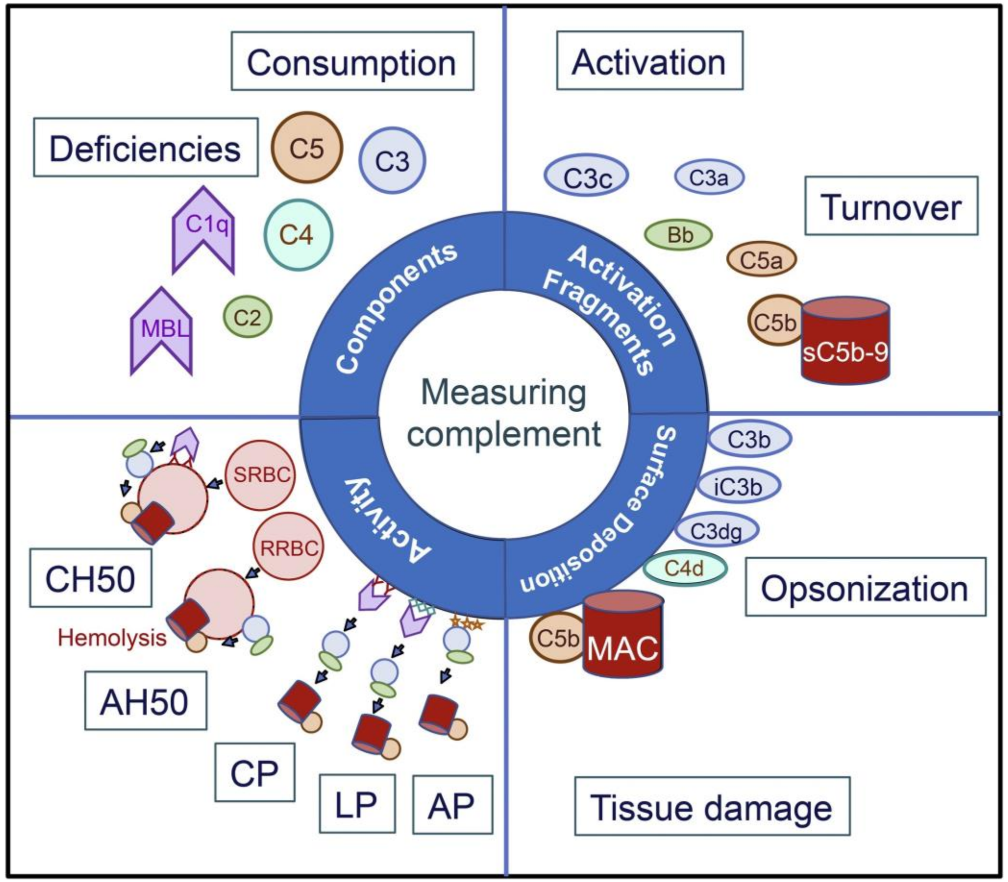
CH50 (<10%)



AH50 (<10%)

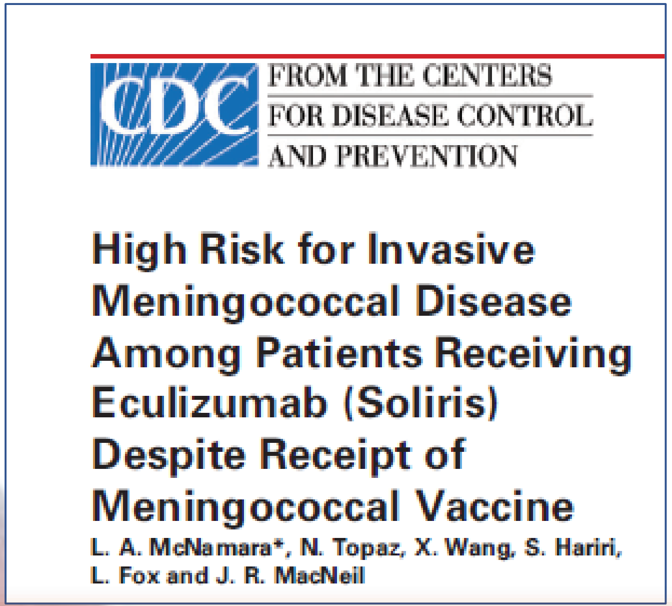
ECL (ELISA) 50-100µg or >100µg/mL?

Free C5
Anti-C5
sC5b-9



Goodschip THJ et al. KDIGO Controversies Conference. Kidney Int 2016/ Ricklin D et al. Mol Immunol 2017

ECL and meningococcal disease



FROM THE CENTERS FOR DISEASE CONTROL AND PREVENTION

High Risk for Invasive Meningococcal Disease Among Patients Receiving Eculizumab (Soliris) Despite Receipt of Meningococcal Vaccine

L. A. McNamara*, N. Topaz, X. Wang, S. Hariri, L. Fox and J. R. MacNeil

INCIDENCE x 1000-5000

14/16 at least 1 vaccination and majority NON-GROUPABLE SEROTYPE

1 death

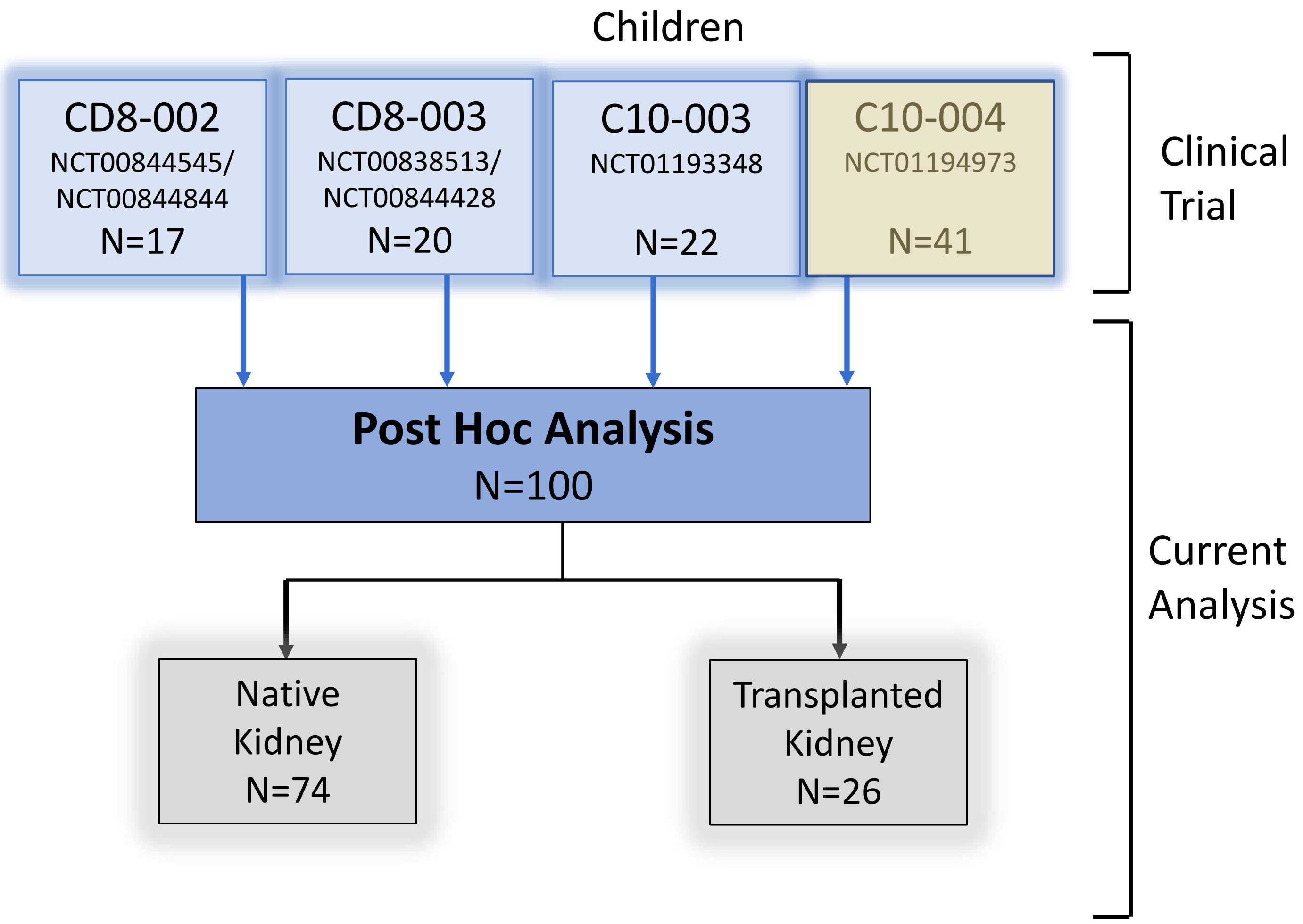
80% Peni-S; 100% Azithro-S

HIGH LEVEL OF SUSPICION EVEN WITHOUT MENINGITIS

INEVITABLE DESPITE…

Am J Transplantation 2017

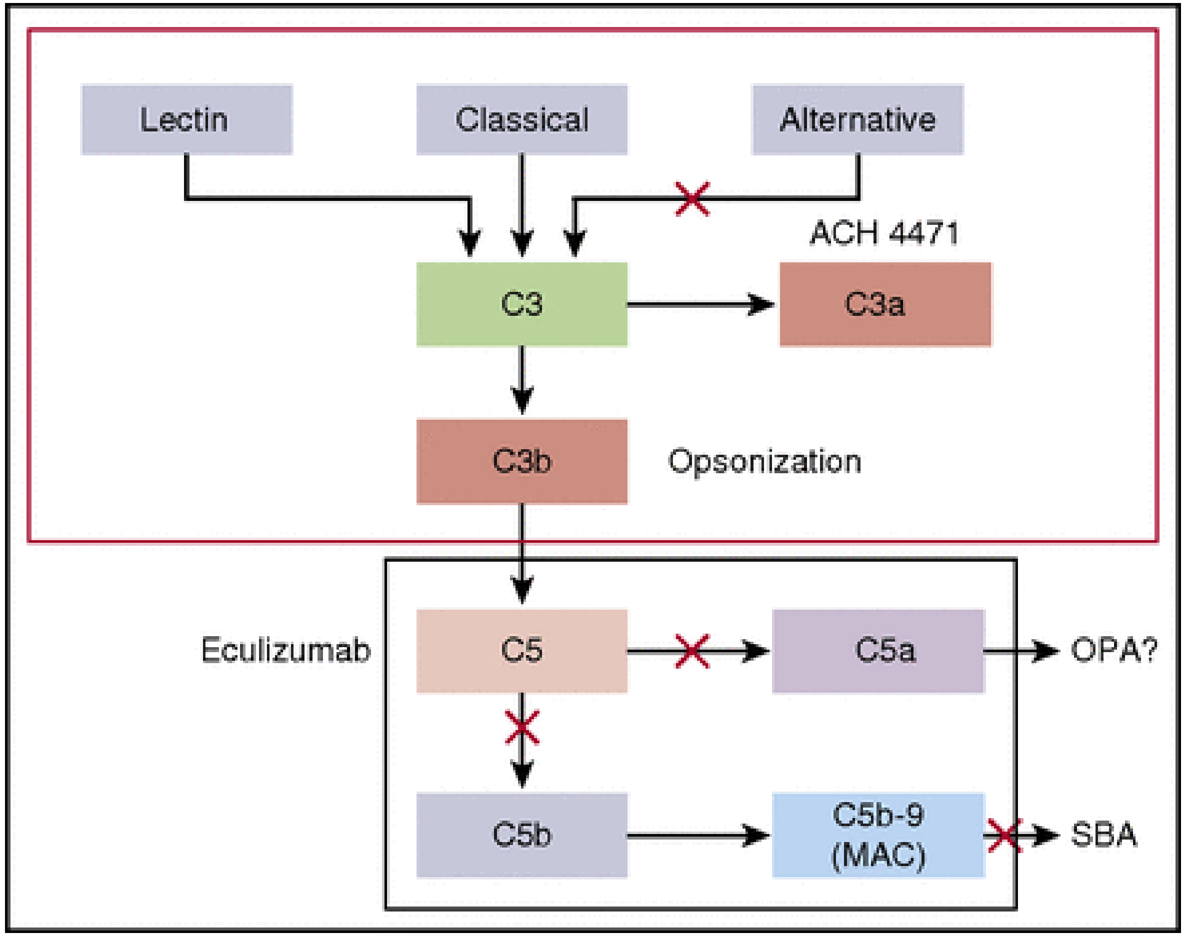
Meningoccal septicemia according to RCT



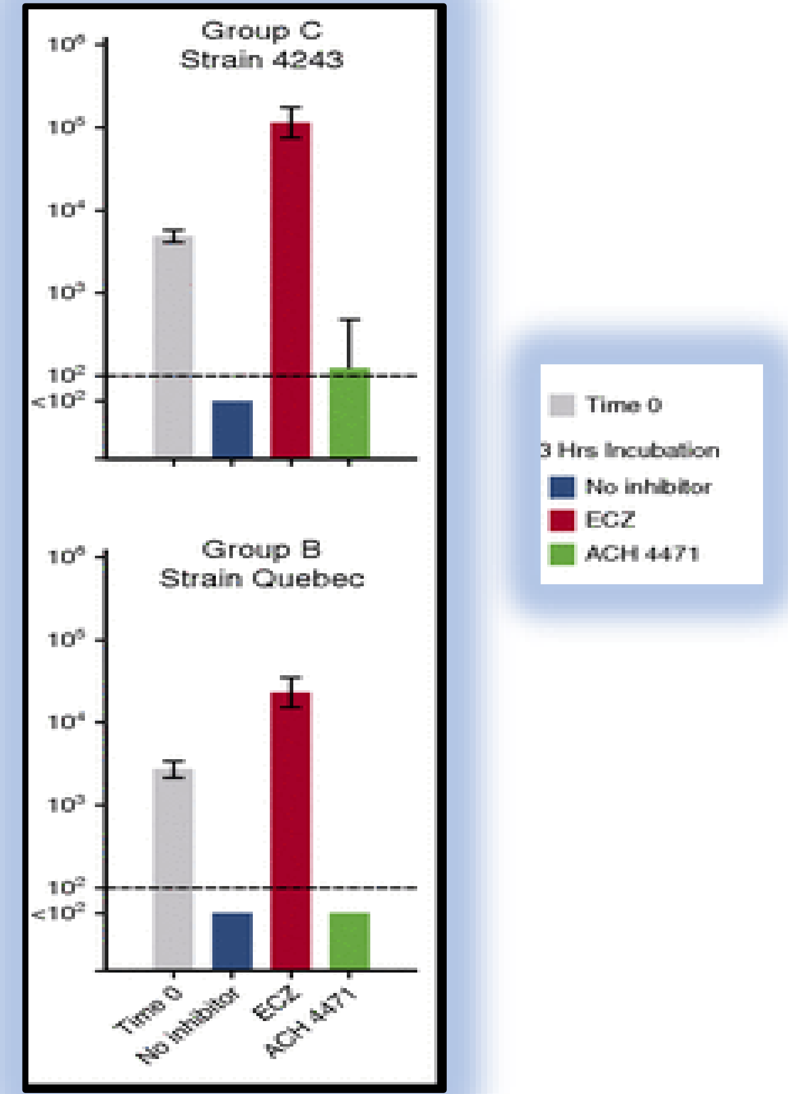
2/100 (no AB prophylaxis)
First 26 weeks
Long-term risk elusive….

Legendre C et al. Transplant Int 2017

The mechanism behind this association



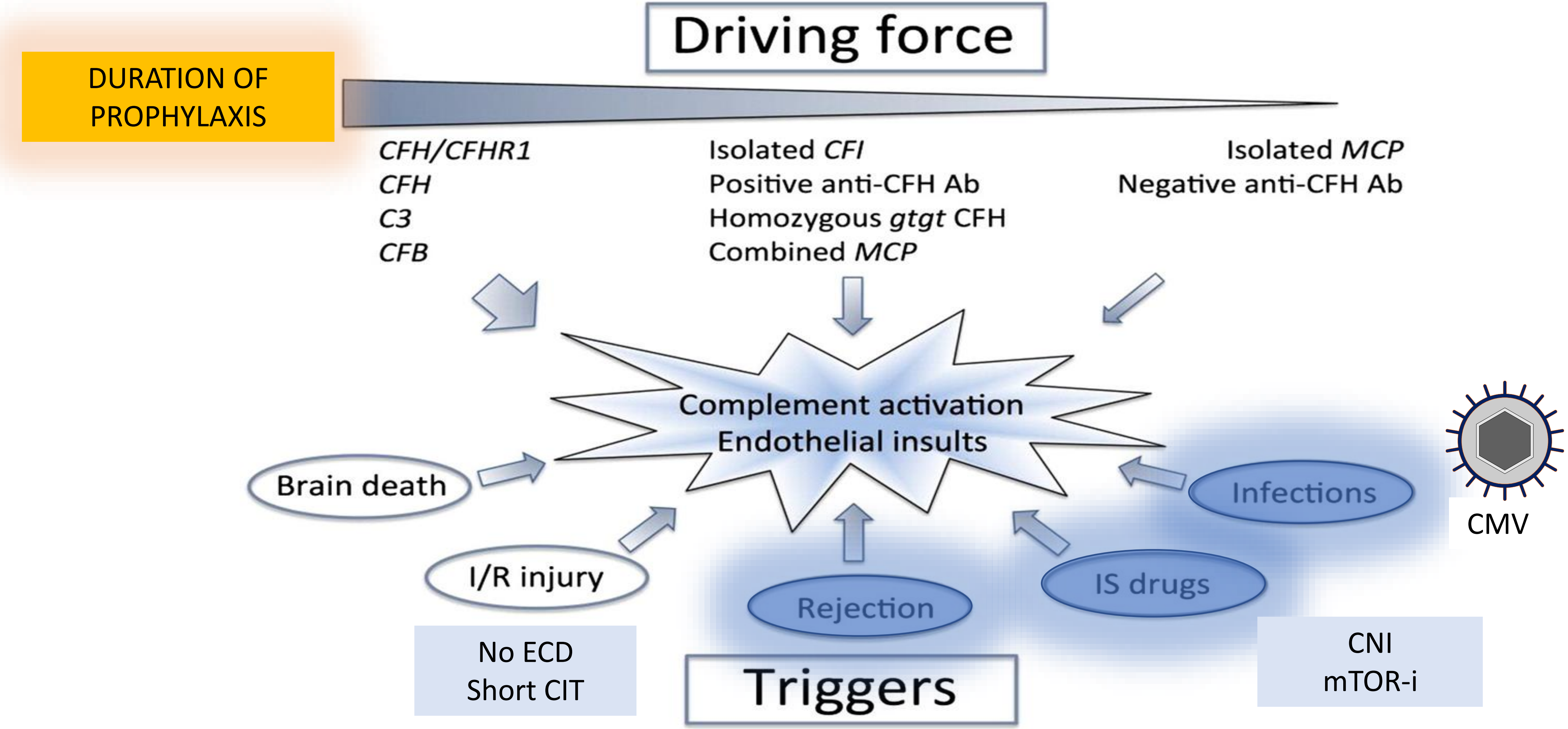
Inhibition of release of C5a
(→upregulation of phagocytosis)



Konar M et al. Blood 2017

aHUS and kidney transplantation

aHUS after transplantation: why at risk?

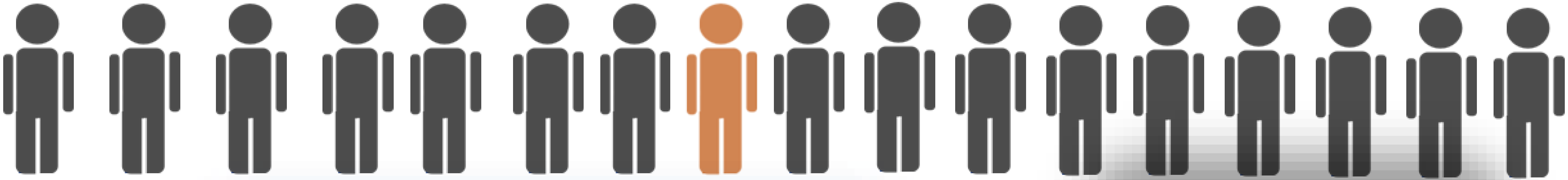


Zuber et al. Transplant Rev 2013

When to stop ECL: the extremes

Living Donor Kidney Transplantation in Atypical Hemolytic Uremic Syndrome: A Case Series

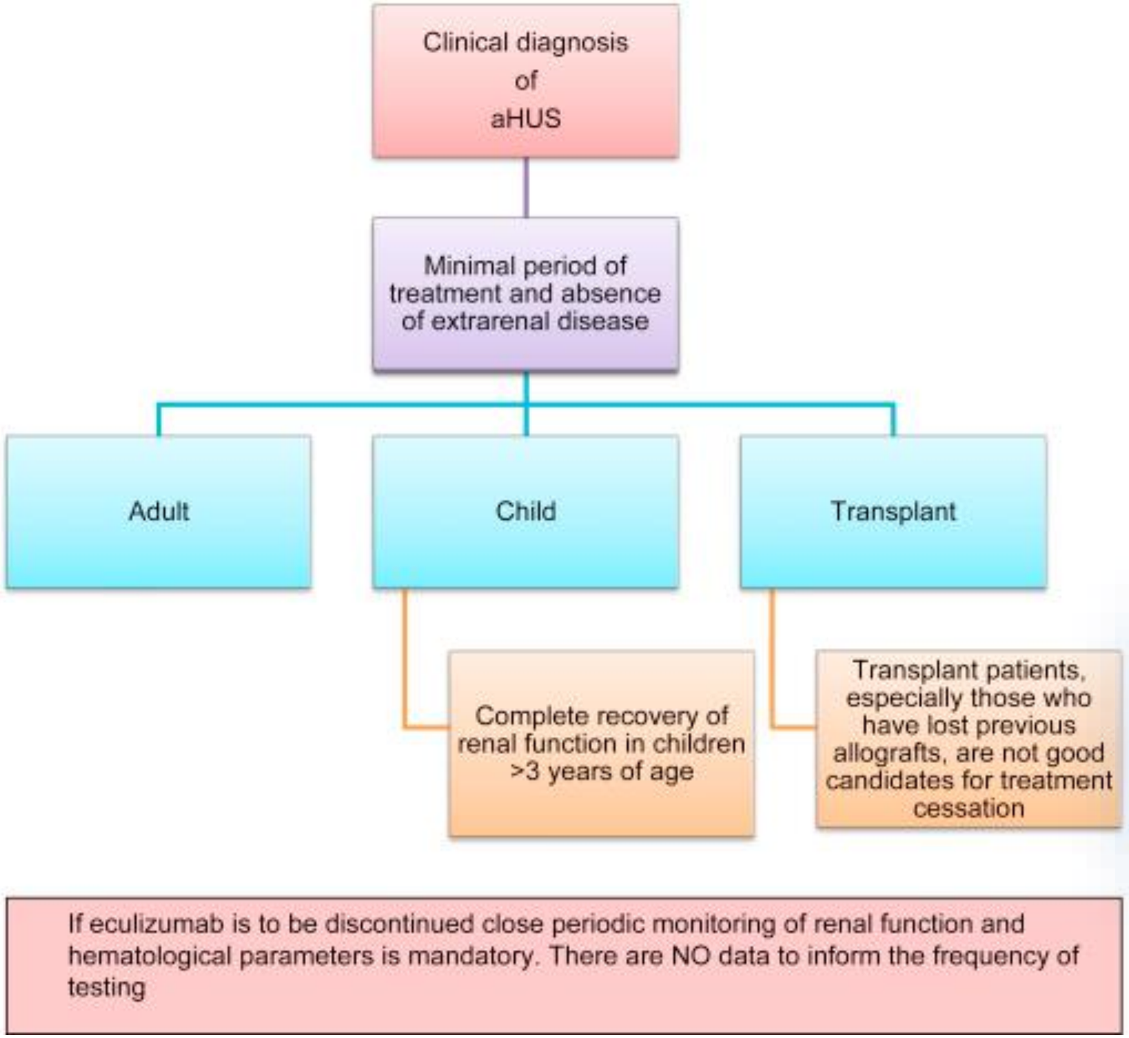
Caroline Duineveld, MD,[1,] Jacobien C. Verhave, MD,[1,*] Stefan P. Berger, MD,[2] Nicole C.A.J. van de Kar, MD,[3] and Jack F.M. Wetzels, MD[1]*



N=17 (mean age 47); 16 pathogenic mutation
ECL only for relapses after tpx
Low dose TAC+aggressive BP control
Median 25m FU (7-68 months)

AJKD 2017

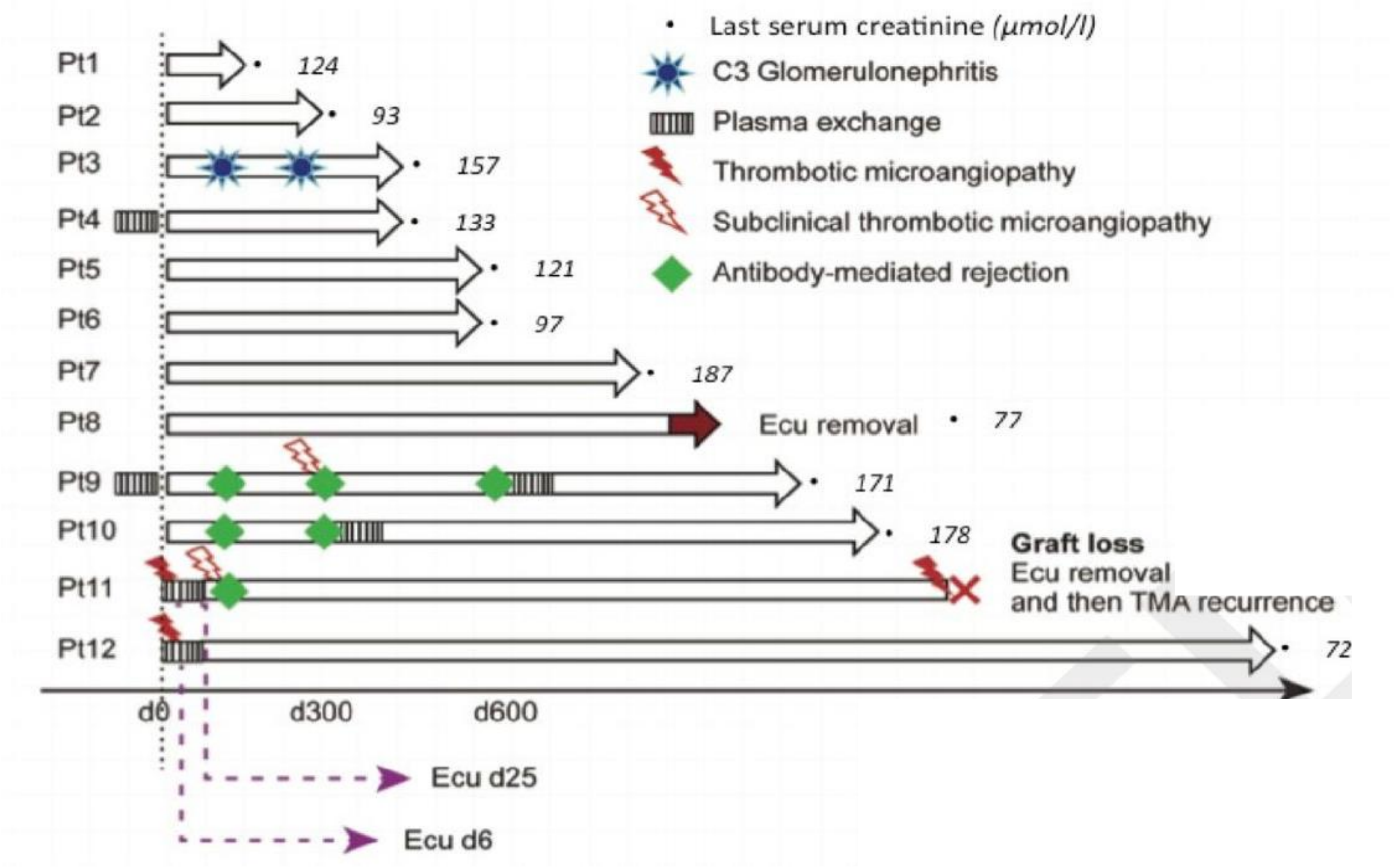
When to stop ECL: the extremes



IS THIS A CONSISTENT POLICY?

Goodschip THJ et al. KDIGO Controversies Conference. Kidney Int 2016

ECL does not prevent ABMR nor C3G



Levi C et al. Transplantation 2017

ORIGINAL ARTICLE

Current evidence on the discontinuation of eculizumab in patients with atypical haemolytic uraemic syndrome

Manuel Macia[1], Fernando de Alvaro Moreno[2], Tina Dutt[3], Ingela Fehrman[4], Karine Hadaya[5], Christoph Gasteyger[6] and Nils Heyne[7]

CASE REPORTS → 16/52 (31%) TMA MANIFESTATION

CLINICAL TRIALS (61/130 DISCONTINUED) → 12/61 (20%) MANIFESTATION WITHIN 24 WEEKS

GLOBAL AHUS REGISTRY (72/296 DISCONTINUED) → 12/76 (overall 16%-10% in adults) TMA MANIFESTATION

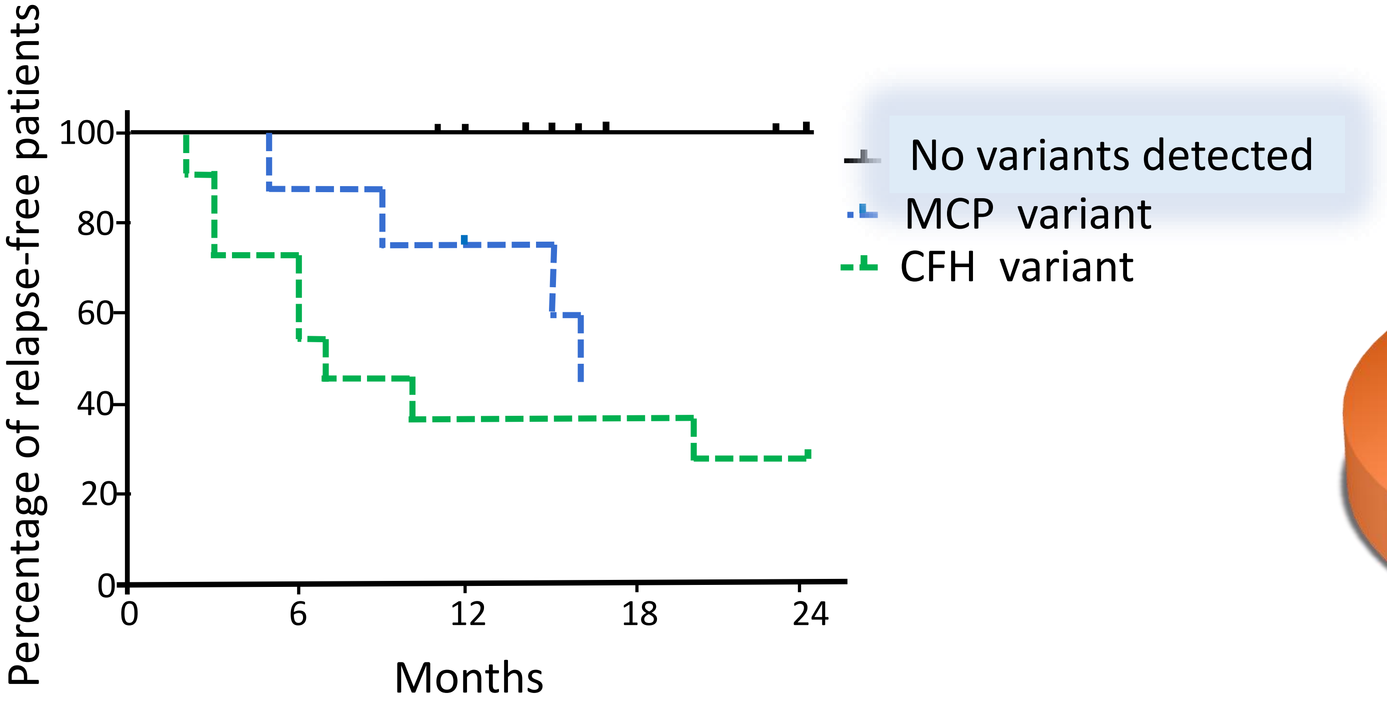
aHUS registry

aHUS Alliance www.aHUSallianceAction.org

Acknowledgements

The authors thank Jimmy Wang of Alexion Pharmaceuticals, Inc. for support with statistical analyses. Medical writing support (funded by Alexion Pharma GmBH) was provided by Matthew deSchoolmeester, PhD, of Bioscript Medical Ltd.

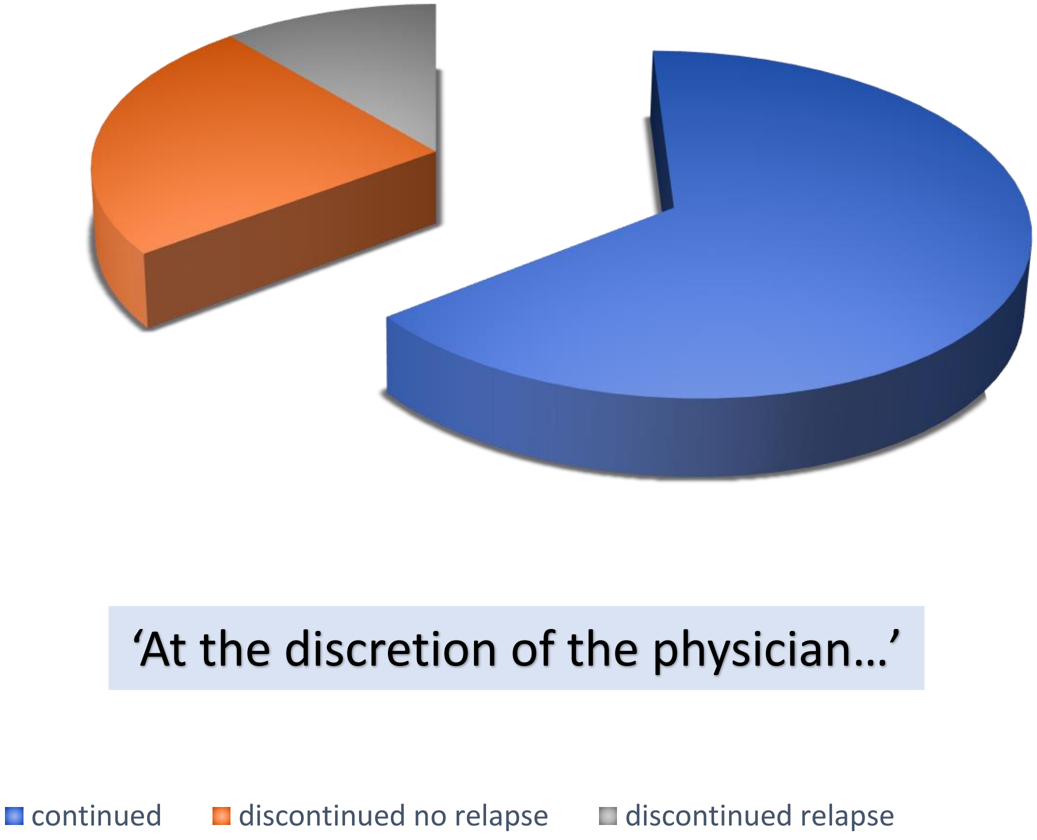
Withdrawal of ECL: data from French registry



Number at risk

CFH	11	7	5	2	0
MCP	8	7	5	3	1
No variant	16	15	14	8	6

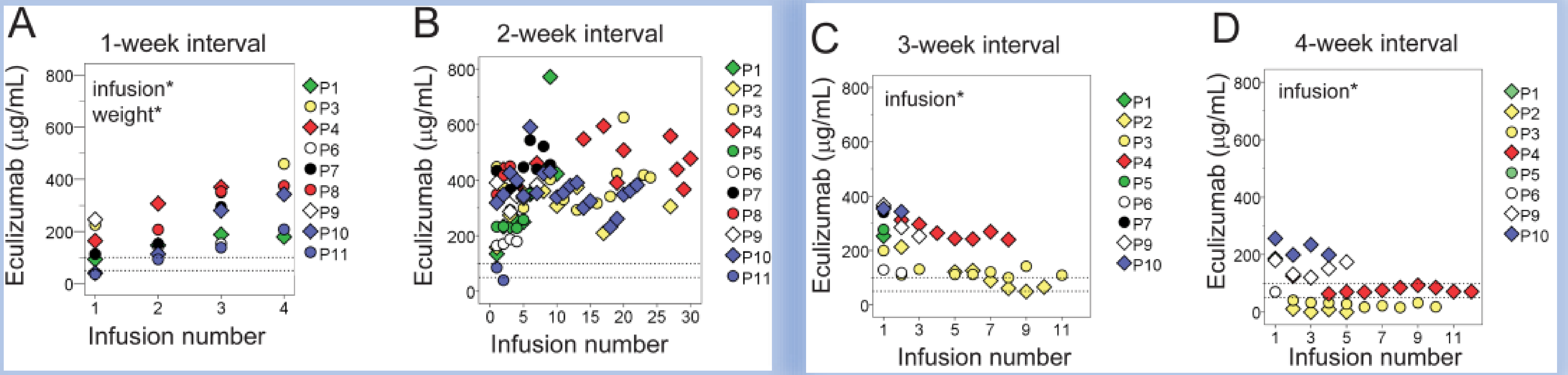
38/108 withdrew ECL



'At the discretion of the physician…'

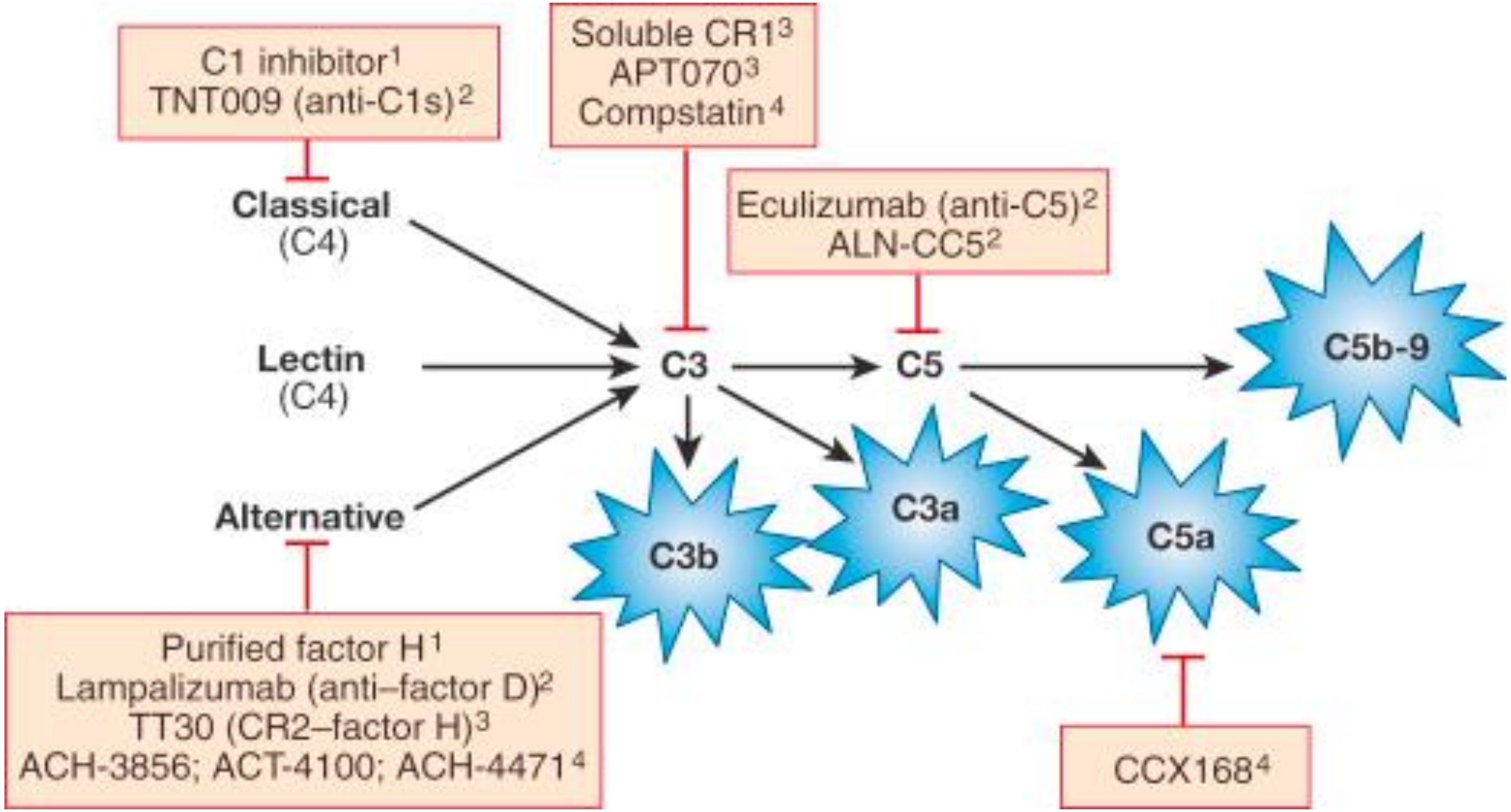
Fakhouri F et al. cJASN 2017

Do we overdose ECL?



Volokhina E et al. Clin Pharmacology and Therapeutics 2017

Novel complement-based therapies: the pipeline



Thurman JM, Le Quintrec M. Kidney Int 2016

Conclusion

- aHUS vs. secondary aHUS: to which extent is complement involved?
- Gene abnormalities only part of the game
- Complement blockade for secondary HUS: CAVEAT bias
- MHT-TMA vs. aHUS with severe hypertension: Criteria? biomarkers? Trials?
- Meningococcal bacteremia in 1-2% medical argument for withdrawal
- Feasibility of withdrawal? Genotyping? LD? Biomarkers?
- The pipeline is not empty.

Thank you for your attention