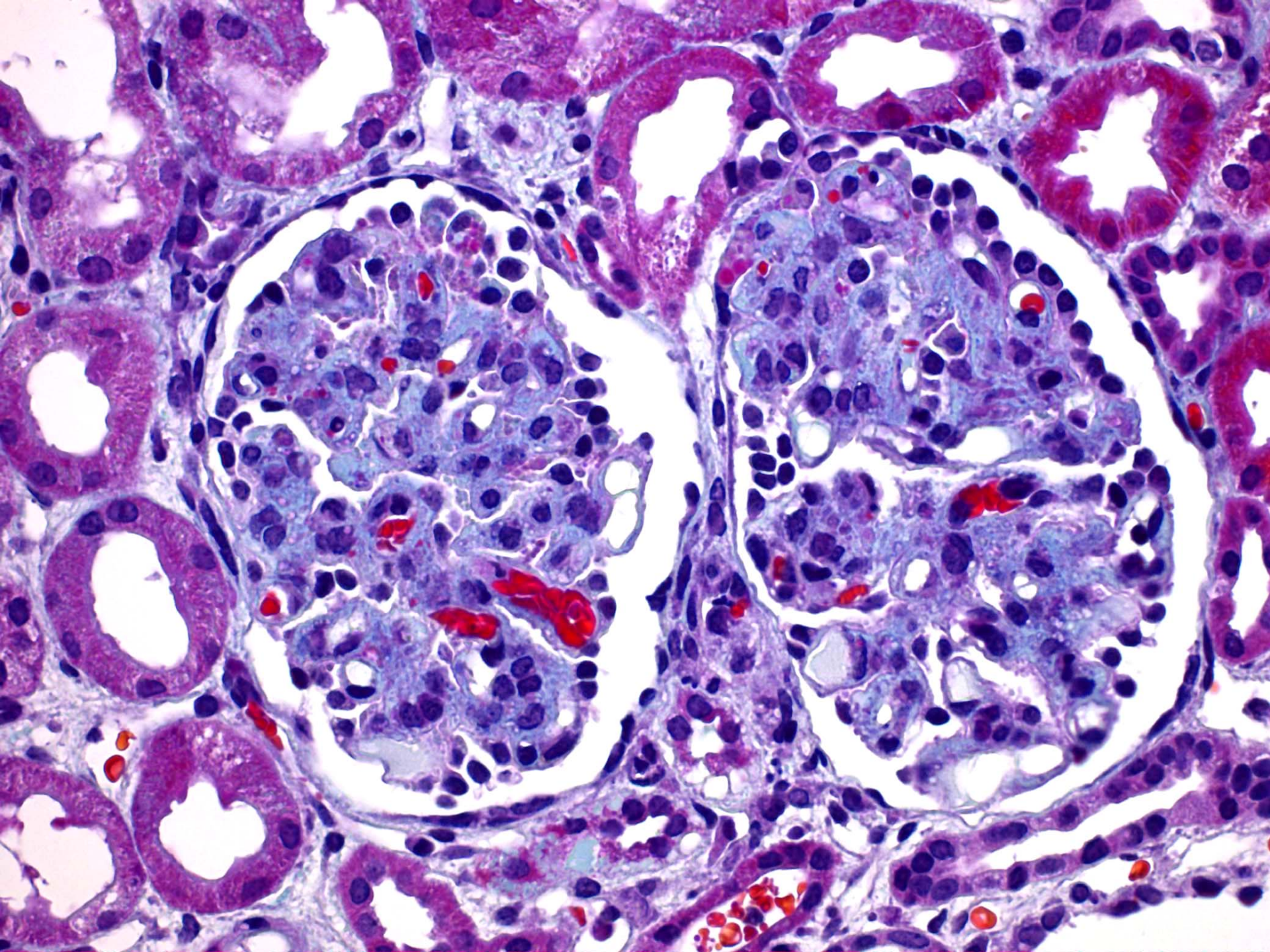




aHUS – what's new?

Christoph Licht
aHUS Canada Meeting
Mississauga, ON – 23.5.2015



An international consensus approach to the management of atypical hemolytic uremic syndrome in children

Chantal Loirat • Fadi Fakhouri • Gema Ariceta • Nesrin Besbas • Martin Bitzan • Anna Bjerre • Rosanna Coppo • Francesco Emma • Sally Johnson • Diana Karpman • Daniel Landau • Craig B Langman • Anne-Laure Lapeyraque • Christoph Licht • Carla Nester • Carmine Pecoraro • Magdalena Riedl • Nicole C. A. J. van de Kar • Johan Van de Walle • Marina Vivarelli • Véronique Frémeaux-Bacchi • for HUS International

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Overview

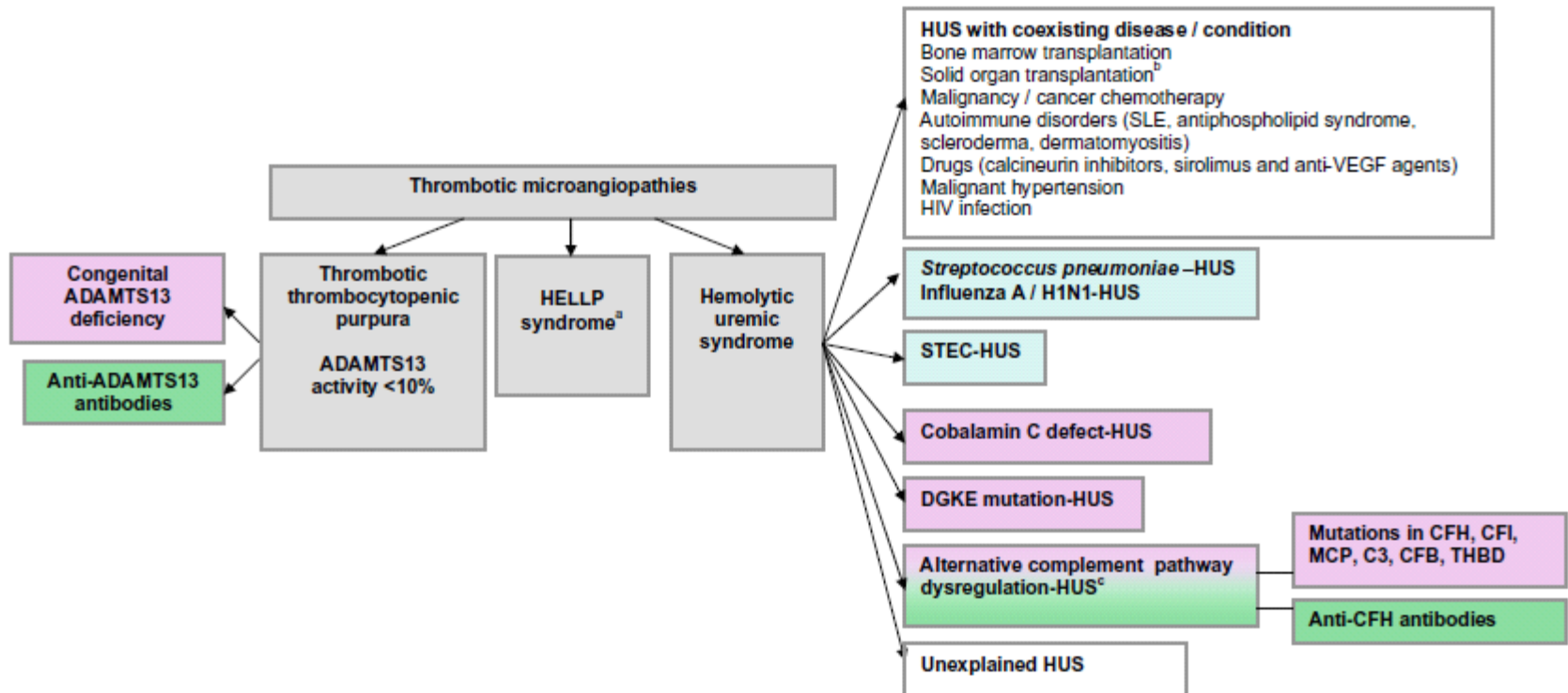
- The complement system – activation and regulation
- The spectrum of complement-mediated disease
- aHUS – a complement-mediated disease
- Diagnosis of aHUS
- Treatment of aHUS

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The spectrum of complement-mediated diseases

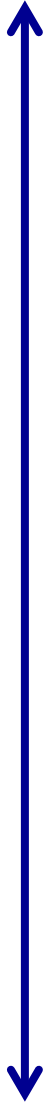
Etiology based classification of TMA



Benefit of complement-targeting treatment supports common pathogenetic role for complement

Thrombotic thrombocytopenic purpura (TTP)
Hemolytic uremic syndrome <ul style="list-style-type: none">- “typical” HUS / STEC HUS- atypical HUS
TMA post solid organ transplantation <ul style="list-style-type: none">- de novo TMA- TMA recurrence
TMA associated with pregnancy
TMA post hematopoietic stem cell transplantation
TMA associated with glomerulonephritis
TMA associated with drugs
TMA associated with metabolic disease
TMA associated with infections
TMA associated with malignant hypertension

Primary complement dysregulation



- Endogenous defects – mutations / autoantibodies
- Conditions resulting in EC activation and secondary complement activation
 - Drugs
 - Malignant hypertension
 - Pregnancy
- Conditions activating complement
 - Immune complexes
 - Autoantibodies
 - Infections
- Conditions inhibiting complement regulators
 - Shiga toxin

Secondary complement activation / dysregulation

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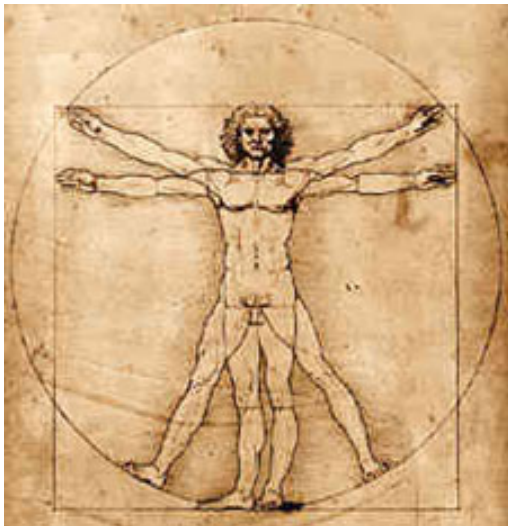
The complement system – activation and regulation

The complement system

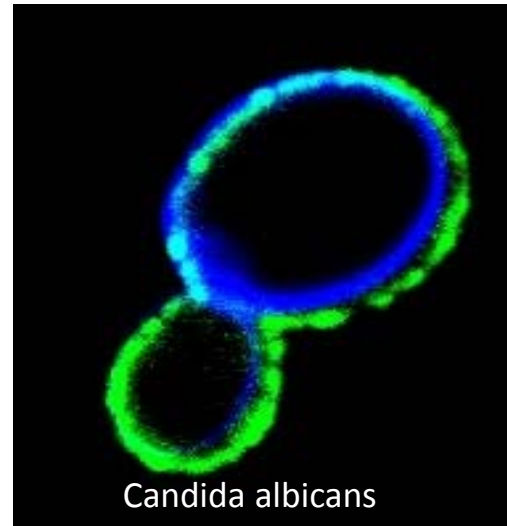
- 1889 – Hans Ernst August Buchner
... detects that a cell free system that can kill bacteria.
- 1896 – Julius Bordet
... detects a heat-insensitive component with specific anti-microbial function (i.e. antibodies) and a heat-sensitive component with unspecific anti-microbial function (i.e. complement).
- 1900 – Paul Ehrlich
... coins the term “complement” (i.e. something that complements the function of antibodies).
- 1930 – Jackie Stanley
... establishes our current understanding of the complement system and its role for innate and acquired immunity.



Injury

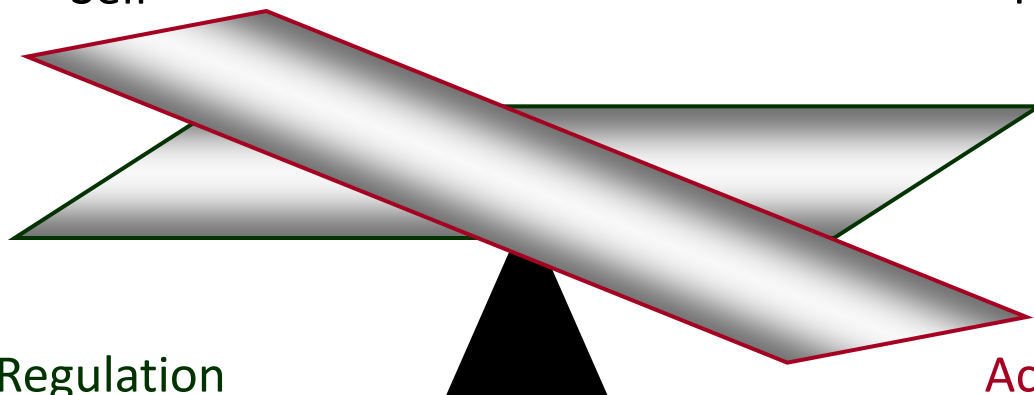


Self



Candida albicans

Foreign

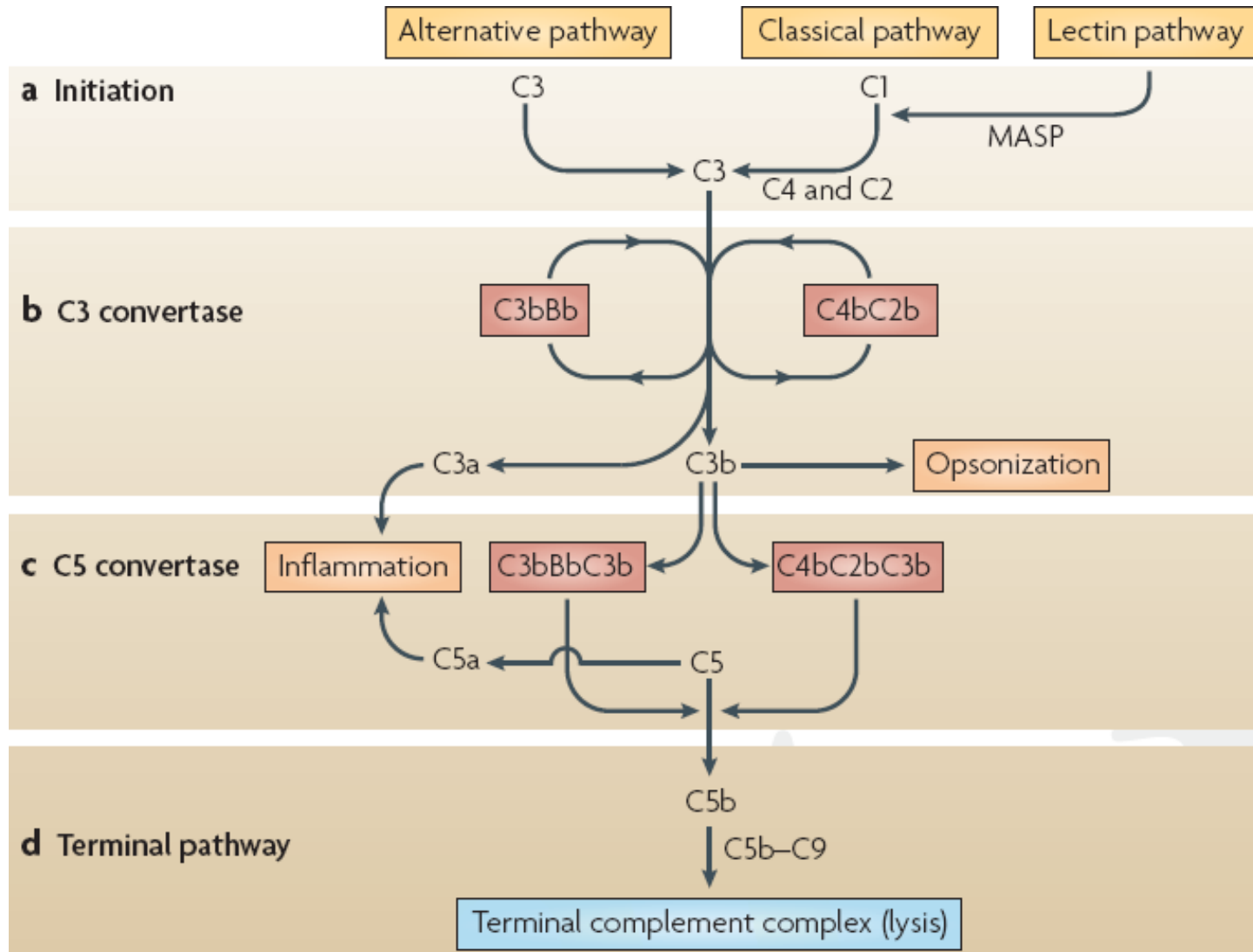


Regulation

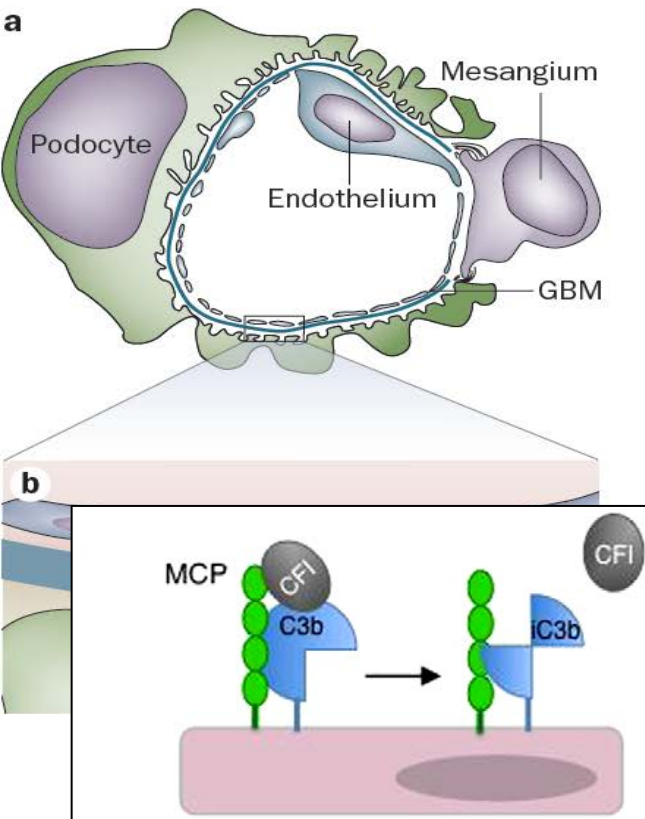
Activation



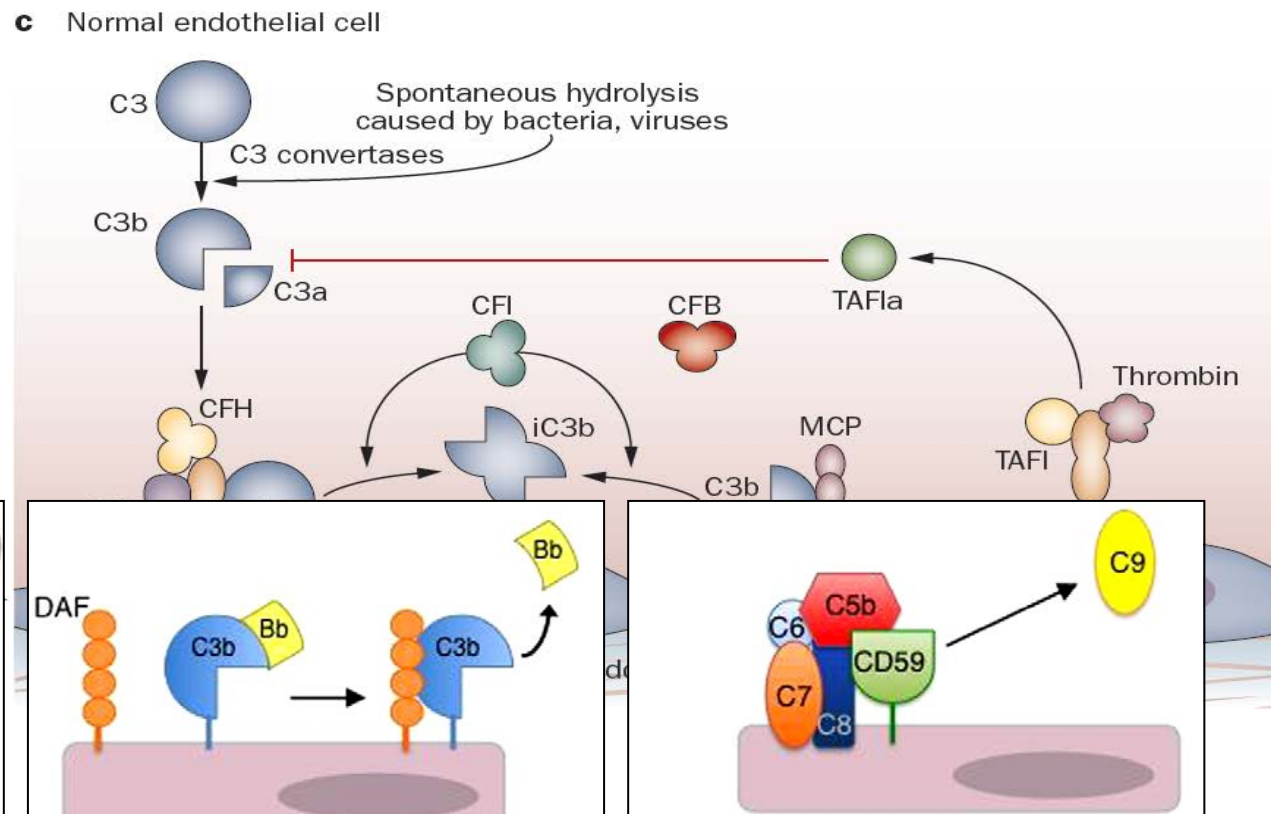
The complement system



Complement alternative pathway: Regulation and dysregulation on the endothelium

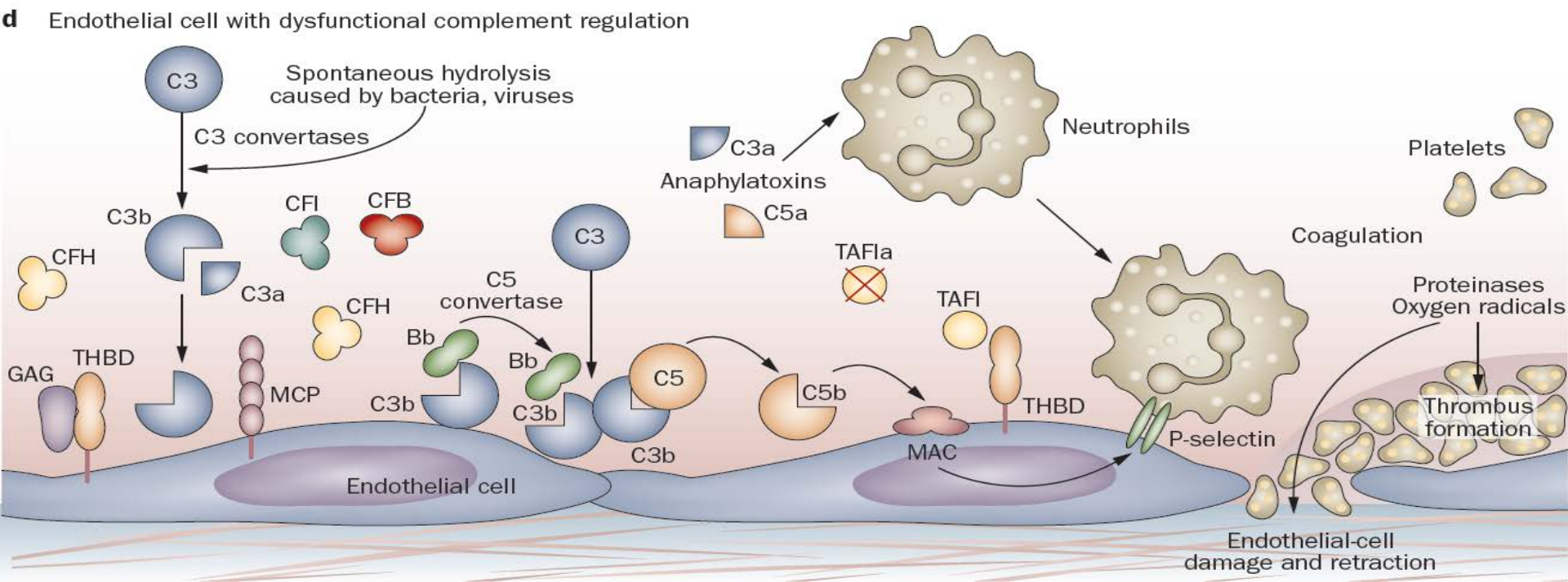
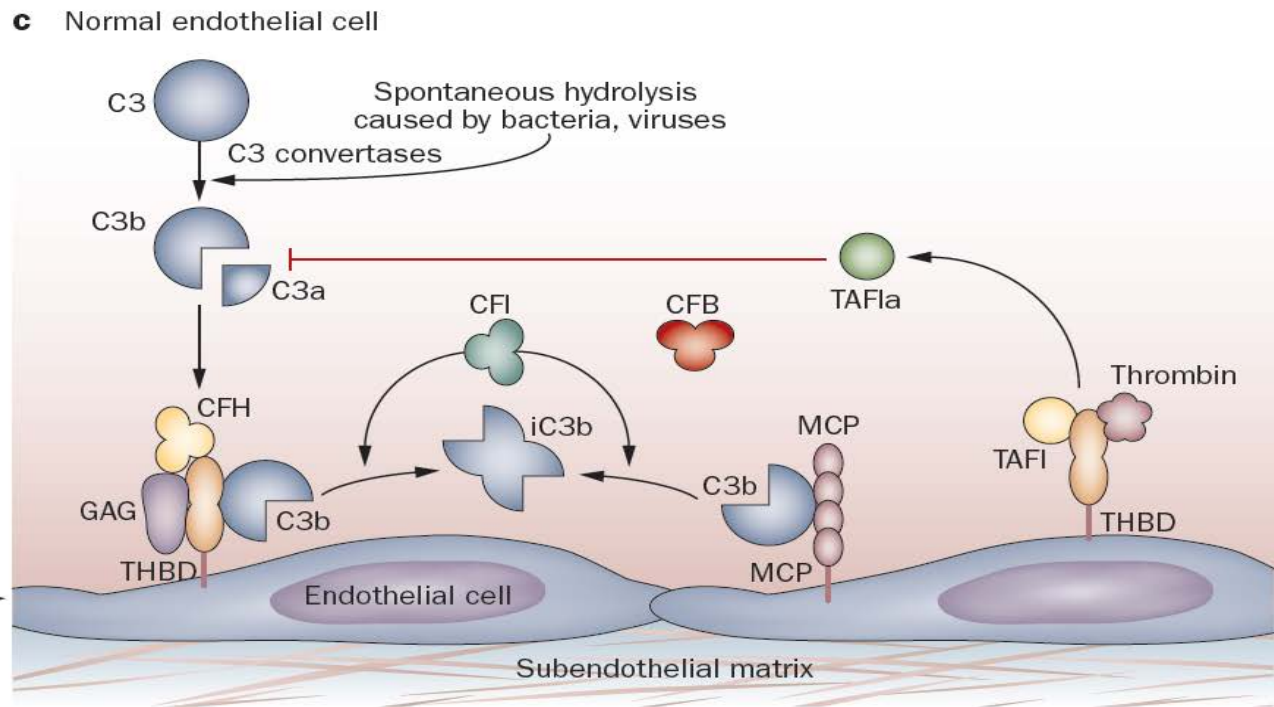
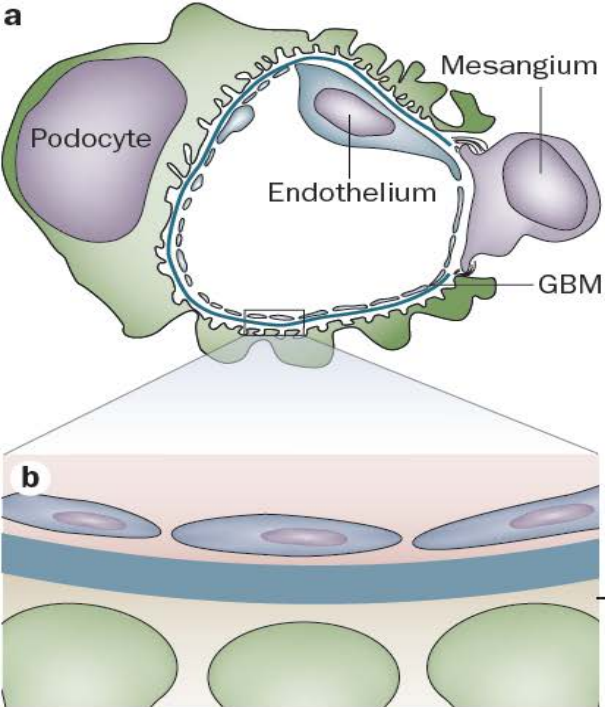


C3b inactivation (CD46/MCP)



Decay of C3 convertase (CD55/DAF)

Prevention of C5b-9 formation (CD59)

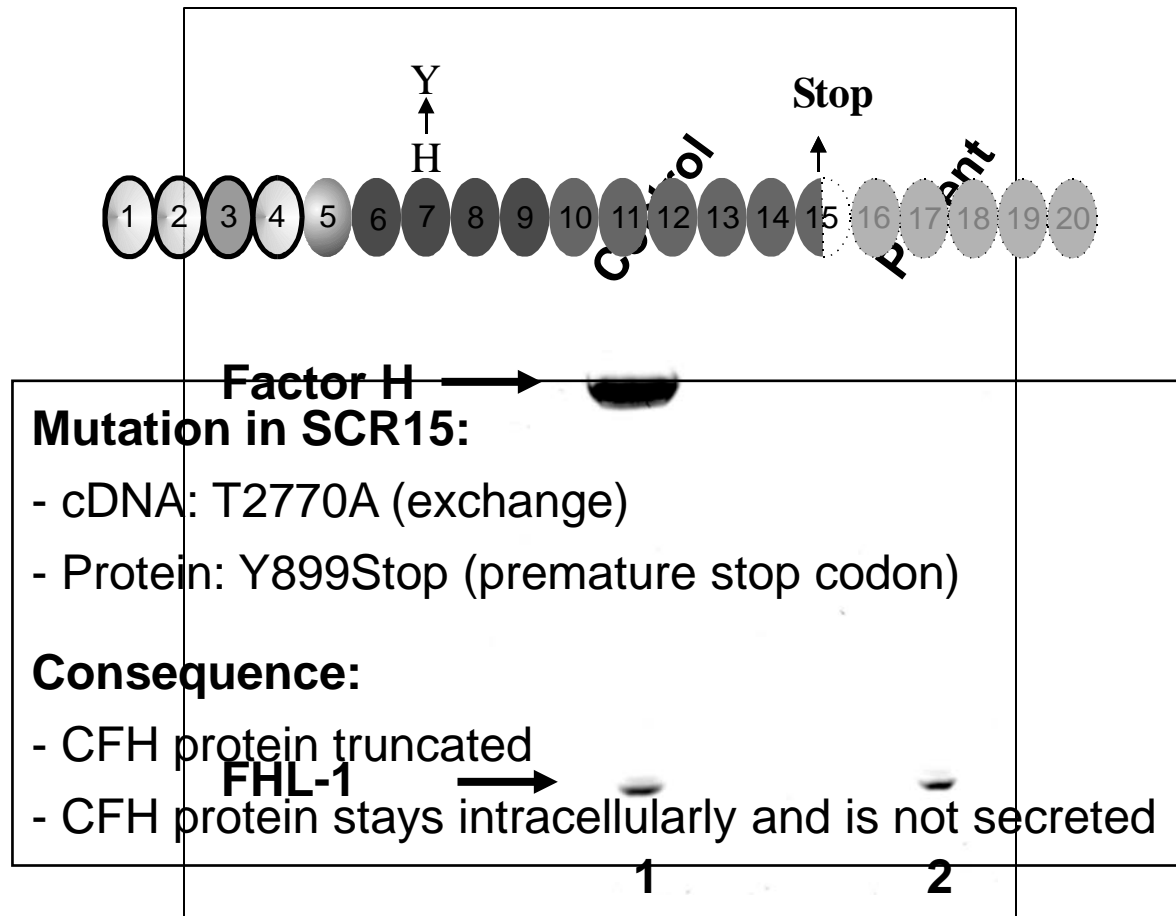


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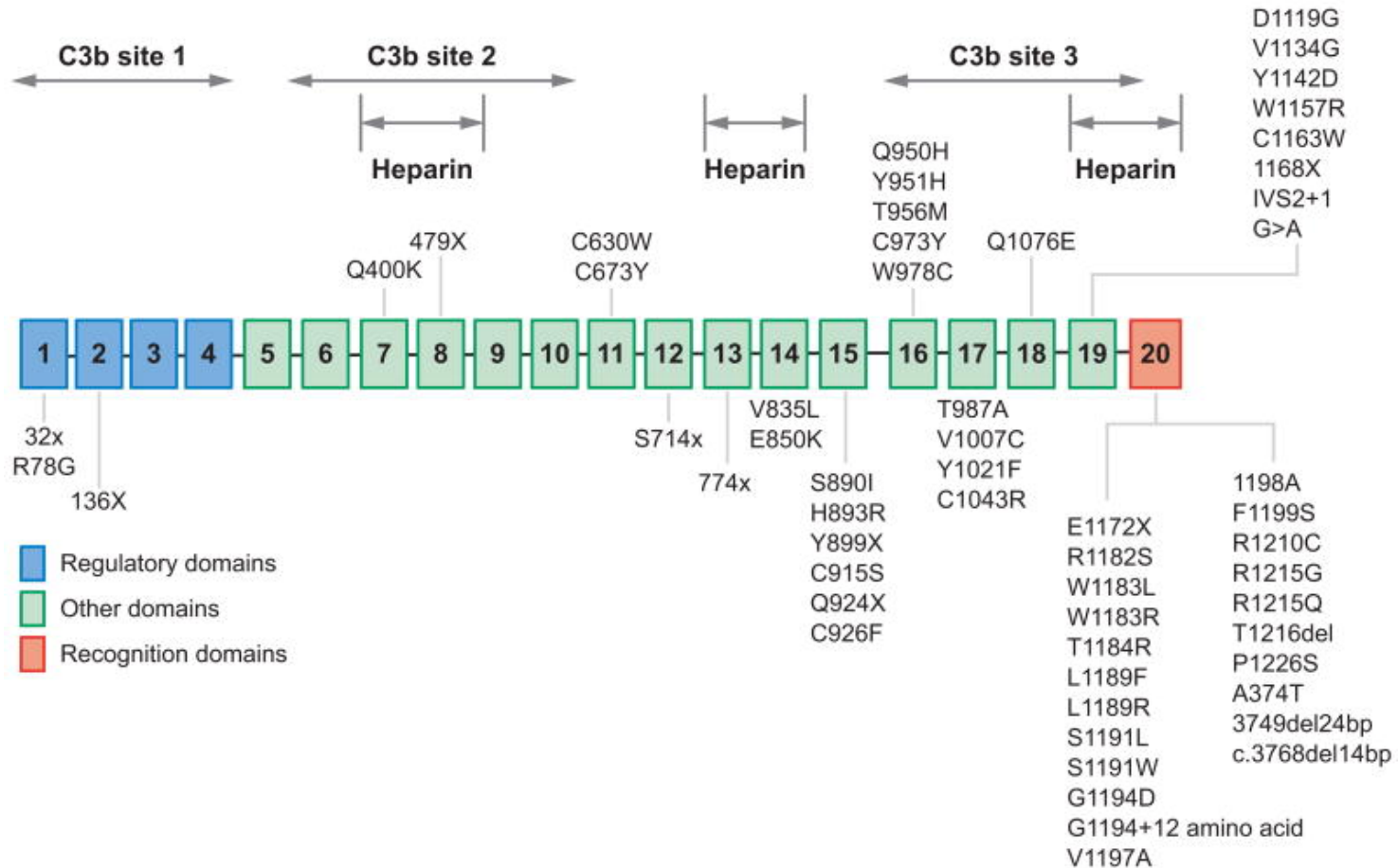


aHUS – a complement-mediated disease

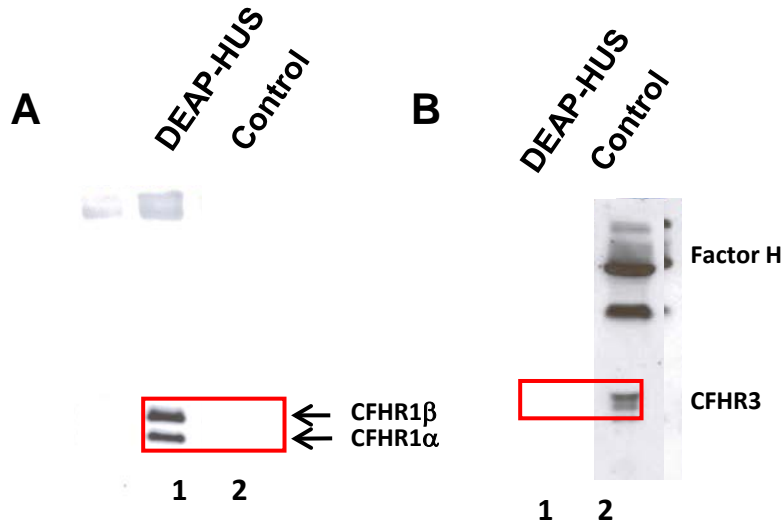
CFH deficiency



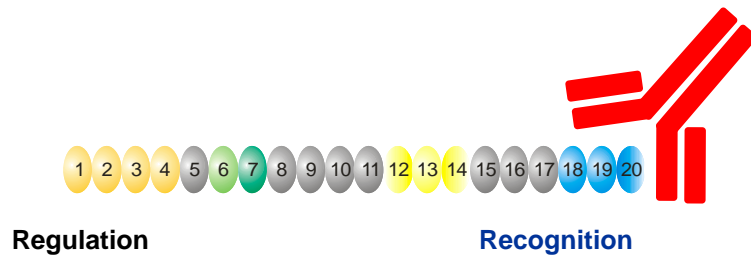
CFH mutations



CFH autoantibodies – DEAP HUS



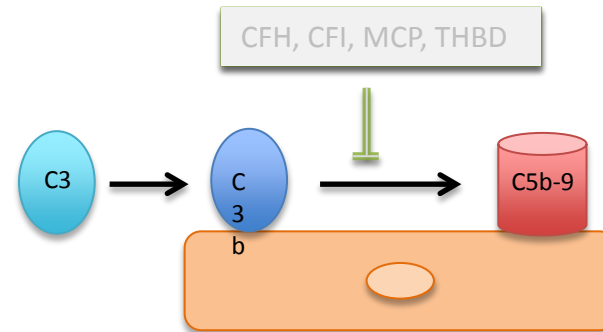
C



- Dragon-Durey et al, J Am Soc Nephrol 2005:
 - Normal CFH levels
 - Decreased CFH activity
 - No CFH mutations
 - CFH autoantibodies in 6% of aHUS patients
- Jozsi et al, Blood 2008:
 - CFH autoantibodies bind and inhibit CFH C-terminus
- Jozsi and Licht et al, Blood 2008:
 - CFH autoantibodies in 11% juvenile aHUS patients
 - Patients lack CFHR1/3 expression
 - New aHUS subgroup: **DEAP HUS**
(deficiency of CFHR and CFH autoantibody positive)
- Abarrategui-Garrido et al, Blood 2009:
 - CFH antibodies associated with CFHR1 deficiency

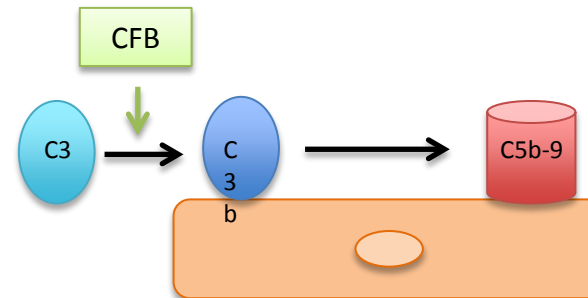
aHUS-associated complement defects

- Loss of function mutations
 - Factor H (CFH)
 - Factor I (CFI)
 - Membrane cofactor protein (MCP/CD46)
 - Thrombomodulin (THBD/CD141)



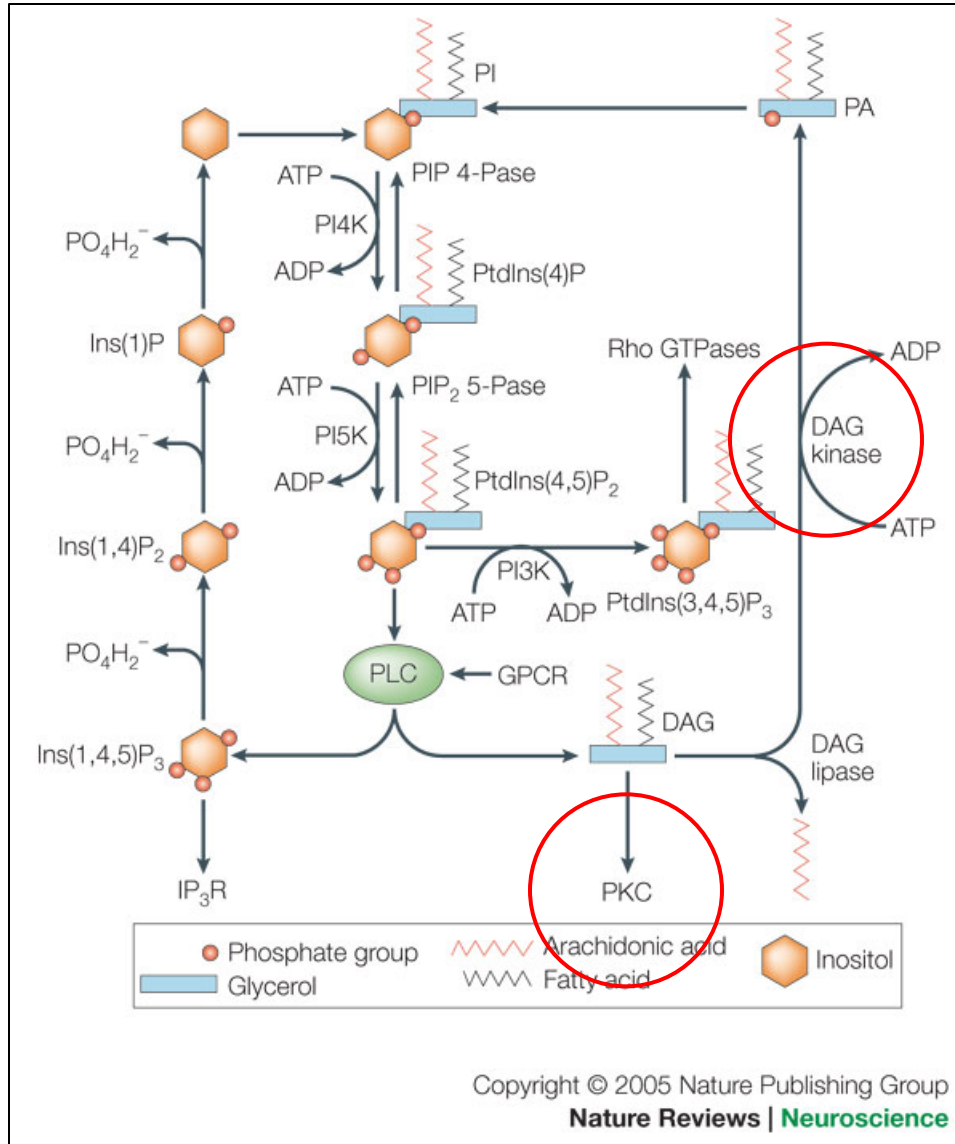
- Autoantibodies
 - CFH (in combination with CFHR3/CFHR1 deletion: DEAP-HUS)

- Gain of function mutations
 - CFB
 - C3



- *Diacylglycerolkinase-ε (DGKE)*
- *Plasminogen (PLG)*

Functional consequences of *DGKE* mutations



Endothelial cells:

- PAF
- PAI-1
- vWF
- TF
- tPA
- **VEGFR2**

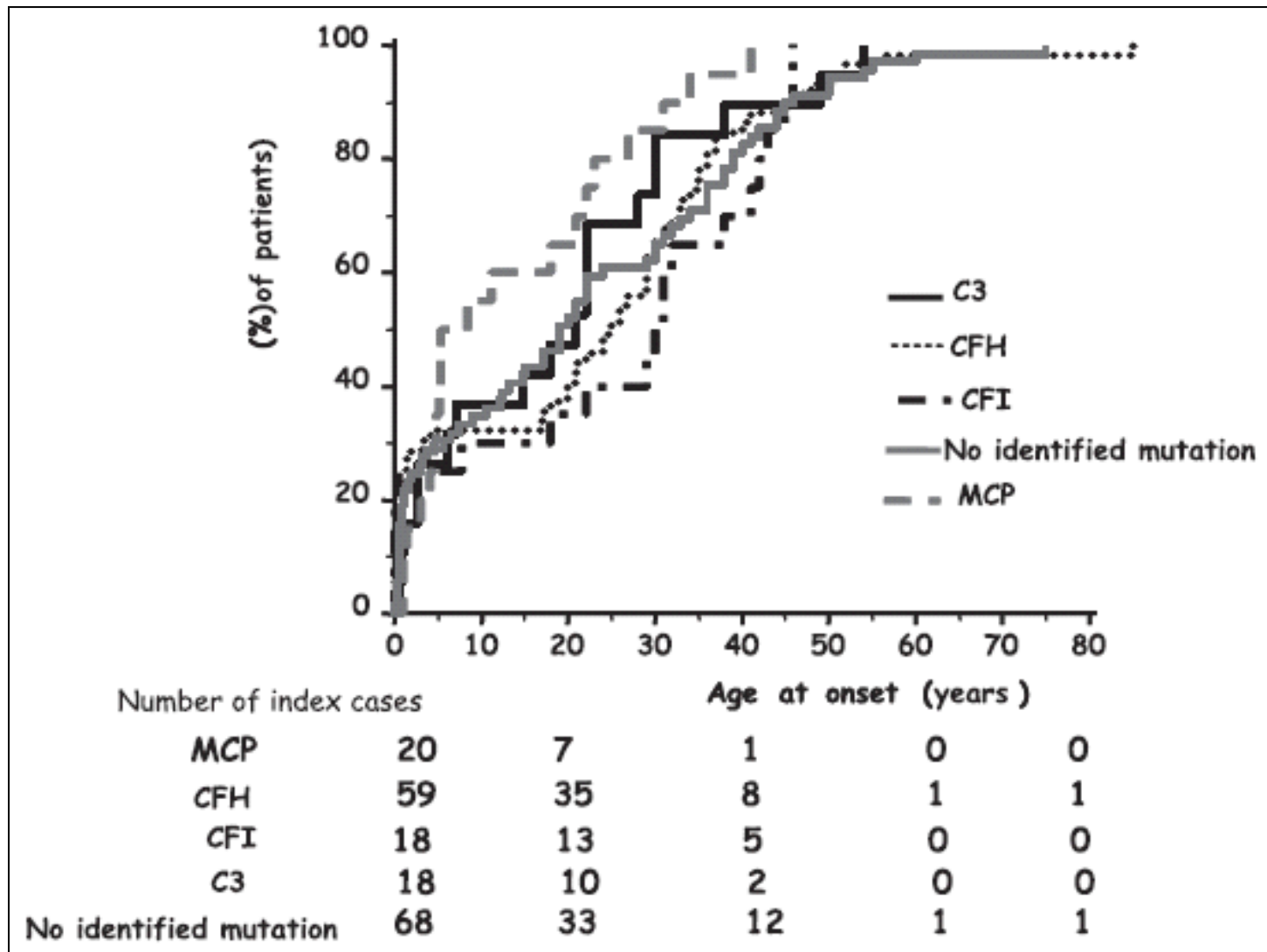
Platelets:

- Granule secretion
- **TA₂**

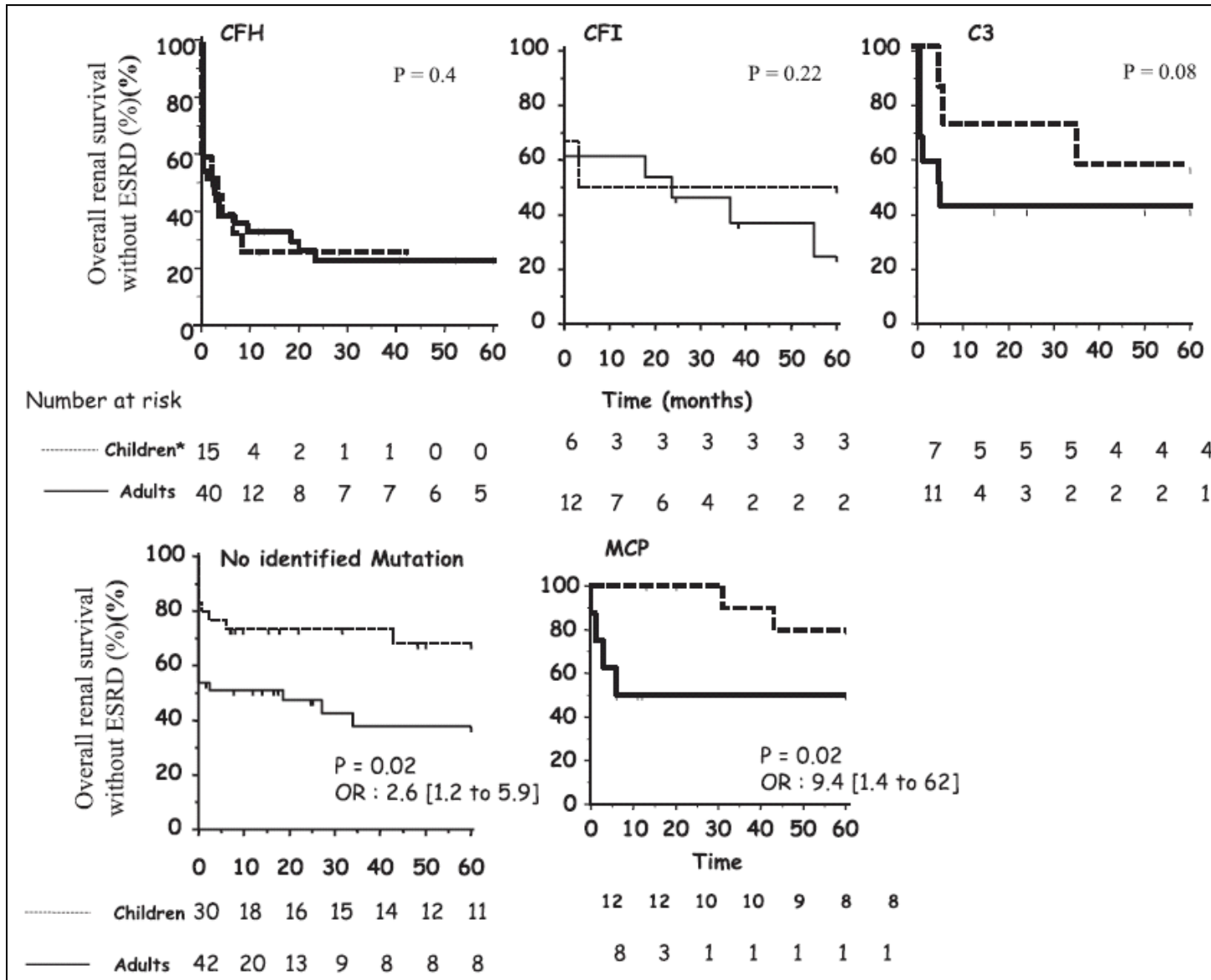
Podocytes:

- Slit diaphragm function
- Nephrin endocytosis

Complement mutation – disease manifestation



Age at disease manifestation and genotype – renal outcome



Long-term outcome

- Relapse:
 - 40% overall risk (43% in children; 35% in adults)
 - 57% of relapses in children and 82% in adults during the first year (!)
(92% of relapses in children with MCP/CD46 mutations)
 - 25% of relapses in all patients after the first year
- ESRD / death:
 - 17% in children and 46% in adults at 1 month
 - 36% in children and 64% in adults at 5 years
- Extrarenal manifestation:
 - Overall 10-30%
 - Most prominent organ system – CNS (11%)
 - Other organ systems – GI (e.g. liver/pancreas), heart, etc.

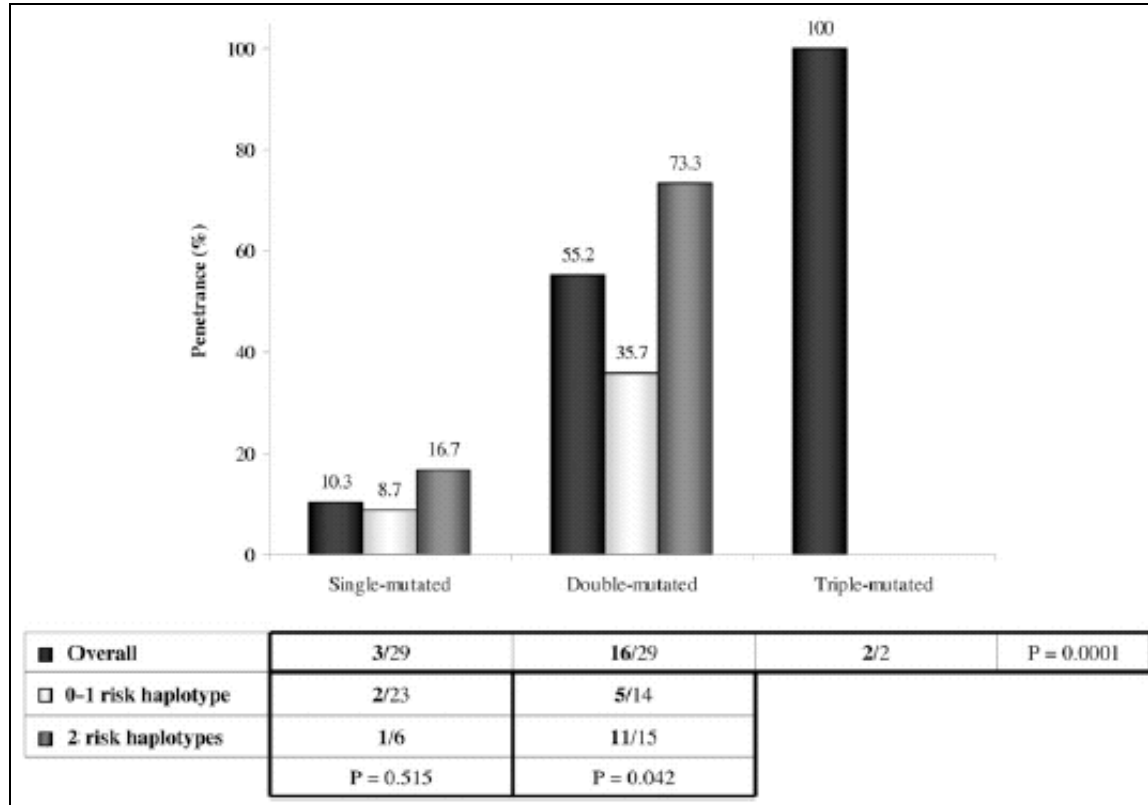
Individual vs. combined complement mutations

Table 2. Prevalence of patients with single and combined mutations in *CFH*, *MCP*, *CFI*, *C3*, and *CFB* in the four cohorts

Genetic Abnormality	CFH	MCP	CFI	C3	CFB
CFH	158				
MCP	7	65			
CFI	4	9	46		
C3	2	1	1	45	
CFB	0	0	1	0	9
Triple-mutated	Two patients				
Combined ^a /single	15/158	19/65 ^{b,c}	17/46 ^{b,c}	4/45	1/9
Combined ^a /single + combined (%)	8.7%	22.6%	27%	8.2%	10%
Single mutation/screened patients	158/795 (19.9%)	65/795 ^{d,e} (8.2%)	46/795 ^{d,e} (5.8%)	45/795 ^{d,e} (5.7%)	9/795 ^d (1.1%)
Combined mutations ^a /screened patients	15/795 ^{c,f} (1.9%)	19/795 ^{c,e} (2.4%)	17/795 ^{c,f} (2.1%)	4/795 (0.5%)	1/795 (0.1%)

- Patients carrying *any* mutation 44% (350/795)
- Patients carrying *single* gene mutation 40.6%
- Patients carrying *combined* mutations 3.4%
- Additional mutation risk *MCP/CD46* 22.6%
- Additional mutation risk *CFI* 27%
- Additional mutation risk *CFH, C3, CFB* 8-10%
- Additional mutations have no impact on overall outcome (except for *MCP/CD46*)
- *MCP/CD46* alone 18.5% vs. *MCP/CD46* combined 50% ESRD at 3 years

Risk haplotypes



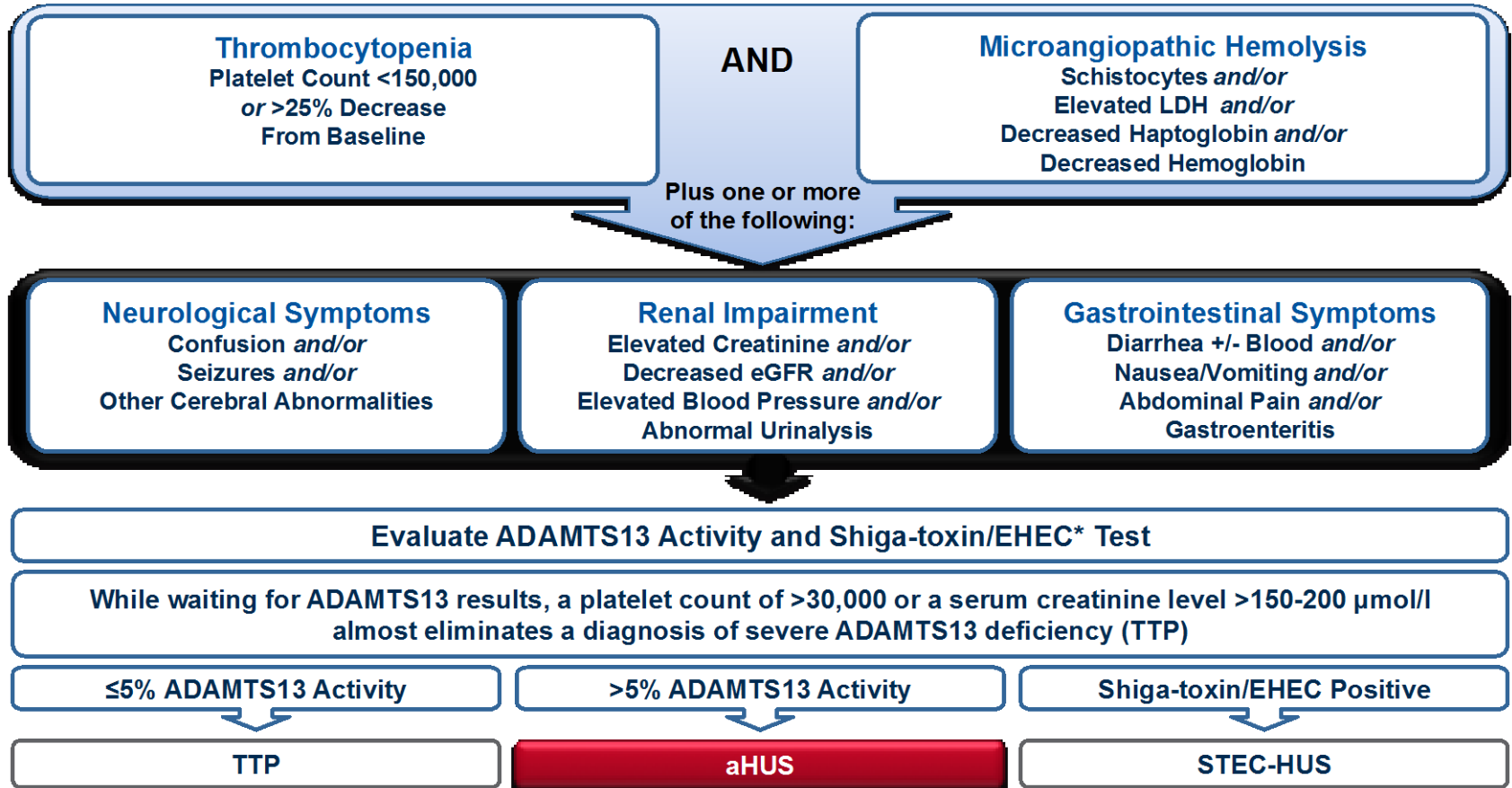
- CFH-H3 tgtgt
- MCP ggaac
- C3 R139W + CFH-H3 tgtgt 4 fold risk
- C3 R139W + MCP ggaac 3 fold risk

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Diagnosis of aHUS

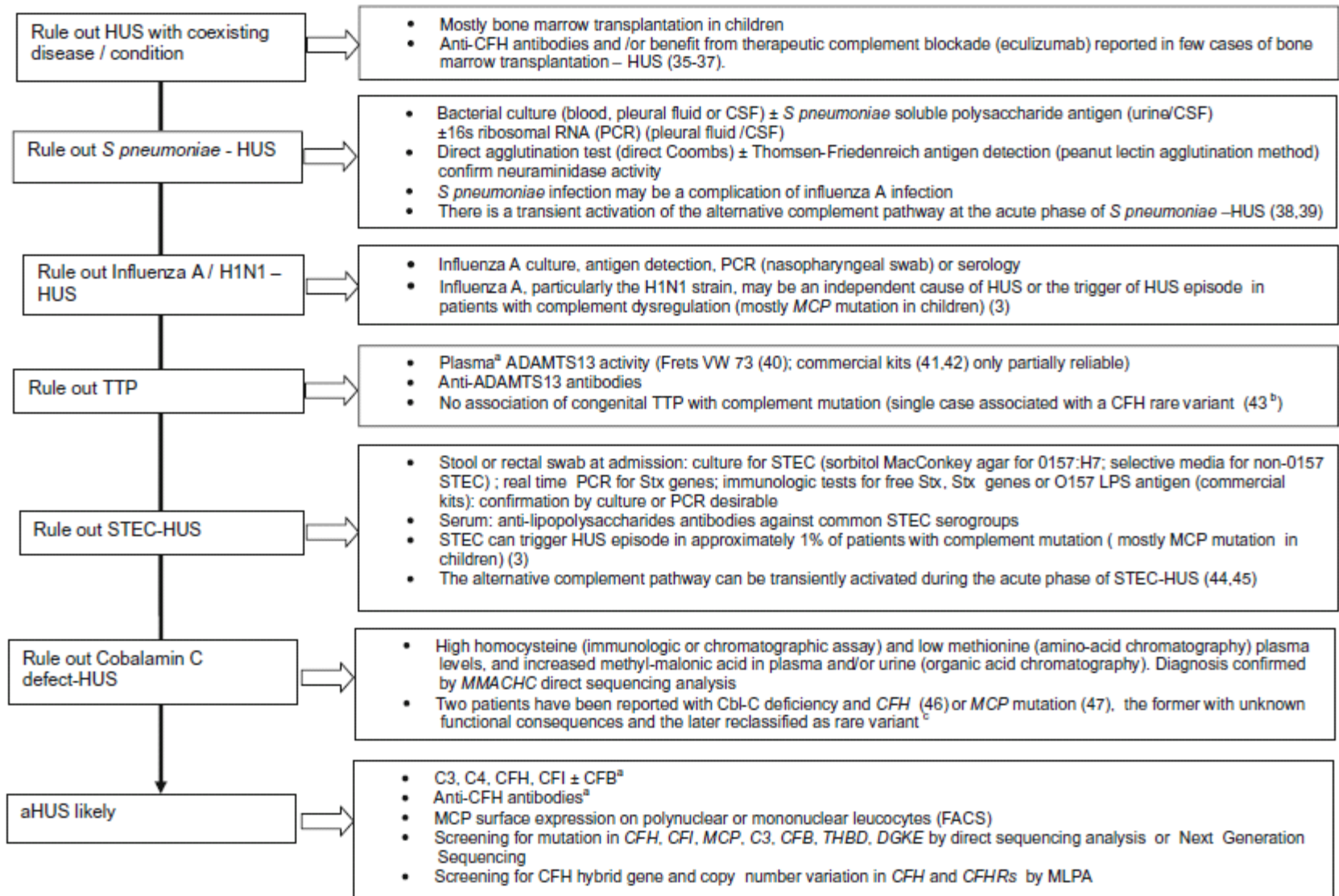
Diagnostic algorithm for aHUS



Diagnostic work up for aHUS includes:

- Screening for mutations in target genes
- MLPA for CFHR1-5
- ELISA for CFH autoantibodies

Diagnostic algorithm for aHUS



Genetic testing of aHUS patients

When

- First episode of aHUS: Start genetic screening after confirmation that there is no causative disease, no STEC infection, no severe ADAMTS 13 deficiency and no hyperhomocysteinemia /methyl-malonic aciduria.
- Start genetic screening without delay if
 - Relapse of HUS
 - Familial history of non synchronous HUS
 - Pregnancy/post-partum-HUS
 - De novo post-transplant HUS
- Genetic screening required before kidney transplantation for aHUS. Not justified before transplantation for STEC-HUS, unless this diagnosis was uncertain/unproven.

Why

- Genetic characterization necessary for
- Confirmation that the disease is complement-dependent or not
 - Establishing prognosis, risk of relapses and of progression to ESRD
 - Genetic counselling to parents and family
 - Decisions for kidney transplantation: choice of the donor, treatment schedule to prevent or treat post-transplant recurrence, decision of combined kidney-liver transplantation
 - Further prospective studies are required to establish the safety of complement blockade treatment discontinuation, according to the genetic background

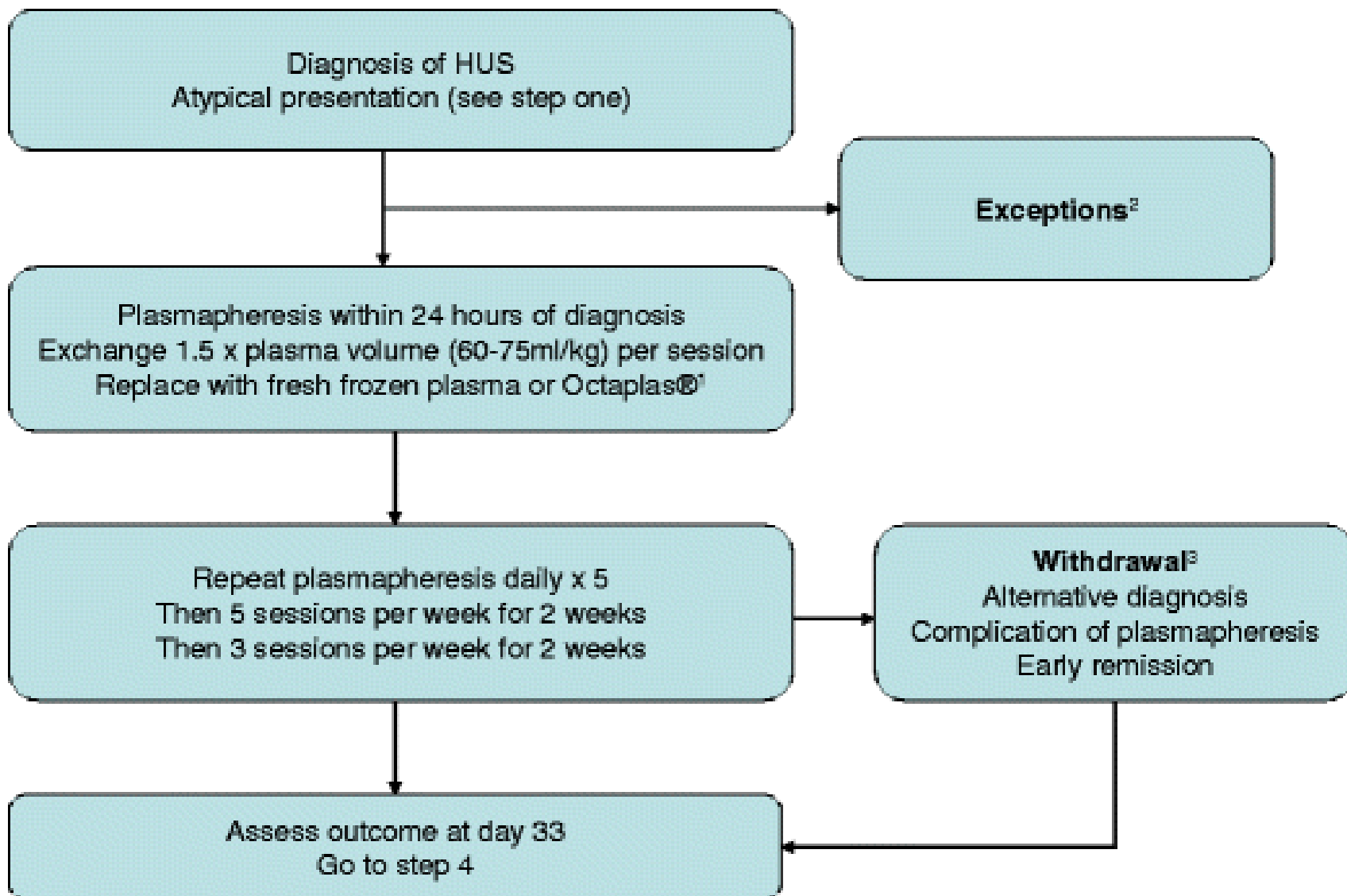
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Treatment of aHUS

Plasma therapy

- First-line treatment (2009)
- Plasma infusion:
 - Replacing deficient and/or defective complement factors
 - Dose limited because of volume challenge
- Plasma exchange:
 - Removing mutant complement factors and/or antibodies
 - Restoring functional complement regulators
 - Providing larger amounts of plasma than with infusion

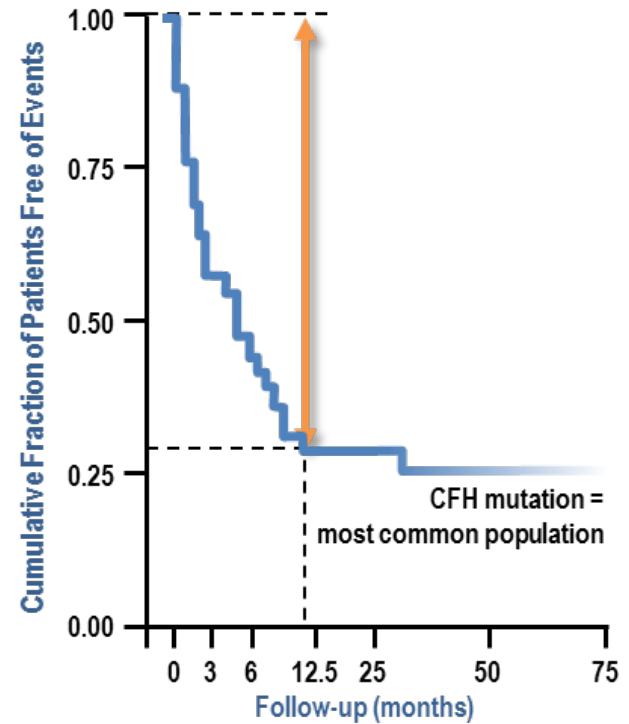


Limitations and complications

- Not all aHUS patients respond to plasma therapy.
- Patients with mutations of membrane-anchored complement regulators (e.g. MCP/CD46; THBD/CD141) may not benefit from plasma therapy.
- Possibility for multiple mutations (e.g. in MCP/CD46 mutation carriers).
(Beresin et al, J Am Soc Nephrol 2013)
- Secondary failure to plasma therapy in patient with CFH mutation.
(Nathanson et al, Pediatr Nephrol 2006)
- Plasma therapy requires central venous access or AV fistula – high complication rate especially in children.

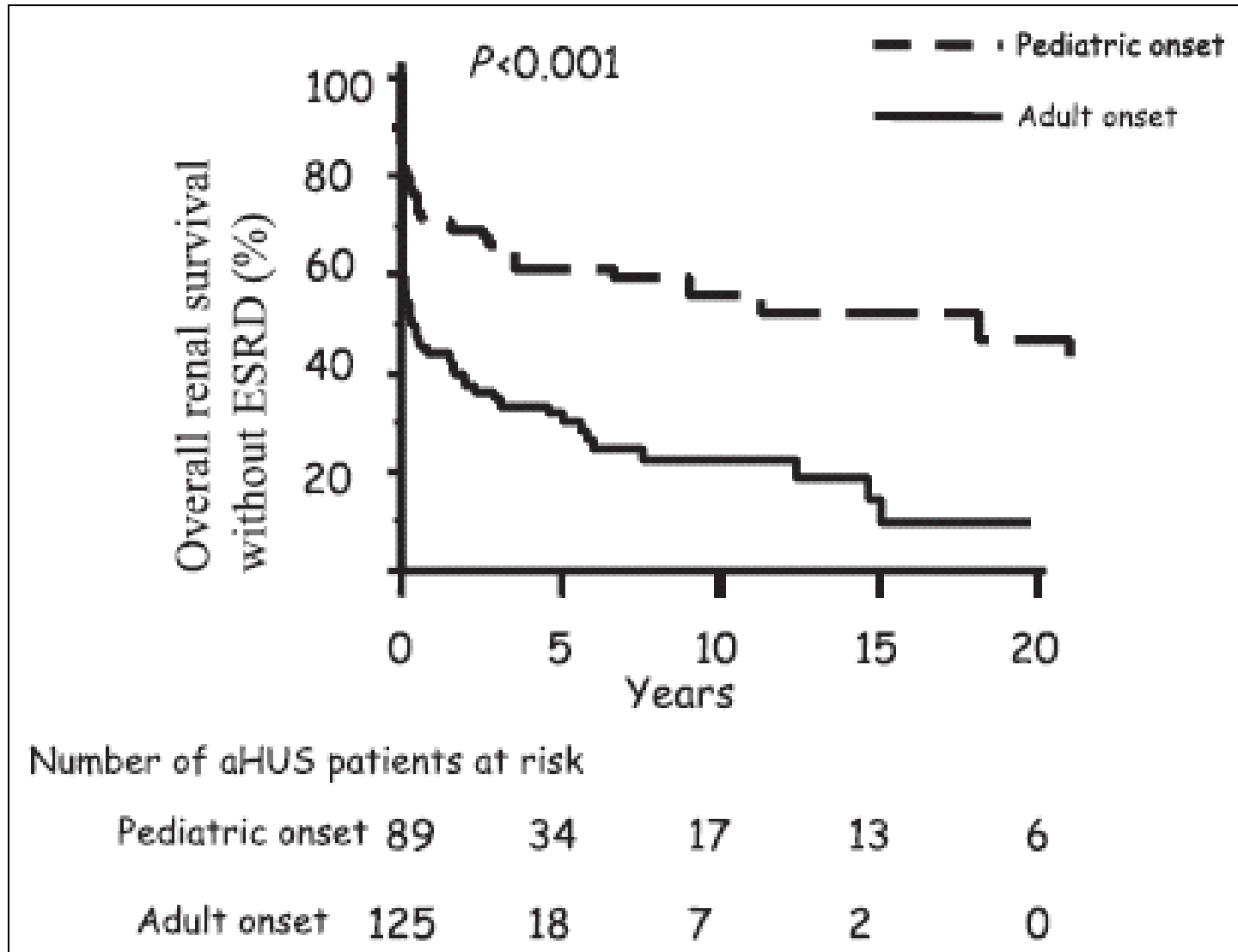
aHUS outcome

- Sudden death and vital organ damage.^{1,2}
- 33-40% of patients die or progress to ESRD with the 1st clinical manifestation.^{1,3}
- Chronic progressive course with premature mortality.^{1,3,4}
- 65% of all patients die, require dialysis or have permanent renal damage within the 1st year after *diagnosis despite plasma exchange or plasma infusion.*¹



No. at Risk 40 27 20 12 7 5 3
Modified from Caprioli et al. *Blood*. 2006;108(4):1267-1272.

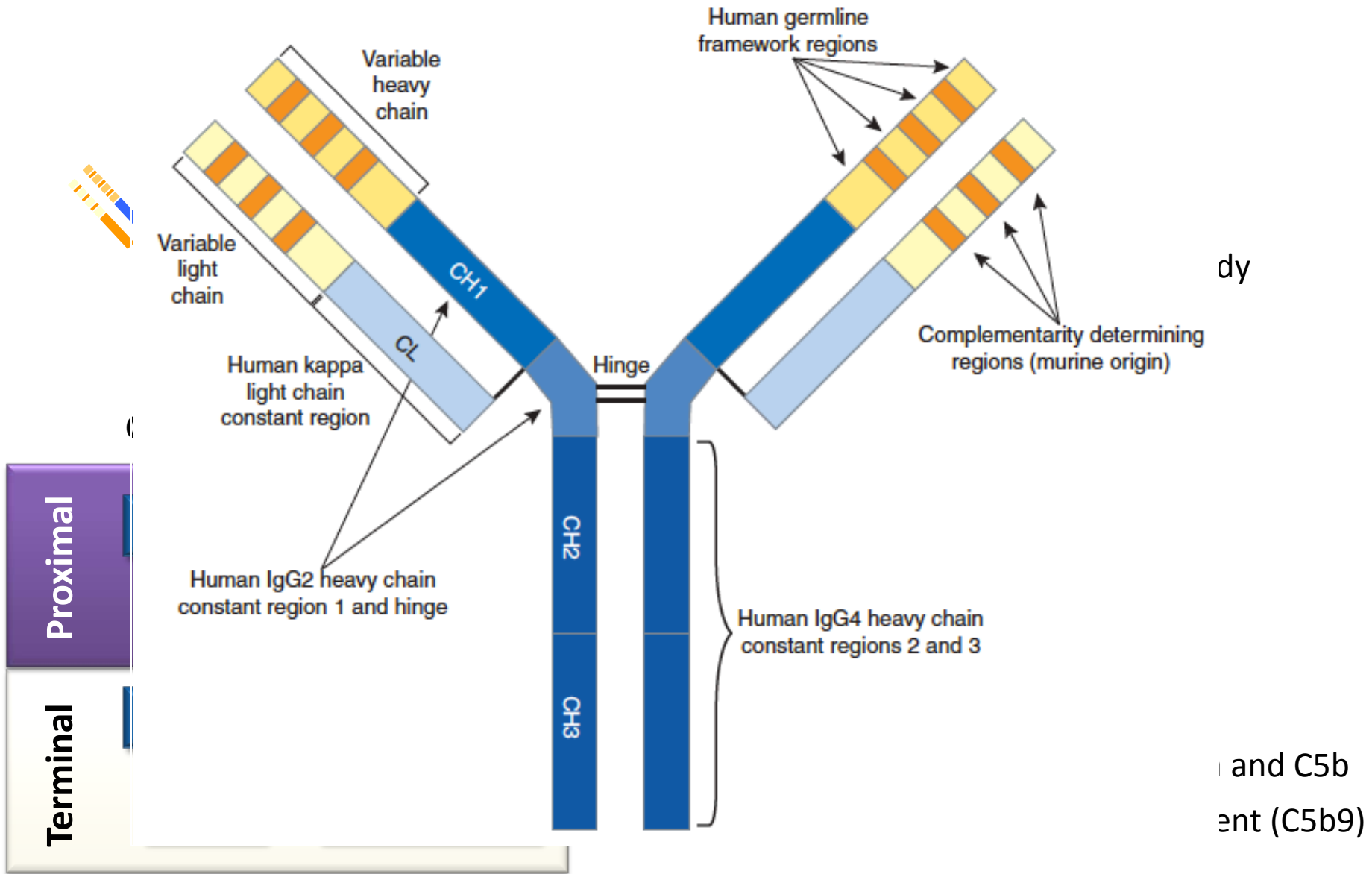
aHUS outcome



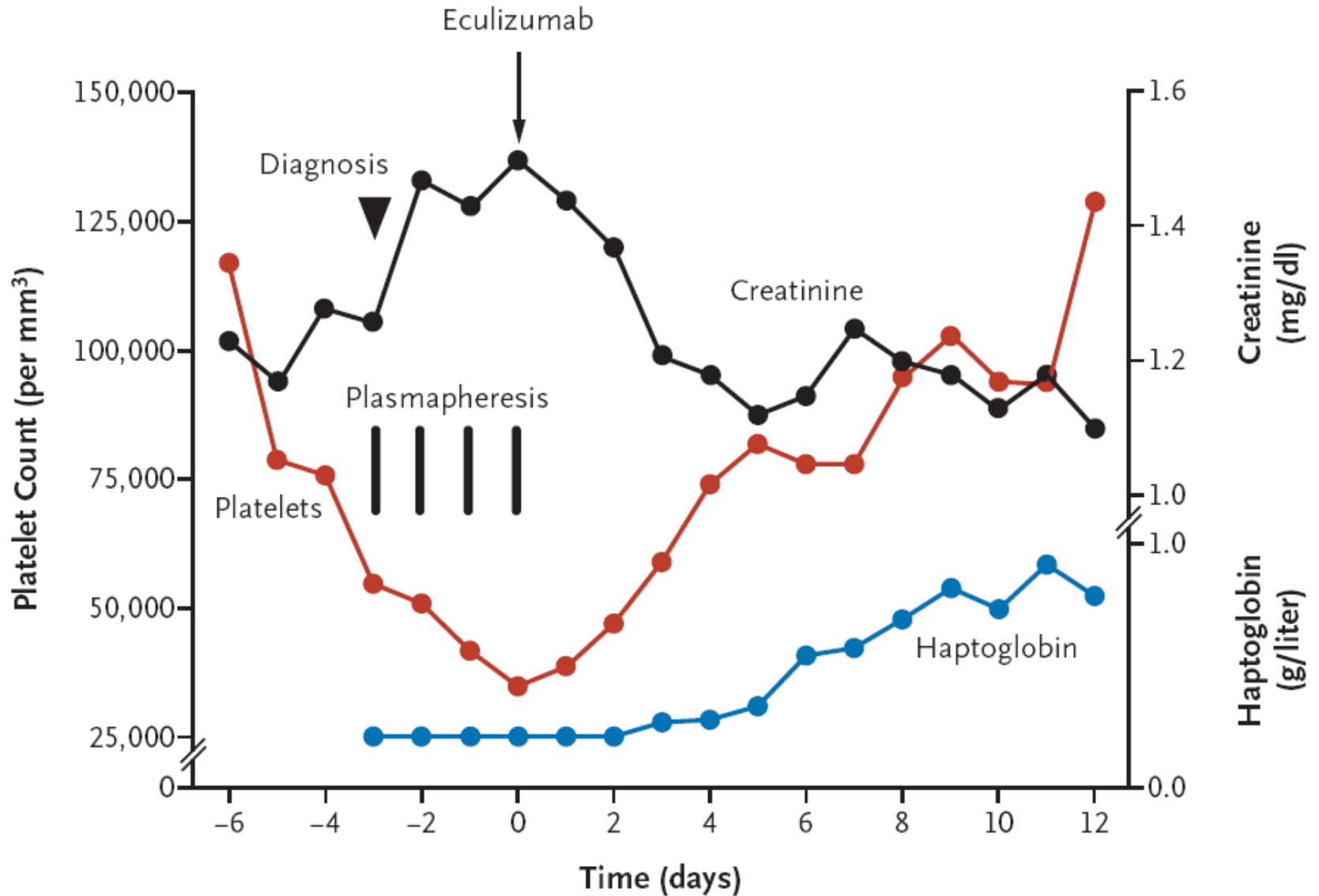
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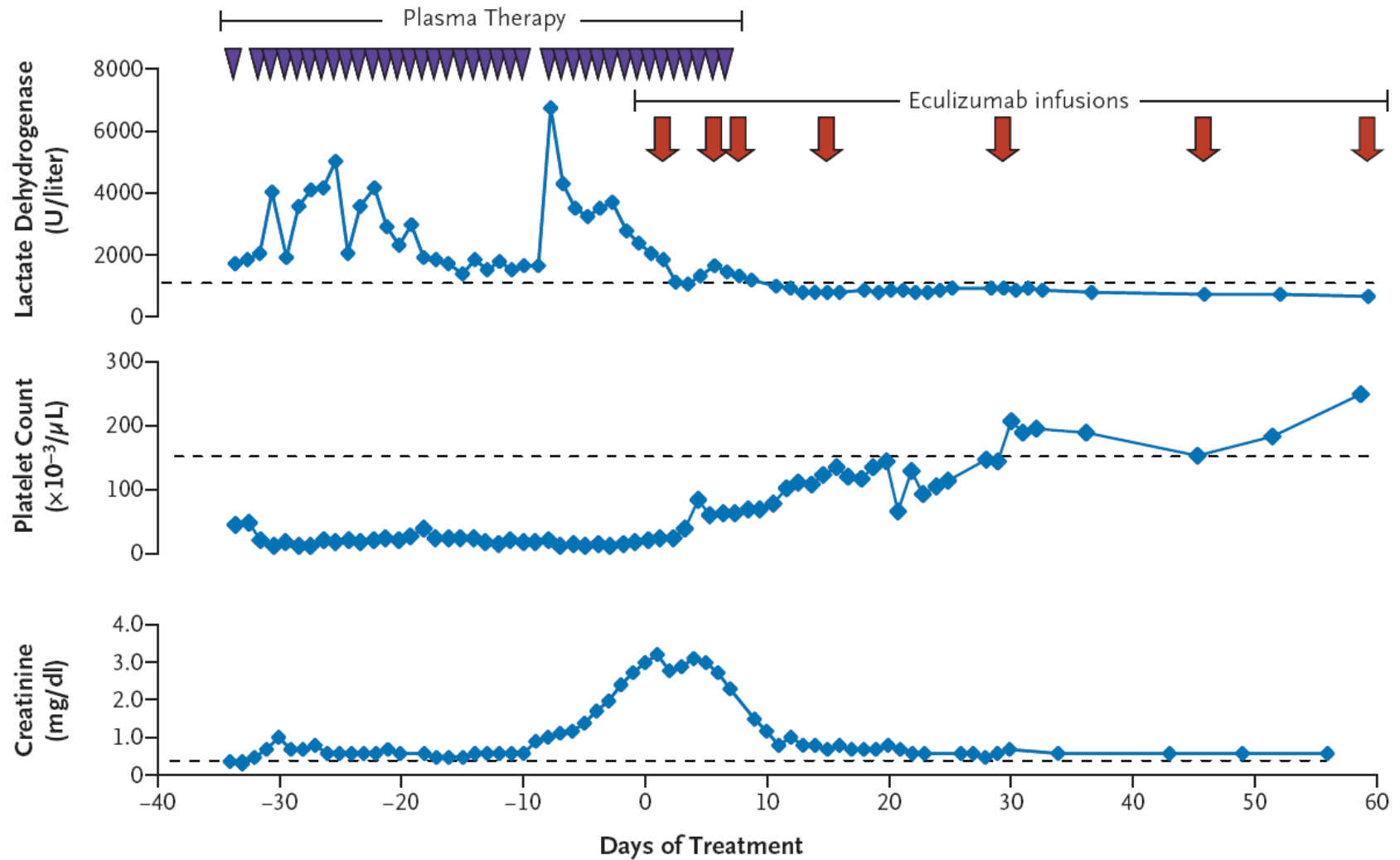
aHIS treatment



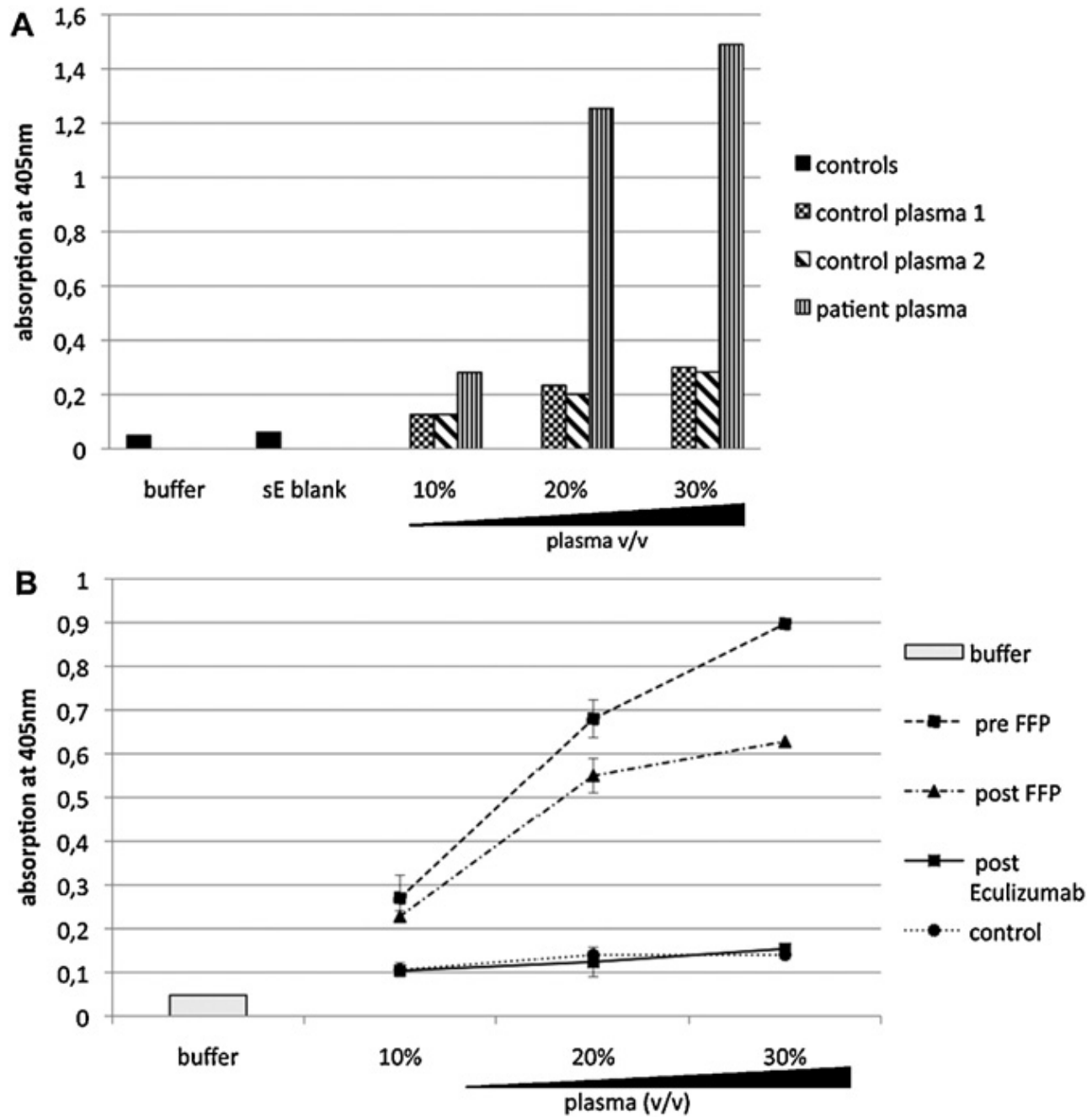
First successful use of eculizumab in aHUS



First successful use of eculizumab in aHUS



Eculizumab is superior to plasma therapy in controlling complement



Meningococcal infection prophylaxis

Meningococcal vaccination

Meningococcal vaccination is mandatory, before eculizumab initiation or as soon as possible if urgent eculizumab therapy is indicated
Quadrivalent conjugate vaccines (anti-A, C, Y, W) (Menactra™ (USA) (age > 9 months), Menveo® (age ≥ 2 years) or Nimenrix® (age ≥ 1 year))
Recent studies showed that Menveo® was well tolerated and highly immunogenic in healthy infants aged 2 to 12 months (103,104)^a
+ **Anti-B vaccine** (Bexsero® (age ≥ 2 months), where available

Efficacy of anti-meningococcal (vaccine) antibodies is uncertain in patients with complement deficiency, complement blockade or immunosuppressive therapy. We therefore recommend additional antibiotic prophylaxis, allowing prompt initiation of eculizumab.
Patients with ESRD due to aHUS should be vaccinated prior to registration on the waiting list (105,106). Also consider vaccination of household close contacts (at least siblings and parents)^b.

Antibioprophylaxis

Which antibiotics?

Methylpenicillin (twice daily, full dose adapted to weight). Despite the reduced sensitivity of approximately 20% of meningococci towards penicillin, methylpenicillin retains its overall efficacy to prevent meningococcal infection.

Macrolides in case of allergy to penicillin (however macrolides interfere with calcineurin inhibitors metabolism in transplanted patients)

Avoid rifampicine or fluoroquinolone for long term prophylaxis, to limit the risk of inducing bacterial resistance (except in case of contact with a patient with invasive meningococcal infection)

Other antibiotics may be recommended by local experts

Which duration?

Obligatory during 2 weeks after vaccination in patients receiving eculizumab

Obligatory in some countries (France, UK) as long as the patient receives eculizumab (+ 60 days after eculizumab discontinuation)

Discrepant current practice in other countries

Continuous antibioprophylaxis is recommended by the majority of authors of this review

Education information card

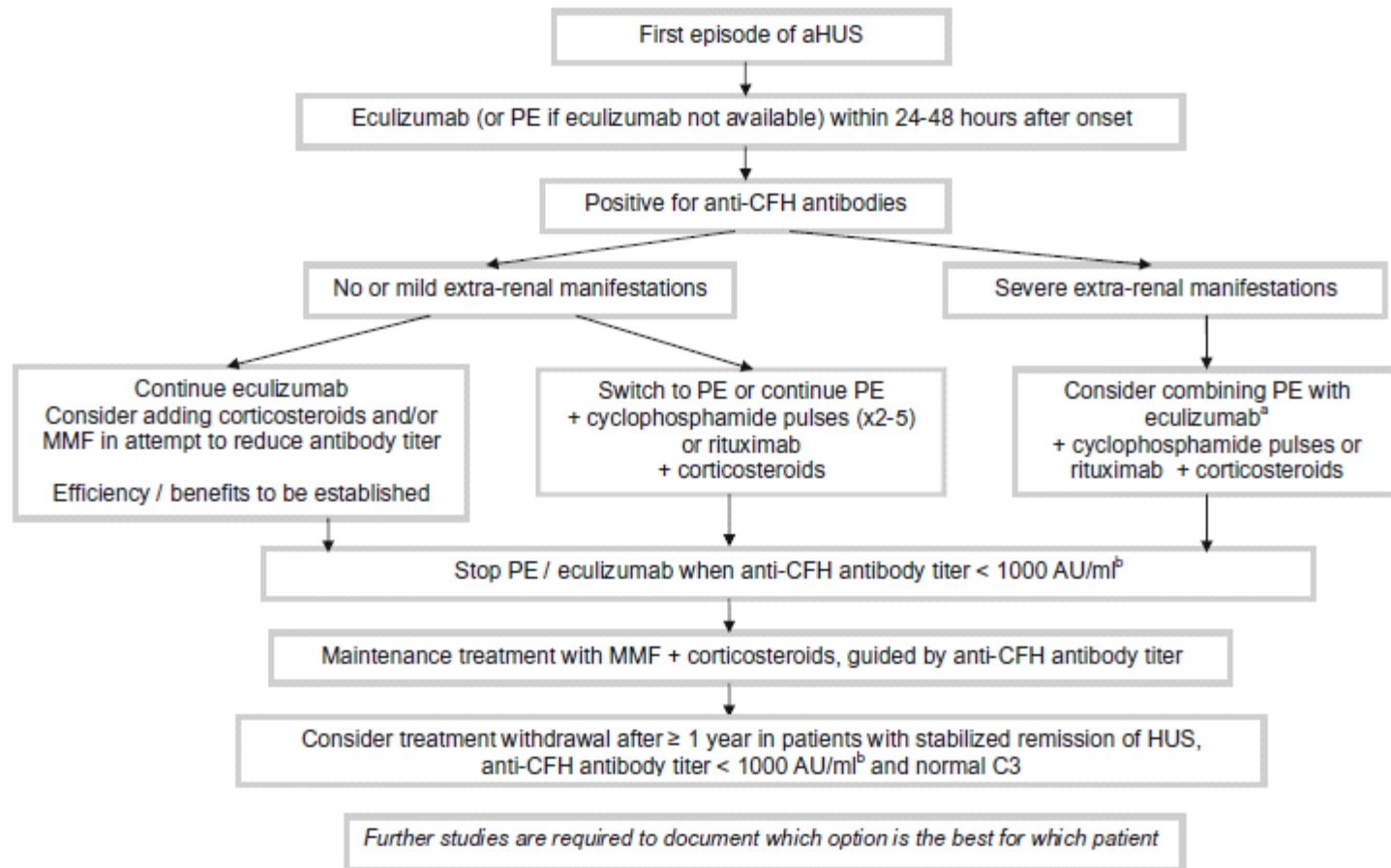
Education on signs of meningococcal infection to ensure early recognition and treatment

Consider prescription of ceftriaxone for immediate access at home in remote areas

Travel/holidays should be carefully prepared (information on meningococcal epidemiology in the visited country, prior written contact with local teams, information to the patient of where to go, which doctor/department/phone numbers...)

Information card to be carried by the patient or his/her care giver, to be shown to medical staff in case of symptoms suggesting infection

Treatment of patients with antibody-mediated aHUS



Treatment duration in aHUS

Risk of relapse

- In the pre-complement blockade period, the risk of relapse after the first year in patients alive without ESRD at 1 year follow-up, was 20-30% in patients with CFH/CFI mutations or no complement mutation identified, while it was 92% in children with MCP mutation. Despite a relapsing course, children with MCP mutation retained a relatively favourable prognosis (17% ESRD at 5 years follow-up) (3)
- Nobody knows what will be the relapse rate after complement blockade discontinuation in patients who survived and have preserved renal function under complement blockade
- Strict monitoring (twice weekly urine dipstix) for early detection of relapse and immediate re-initiation of complement-blockade treatment in case of relapse can limit the risk of poor outcome and renal sequel (142)

Risk of vascular complications

- The frequency of cardio/cerebro vascular complications and of arterial stenosis in aHUS patients compared to patients with CKD due to other causes is not documented. Therefore this problem currently is not demonstrated as a reason for life-long complement blockade

Risk of meningococcal infection under complement blockade therapy

- Neither vaccination nor antibioprophyllaxis guarantee protection against meningococcal infection in patients receiving terminal complement blockade therapy

Complement blockade treatment burden and cost

- Long term IV infusions may lead to vascular access obstacles
- Twice monthly IV treatment—particularly if performed in hospital- may be unacceptable as a life-long social commitment
- Access to eculizumab both logistically and financially may be limited in some settings

Management of aHUS patients with kidney transplants

