

Hemolytic Uremic Syndrome (HUS) and Thrombotic Thrombocytopenic Purpura (TTP)

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 - Clinical focus: kidney and pancreas Transplant
 - Research focus: Thrombosis/TMA

DISCLOSURE

Relevant Financial Relationships

Advisory board and consulting: Alexion
Vertex, Novartis, Apellis, UpToDate

Off Label Usage

Yes

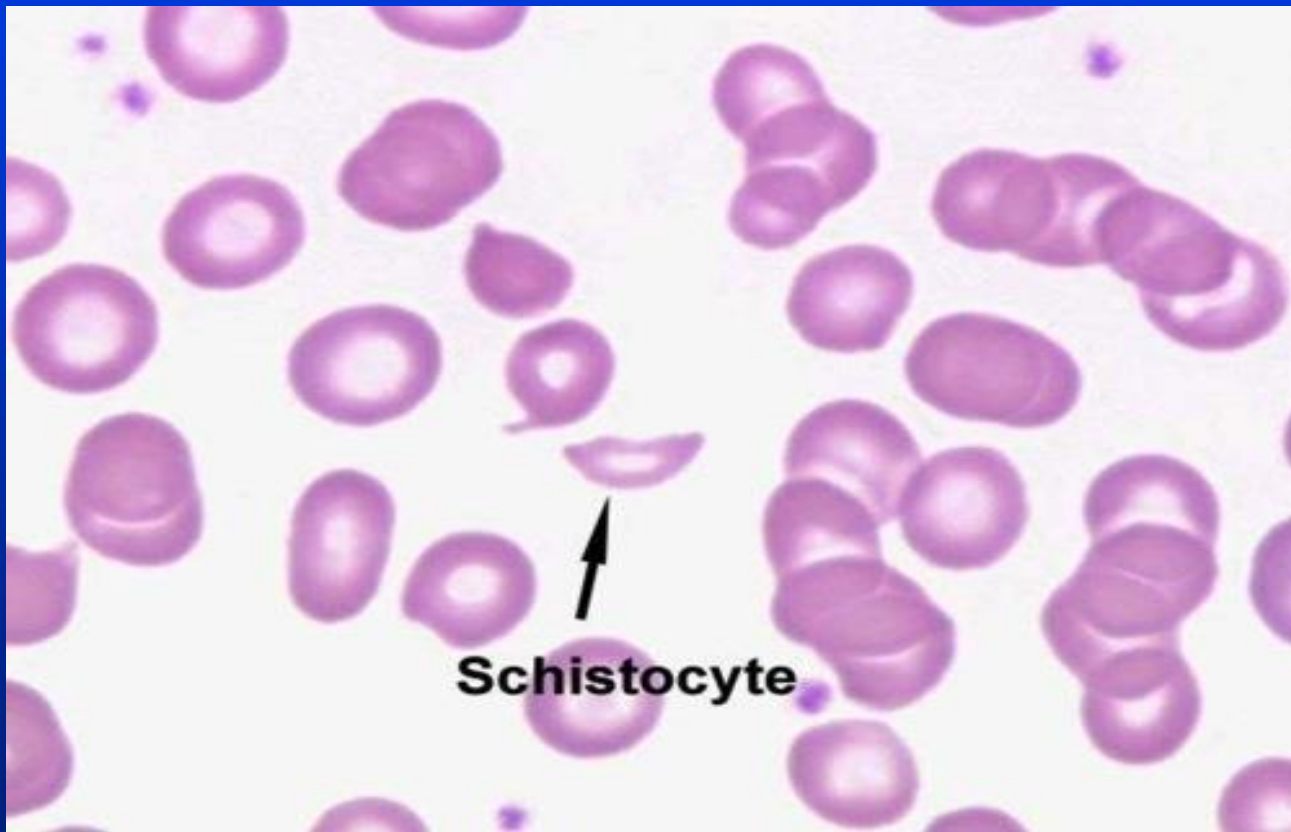
Case Presentation: 1

- 44 years old previously healthy woman admitted to the hospital with weakness, fatigue, and malaise for few days. She had no fever, chills, and no recent travel or sick contacts. She reports that a week ago she developed some upper respiratory viral infection which resolved in 3 days.
- She has no known past medical history and currently she is not taking any medications.
- Physical exam: BP 157/87, HR 98, Temp 99F, RR 16, Pale, no icterus, AAOx3
- Lungs CTA bilaterally
- Heart: normal exam, except for mild tachycardia
- GI: Normal exam
- Skin no rash
- Neurological exam: normal

Case Presentation: 1

- Blood workup demonstrated:
- AKI, anemia and thrombocytopenia
 - Creatinine 3.9 mg/dL from baseline 1.0 mg/dL
 - Platelets 64 k/uL, Hb 6.8 g/L, PT and PTT normal, fibrinogen normal,
- Workup of anemia: LDH 648, haptoglobin <8
- Coombs negative
- Schistocytes seen on peripheral smear
- Serum creatinine continued to increase
 - Creatinine 8.5 mg/dL on Hospital Day #5
 - C3 and C4 normal
 - ANA, dsDNA negative, SS-A, SS-B neg

Peripheral Smear



2 or > schistocytes/hpf on blood smear

Case Presentation: 1-

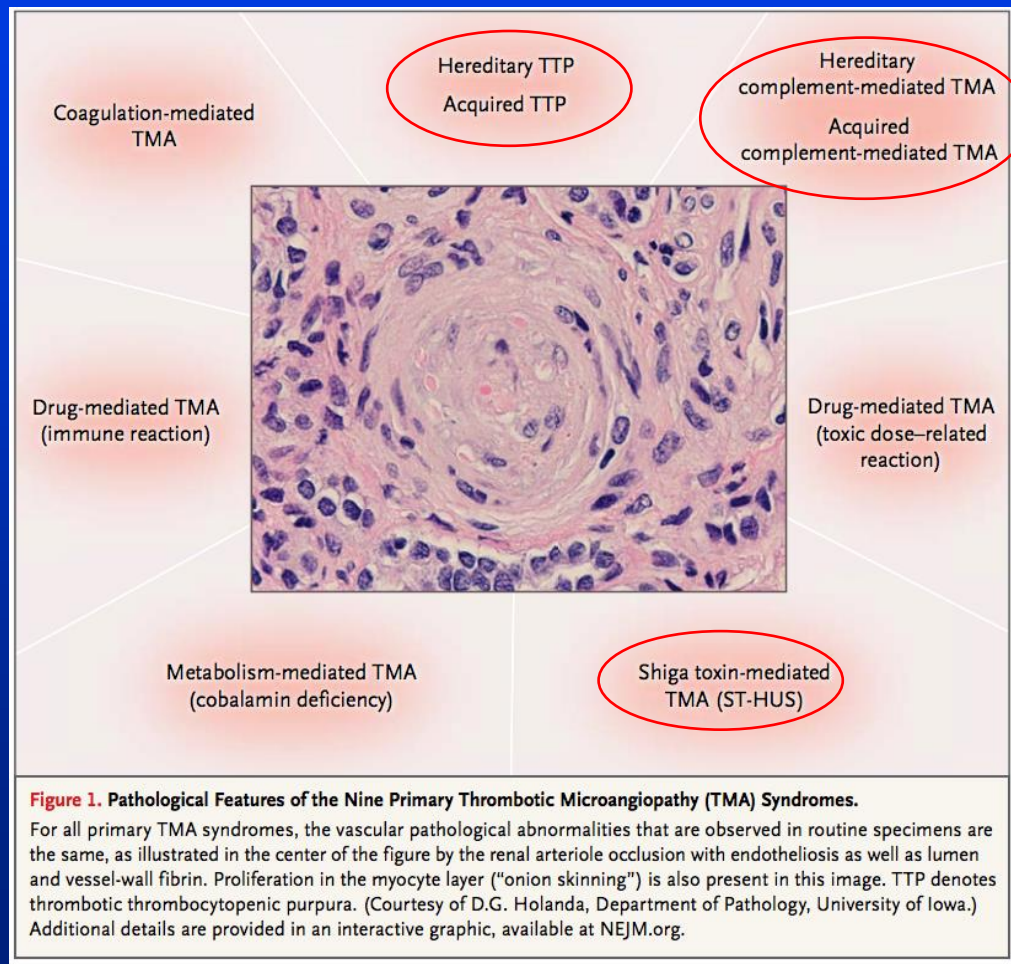
Question 1

- What is the underlying pathophysiologic entity associated with this presentation:
 - a- Autoimmune hemolytic anemia
 - b- Thrombotic microangiopathy (TMA)
 - c- Hemolytic uremic syndrome (HUS)
 - d- Thrombotic thrombocytopenic prurpura (*TTP*)

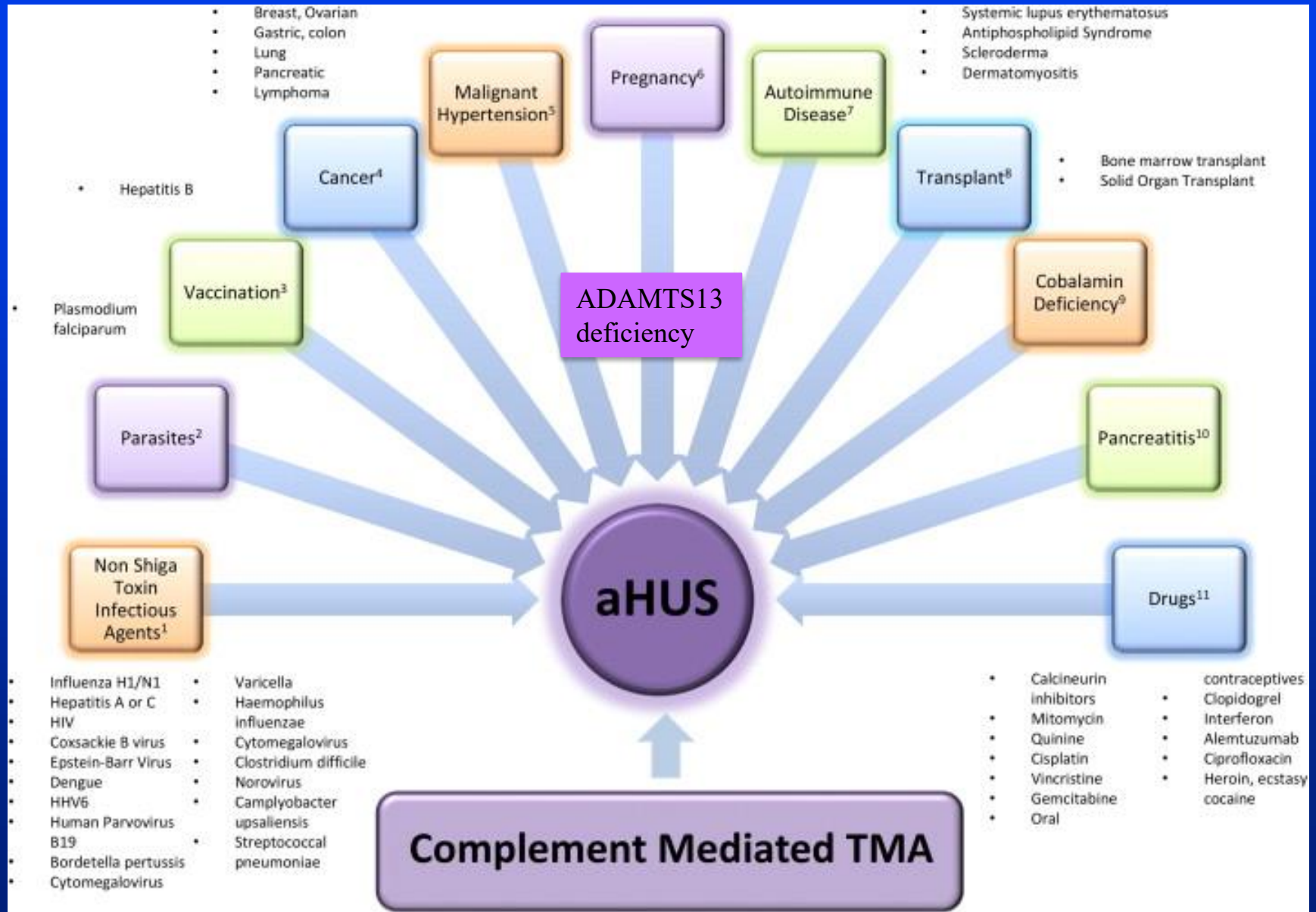
TMA syndromes

- Extremely diverse syndromes
- Hereditary or acquired
- Affect children and adults
- Clinically: Microangiopathic hemolytic anemia (MAHA), thrombocytopenia, organ injury
- Pathology: arteriolar and capillary microthrombi, endothelial injury

TMA Pathology

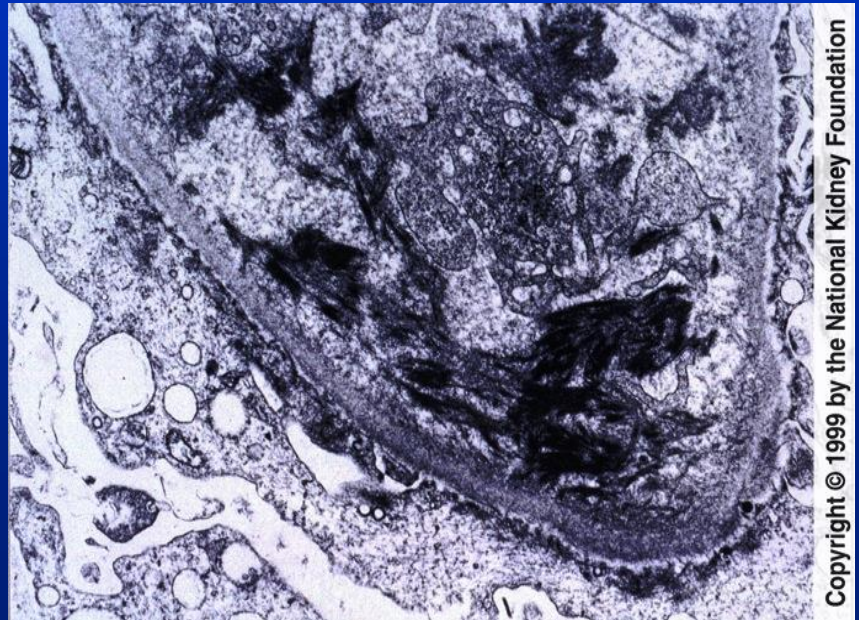
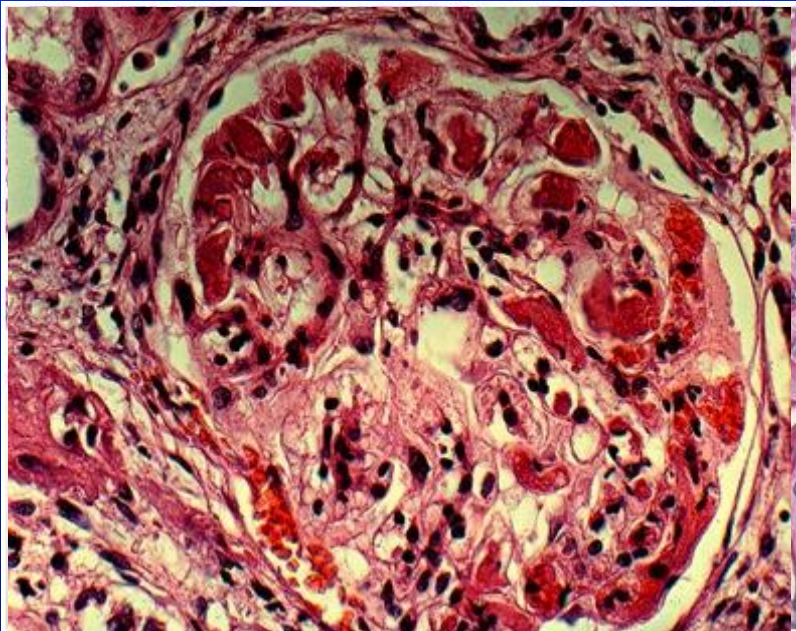


Differential Diagnosis of TMA



Case 1 continued...

- Kidney biopsy performed on hospital day #5
- Demonstrated active and chronic TMA



Case Presentation: 1-

Question 2

- Plasma exchange (PEX) started on Hospital Day #5
- Hemodialysis initiated on HD #5
 - MAHA and thrombocytopenia persisted despite PEX therapy daily for 5 days, and patients remained dialysis dependent
 - ADAMTS13 78% and APLA neg, STEC neg

What is the best next step?

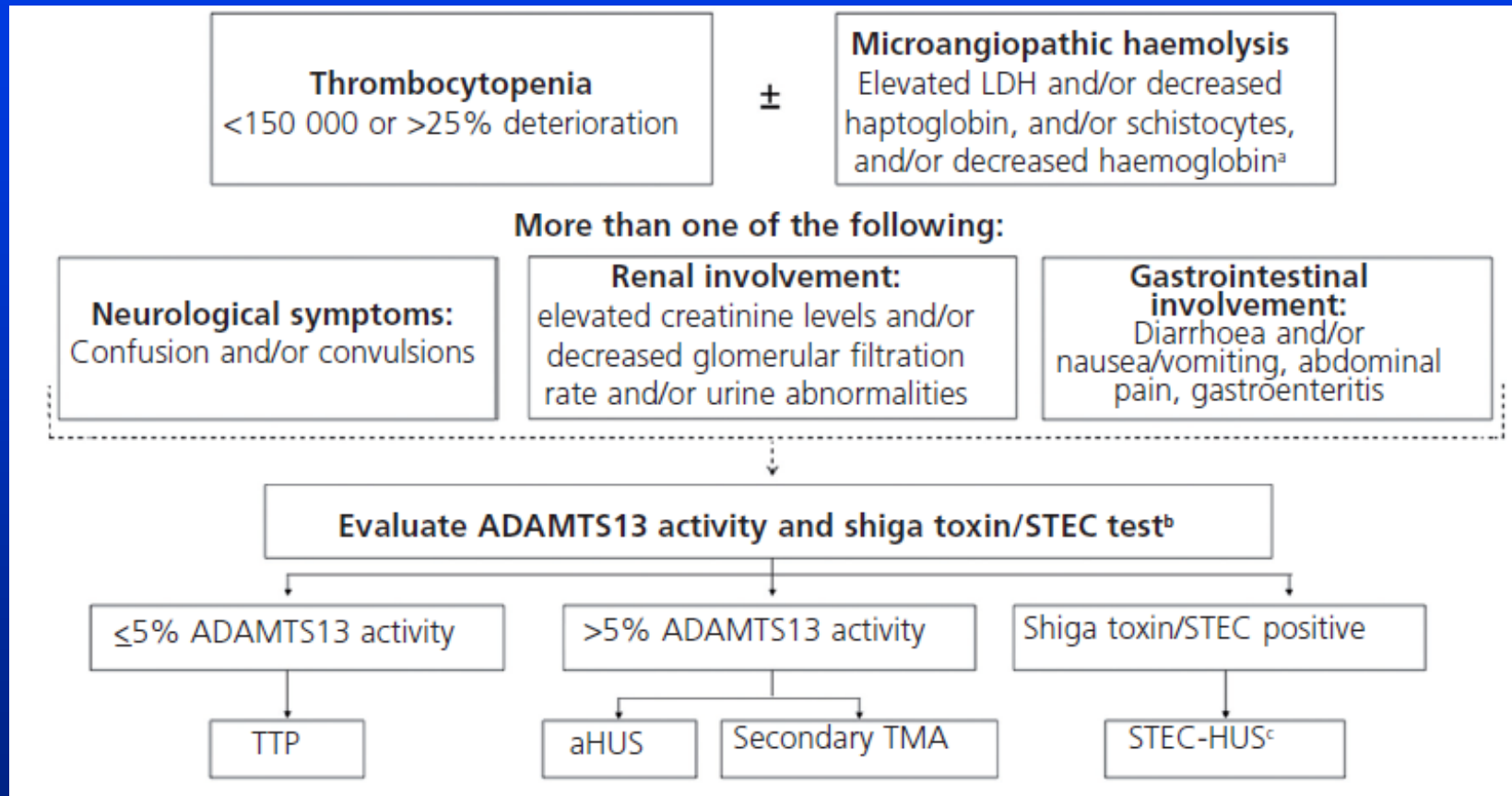
- a- continue PEX for another week
- b- Start plasma infusion
- c- Consider initiation of rituximab
- d- Eculizumab

Case Presentation: 1-

Question 3

- Before the administration of eculizumab, you should:
 - a- vaccinate the patient for *Neisseria meningitidis*
 - b- vaccinate the patient for *Neisseria meningitidis* and start at least 2 weeks of antibiotic prophylaxis for *N. Meningitidis* (e.g ciprofloxacin)
 - c- Monitor for any signs of meningitis and treat as needed
 - d- no further intervention is needed, proceed with eculizumab

Summary: Evaluation of TMA



While waiting for
ADAMTS13 result Plts>
30,000 and creatinine >2.25
mg/dl almost rules out TTP

Campistol Nefrologia 2013, Nester C Blood Purif 2013

Cataland et al, blood, 2014 x Volume 123, Number 16

Plasmic Score

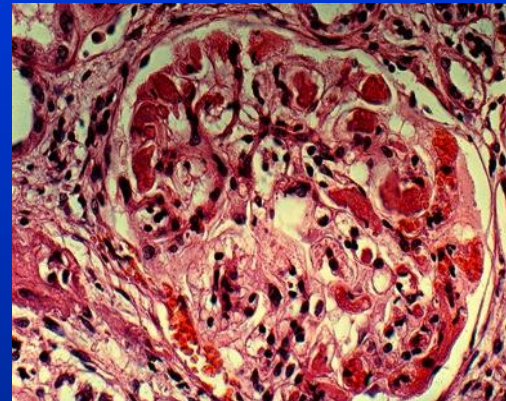
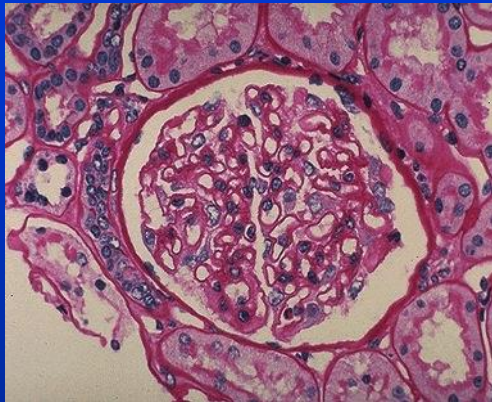
Variables	Points*
Platelet count <30 x 10 ⁹ per L	1
Hemolysis variable†	1
No active cancer	1
No history of solid-organ or stem-cell transplant	1
MCV <90 fL	1
INR <1.5	1
Creatinine <2.0 mg/dL	1
INR: International normalized ratio. MCV: Mean corpuscular volume.	
†Reticulocyte count >2.5%, or haptoglobin undetectable, or indirect bilirubin >2.0 mg/dL.	

Score	Risk Category	Risk of severe ADAMTS13 deficiency (≤ 10%)
0-4	Low	4.3%
5-6	Intermediate	56.8%
7	High	96.2%

Hemolytic Uremic Syndrome (HUS)

A thrombotic micropathology manifesting with:

- Micro-angiopathic hemolytic anemia
- Thrombocytopenia
- Acute renal failure



Classic HUS-D⁺ - diarrheal prodrome associated with shiga toxin producing 0157:H7 E.coli; most cases recover.

Atypical HUS - May be associated with mutations in complement regulatory proteins. Poor prognosis, 50% ESRD, may recur after transplantation.

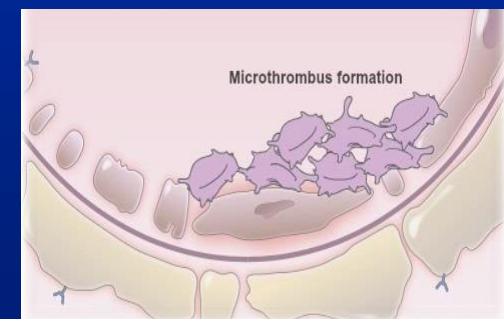
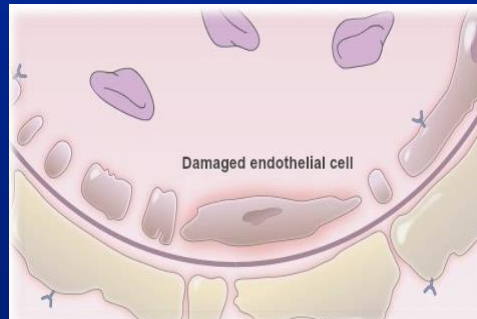
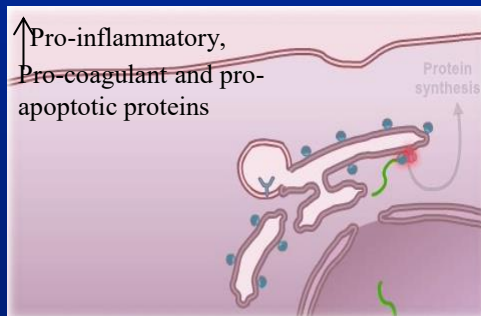
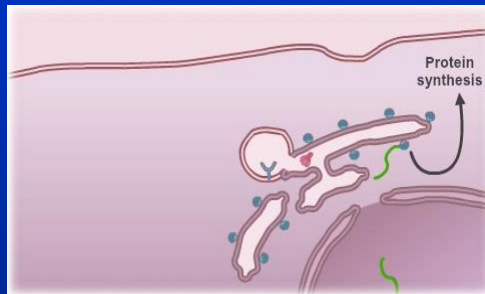
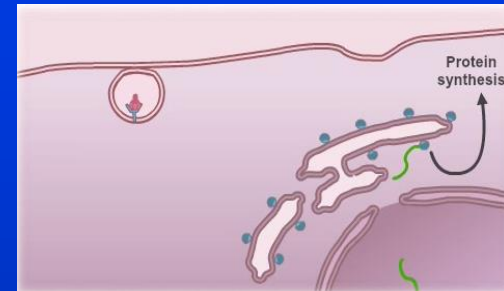
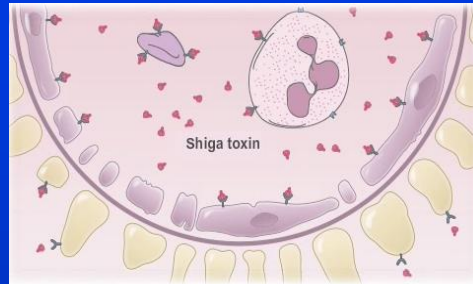
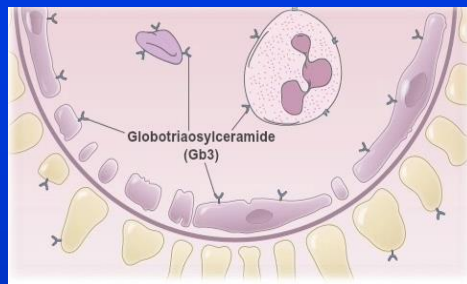
Shiga Toxin HUS

- Induced by enteric infection with shiga toxin secreting strain of Enterohemorrhagic E Coli (O157:H7, O104:H4) or Shigella (contaminated water, vegetables, beef products etc..)
- Common in children presenting with AKI
- 6-9% of STEC infected children develop HUS

STEC-HUS

- Bloody diarrhea prodrome 5-10 days
- 60% require dialysis, mean time on dialysis: 10 d.
- 25% of affected patients have neurological symptoms
- 4% mortality
- 5-25% with long term morbidity (HTN, proteinuria, decreased GFR)
- Treatment is supportive
- Role of PEX or complement inhibition uncertain

Shiga Toxin HUS: Pathophysiology



Case Presentation: 1-

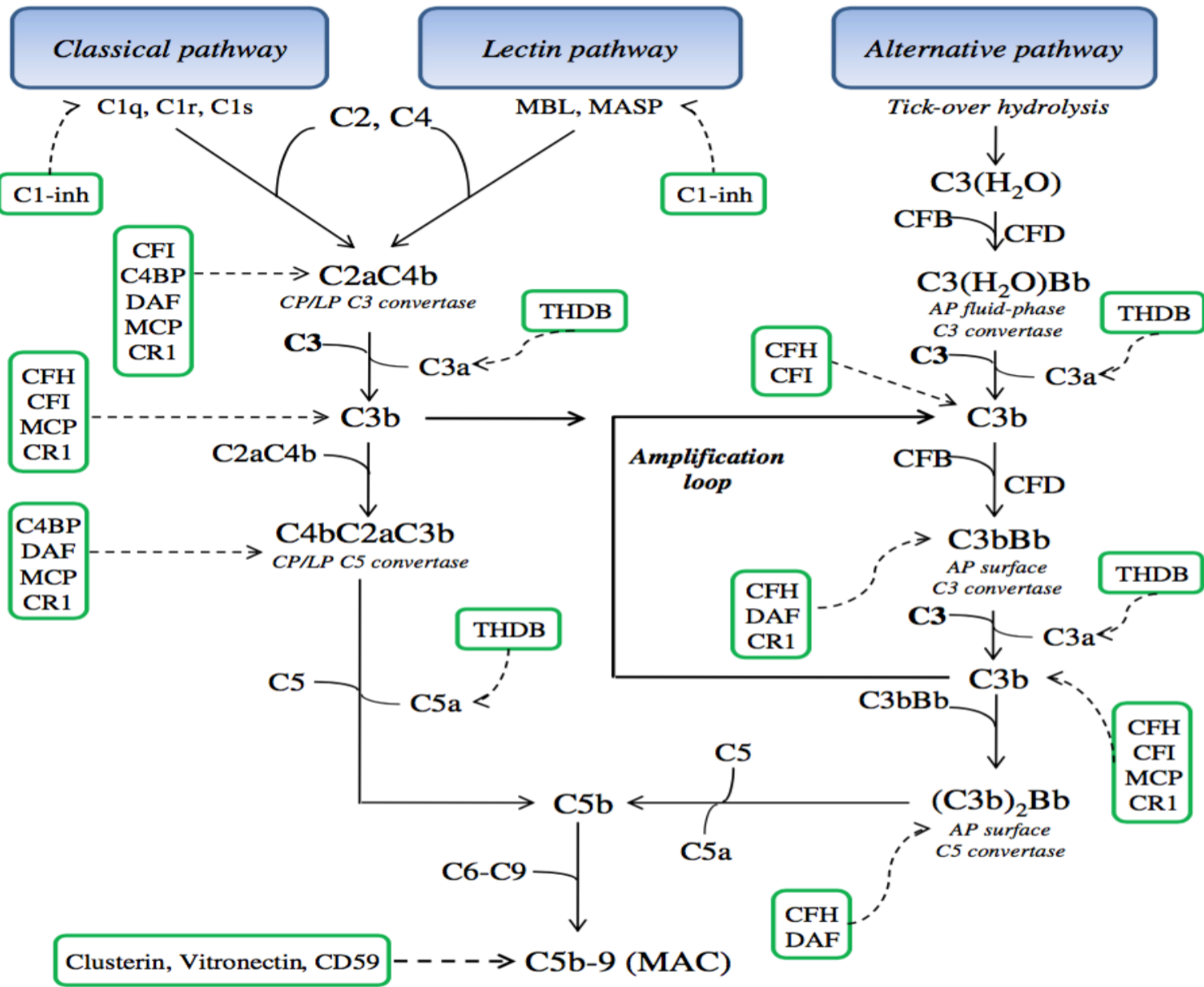
Question 4

- Which one of the following statements is correct:
 - a- Normal complement levels rule out aHUS
 - b- The absence of complement system related genetic mutations rules out aHUS
 - c- the absence of family history of aHUS, rules out aHUS
 - d- none of the above

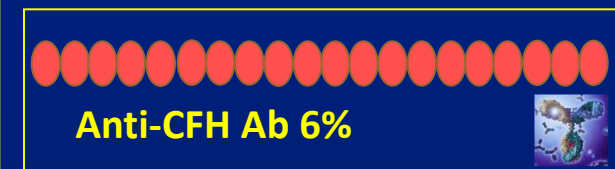
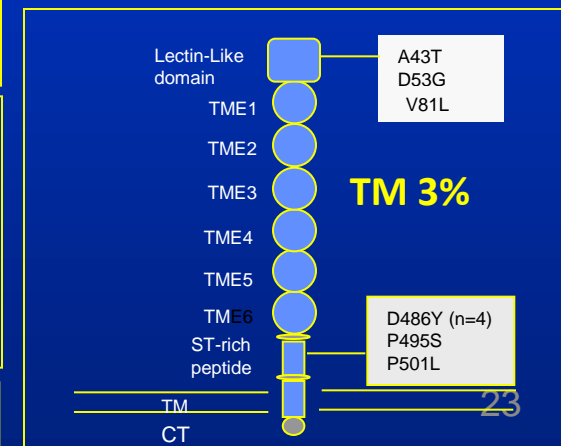
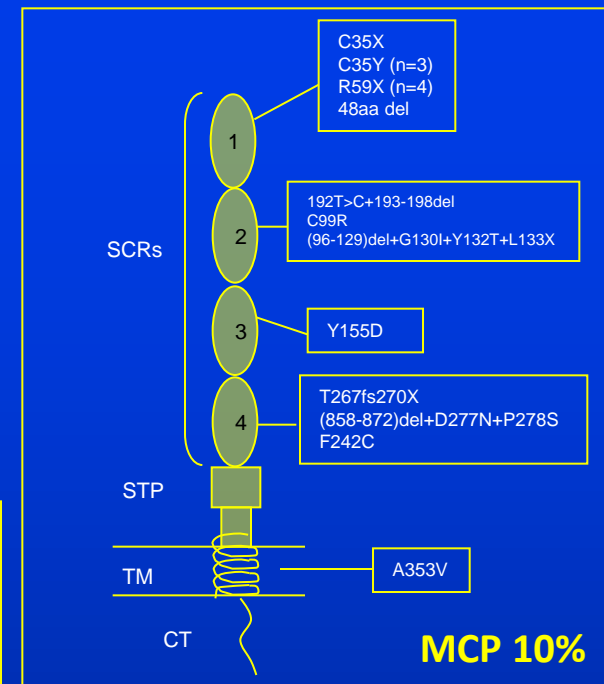
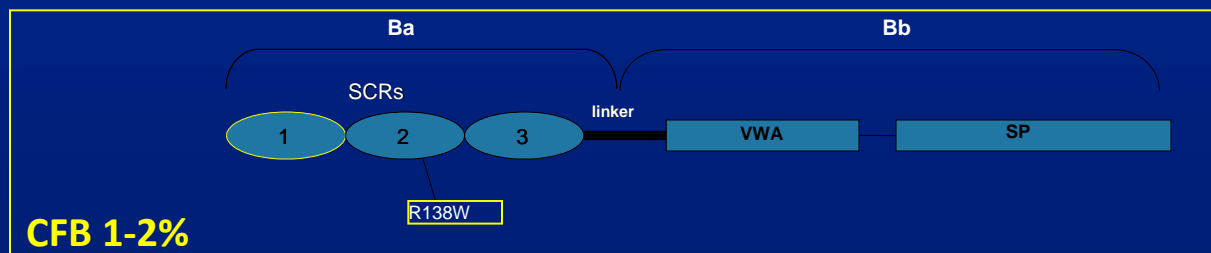
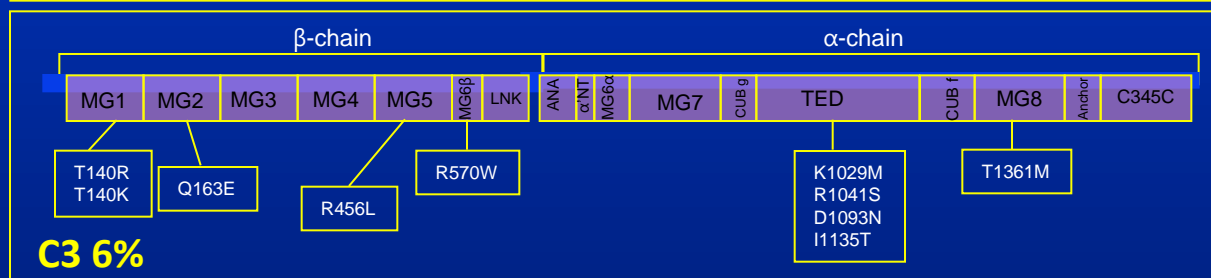
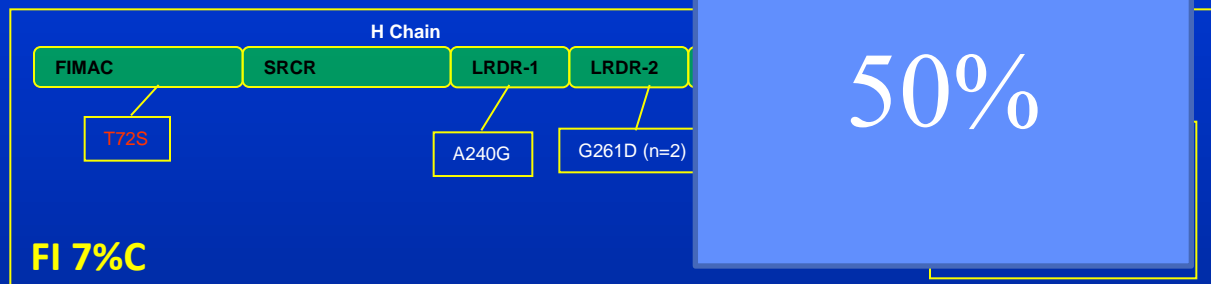
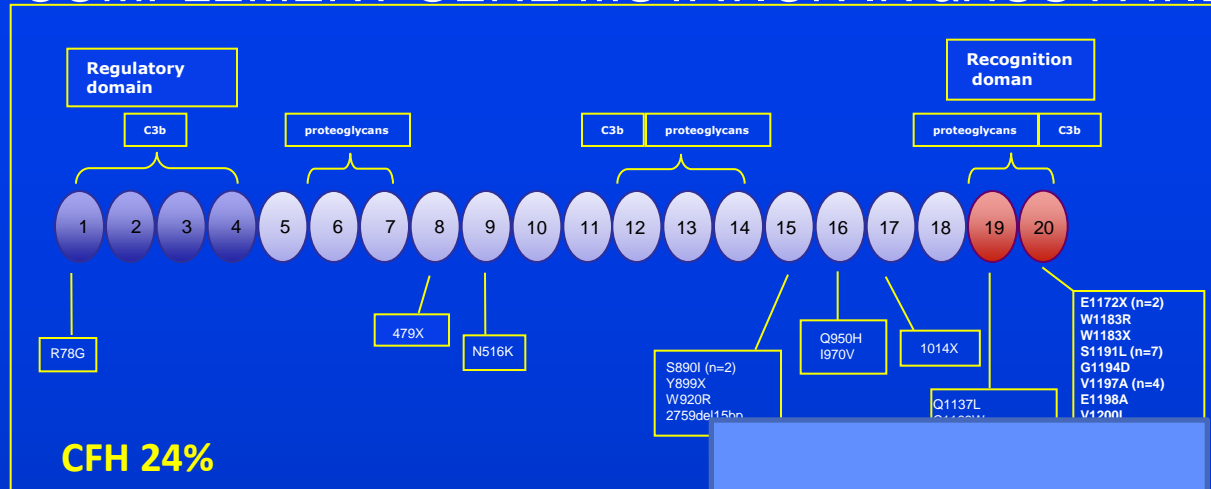
Atypical HUS

Atypical HUS:

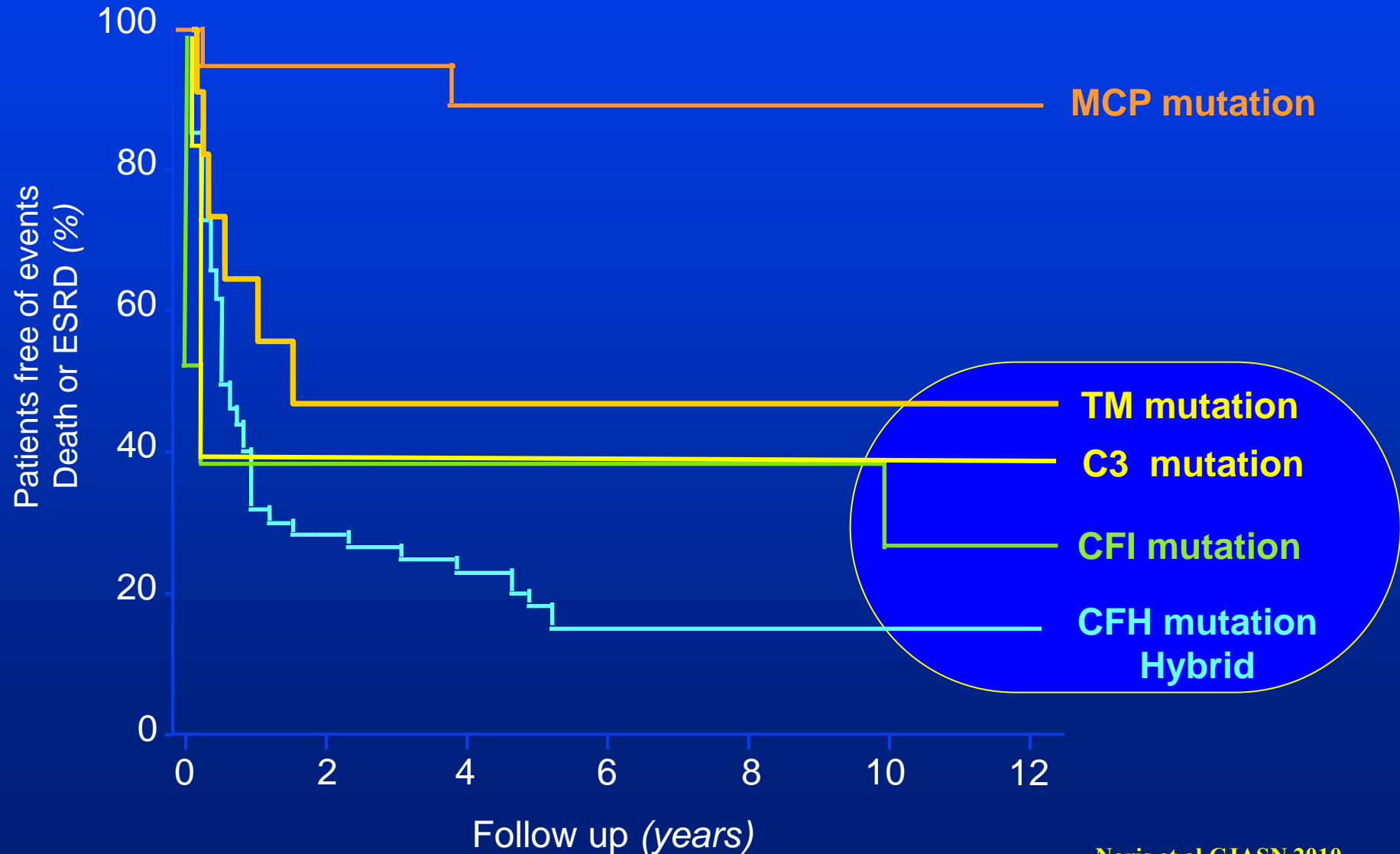
- is not induced by Shiga toxin+
- is often recurrent, 50% of patient have normal complement level and normal sC5b-9 (sMAC)
- may cause permanent kidney damage
- may cause neurological and other organ damage
- frequently recurs after transplantation
- may be sporadic or familial
- linked to abnormalities of complement regulation



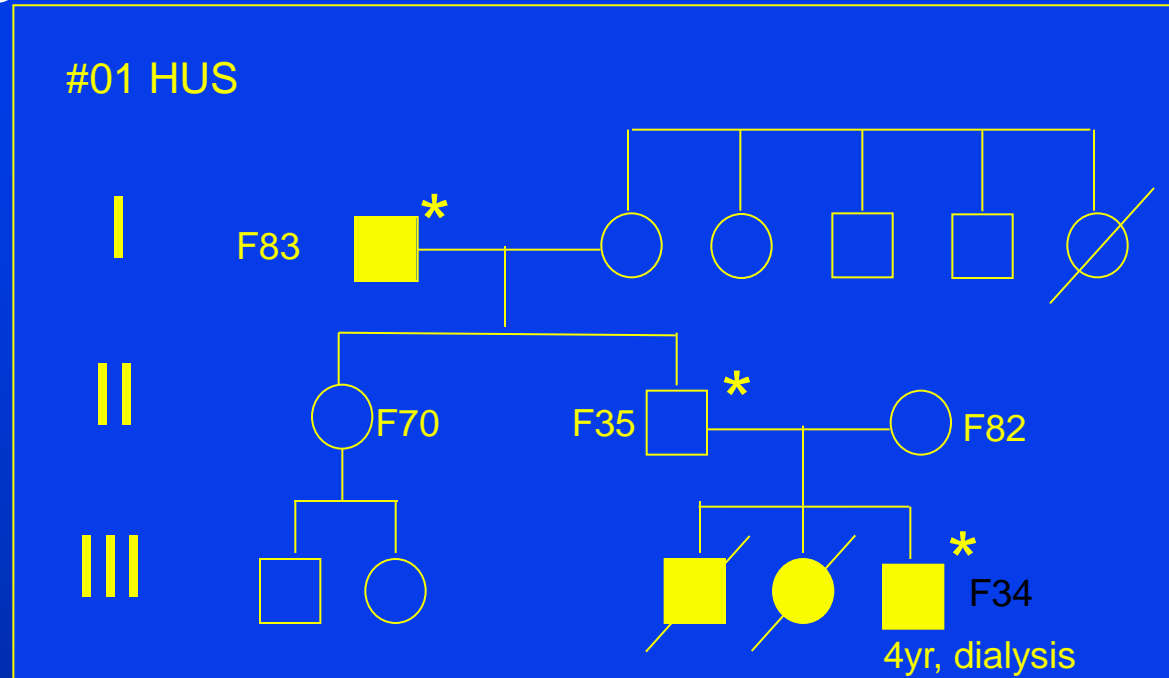
COMPLEMENT GENE MUTATION IN aHUS PATIENTS



LONG TERM OUTCOME OF aHUS PATIENTS



INCOMPLETE PENETRANCE OF aHUS IN MUTATION CARRIERS



* R1215Q change in CFH

- 3 subjects in the III generation developed aHUS in infancy: 2 died, 1 reached ESRD
- F35 never developed aHUS
- Subject F83, carrier of the R1215Q mutation developed aHUS and died at 82 years of age

Atypical HUS may arise when there is:

- Deficiency, dysfunction or autoantibody-mediated inhibition of one or more of the regulatory proteins
- Resistance of C3b or factor B to decay by factors H, I and MCP
- Mutation of thrombomodulin, an endothelial glycoprotein with cytoprotective and anticoagulant properties
- The disease may be quiescent for months or years, even in patients with homozygous mutations and complete deficiency, only to be triggered by an otherwise innocuous infection, drug exposure or pregnancy

Eculizumab/Ravulizumab

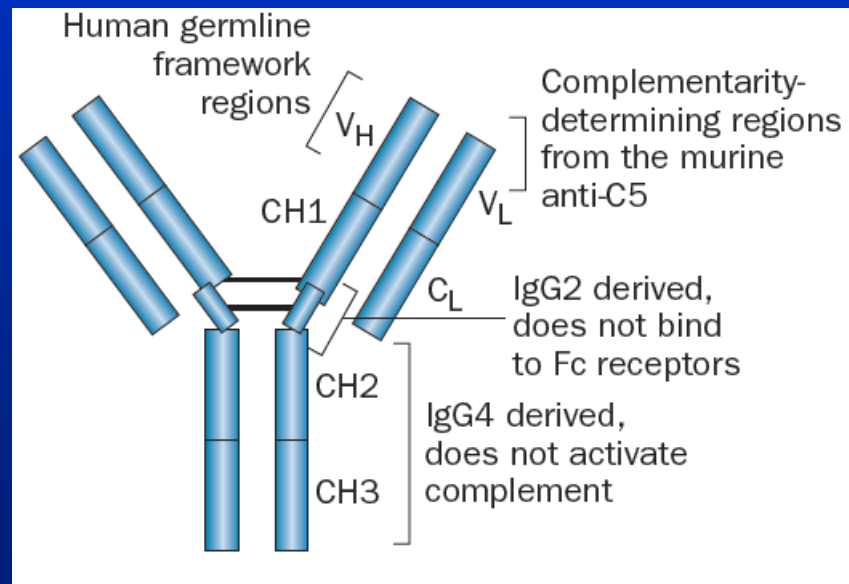
Eculizumab/Ravulizumab

A humanized monoclonal antibody that binds to C5

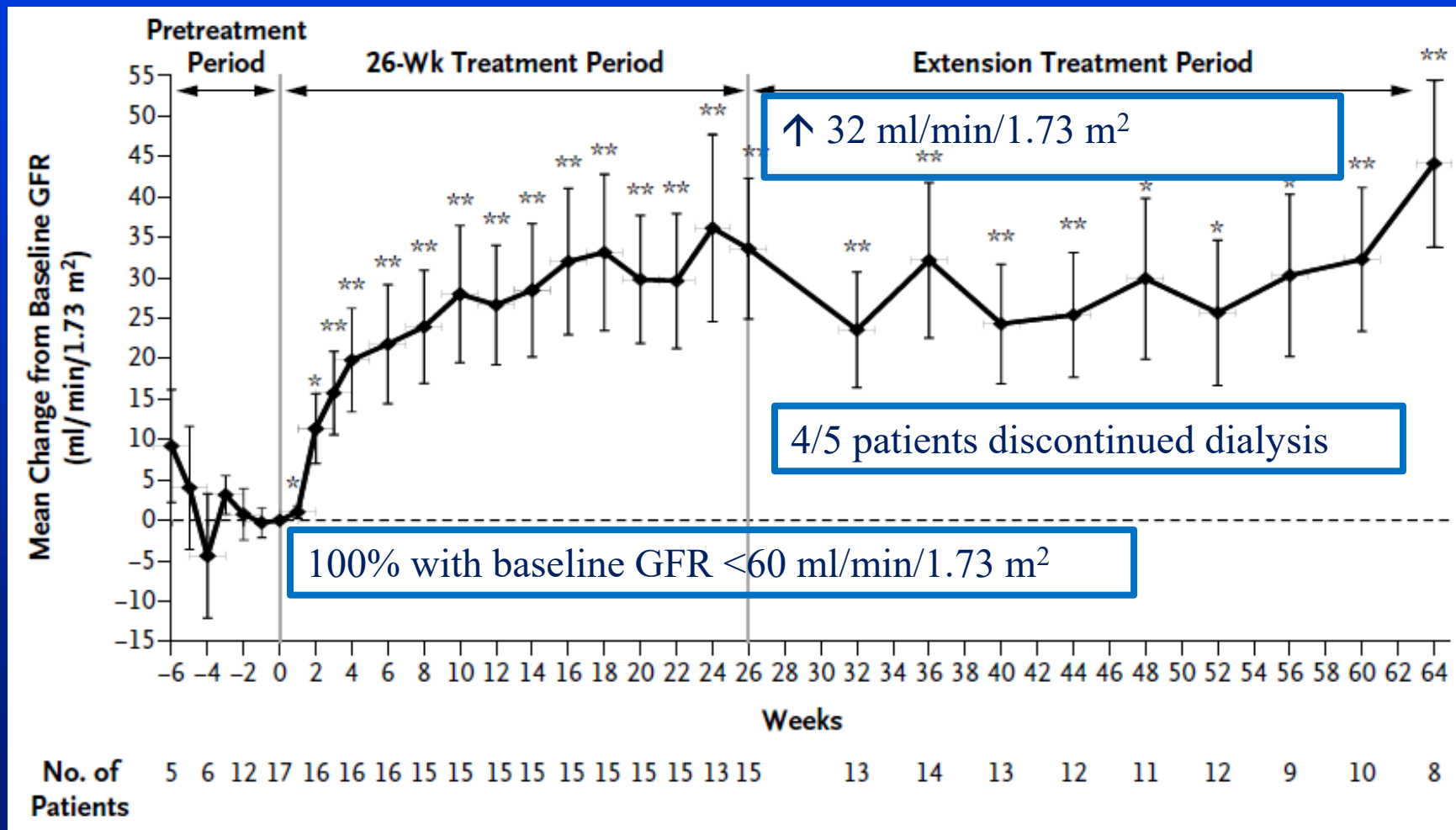
Legendre CM et al., *N Engl J Med*, 2013
Licht C et al., *Kidney Int*, 2015

Eculizumab

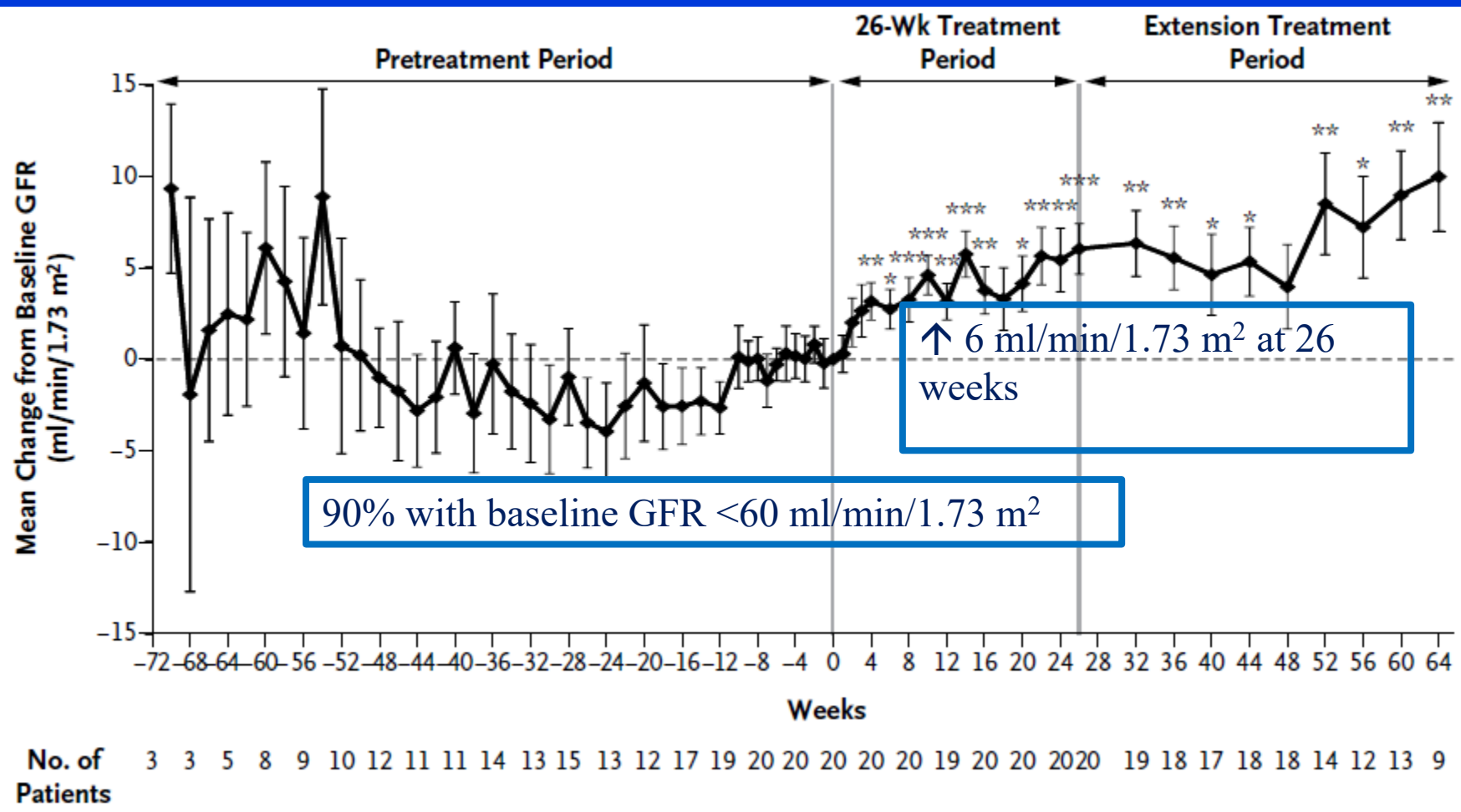
- Recombinant fully humanized hybrid IgG2/IgG4 monoclonal antibody against C5
- Prevents formation of C5a and C5b, component of the membrane attack complex



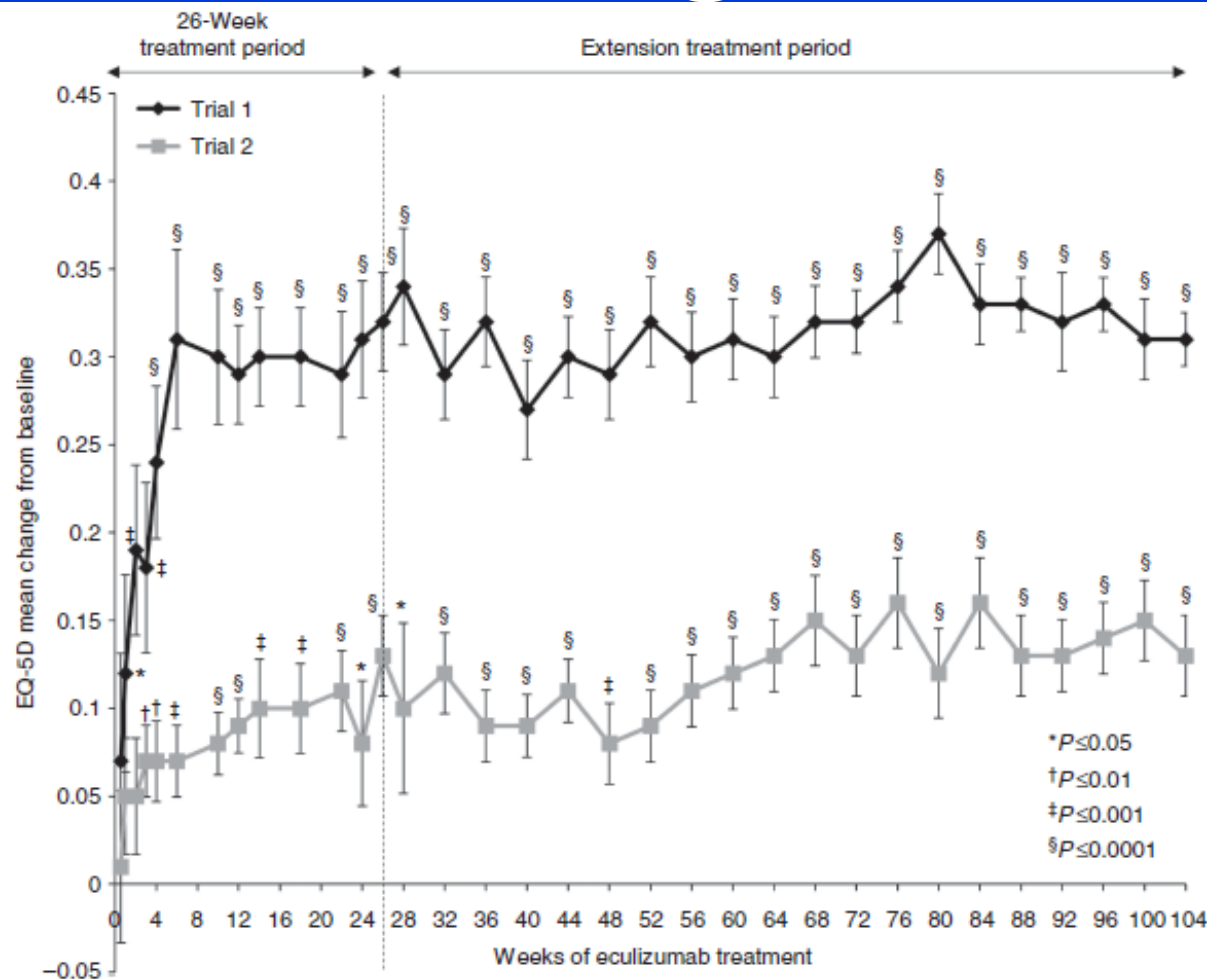
Plasma-Resistant Trial: eGFR



Plasma-Sensitive Trial: eGFR



Change in HRQoL



Clinically meaningful increase in 87%

Clinically meaningful increase in 73%

* $P \leq 0.05$

† $P \leq 0.01$

‡ $P \leq 0.001$

§ $P \leq 0.0001$

Trial 1 8 15 14 14 12 13 13 13 12 7 12 4 9 9 9 8 8 10 11 8 9 11 10 11 11 10 9 9 7 7 8
 Trial 2 18 20 20 19 19 19 17 16 18 5 17 3 19 17 19 18 19 18 17 17 16 18 18 18 16 17 18 17 16 15

Black Box Warning

PATIENT SAFETY CARD

PATIENT SAFETY INFORMATION CARD



Important Safety Information for Patients Taking Soliris®

Soliris can lower the ability of your immune system to fight infections, **especially meningococcal infection, which requires immediate medical attention.** If you experience any of the following symptoms, you should immediately call your doctor or seek emergency medical care, preferably in a major emergency medical care center.

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever of 103°F (39.4°C) or higher
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light



Get emergency medical care right away if you have any of these signs or symptoms and show this card.

Even if you stop using Soliris, keep this card with you for 3 months after your last Soliris dose. Your risk of meningococcal infection may continue for several weeks after your last dose of Soliris.

TRANSPLANTATION OUTCOMES

*aHUS recurrence
(% failure)*

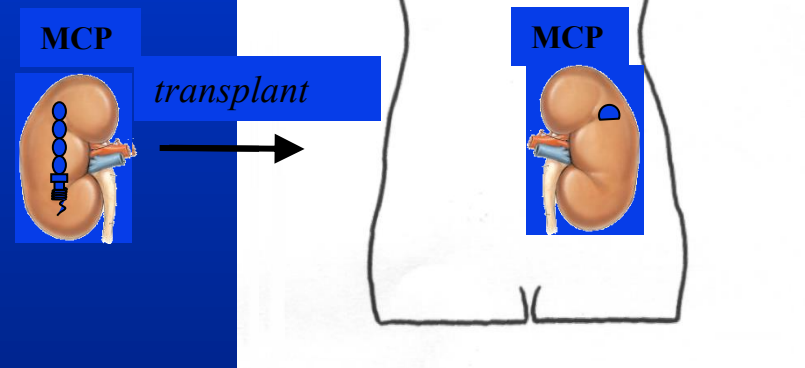
Patients with :

- CFH	mutations	49 out 76 (82%)
- CFI	mutations	19 out 26 (95%)
- CFB	mutations	4 out 4 (100%)
- C3	mutations	16 out 30 (75%)
- CFH	antibodies	5 out 17 (80%)
- MCP	mutations	3 out 17 (66%)

22.6%
■ single
combined



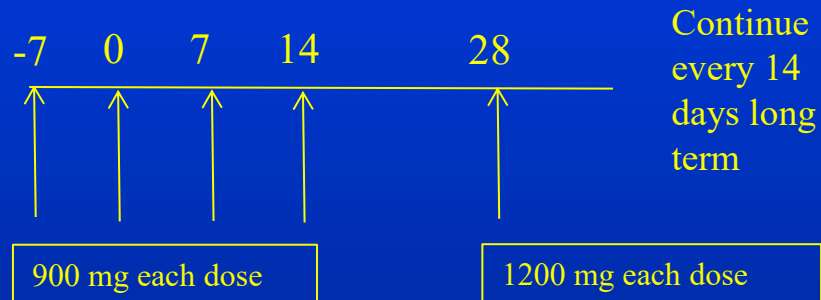
MCP?



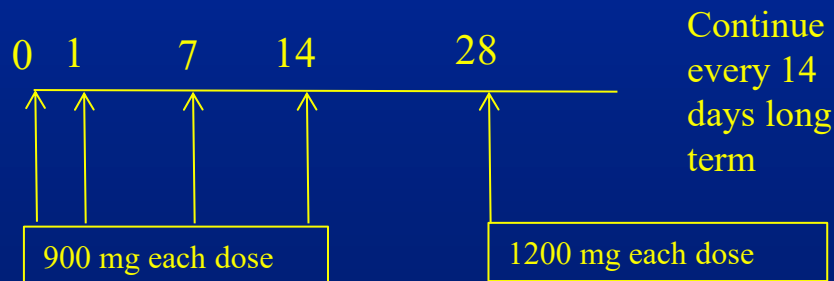
FH normal
FH mutated

Treatment Plan

- *Living donor*

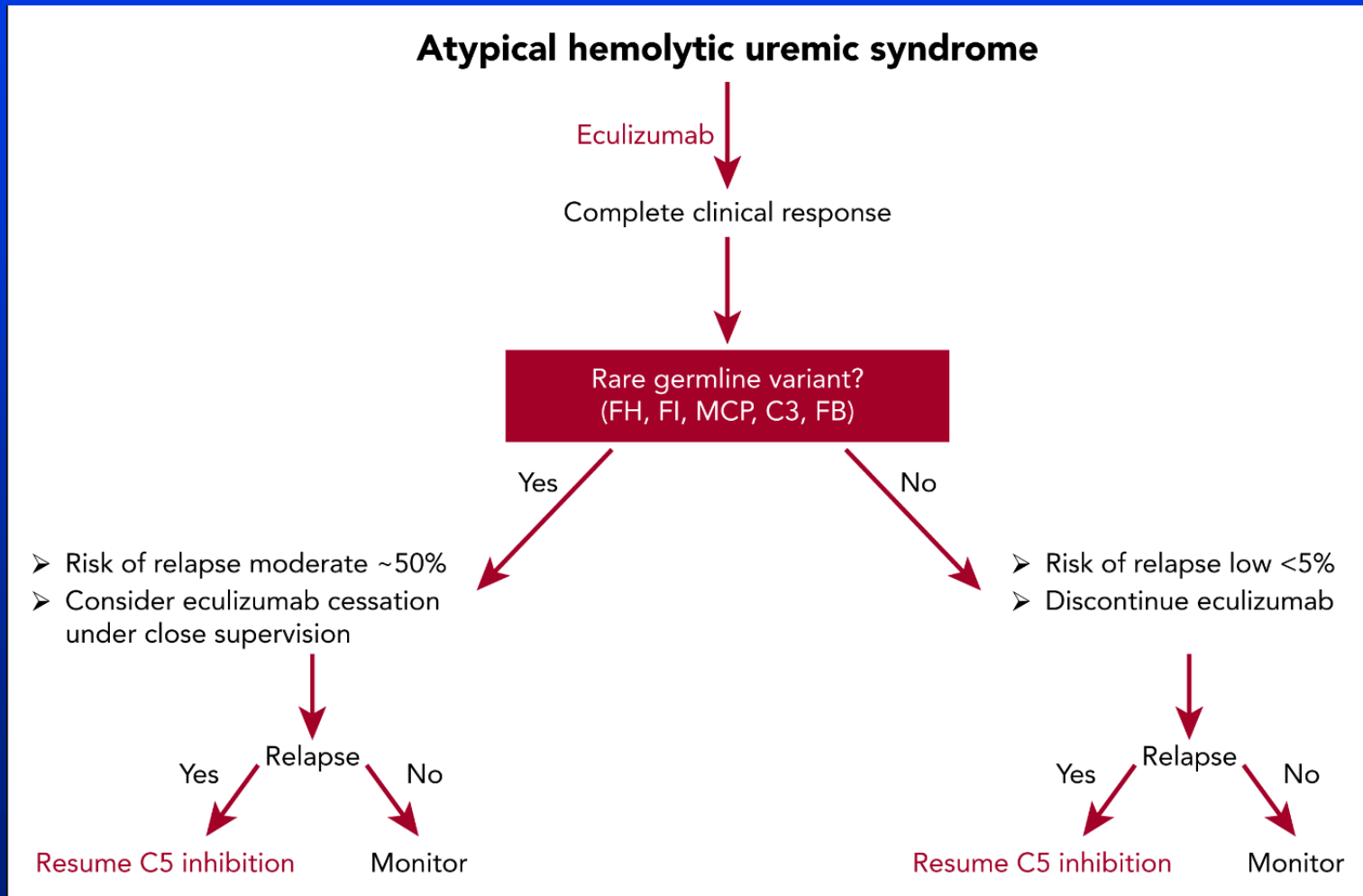


- *Deceased donor:*



Laboratory test samples must be drawn before plasma therapy and before eculizumab pre-transplant, 24 hours before transplant and post transplant to monitor eculizumab therapy

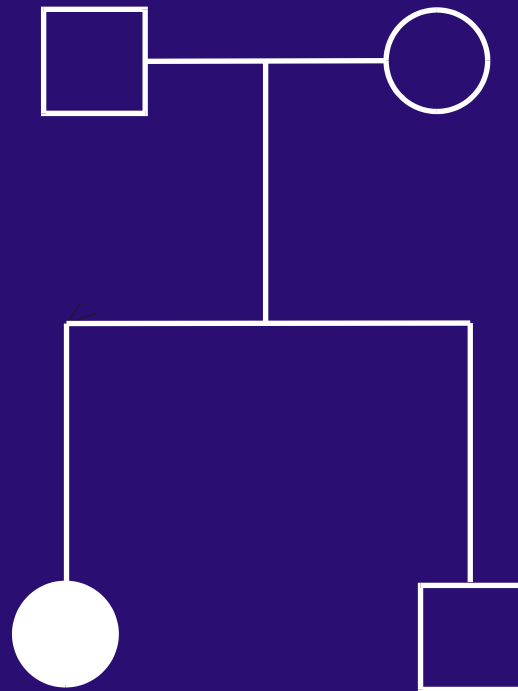
Can we stop Eculizumab?



Case 3

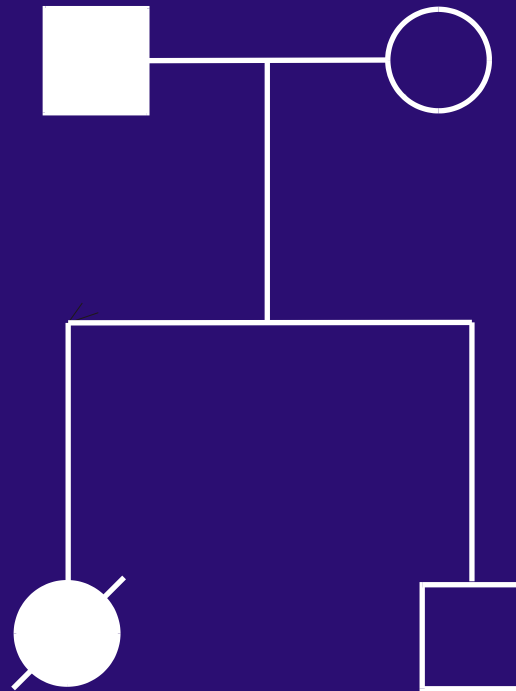
- 12 years old male patient who developed ESRD secondary to aHUS. He is now undergoing an evaluation for kidney transplantation at your center. Which of the following statement is correct:

- A- Living unrelated kidney donor should be avoided
- b- Living related kidney transplant should be avoided
- c- He can be transplanted regardless of the source of donor as long as he receives eculizumab after kidney transplantation
- d- The risk of recurrent aHUS after kidney transplantation is very low



Sporadic HUS
a. 2. LRD from
father

Father 1y later
develops HUS



Graft lost to
recurrent HUS

Mutations in Complement System Proteins in Atypical HUS

Protein	Synthesis Site	Function	Effect of Mutation	Mutation (%)
CFH	Liver (plasma)	Cofactor	Inactivating	30
MCP	Cells	Cofactor	Inactivating	12
CFI	Liver (plasma)	Protease	Inactivating	5-10
C3	Liver (plasma)	Component	Activating	5
CFB	Liver (plasma)	Component	Activating	rare
THBD	Cells	Cofactor	Inactivating	3-5
CFHR1 /CFH	Liver (plasma)	-	Competitor	3-5

Kidney transplant alone with Eculizumab or Combined liver Kidney Transplant

Isolated kidney with chronic eculizumab	Combined liver – kidney transplant
Lower short-term risk	Higher short-term mortality
Long-term outcomes unknown	Long-term outcomes stable over 10-20 years
Long-term dependence on eculizumab to prevent recurrences of aHUS	aHUS recurrence unlikely
Complications of immunosuppressive agents	? Fewer complications of immunosuppressive agents
Chronic rejection	? Reduced risk of chronic rejection
IV infusion every 2 weeks	Better lifestyle with no infusions
Limited worldwide availability	More widely available But scarce liver plus kidney availability
Extremely expensive	Less expensive

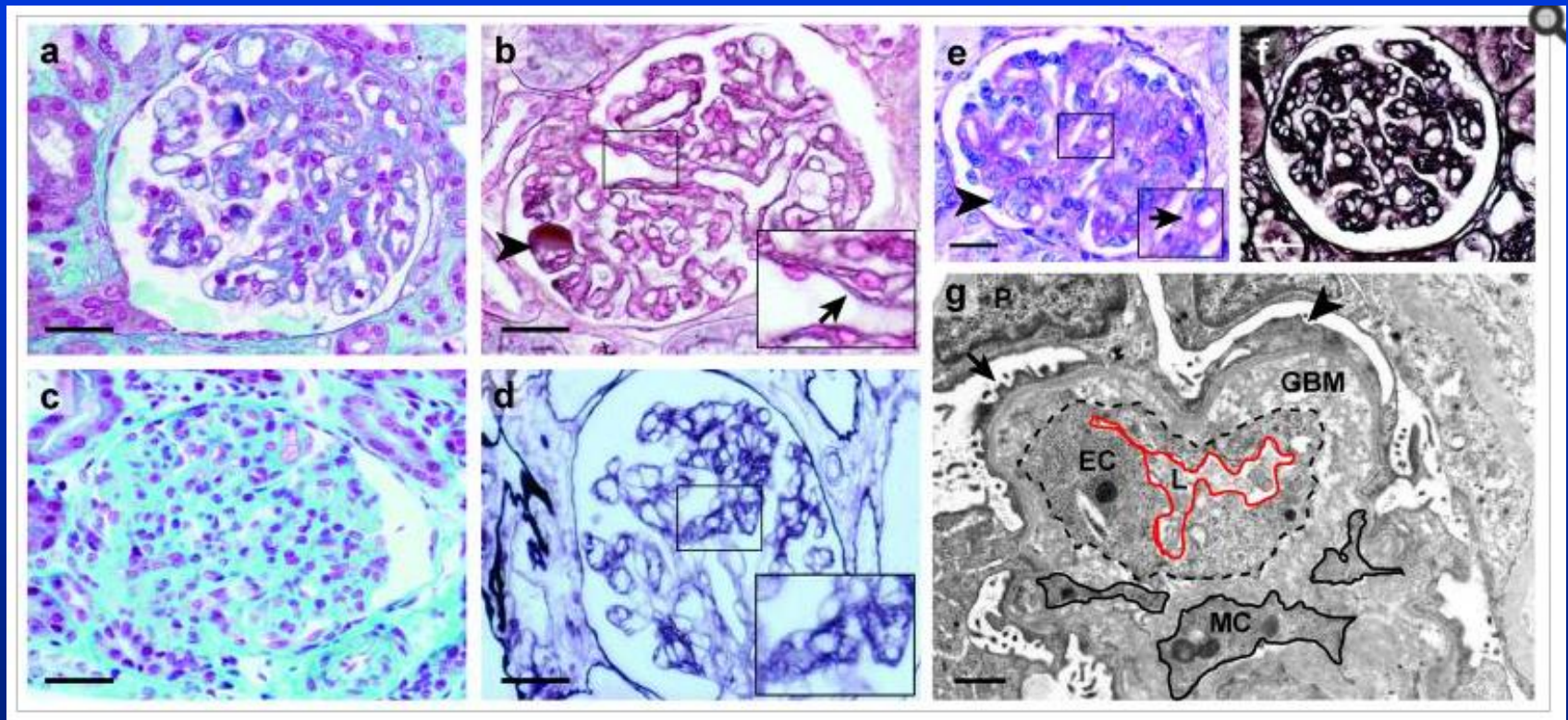
Complement based therapeutics in the pipeline for renal disorders none FDA approved for aHUS yet

Drug Class	Name	Current use	Potential use
C1 Esterase Inhibitor	Berinert, Conestat Alfa, Cinryze	- Acute and chronic graft injury [Transplantation]	
MASP2 Inhibitor	OMS721	- TMA	- aHUS, HSCT-TMA - IgA Nephropathy
Anti-C5 antibody	Eculizumab	- PNH - AHUS	- Delayed AMR - Transplant associated TMA - Idiopathic Membranous GN
C5aR antibody	CCX168		- ANCA vasculitis - AHUS [with congenital complement abnormality]
C3 inhibiting peptide	AMY 101 Compstatin, Pegcetacoplan		- PNH - C3GP, aHUS
C3 soluble complement receptor	TP 10		- DDD
C5 inhibitor	Coversin		- PNH
Factor D inhibitor	ACH-4471 (Danicopan)		- PNH

Case 4

- 10 months old male enfant presents with MAHA, thrombocytopenia, and AKI. He has no known family history of aHUS. The patient had persistent hypertension, hematuria and also nephrotic range proteinuria. All genetic complement testing for aHUS were negative and he had no circulating anti-CFH antibodies. C3 and C4 are normal.
- a Kidney biopsy was performed.

Case 4



Case 4: Question 1

- What is the most likely diagnosis:
 - a- complement mediated aHUS
 - b- TTP
 - c- HUS secondary to diacylglycerol kinase ϵ (DGKE) mutation
 - d- Lupus nephritis

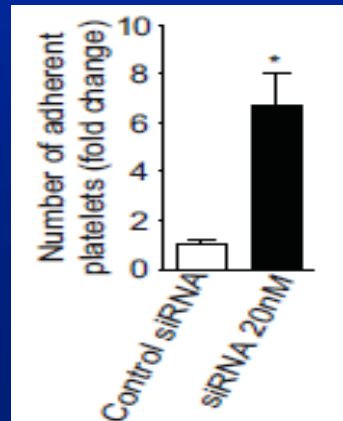
RECESSIVE MUTATIONS IN *DGKE* CAUSE aHUS SYNDROME

- Homozygous or compound heterozygous mutations in *DGKE* (encoding diacylglycerol kinase ϵ) were found in 27% of aHUS cases with onset in the first year of life
- Peculiar clinical phenotype: recurrent disease in childhood, development of proteinuria sometimes with the nephrotic syndrome
- *DGKE* is not an integral protein of complement and patients did not show complement consumption and one relapsed while on eculizumab

Lemaire M et al, Nature Genet 2013

Consequences of *DGKE* deficiency

- *DGKE* knock down in endothelial cells up-regulated ICAM-1 and tissue factor expression and resulted in platelet adhesion without inducing complement deposition.



Bruneau et al, Blood, 2015

TTP

- Described in 1924 by Moschowitz
- Associated with CNS involvement
- In the 1980's TTP was a disease in search of an etiology
- Large von Willebrand multimers were initially identified.

TTP Pentad

- Severe Thrombocytopenia (10-30k)
- MAHA
- Neurological involvement (headache, confusion, TIA, seizure, etc..)
- Renal failure
- Fever

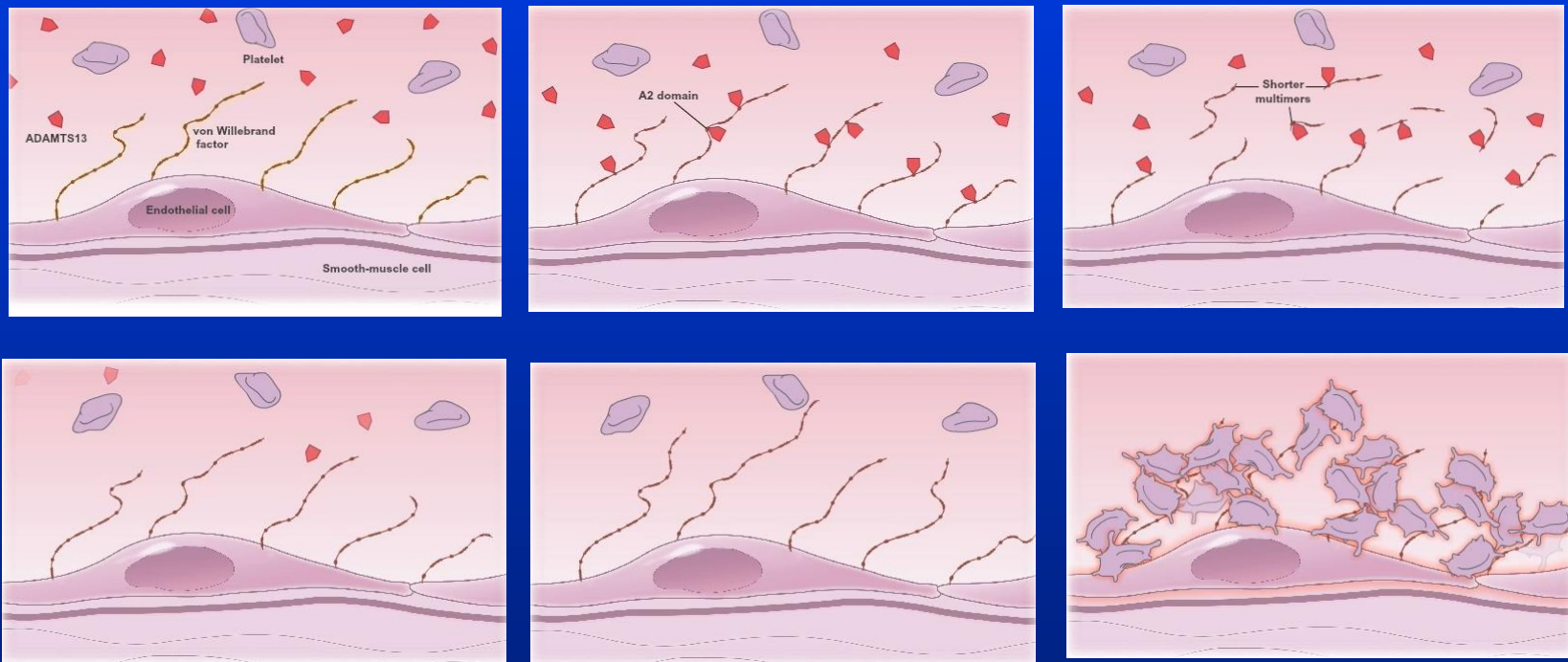
Von Willebrand Factor (vWF)

- Large glycoprotein
- Dimers form in the ER
- Multimers form in the Golgi
- vWF is released in the plasma as large multimers with high MW, the biologically active form
- A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) usually cleaves vWF multimers

Hereditary Thrombotic Thrombocytopenic Purpura (TTP)

- Homozygous or compound heterozygous mutations of ADAMTS13 (Upshaw-Schulman syndrome) causing ADAMTS13 deficiency in the absence of auto-antibody
- Usually presents in children can present in adults (e.g. precipitated by pregnancy)
- Patients with heterozygous mutations are normal

Hereditary TTP: Pathophysiology

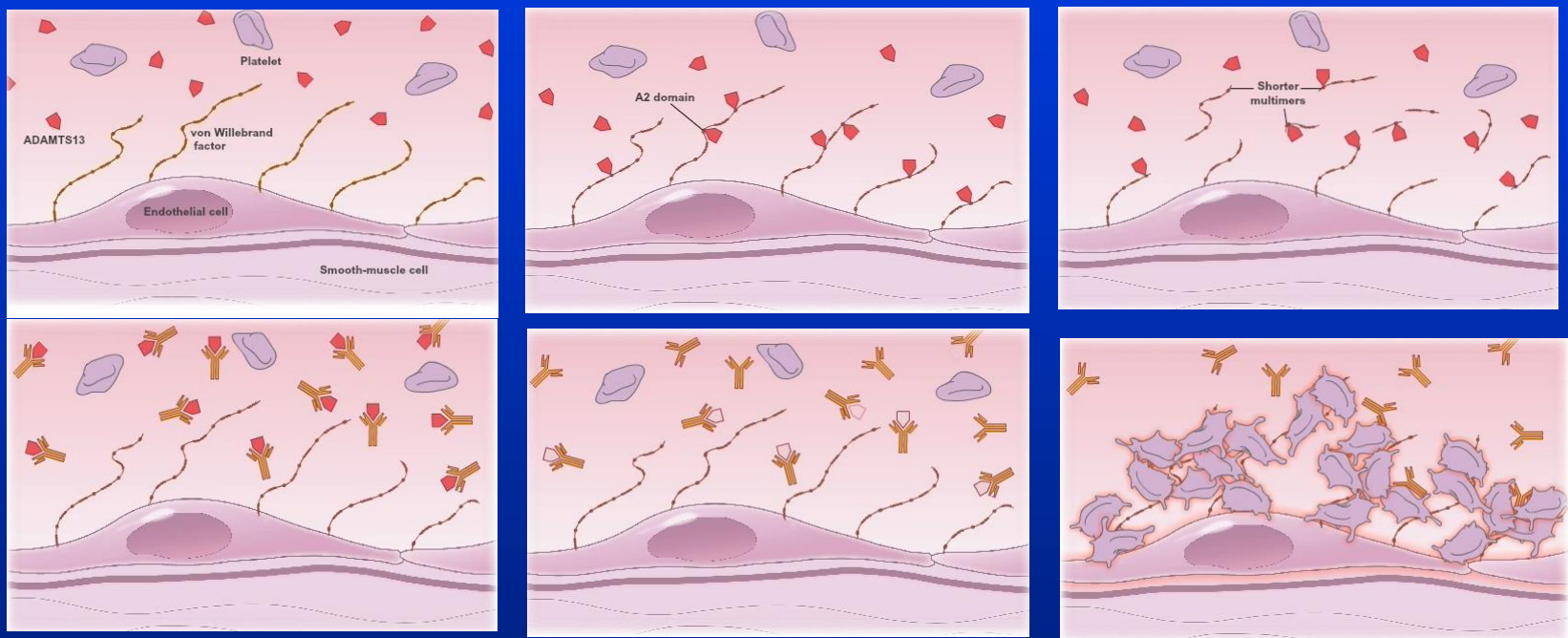


Treatment: Plasma infusion or Plasma derived factor VIII concentrate (if plasma allergy) which contains ADAMTS13

Acquired Thrombotic Thrombocytopenic Purpura (TTP)

- Variable presentation (weakness, GI symptoms, purpura, focal neurological deficit)
- Normal or transient mild renal failure!
- 1/3 have no neurological findings
- ADAMTS13 activity $<10\%$ caused by an autoantibody blocking ADAMTS13 or accelerating its clearance

Acquired TTP: Pathophysiology

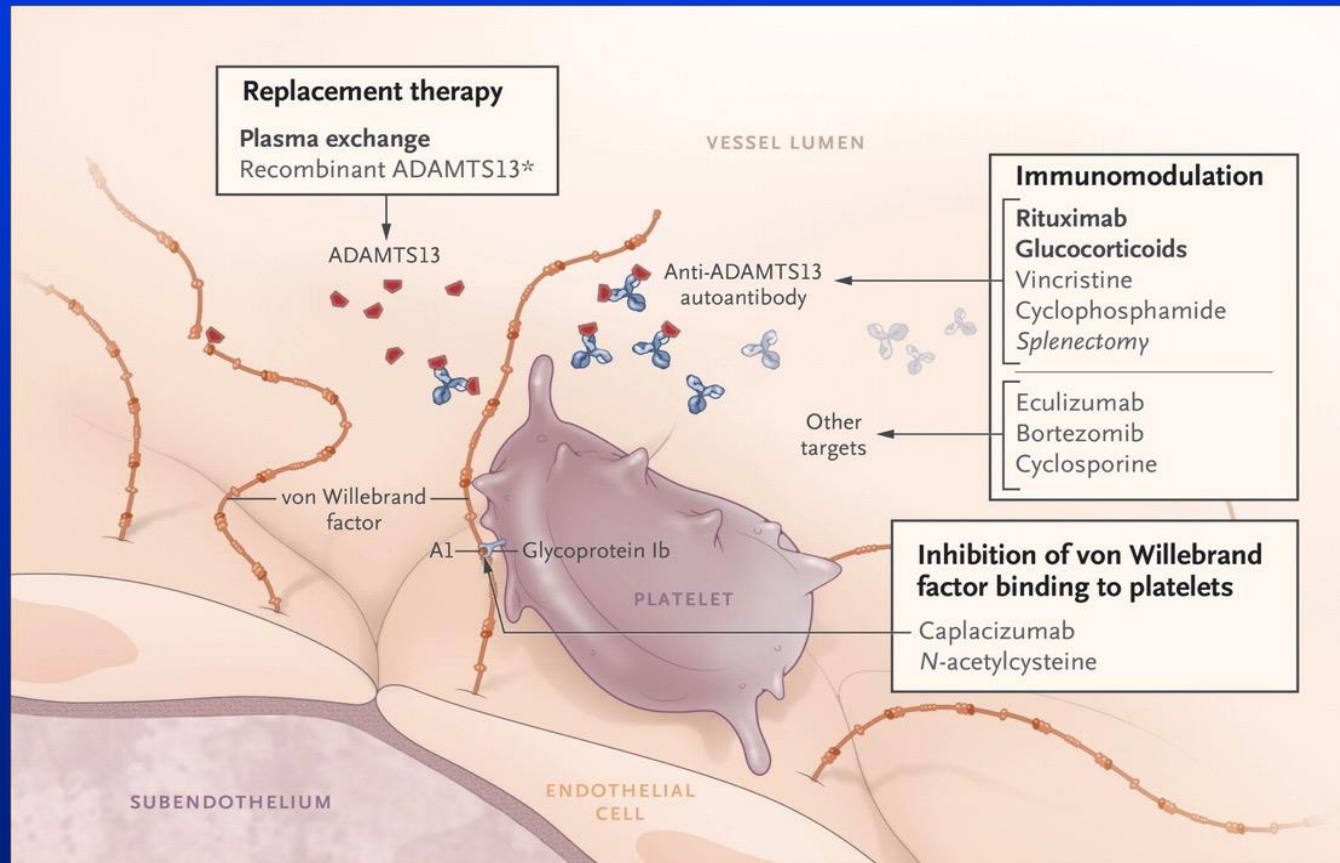


Treatment: without PEX mortality close to 90%, PEX (standard of trt) 60-90% survival. Steroids, rituximab, bortezomib, other IS can be used. Dialysis rarely required

Therapy of Acquired TTP

- Adults with TTP- plasma exchange (removes large multimers of vWF and autoantibodies to ADAMTS13 and allows infusion of metalloprotease), 90 % survival with PEX for TTP (mortality 90% in the past), PEX performed daily and continued until platelets are normal (>150000)
- Steroids are frequently used
- Rituximab (Anti-CD 20) often used for severe cases (severe neurological symptoms)
- Aspirin or anticoagulants may increase bleeding risk , platelets transfusion can be used in severe thrombocytopenia

Treatment for TTP



Case 5

35 y/o female with no PMH presents with 5d headache, N/V and non-bloody diarrhea

- No recent travel
- Husband and kids are healthy, and ate same foods
- Has never had this constellation of symptoms before

Case 5, continued

Medications: none

PMH: 3 full-term vaginal deliveries, no miscarriages

SH: occasional EtOH, no tobacco, no illicit drugs

FH: father with HTN, CAD; siblings and children healthy

Physical Exam

VS: T 100.0 HR 90 BP 145/90 RR 16 O₂ sat 98%
(RA)

60 kg, no apparent distress, mild pallor

Lungs: clear

Heart: RRR, no MGR, normal pulses

Abd: diffusely tender with deep palpation, no rebound

Extr: no edema, no rashes

Neuro: no focal deficit

Laboratory tests

Creatinine 2.0, BUN 36

WBC 11.0 / Hgb 9.0 / Plts 30

LDH 1800, haptoglobin <8

Normal amylase, lipase, LFTs

UA: SG 1.015, pH 5.5, 1+ protein, 2+ blood, trace
LE

> 20 RBC/hpf, > 10 WBC/hpf, several granular casts

Case 5, continued

- Blood and urine cultures negative
- Stool cultures negative for bacterial dysentery, STEC negative
- INR 1.1, PTT 28, D-dimer normal
- Samples sent for ADAMTS13 activity and anti-phospholipid antibodies

Case 5: Question 1

- What is your first therapeutic approach?
 - a- Plasma exchange with steroids
 - b- plasma infusion
 - c- steroids and rituximab
 - d- Eculizumab

Case 5, continued

- Plasma exchange initiated with FFP
- Rapid improvement in headache
- Platelet count 180 by day 4, LDH down to 280
- On day 5, prior to plasma exchange, Plts dropped to 140
- LDH increased to 480
- Return of headache and < 10 min episode of left-sided weakness
- ADAMTS13 activity returned < 5% of normal
- ADAMTS13 inhibitor present, consistent with acquired TTP

Case 5, Question 2

- What is the best therapeutic approach for this refractory TTP
 - a- Increase the dose of PEX to twice daily
 - b- Continue current dose of PE, high dose steroids and rituximab given at end of PEX
 - c- Eculizumab
 - d- reconsider your diagnosis.

Case 6

- The best treatment of the first relapse of acquired TTP (usually occurring >30 day after initial episode recovery), after an initial good response to PEX and steroids during the first presentation is:
 - a- PEX and steroids
 - b- PEX/steroids and Rituximab
 - c- splenectomy
 - d- cyclophosphamide

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Thank you!

- *Questions*