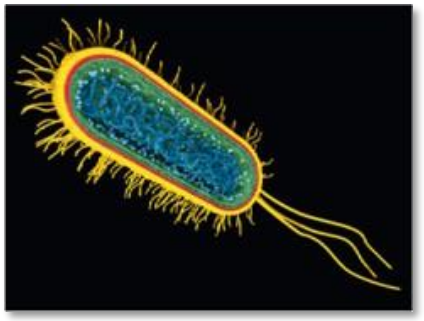
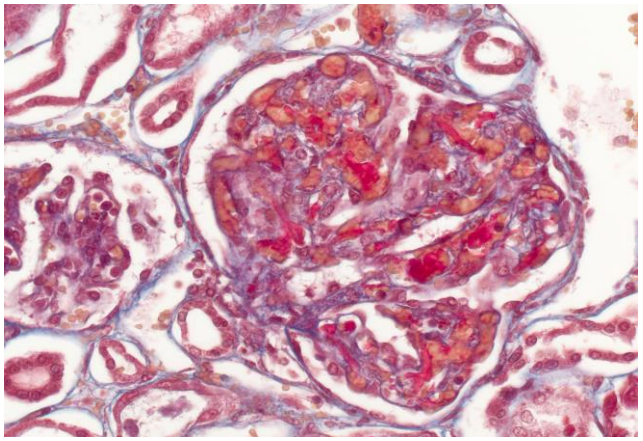
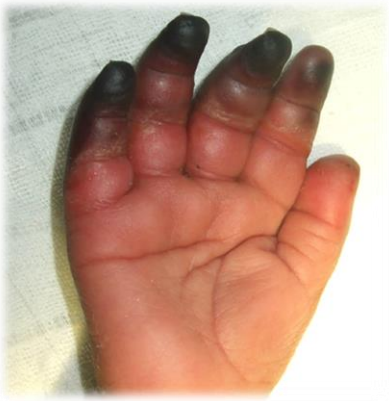
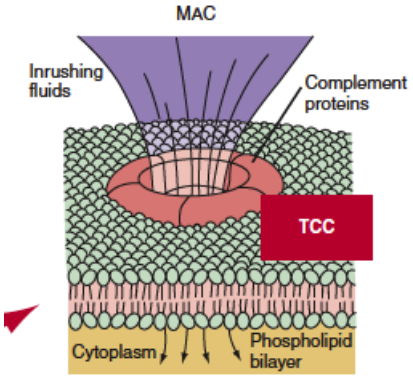


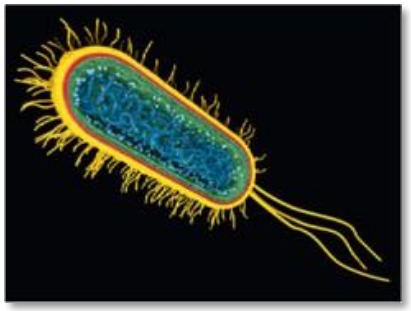


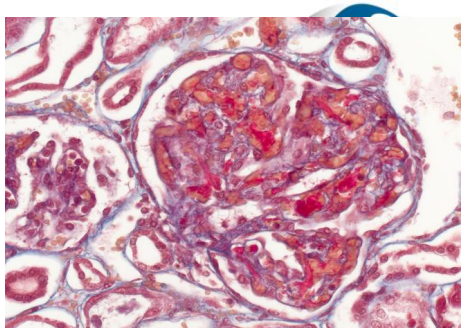
Hemolytic Uremic Syndrome

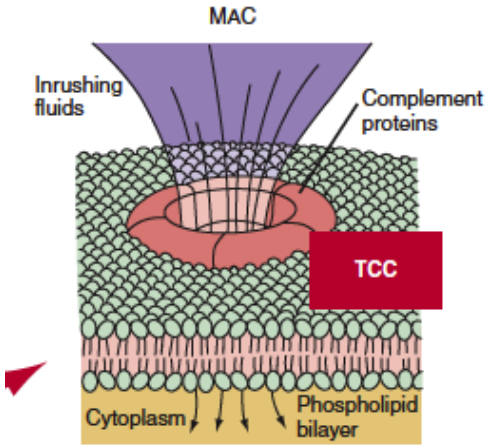
Diagnosis and Treatment







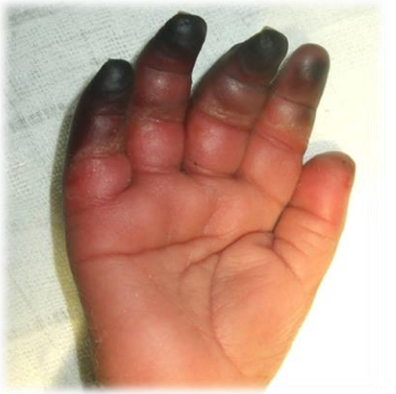




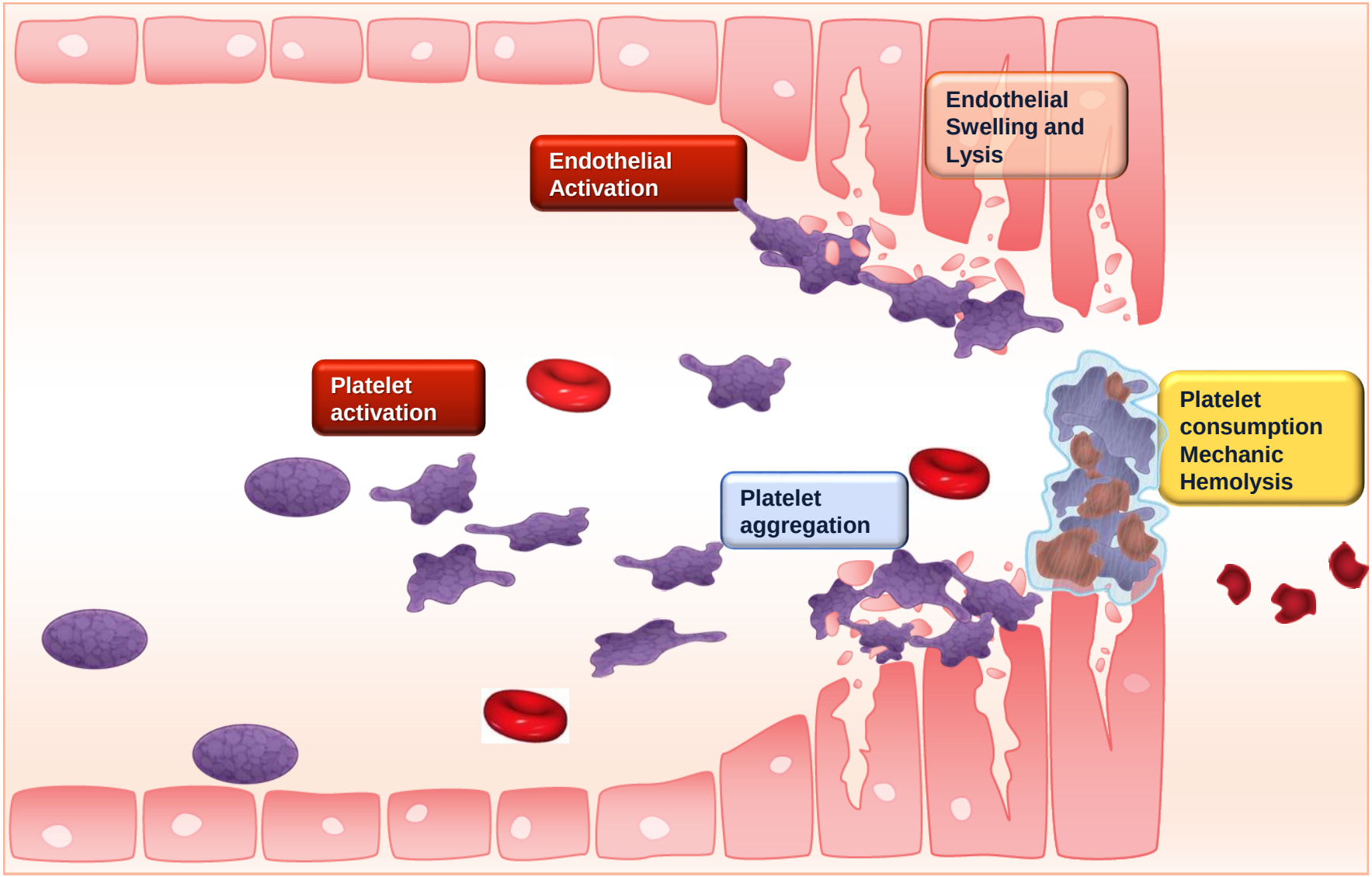
Síndrome Hemolítico Urémico
Diagnóstico y Manejo

Franz Schaefer

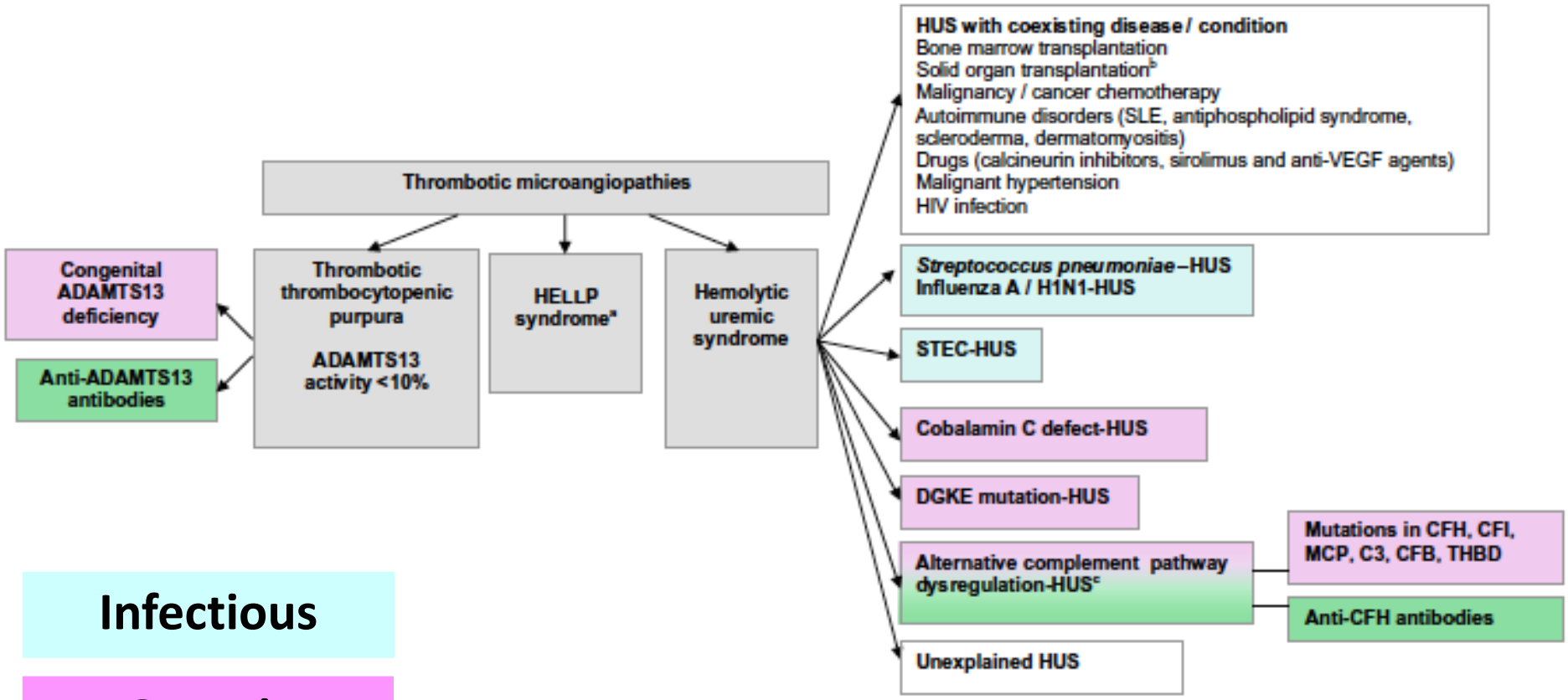
Division of Pediatric Nephrology
Center for Pediatric and Adolescent Medicine
Heidelberg, Germany



HUS: Thrombotic Microangiopathy



Spectrum of Etiologies in TMA/HUS



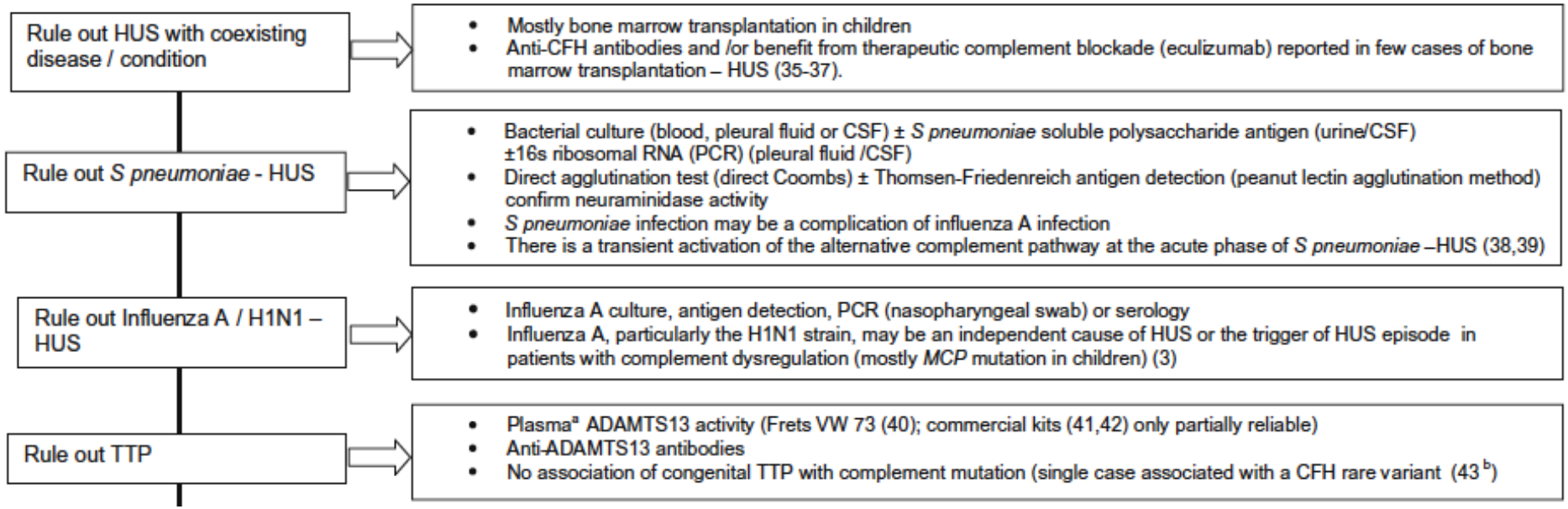
Infectious

Genetic

Autoimmune

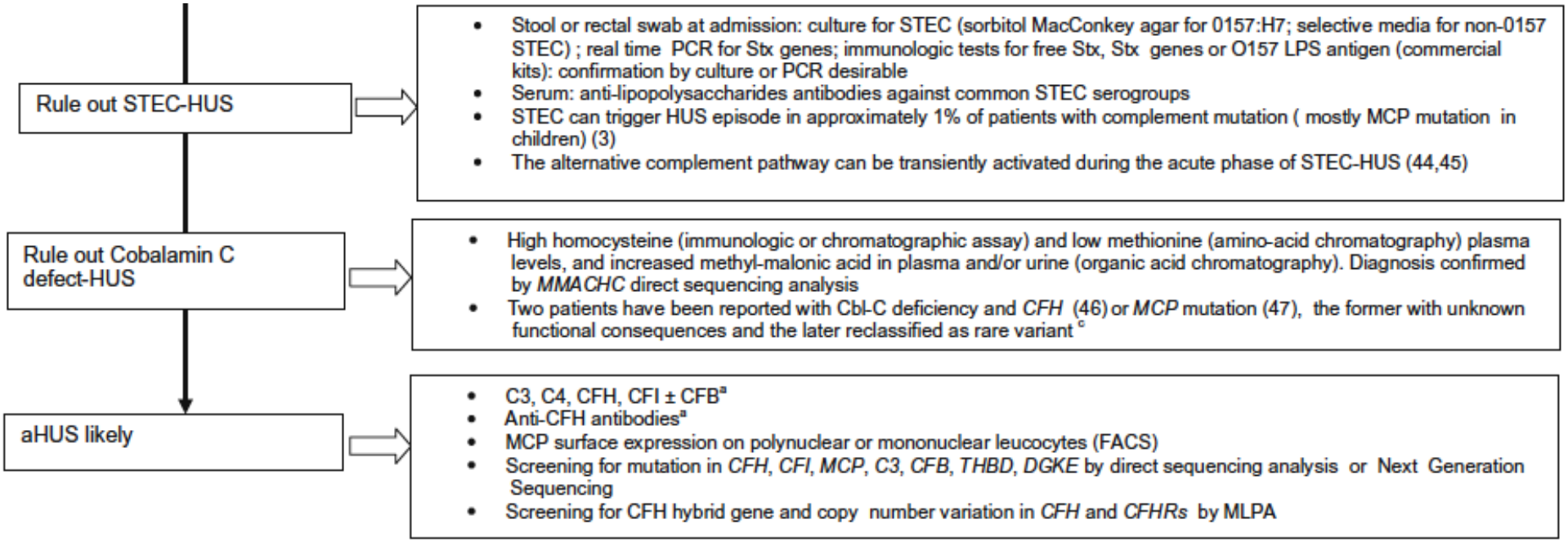
Loirat et al. Pediatr Nephrol 2015

Diagnostic Workup of HUS



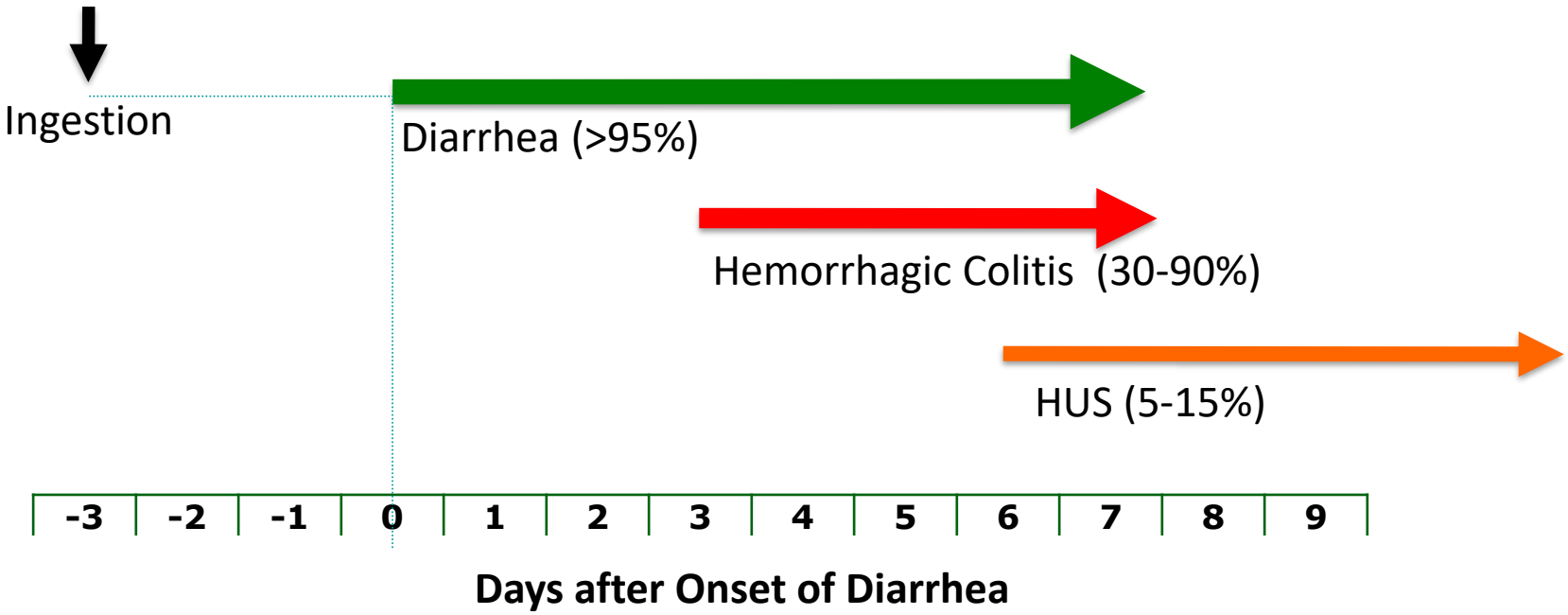
Loirat et al. Pediatr Nephrol 2015

Diagnostic Workup of HUS



Loirat et al. Pediatr Nephrol 2015

STEC Disease Course



Wong et al. Clin Infect Dis 2012; 55:33

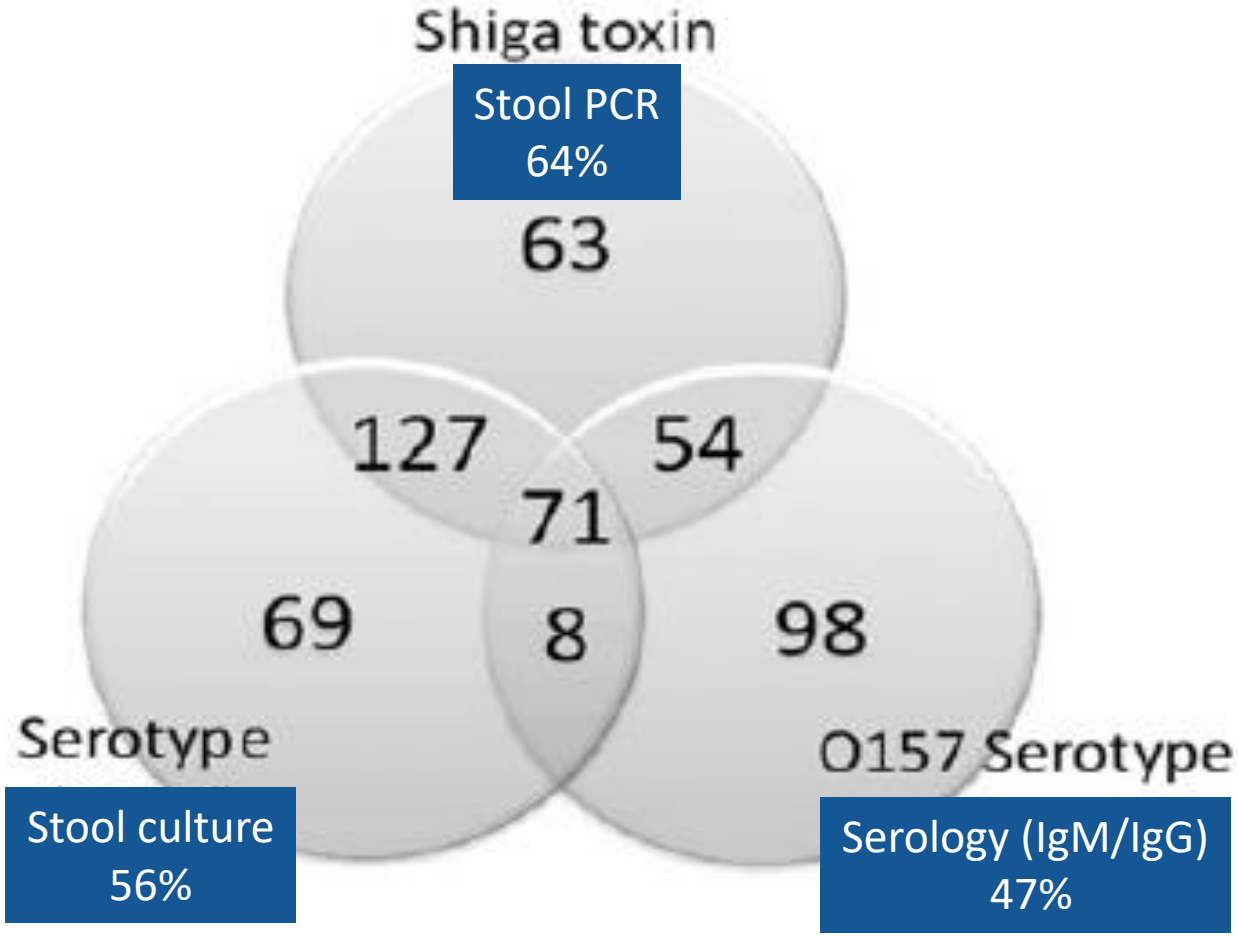
Prospective study in 259 children with STEC O157:H7

Bloody diarrhea:	90%
HUS:	14%
Oligoanuric HUS/Dialysis:	4%

Age	*n*	*% HUS*
0-1	64	12
2-3	**73**	**22**
4-6	49	14
7-10	73	7

Diagnostic Assessment of STEC-HUS

German-Austrian Registry (n=490)



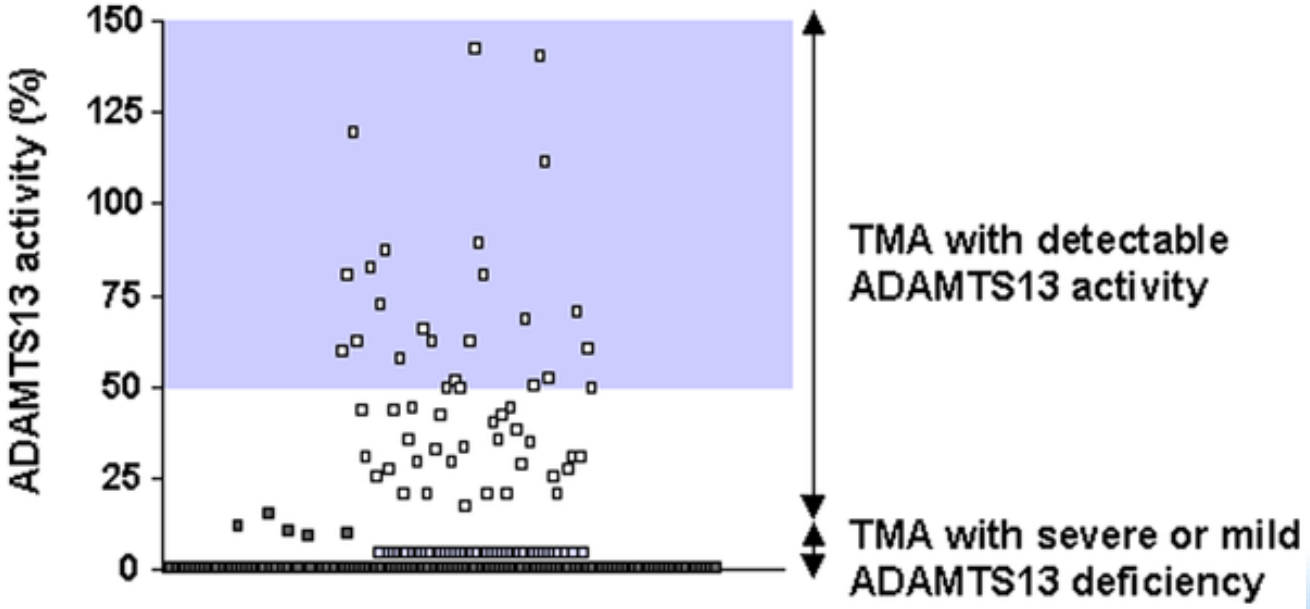
Rosales A, et al. Clin Infect Dis 2012;54:1413-21

ADAMTS13 vWF Cleavage Protease Deficiency

Adults: Autoantibodies against ADAMTS13

Children: Autosomal recessive mutations in ADAMTS13 gene

Diagnosis: ADAMTS13 activity > 5 % of normal



Coppo P, et al. PLoS ONE 2010;5:e10208

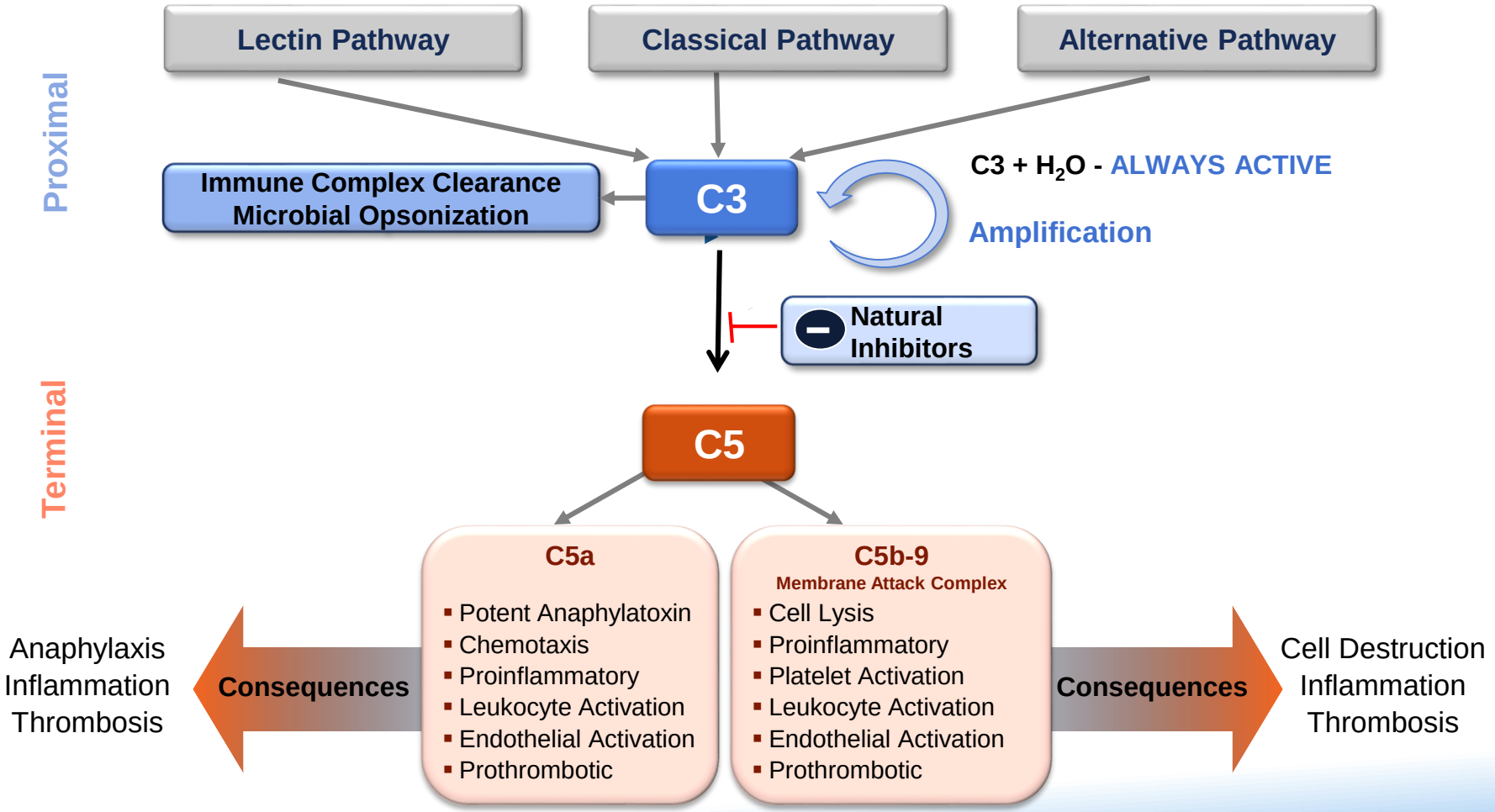
Platelet count >30,000 mm^3 or serum creatinine >150–200 µmol/L almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)

Patient characteristics	ADAMTS13 deficiency group (n=160)	ADAMTS13 detectable group (n=54)	P value
Platelet count, $\times 10^9$/L	17.4 (14.2)	66.6 (49.3)	<0.0001
Serum creatinine, µmol/L	114 (68.4)	454 (326)	<0.0001
mg/dL	1.29 (0.77)	5.13 (3.68)	

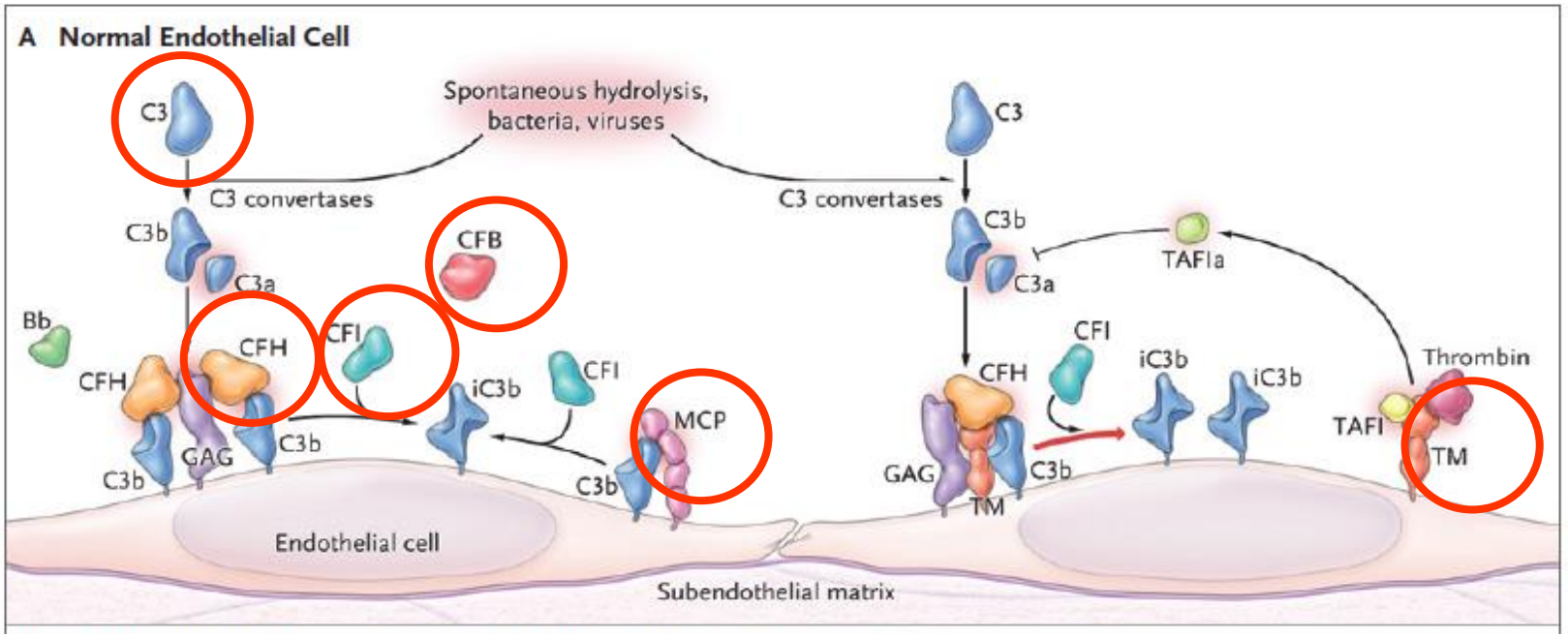
Patient characteristics	Adjusted odds ratio	95% CI	P value
Platelet count ≤30×10^9/L	23.4	3.4–24.2	<0.001
Serum creatinine ≤200 µmol/L (2.26 mg/dL)	9.1	8.8–62.5	<0.001

Table adapted from Coppo P, et al. PLoS ONE 2010;5:e10208
Zuber J, et al. Nat Rev Nephrol 2012;8:643-57

Loss of Endogenous Inhibitors Leads to Uncontrolled Complement Activation



Complement Dysregulation in aHUS



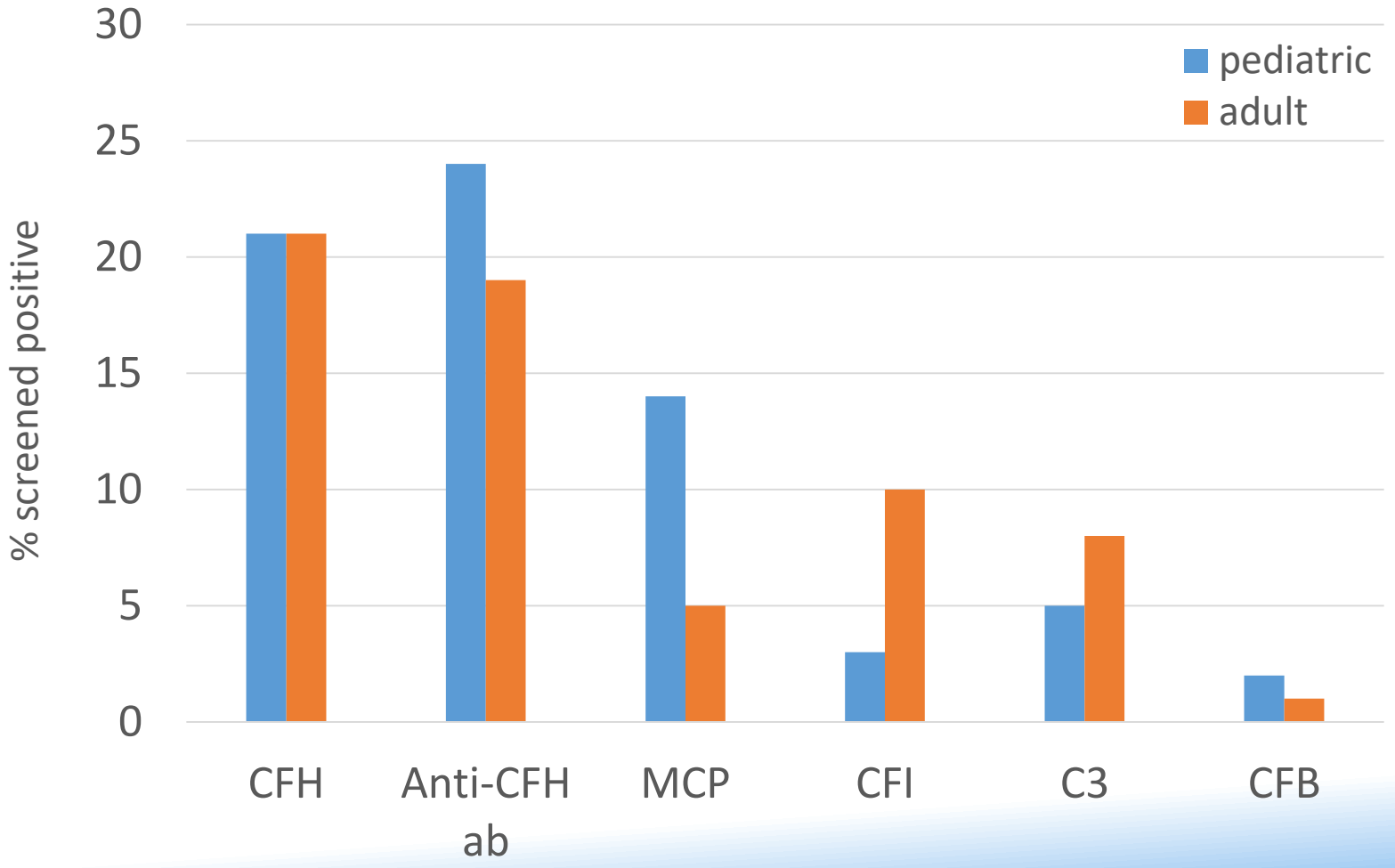
Noris and Remuzzi, New Engl J Med 2009; 361:1676-87

50-60 % explained by mutations in CFH, CFI, MCP, C3, CFB, TMBD

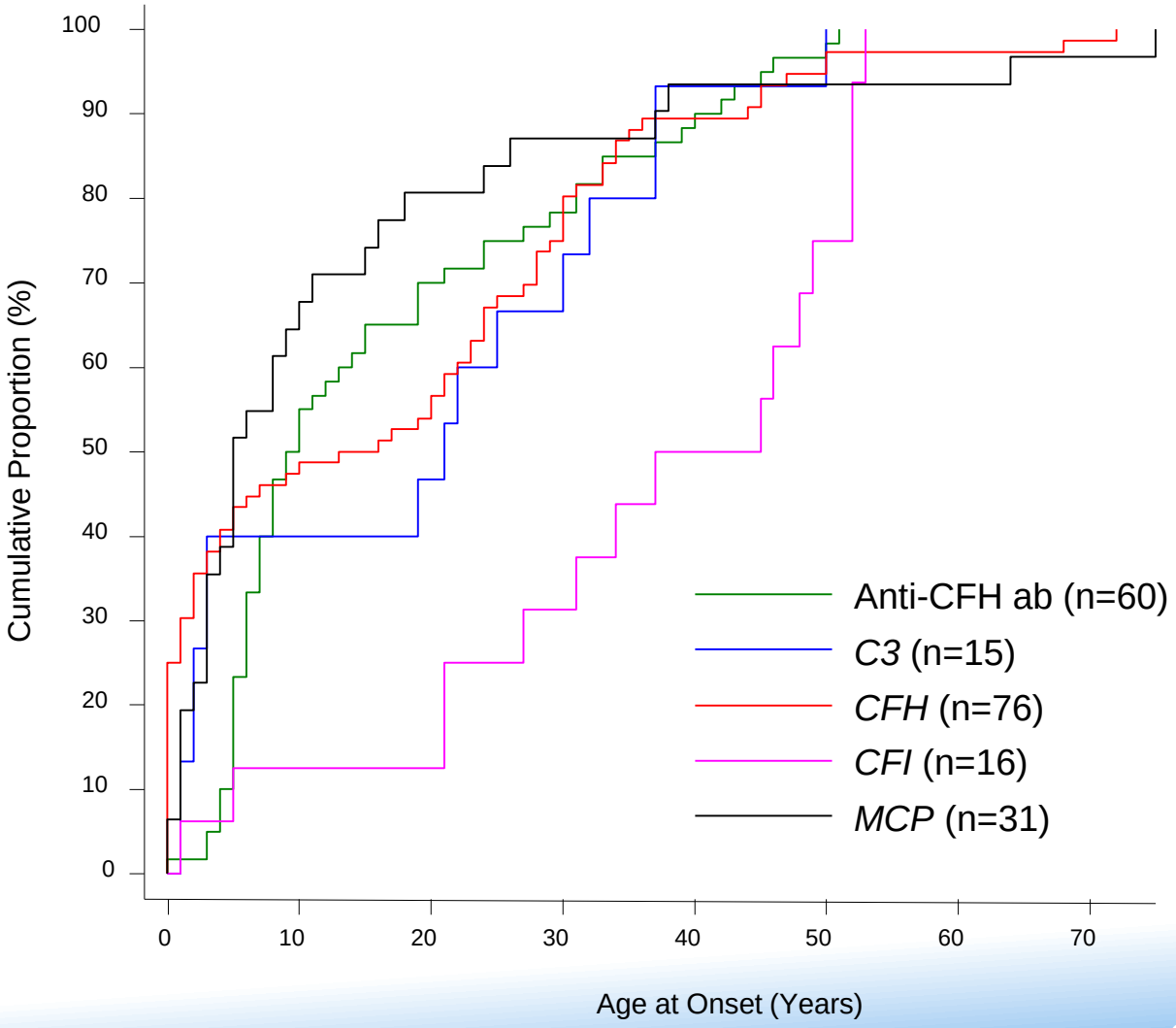
-> autosomal dominant transmission with incomplete penetrance

15-25% explained by factor H autoantibodies

Most Common Causes of aHUS



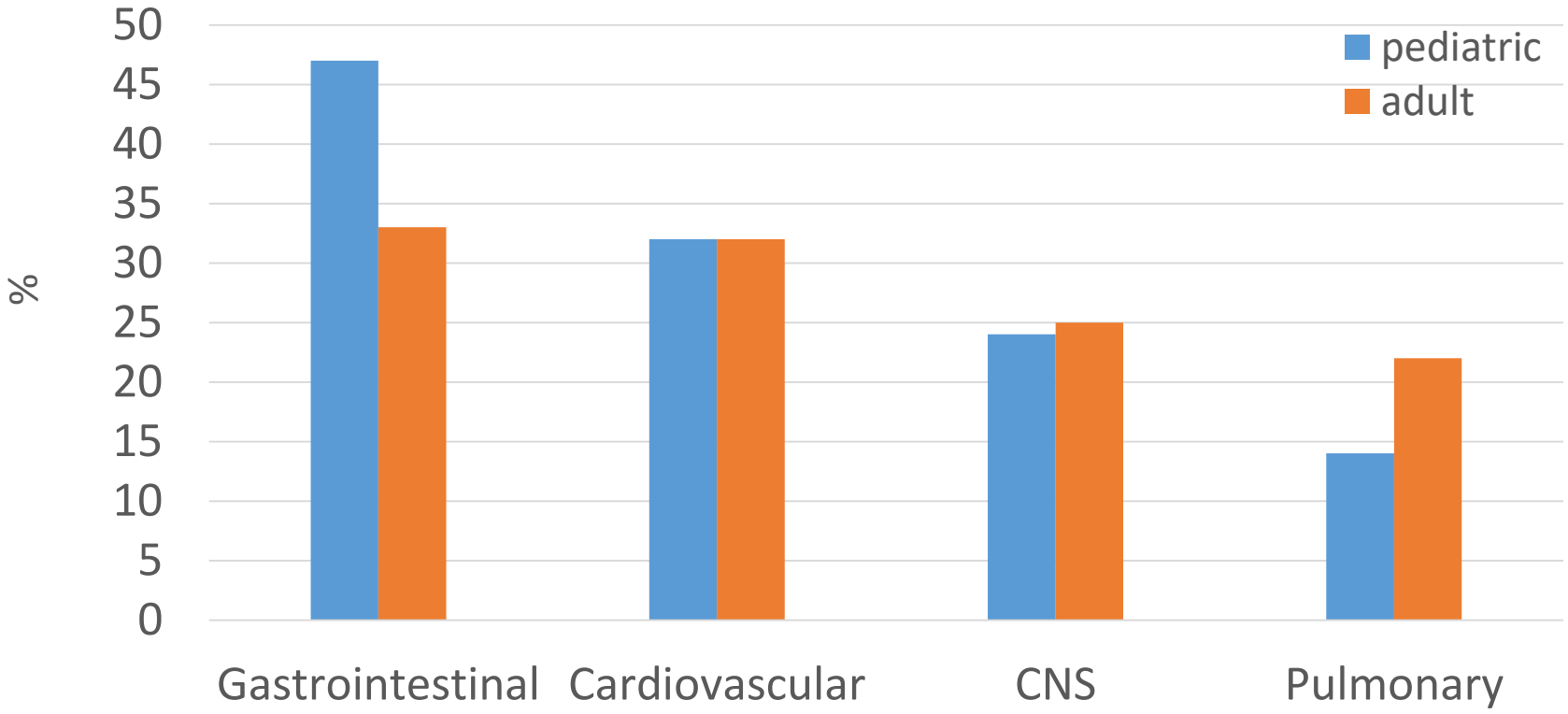
Age at Onset by Complement Disorder



Mutation	Median Age at Onset (Years)
MCP	7.2
C3	7.7
Anti-CFH abs	8.4
CFH	18.5
CFI	34.3

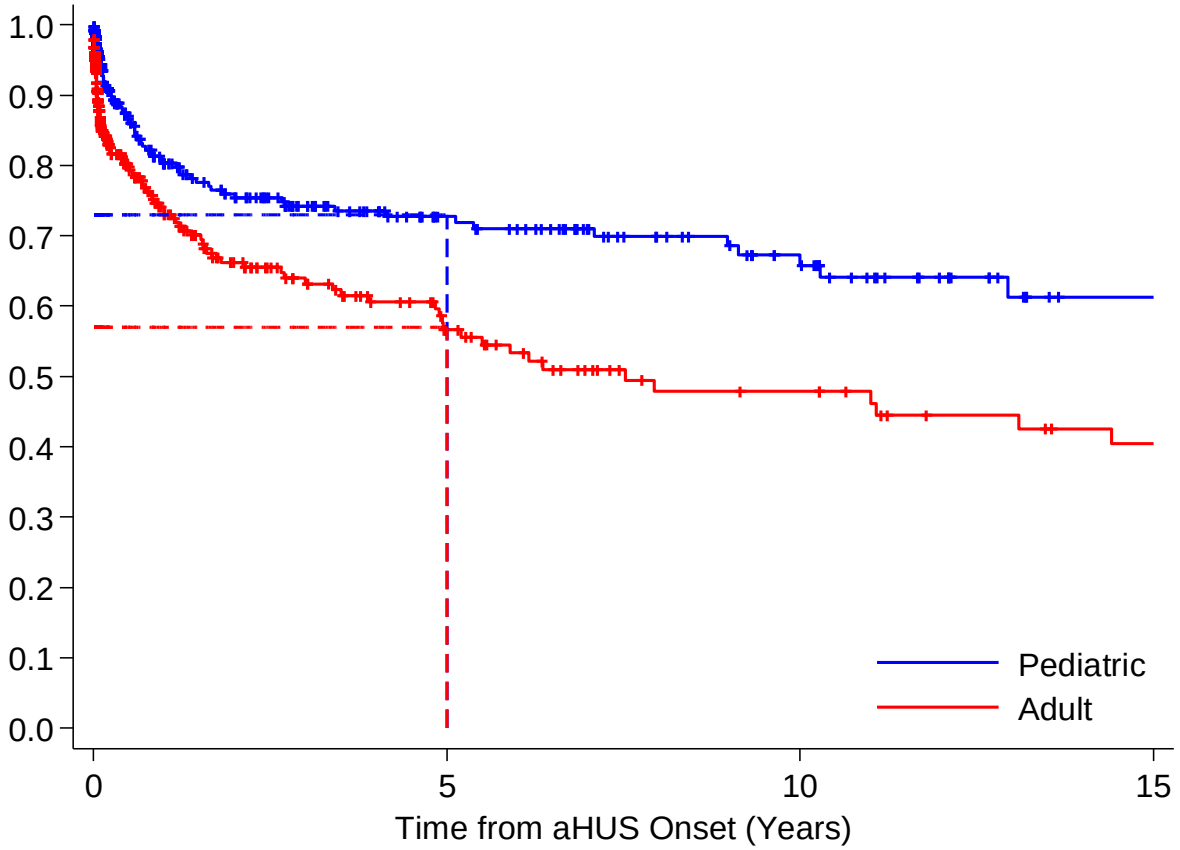
Schaefer et al. Kidney Int 2018

Extrarenal Manifestations of aHUS



Schaefer et al. Kidney Int 2018

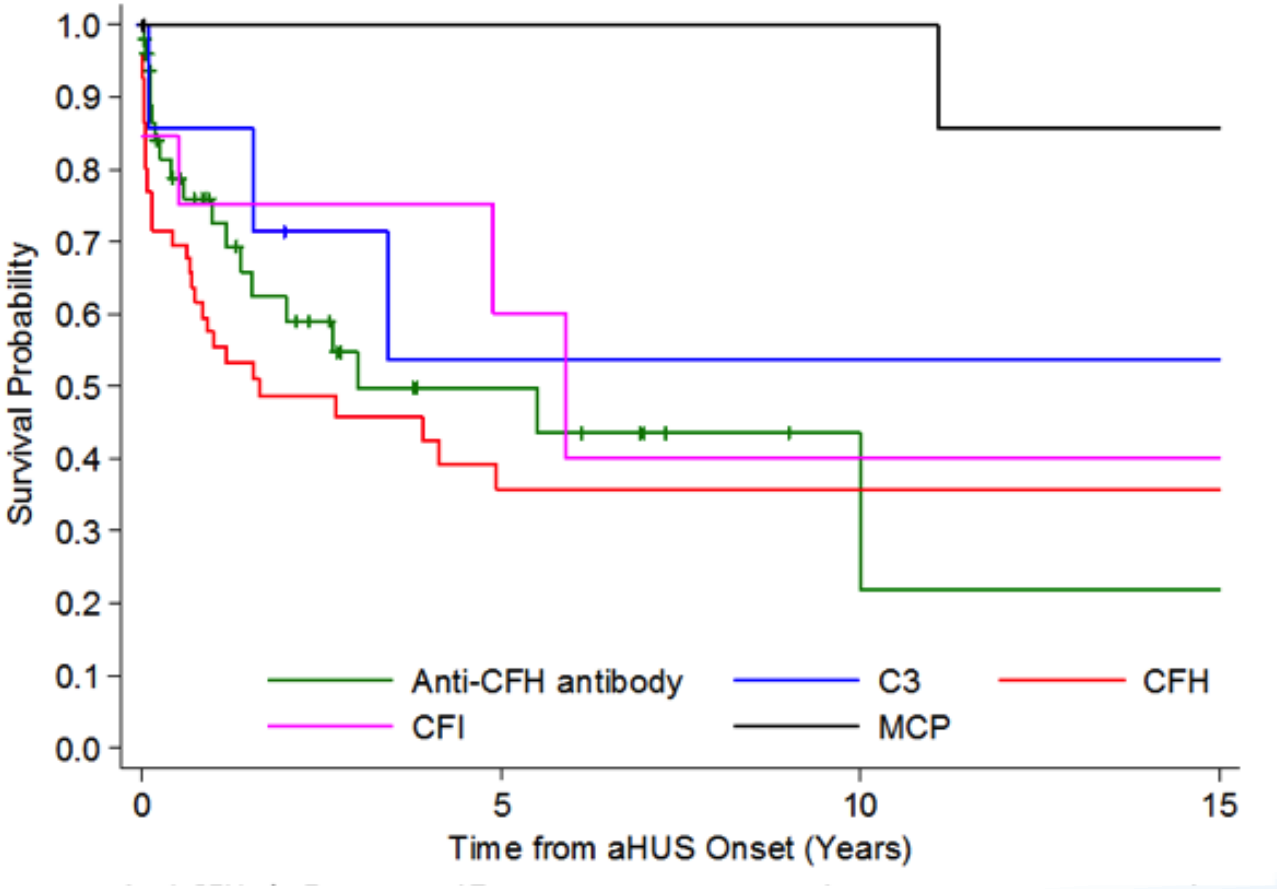
Better Renal Outcome in Pediatric Onset aHUS



aHUS registry

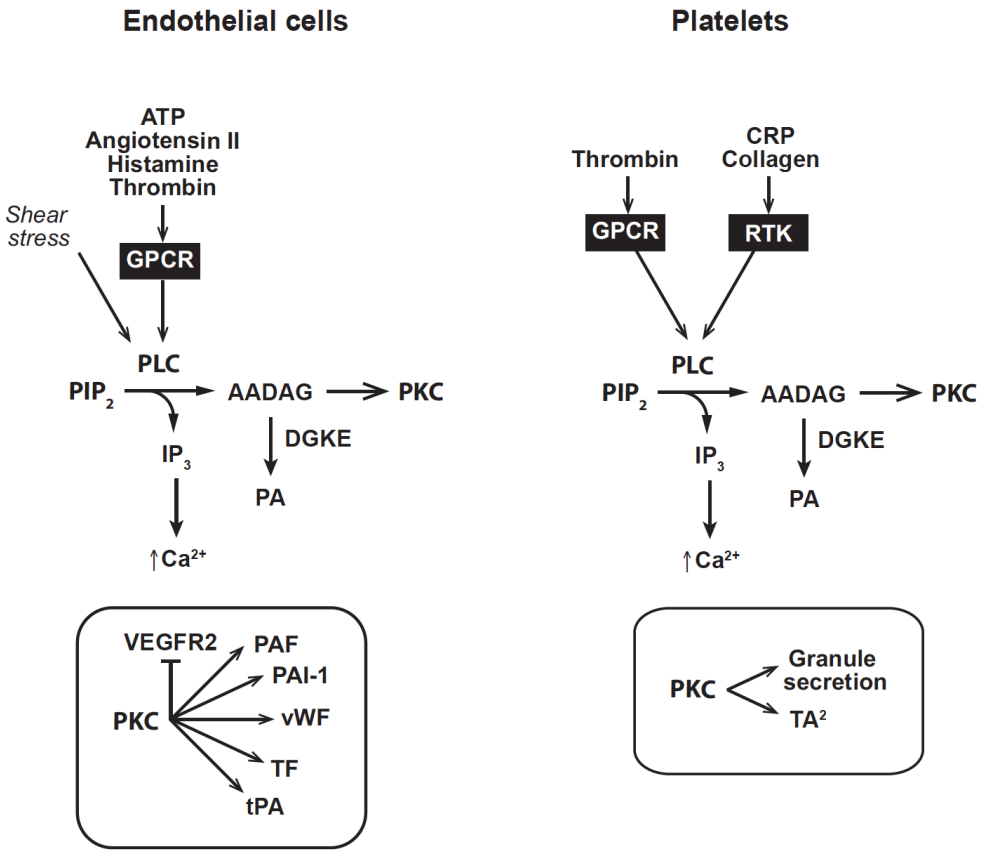
Schaefer et al. Kidney Int 2018

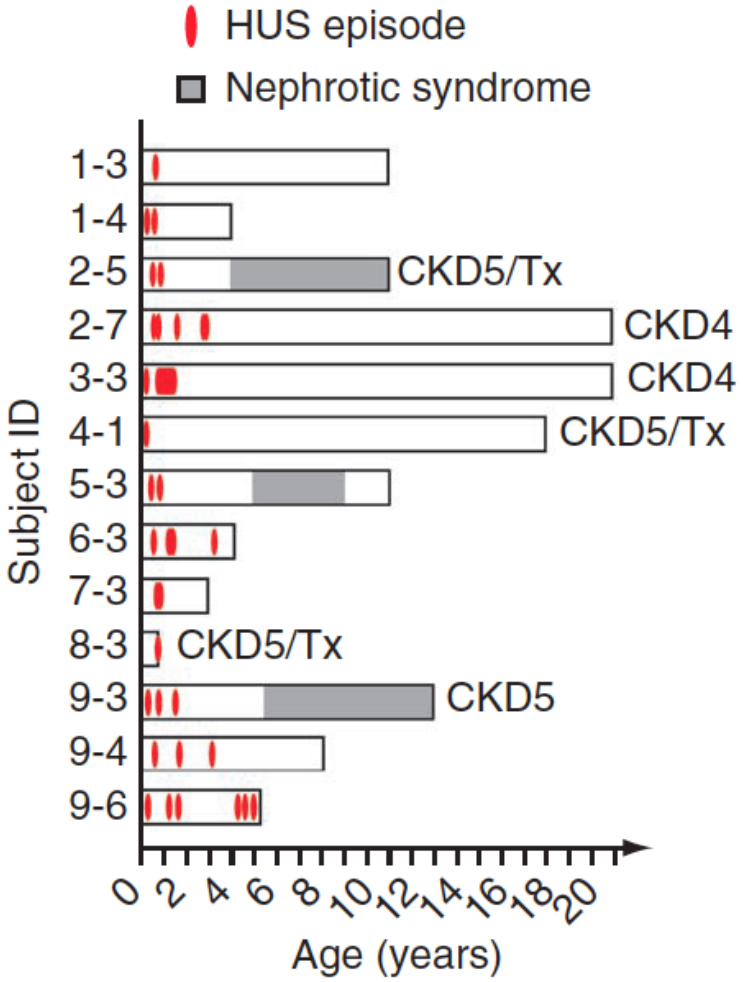
Renal Survival by Causative Anomaly



Schaefer et al. Kidney Int 2018

DGKE Nephropathy: Complement-Unrelated Form of aHUS

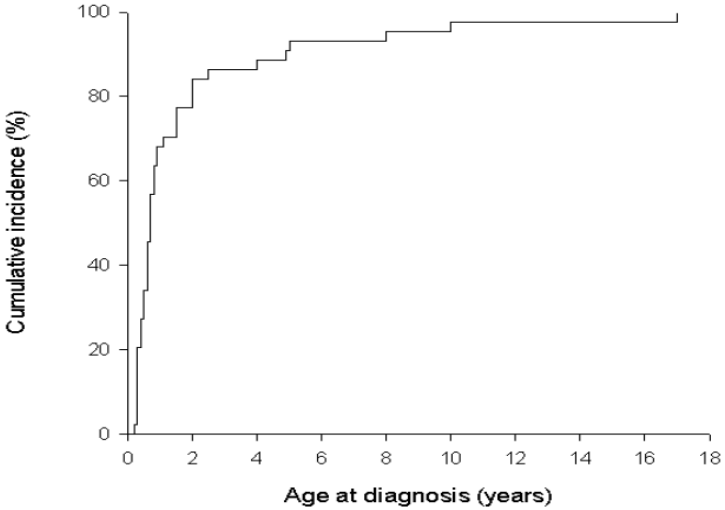


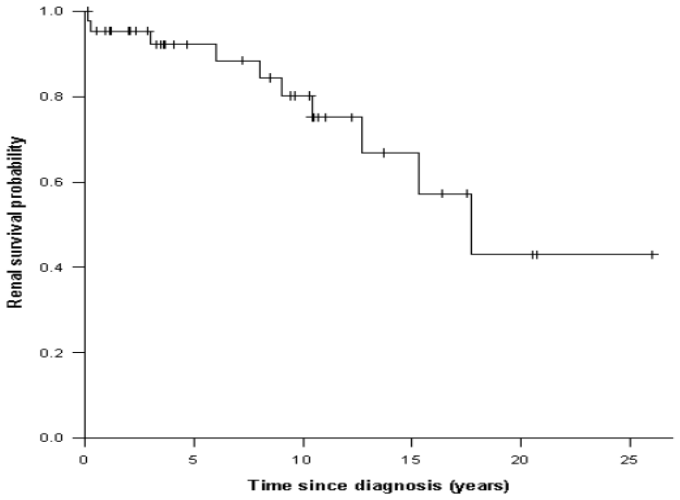


Lemaire M, et al. Nature Genetics 2013;45:531-6

DGKE Nephropathy: Complement-Unrelated Form of aHUS

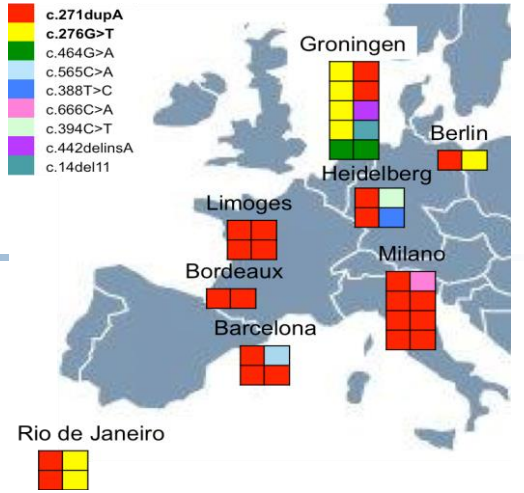
- Autosomal recessive disease
- HUS typically accompanied by heavy proteinuria
- Sometimes MPGN without TMA
- 1st manifestation in first 3-4 years of life
- Slowly progressive proteinuric nephropathy, 80% 10-year ESKD-free survival
- HUS remits without specific treatment
- Recurrences on complement inhibition observed
- No post-transplant recurrence





Azukaitis et al. JASN 2018

‘Metabolic’ aHUS: Cobalamin C Deficiency



19 cases identified in ESCAPE Network:

- Age at onset: 7 days to 14 years (median 0.9 y)
- Phenotype: 10 isolated aHUS, 9 associated pulmonary hypertension
- Plasma homocysteine: 145 (53-207) uM (nl <12)
- Diagnosis: n=4 post mortem, n=3 6-19 y after 1st manifestation !
- Treatment: 14/19 Vit B12, folate supplementation
  1/19 Eculizumab, ineffective
- Outcome: 7 dead (5 without substitution therapy)
  4 CKD2-5, 2 post-transplant
  6 normal kidney function (all diagnosed and treated early)
  7/12 survivors with cognitive deficits

Indications for Genetic Screening

NGS Screening
for CFH, CFI, CFB, C3, MCP, TM, DGKE recommended in:

- First aHUS episodes after ruling out STEC infection, ADAMTS13 deficiency, CbC deficiency and CFH antibodies
- HUS relapse
  Family history of non synchronous HUS
  Pregnancy/post-partum HUS
  de novo post-transplant HUS
- STEC-negative cases with ESRD as part of pre-transplant workup

Loirat et al. PN 2015

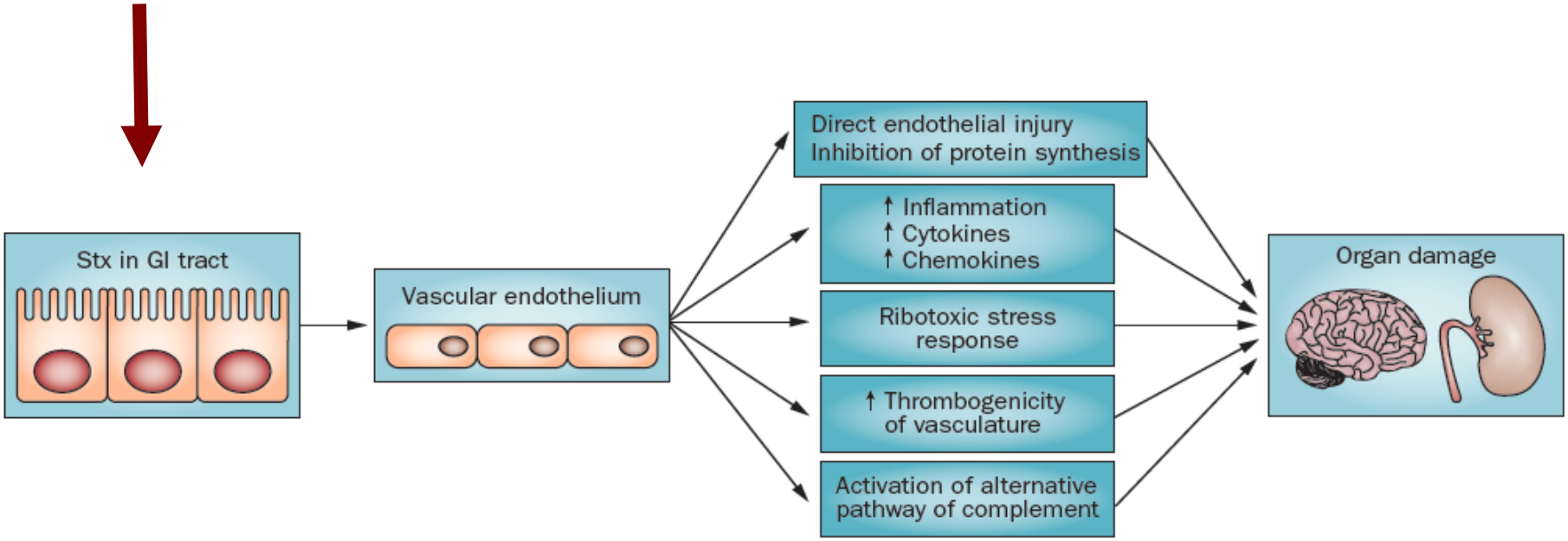
Relevance of Genetic Screening

- Establishing prognosis (risk of relapses, CKD progression)
- Genetic counselling to parents and family
- Decisions concerning kidney transplantation:
  - choice of donor
  - planning of post-transplant management
  - decision of combined kidney-liver transplantation
- Assessment of risks of treatment discontinuation

Loirat et al. PN 2015

Potential Therapeutic Strategies for STEC HUS

Antibiotics?



Antibiotic Use Increases HUS Risk in Children with STEC 0157:H7 Infections

Table 4. Multivariable Analysis for Risk Factors Associated With Hemolytic Uremic Syndrome

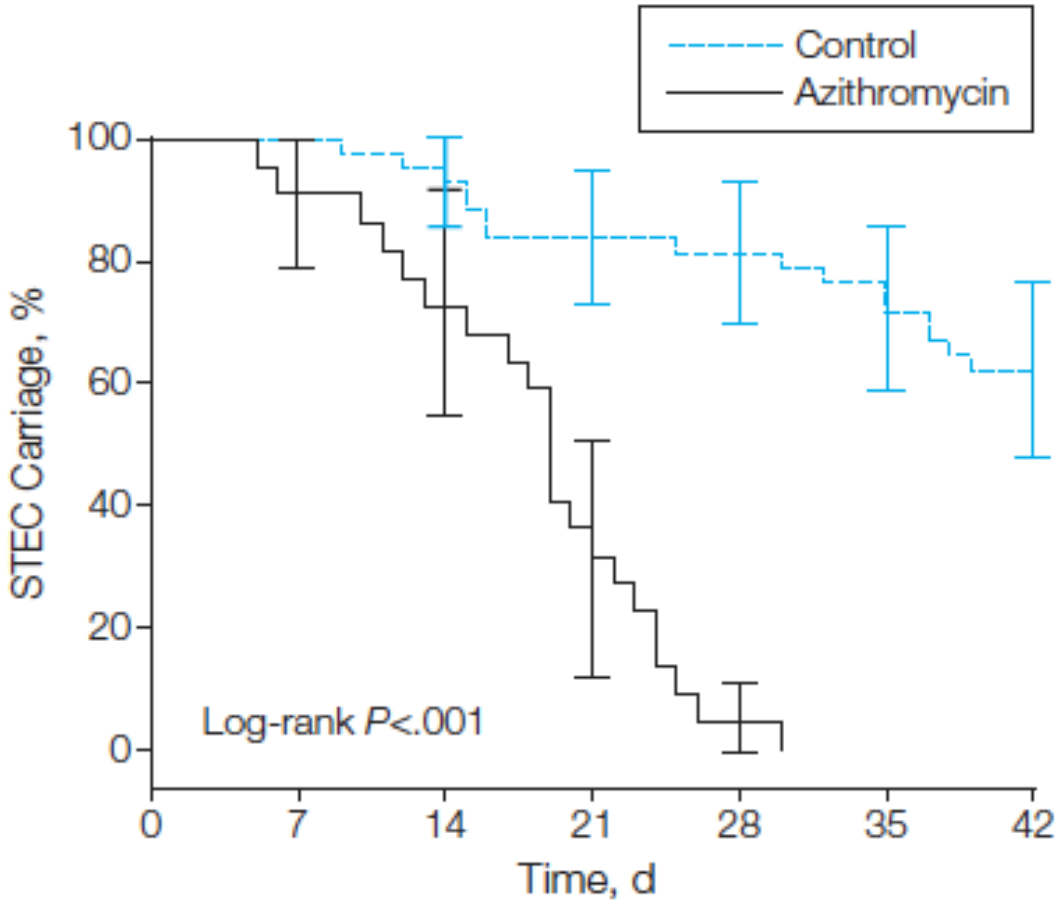
Risk Factor[a]	Multivariable OR (95% CI)[b]	*P* Value
Age[c]	0.89 (0.77–1.04)	.15
Vomiting before enrollment	3.05 (1.23–7.56)	.02
Initial leukocyte count[c]	1.10 (1.03–1.19)	.008
Days from onset of diarrhea to first leukocyte count determination	0.87 (0.63–1.20)	.40
Days from onset of diarrhea to stool culture	0.98 (0.65–1.48)	.94
Acetaminophen	1.39 (0.58–3.34)	.46
Antibiotics	3.62 (1.23–10.6)	.02

Table 6. Probabilities of Hemolytic Uremic Syndrome (HUS) by no HUS → Nonoligoanuric HUS → Oligoanuric HUS

Grouping	No HUS[a] (%)	Nonoligoanuric HUS[a] (%)	Oligoanuric HUS[a] (%)
No antibiotics + low leukocyte count	92.3	5.6	2.1
No antibiotics + high leukocyte count	84.0	11.3	4.7
Antibiotics + low leukocyte count	77.4	15.5	7.0
Antibiotics + high leukocyte count	60.0	25.3	14.7

Wong et al. Clin Infect Dis 2012; 55: 33

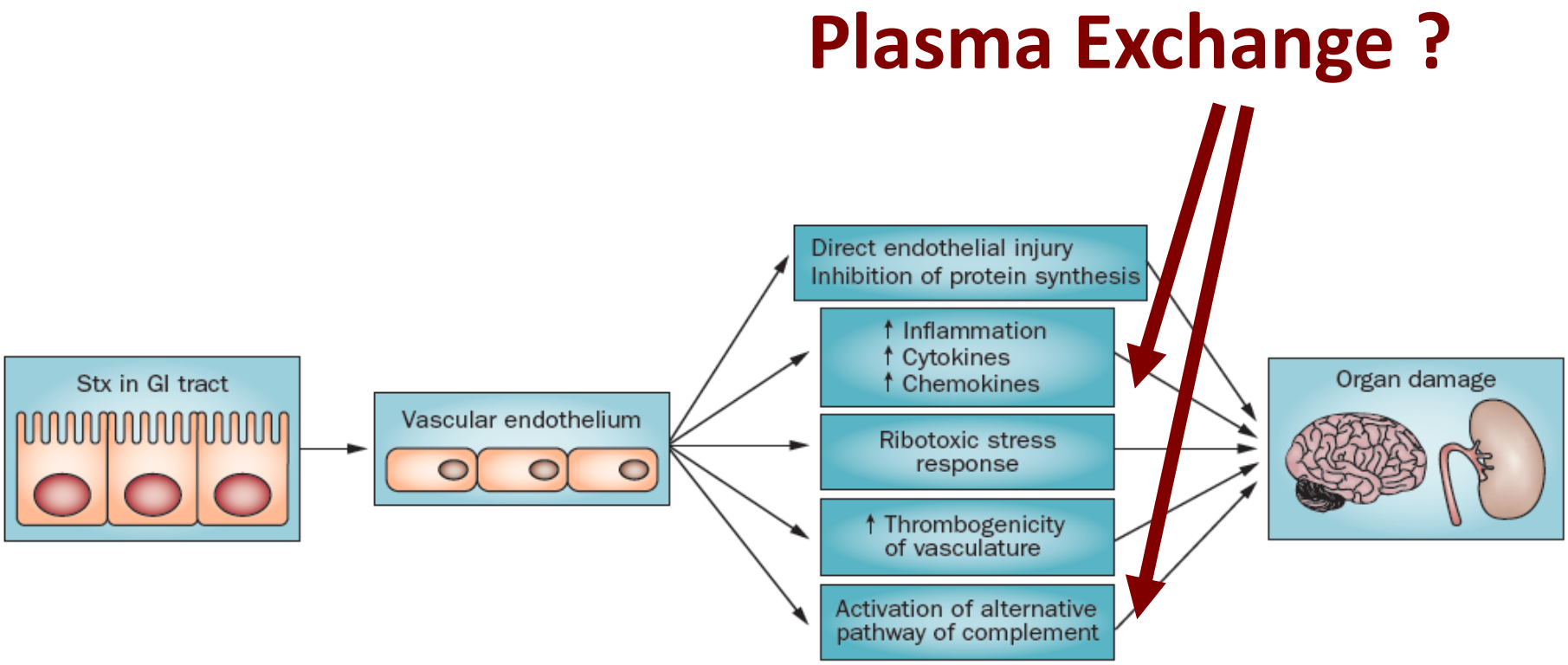
Azithromycin Efficiently Eradicates STEC 0104:H4



No. at risk							
Control	43	43	41	36	35	32	25
Azithromycin	22	20	16	8	1	0	0

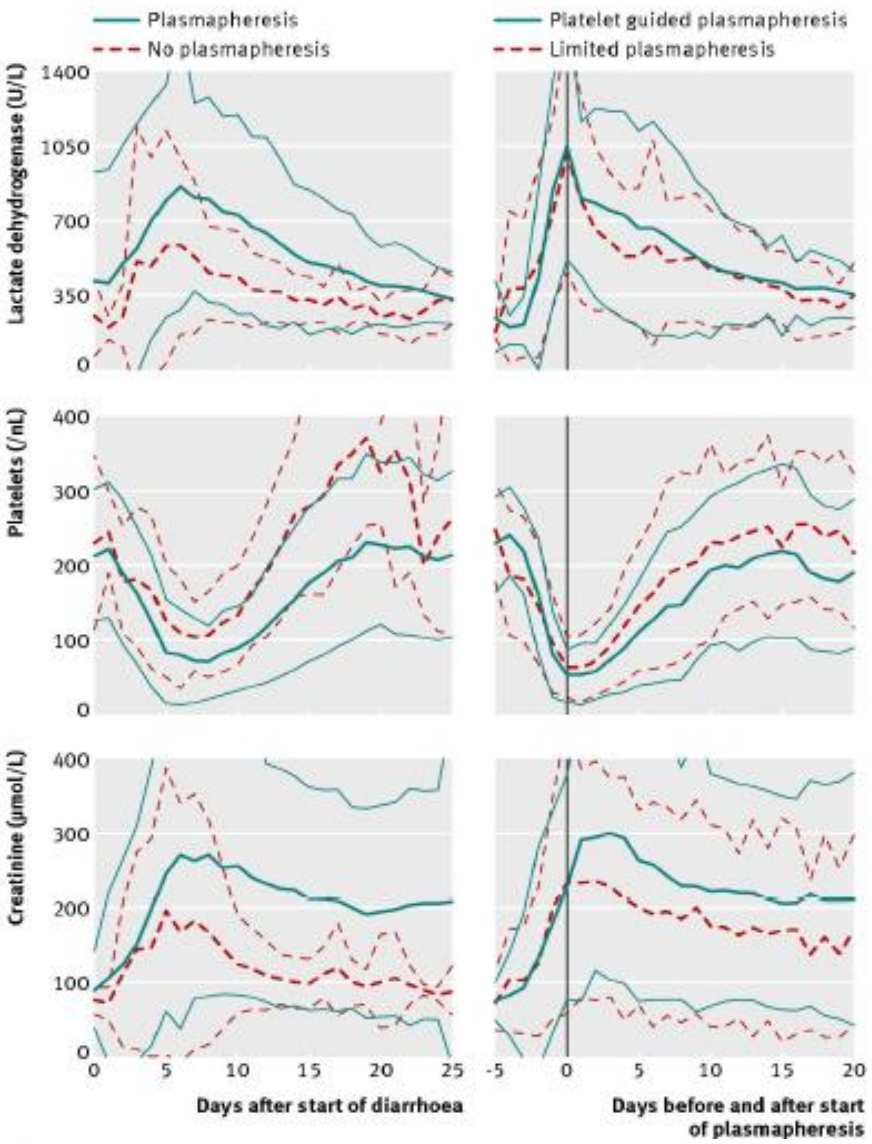
Nitschke et al. JAMA 2012; 307:1046

Potential Therapeutic Strategies for STEC HUS



Case-Control Analysis of Applied Therapies in 298 Adult Patients with HUS due to STEC 0104:H4

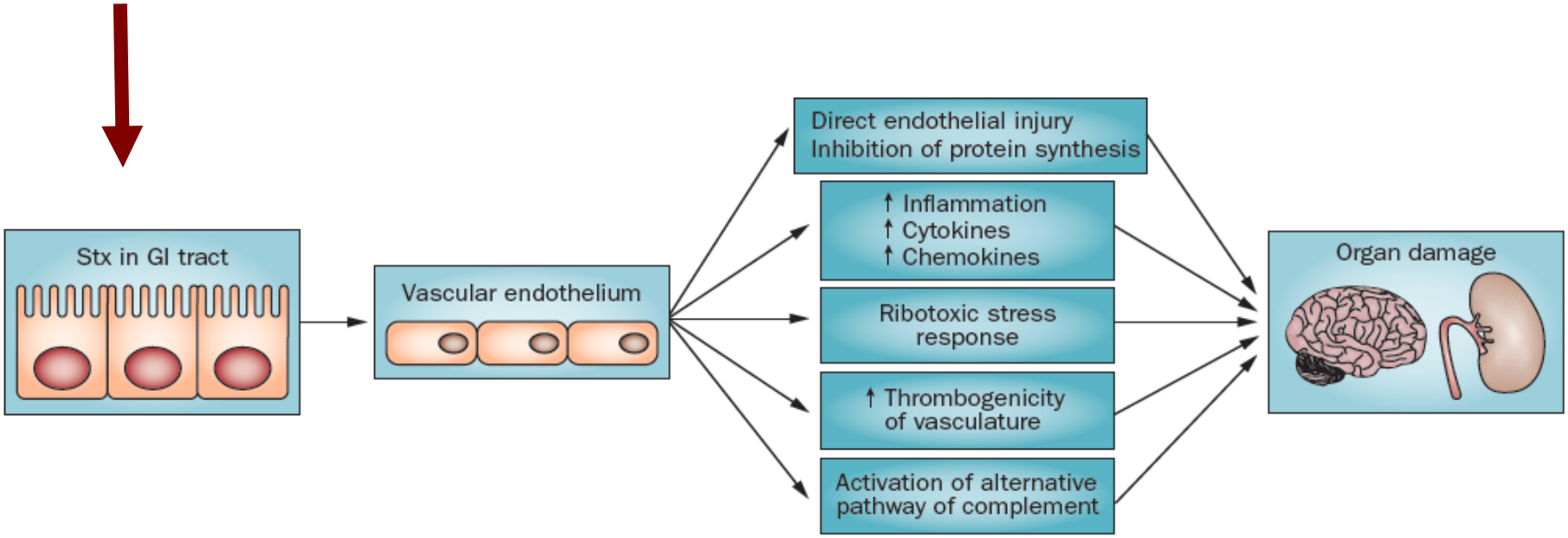
No clear benefit from plasmapheresis



Menne et al. BMJ 2012;345:e4565

Potential Therapeutic Strategies for STEC HUS

Prevention?



Potential Therapeutic Strategies for STEC HUS

ito.com ECONOMÍA FINANZAS POLÍTICA NEGOCIOS OPINIÓN LIFESTYLE SUSCRIBI

Argentinos, cerca de lanzar el primer medicamento del mundo contra el síndrome urémico hemolítico

11 Abril 2019

Se trata de un suero que actúa neutralizando la
fue comprobada y ahora se espera corroborar
una terapia específica contra este cuadro, que
especialmente en niños.

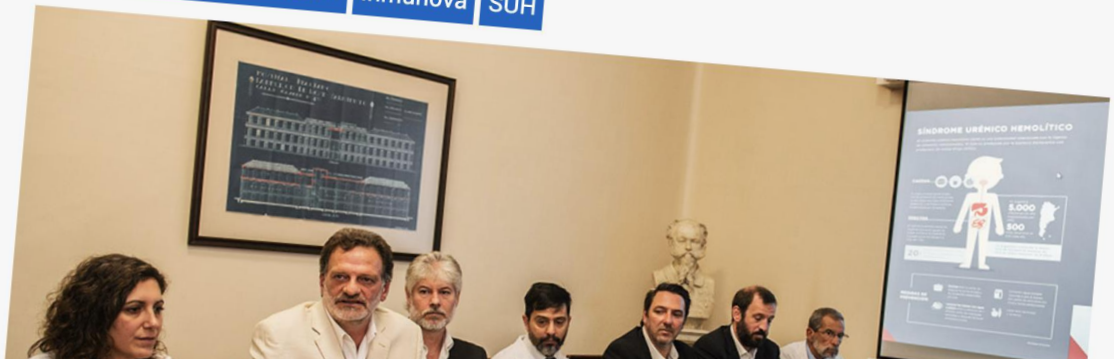
CIENCIAS BIOLÓGICAS Y DE LA SALUD

Avanzan en la aprobación de un suero para prevenir el Síndrome Urémico Hemolítico

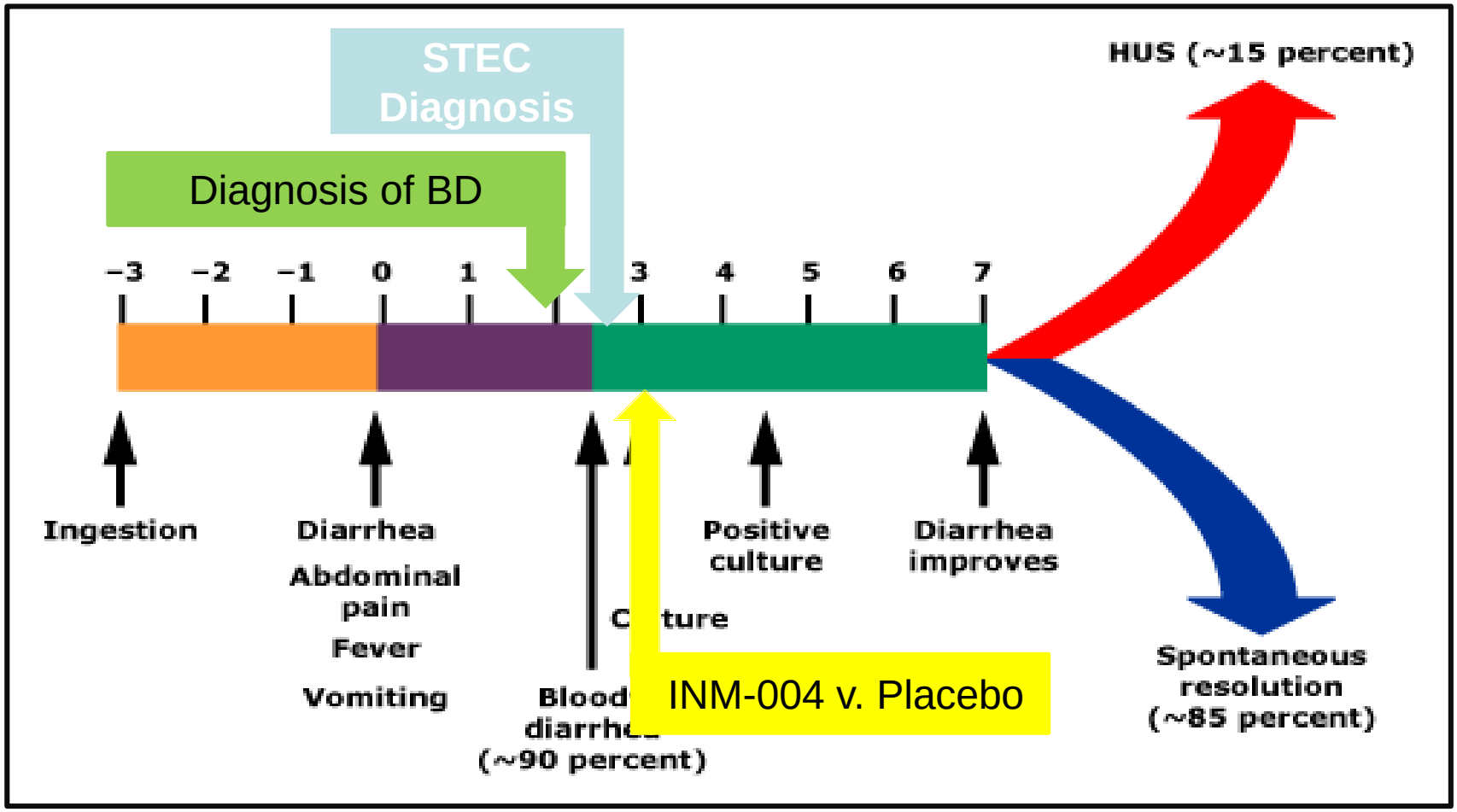
El investigador del CONICET, Fernando Goldbaum, es una de las cabezas del desarrollo del medicamento que ahora pasará a la etapa clínica en pacientes.

Publicado el 12 de abril de 2019

Tags: Fernando Goldbaum | Inmunova | SUH



Potential Therapeutic Strategies for STEC HUS



Rep.:Tarr, PI, Gordon, CA, Chandler, WL. Shiga-toxin-producing Escherichia coliand haemolytic uraemic syndrome. Lancet 2005; 365:1073. Copyright ©2005 Elsevier.

Therapeutic Options in Atypical HUS

- **Plasma Therapy**

  Plasma infusions (-30 ml/kg)

  Plasma exchange (150% of plasma volume q. 2d)

  - Substitution of lacking or dysfunctional proteins

  - Removal of autoantibodies or activating factors

  → Maintenance therapy required

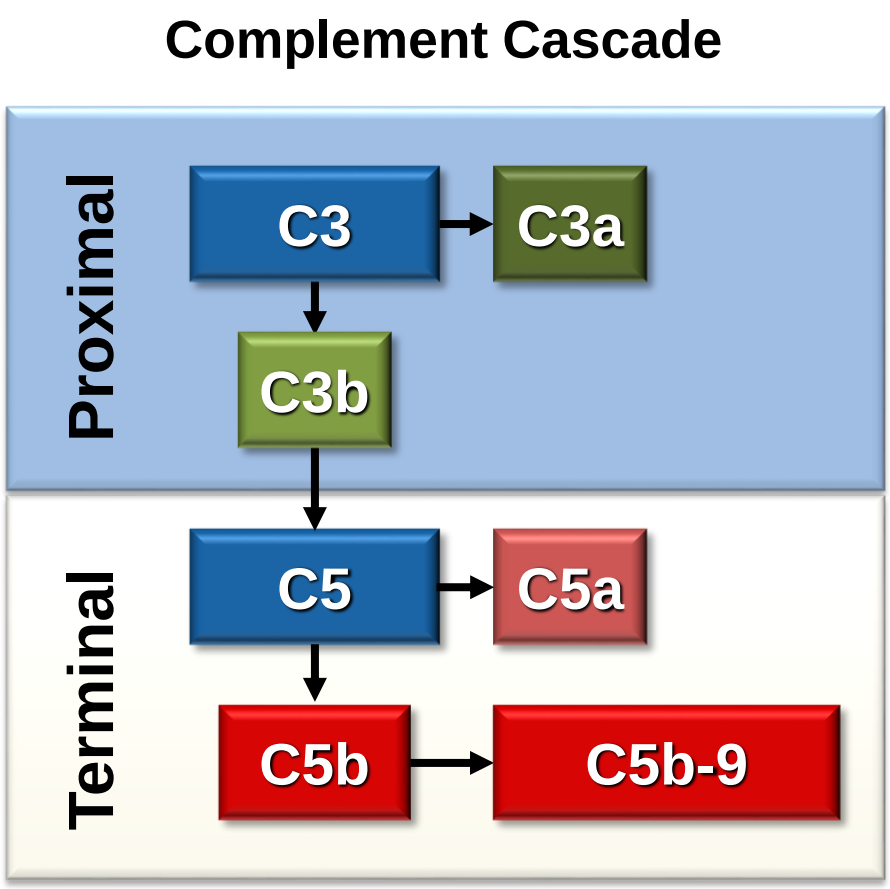
- **Immunosuppression**

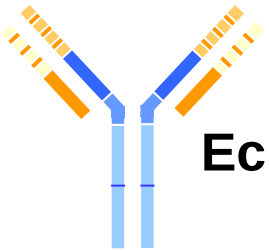
  Anti B-lymphocyte therapy for autoantibody-mediated disease

- **Combined liver-kidney transplantation**

- **Monoclonal anti-complement antibody Eculizumab**

Eculizumab Blocks Terminal Complement





- Eculizumab binds with high affinity to C5
- Terminal complement - C5a and C5b-9 activity blocked
- Proximal functions of complement remain intact
  - Weak anaphylatoxin
  - Immune complex clearance
  - Microbial opsonization

Eculizumab Multinational, Multicenter Clinical Program in aHUS

Clinical Diagnosis of aHUS with

- TMA (measured by platelet count, hemolysis)
- Organ damage (serum creatinine ≥ULN)
- ADAMTS13 >5%; no positive STEC test
- No requirement for identified genetic mutation

Prospective (26 weeks)

Acute, progressing TMA
Study C08-002 (N=17)
Adult/adolescent

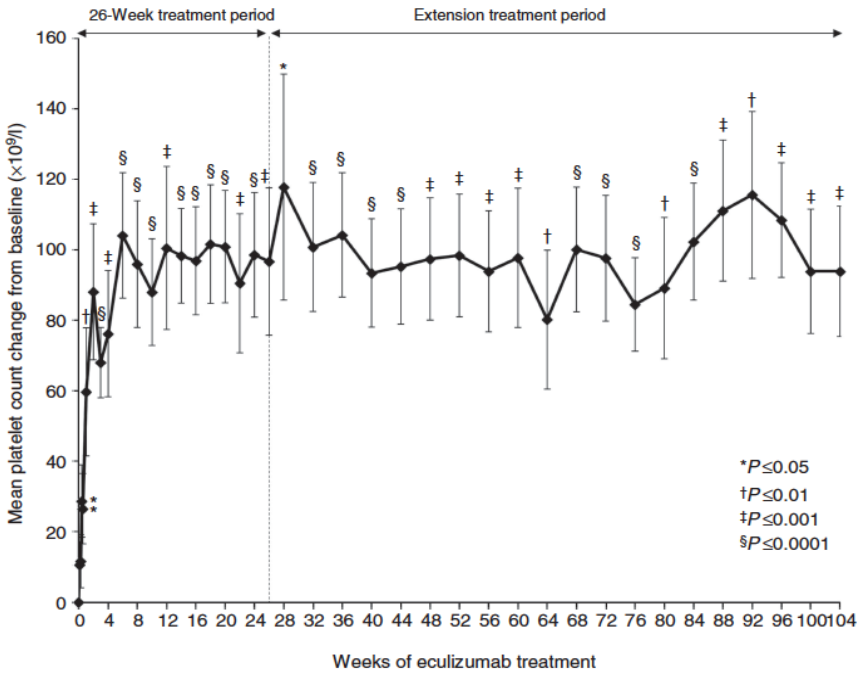
Long-standing aHUS
Study C08-003 (N=20)
Adult/adolescent

Long-Term Extension Studies

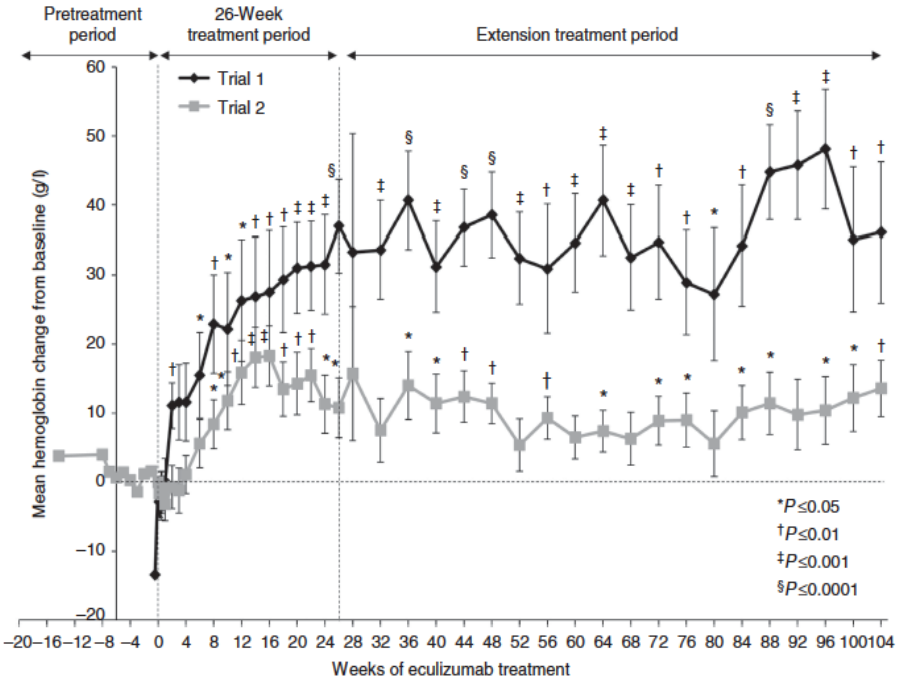
32 of 37 patients (86%) continued chronic eculizumab treatment in extension studies

Hematological Normalization

Change in Hemoglobin

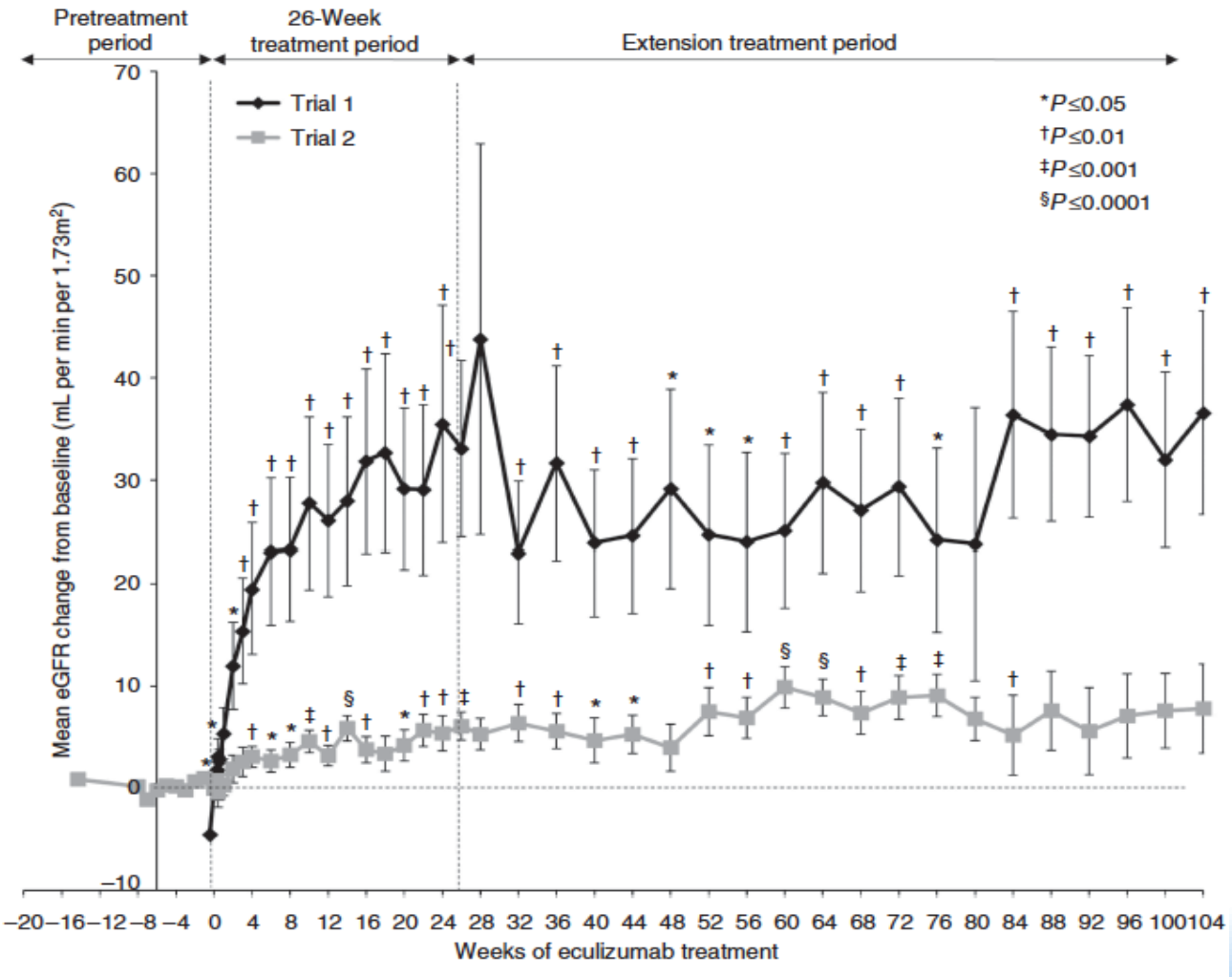


Change in Platelets



Licht et al. Kidney Int 2015

Improvement of eGFR



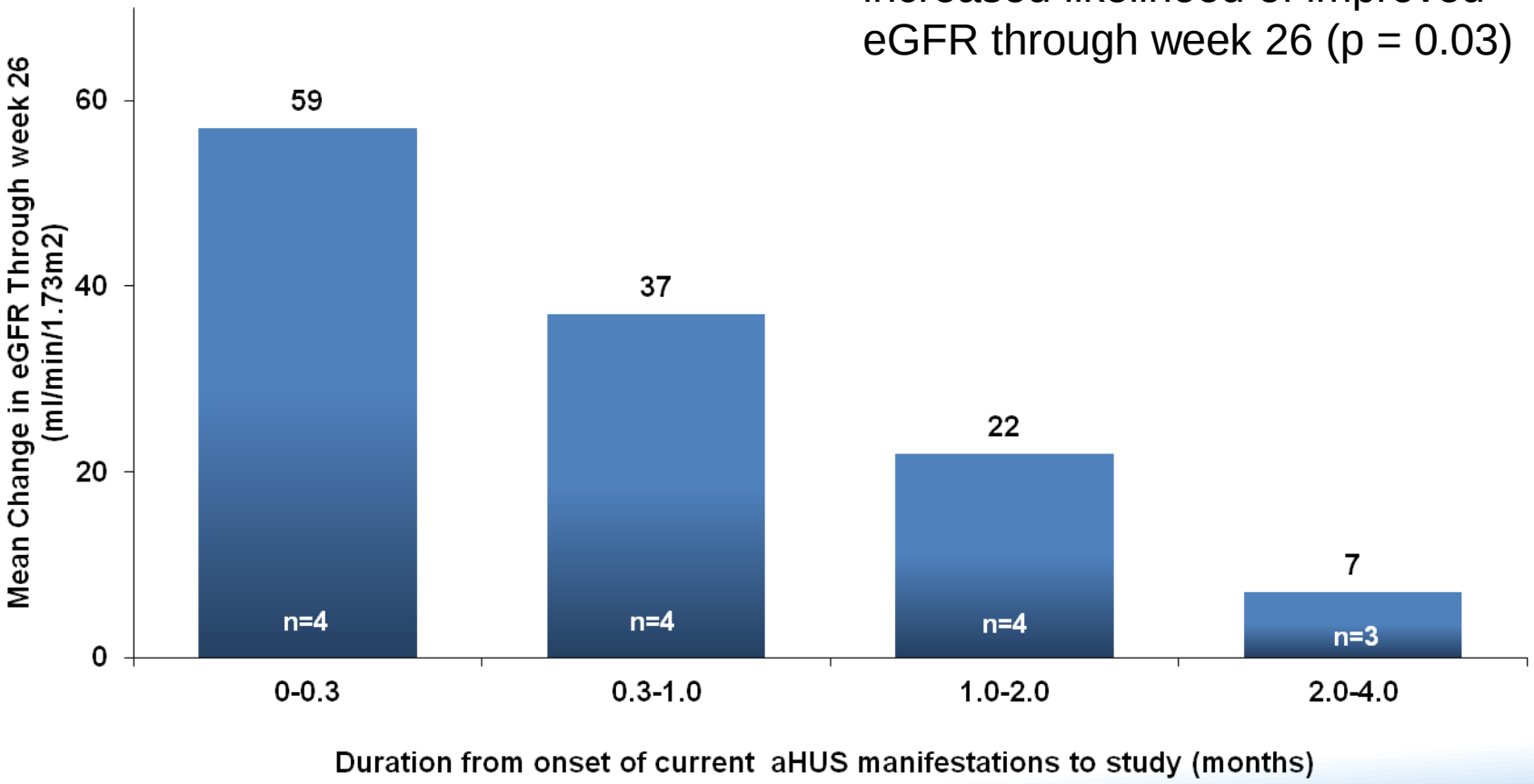
‚Acute' HUS Trial

‚Chronic' HUS Trial

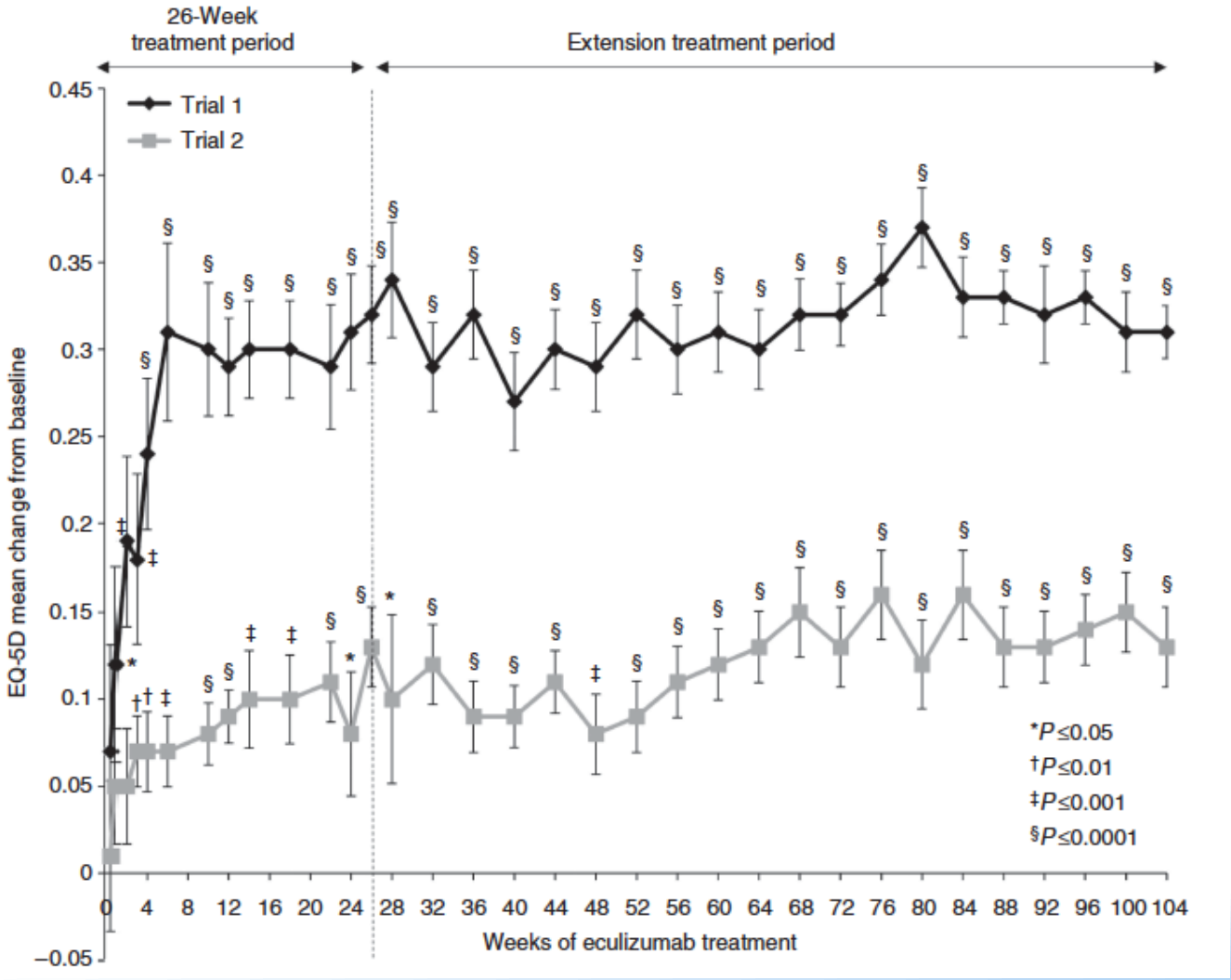
Licht et al. Kidney Int 2015

Earlier Treatment With Eculizumab Leads to Greater Improvement in Renal Function

Earlier intervention with eculizumab: increased likelihood of improved eGFR through week 26 (p = 0.03)



Improved Quality of Life



‚Acute' HUS Trial

‚Chronic' HUS Trial

Prevention of Meningococcal Infections on Eculizumab Therapy

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…)

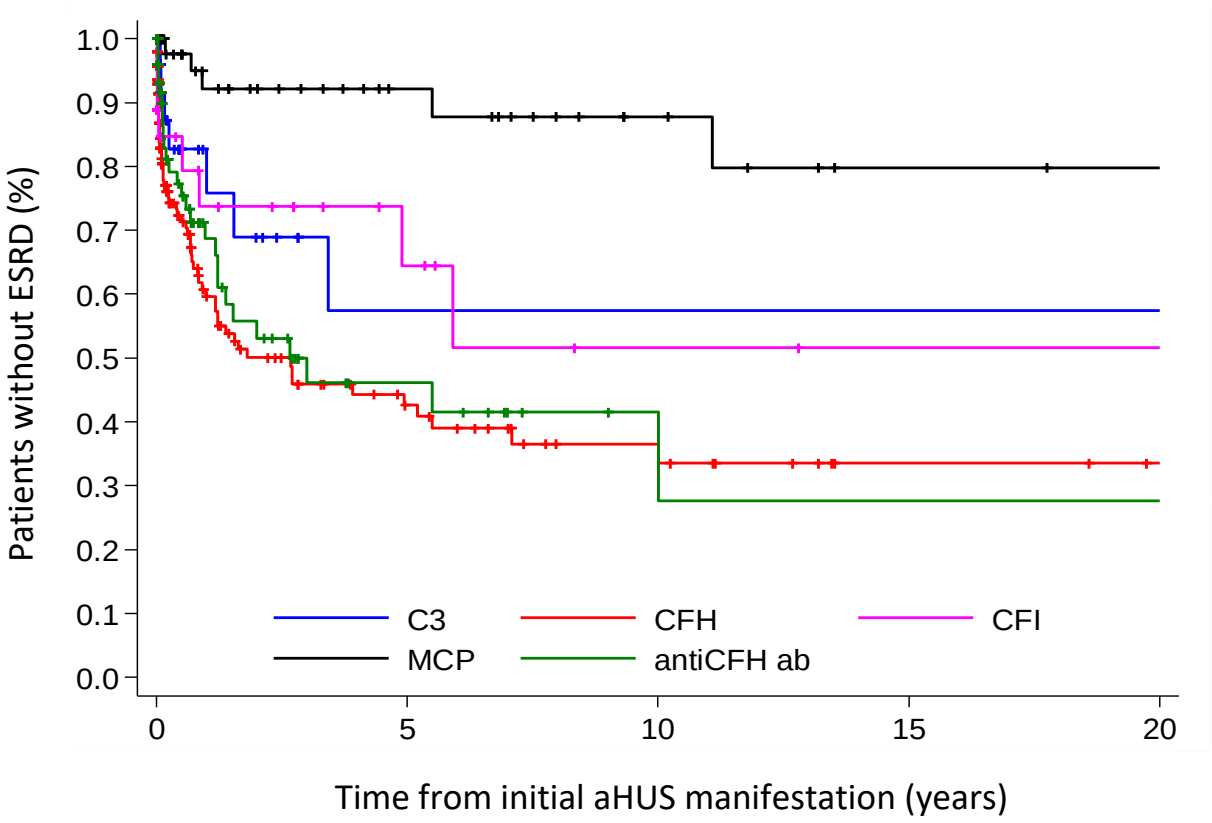
Information card to be carried by the patient or his/her care giver, to be shown to medical staff in case of symptoms suggesting infection

CFH Autoantibody Associated aHUS

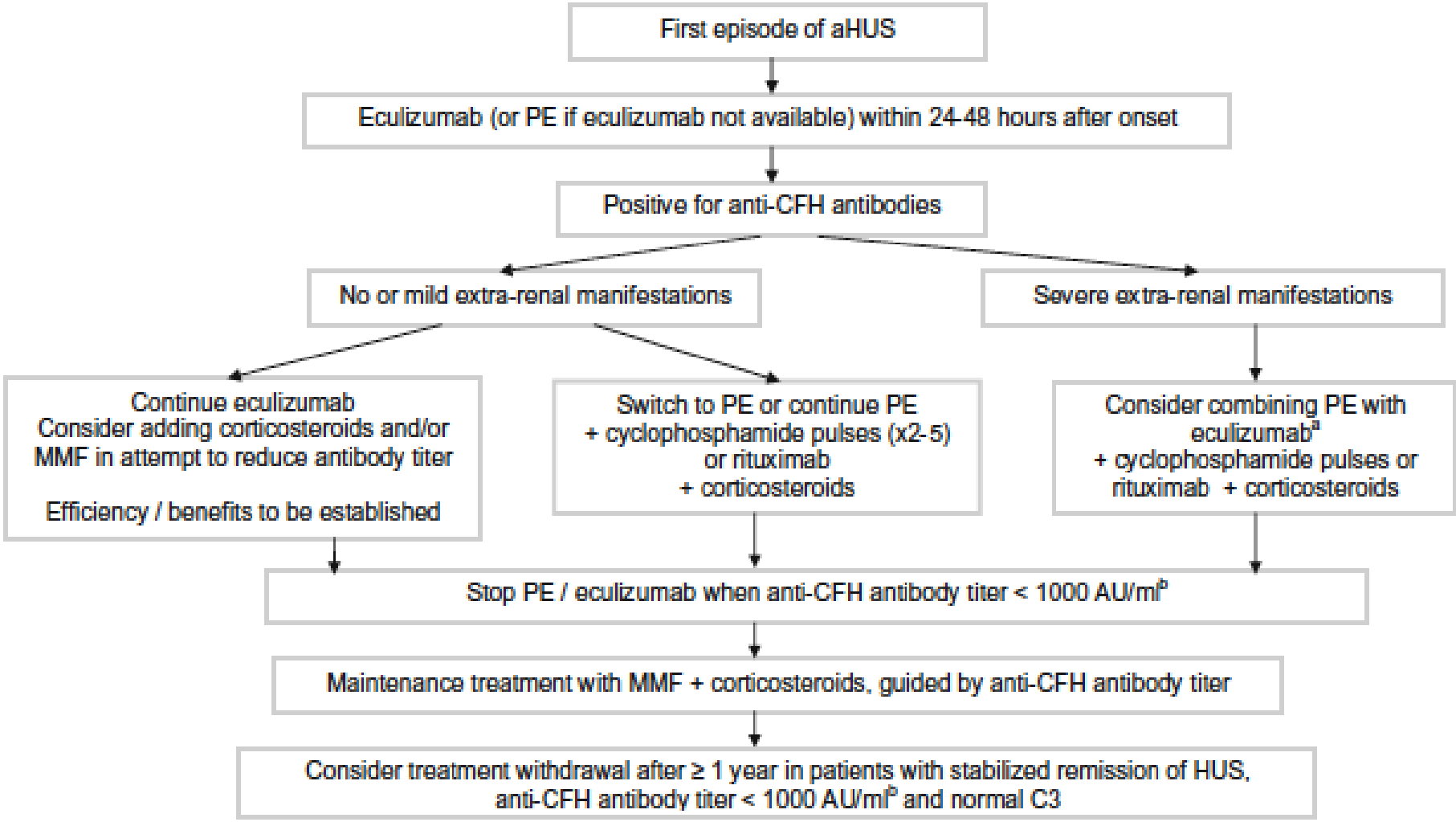
- Indian experience: 138 children (56% of all HUS!)
- Homozygous CFHR1 gene deletion in 60/68
- **Therapy:** 119 dialysis, 105 PE, 26 IVIG,
  87 induction immunosuppression (pred ± iv CPH or rituximab)
- **Adverse outcome (CKD 4-5 or death):** 41/122 by last follow up
- **Risk factors:** Anti-CFH >8000 AU/ml, low C3, delayed PE
- **Maintenance IS** (oral pred + MMF/AZA) reduced relapse risk

Sinha et al. KI 2014

Poor Long-Term Renal Prognosis in CFH Auto-Antibody Mediated aHUS



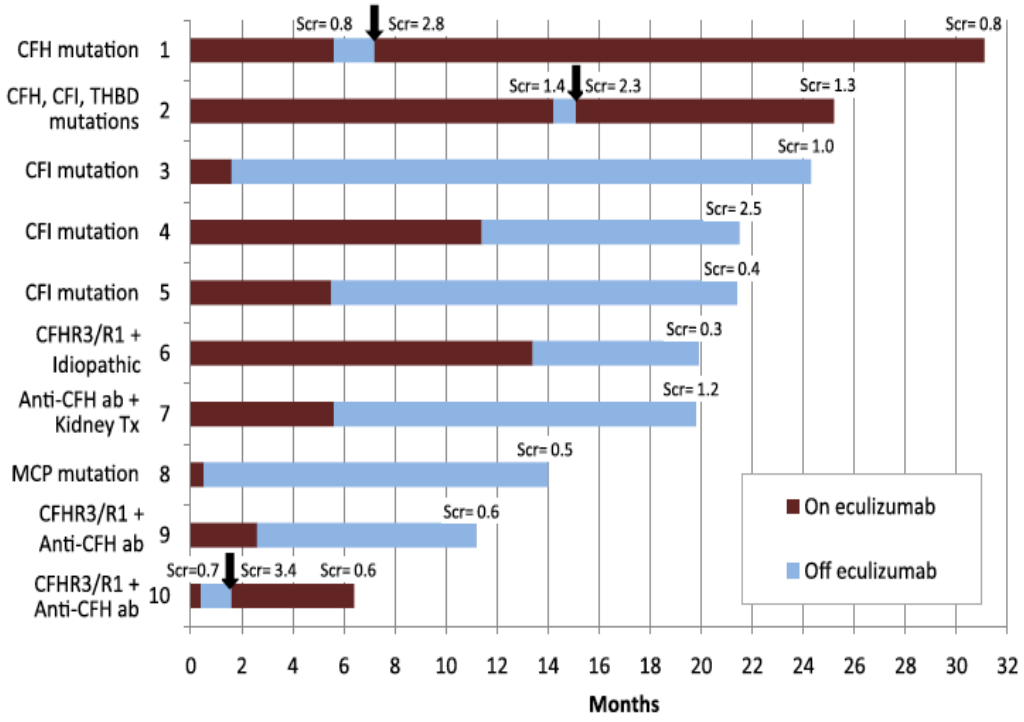
International Consensus Paper 2015: Initial Therapy of aHUS in Children



Eculizumab Treatment Discontinuation

Milano Experience

- Ecu discontinued in 10 of 22 aHUS patients
- "Watchful waiting" policy: Thrice weekly home dipstick monitoring
- 3 out of 10 patients experienced TMA episodes within 3-6 weeks after discontinuation



Ardissino et al. AJKD 2014

Eculizumab Treatment Discontinuation

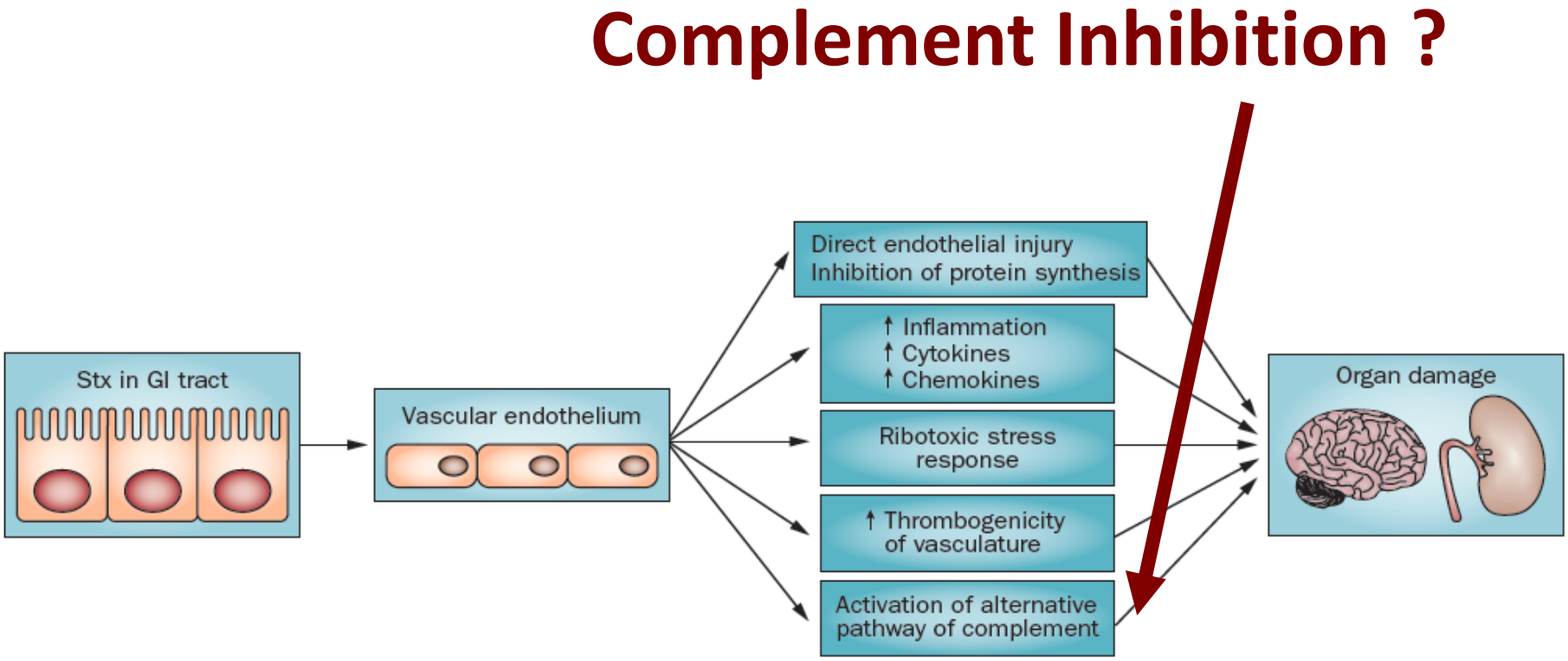
Clinical Trial Results:

- 5 out of 18 patients experienced TMA episodes following a missed dose
- 1 patient rapidly deteriorated to ESRD
- Eculizumab was reinitiated in 4 of 5 patients

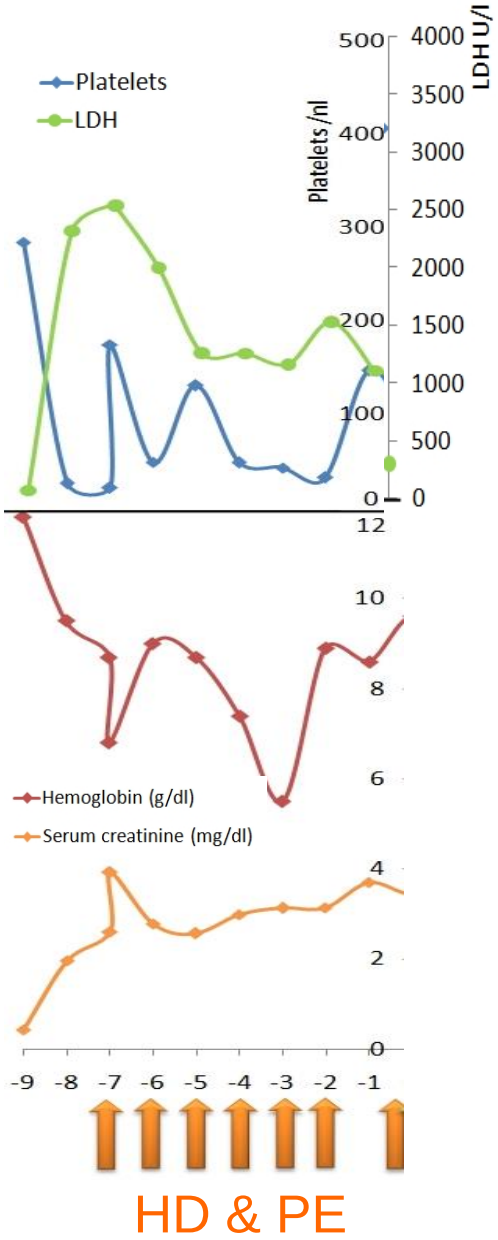
Conditions Justifying Discontinuation (or Withholding) of Eculizumab

- CbC Deficiency
- DGKE mutation
- MCP mutation
- CFH auto-antibody mediated disease with low autoantibody titres on immunosuppressive treatment
- Absence of genetic abnormalities in gene panel screening (?)

Potential Therapeutic Strategies for STEC HUS



A Case of Complicated STEC HUS

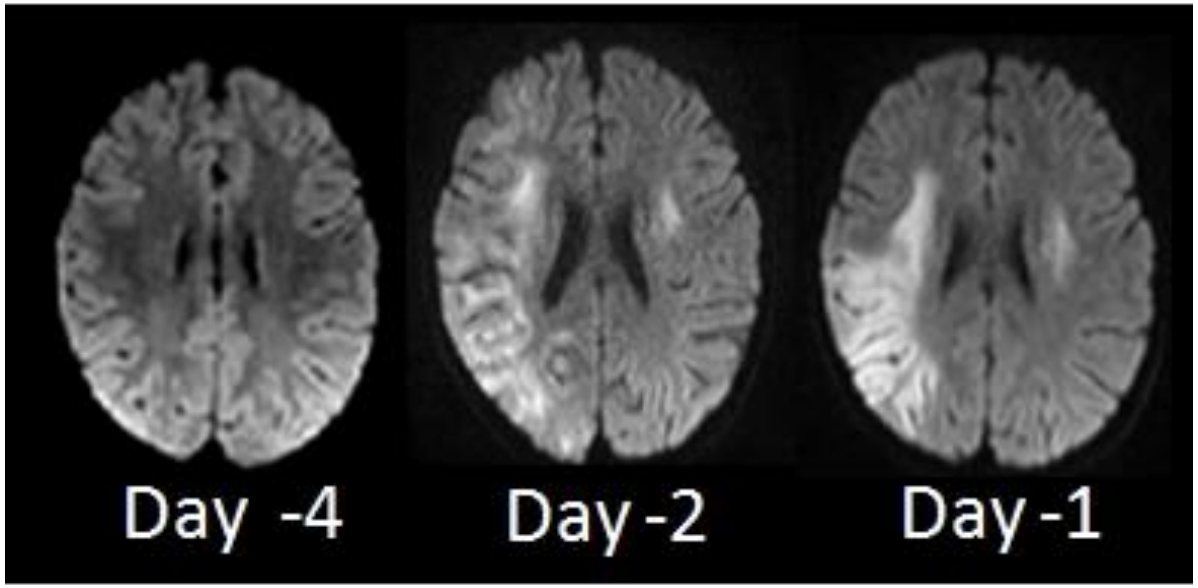


4yo girl, D+ HUS, STX2 positive

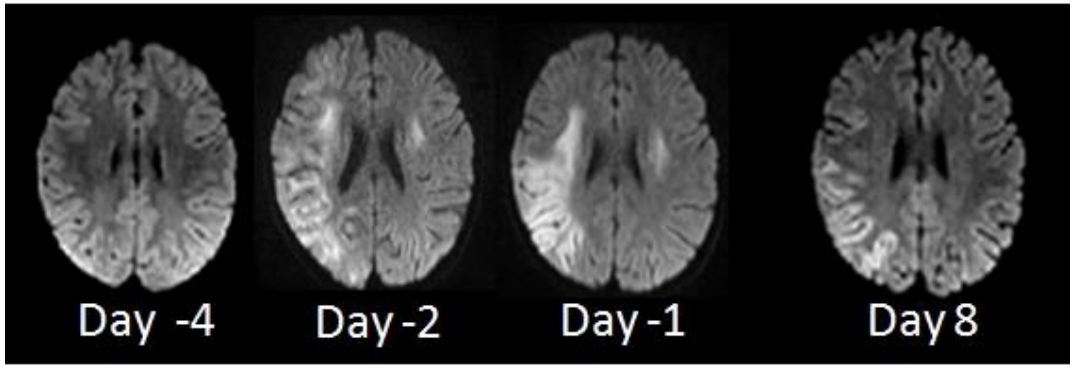
Anuric renal failure

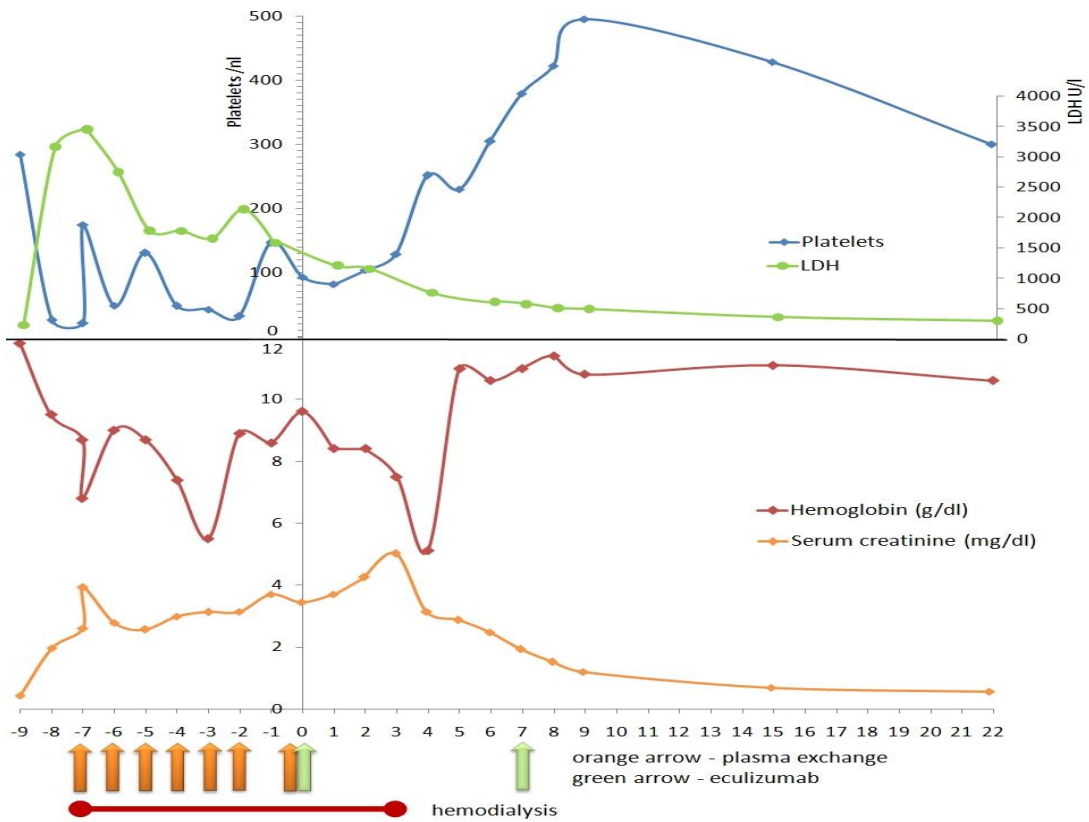
Signs of complement activation
PE with each HD session

Progressive neurological symptoms:
Focal seizures -> hemiplegia -> coma



- **Eculizumab infused**
- Improved vigilance, motor responses within few hours after infusion
- Urine output starting within 24h
- Dialysis stopped after 3d
- Fully regained speech, motor control within 7d
- Discharged after 9 days with completely normalized neurological status, normal GFR
- Complement status normalized
- No gene abnormalities found



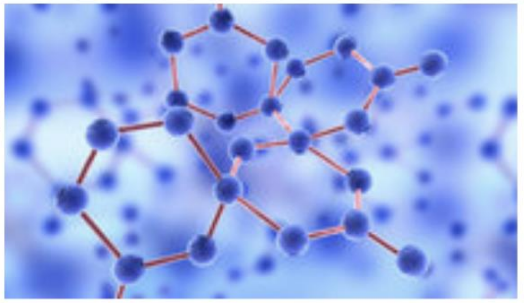


Lapeyraque et al. NEJM 2011

Therapeutic Complement Inhibition beyond Eculizumab

Russian approval for non-originator eculizumab

Posted 24/05/2019



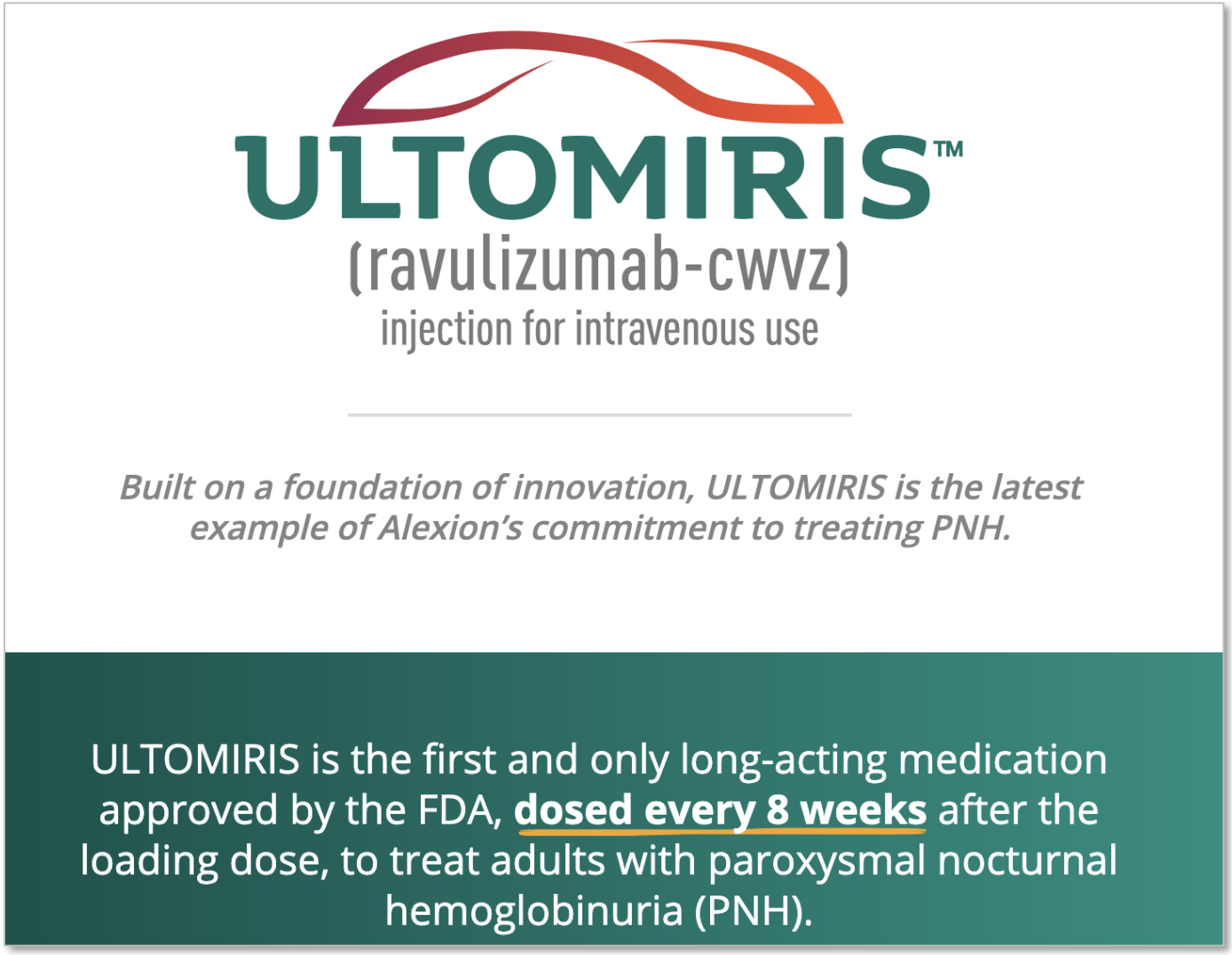
Russian biotechnology company Generium and Swiss-based cell-line producer Selexis announced on 9 April 2019 that the Russian Ministry of Health had approved their eculizumab non-originator biological drug, Elizaria. The drug is a non-originator biological of Soliris (eculizumab), which is made by Alexion Pharmaceuticals.

Eculizumab is a humanized monoclonal antibody that is a terminal complement inhibitor. It is used to treat people with paroxysmal nocturnal haemoglobinuria (PNH), for whom it improves quality of life but does not appear to affect the risk of death. It is also indicated for the treatment of patients with atypical haemolytic uremic syndrome (aHUS) – a disease that primarily affects kidney function – to inhibit complement-mediated thrombotic microangiopathy.

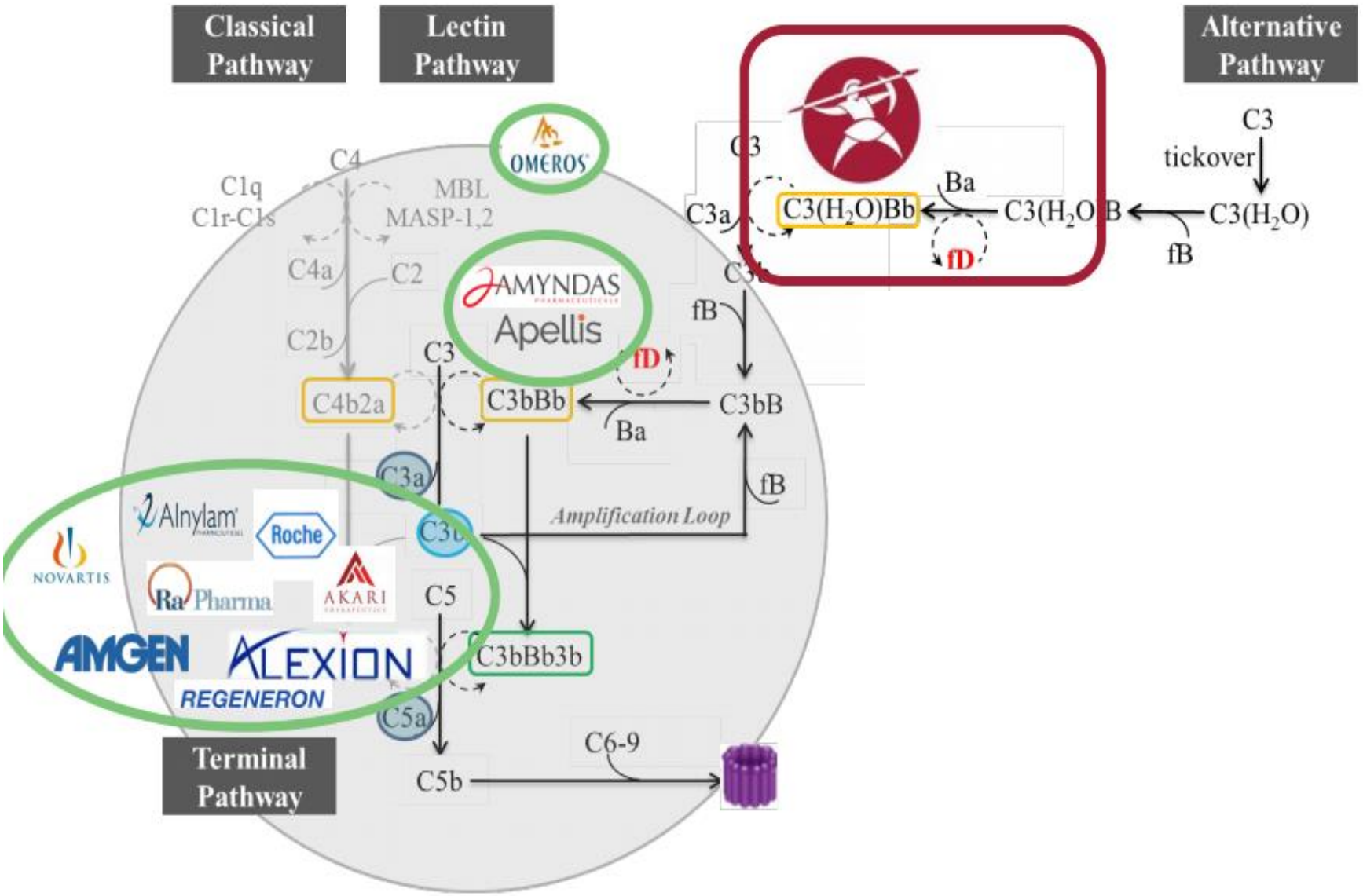
Elizaria is generated using the SUREtechnology Platform developed by Selexis, and is the fifth biological product to be marketed using this technology. According to Igor Fisch, President of Selexis, this validates the company's 'ongoing scientific innovation' and its commitment to helping their 'partners address complicated and intractable diseases by developing complex protein therapeutics faster, safer and more cost efficiently'.

No information was given by the companies as to what data the approval was based on. It was also not clear if the design of the clinical trials was developed in accordance with European Medicine Agency or US Food and Drug Administration guidelines.

Therapeutic Complement Inhibition beyond Eculizumab



Therapeutic Complement Inhibition beyond Eculizumab



Therapeutic Complement Inhibition beyond Eculizumab

Novartis	LFG316	C5 antibody	Phase 2 - PNH
Regeneron	REGN3918	C5 antibody	Phase 2 - PNH
Roche	Crovalimab	C5 antibody, long-acting	Phase 1/2 - PNH
Ra Pharma	Zilocuplan	C5 inhibitor, cyclic peptide	Phase 2 – PNH, MG
ChemoCentryx	Avacopan	C5a receptor blocker, oral	Phase 2 – aHUS, C3G, IgAN
Akari	Coversin	C5 / TLP4 inhibitor, s.c.	Phase 2 – PNH, aHUS
Alnylam	Cemdisiran	C5 RNAi, 3-monthly s.c.	Phase 2 aHUS, IgAN
Apellis	APL-2	C3 inhibitor, daily s.c.	Phase 2/3 – Glomerulopathies/PNH
Amyndas	AMY-101	C3 inhibitor, daily s.c.	PNH, C3G
Achillion	Danicopan	Factor D inhibitor, oral	Phase 1 - PNH, C3G
Omeros	Narsoplimab	MASP-2 antibody	Phase 3 - TMAs, IgAN