

# aHÜS Yönetimi

Dr.Figen ATALAY

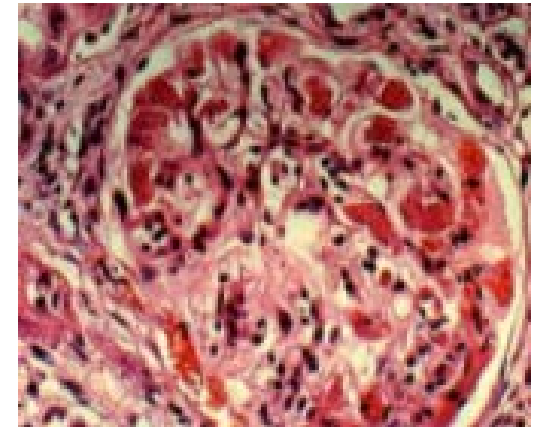
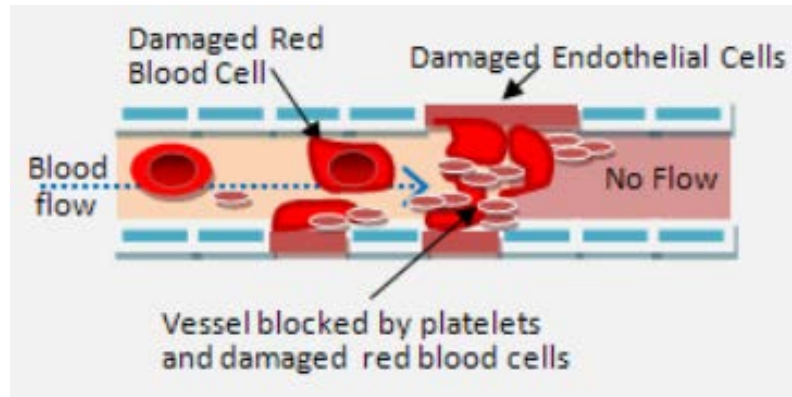
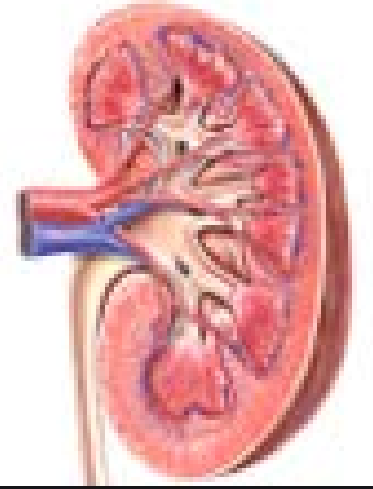
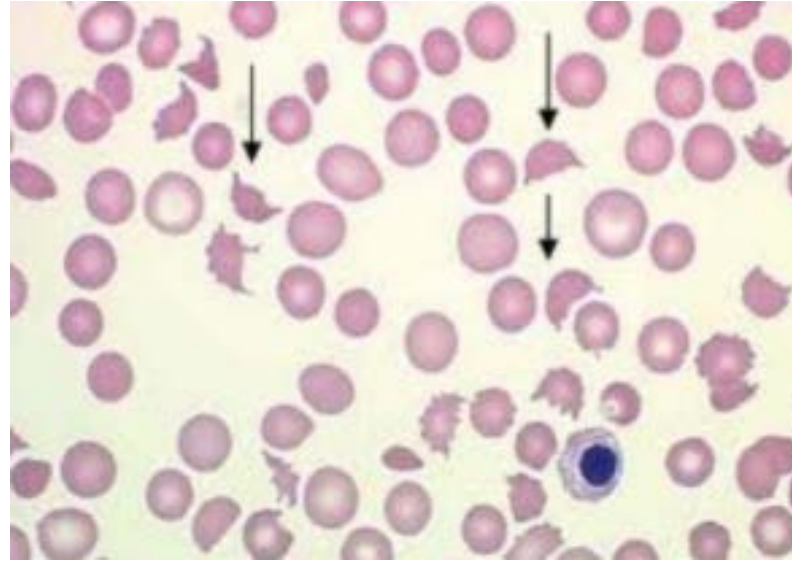
Başkent Üniversitesi Tıp Fakültesi

# Trombotik Mikroanjiopati

Mikroanjiopatik  
Hemolitik Anemi

Trombositopeni

Son organ hasarı



# **Trombotik Mikroanjiopati**

**TTP**

**Hemolitik Üremik  
sendrom**

ADAMTS13 fonksiyonunun azalması  
(<%10)

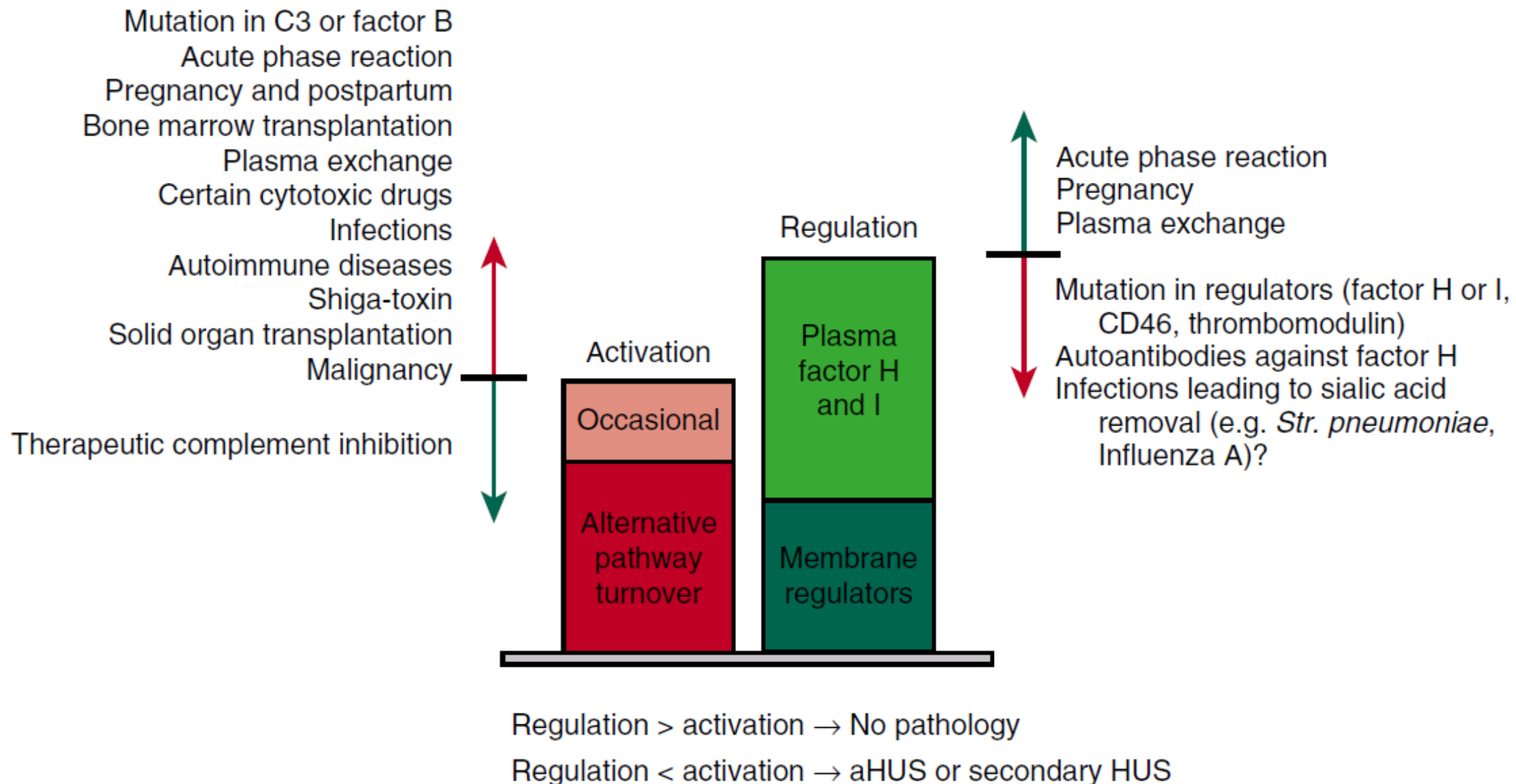
Sistemik bir hastalık  
Multiorgan hasarı  
(SSS, kalp, daha az böbrek)

# **Hemolitik Üremik Sendrom**

**Tipik HUS  
(STEC-HUS)**

**Atipik HUS**

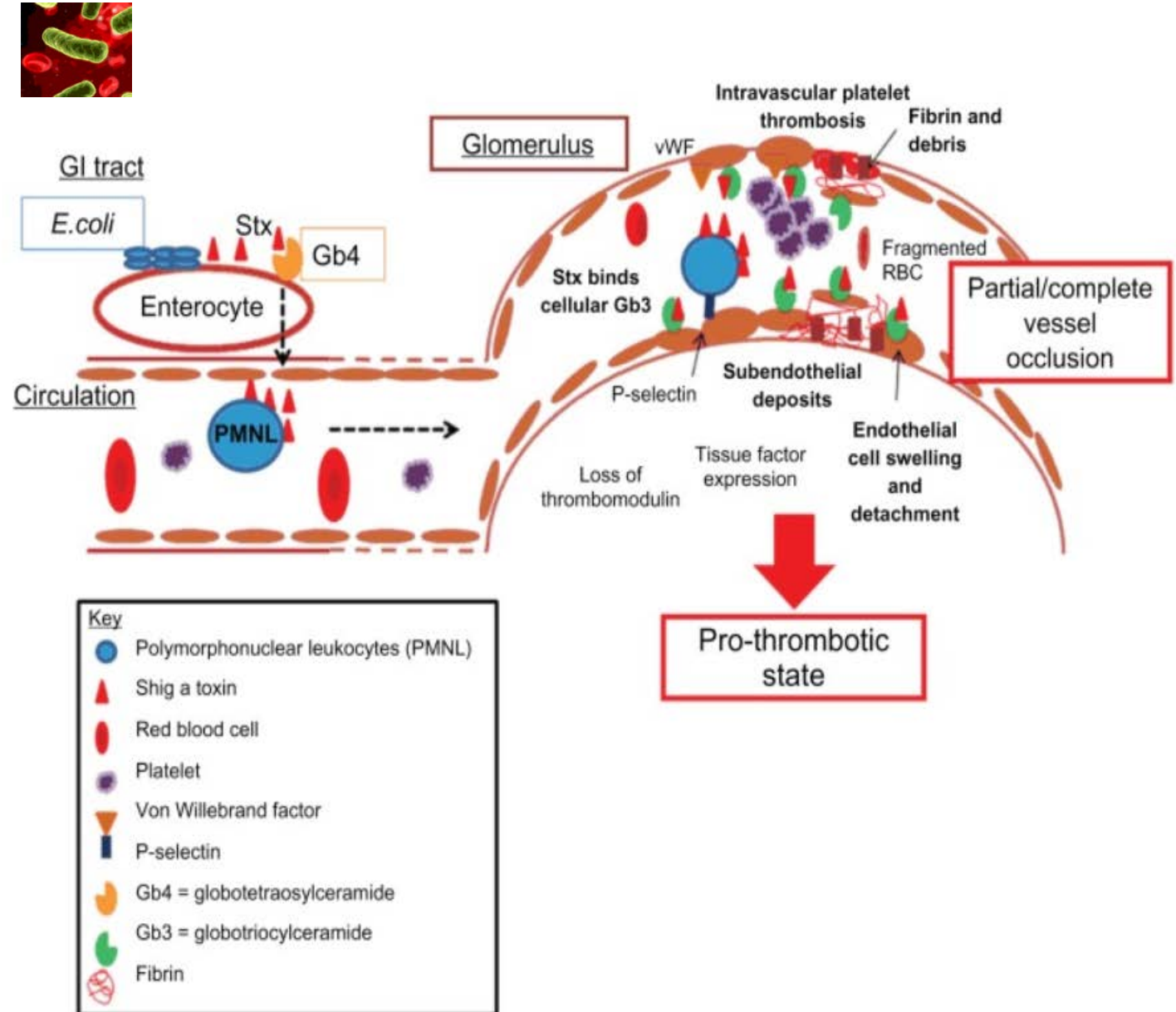




## Tipik HUS (STEC-HUS)

STEC (shiga toxin  
üreten E.Coli)  
Pnömonok enfeksiyonları

- Çocuklarda daha sık
  - Kanlı diare
- ~%15 akut renal yetmezlik
- Renal fonksiyonlarda kalıcı hasar nadir

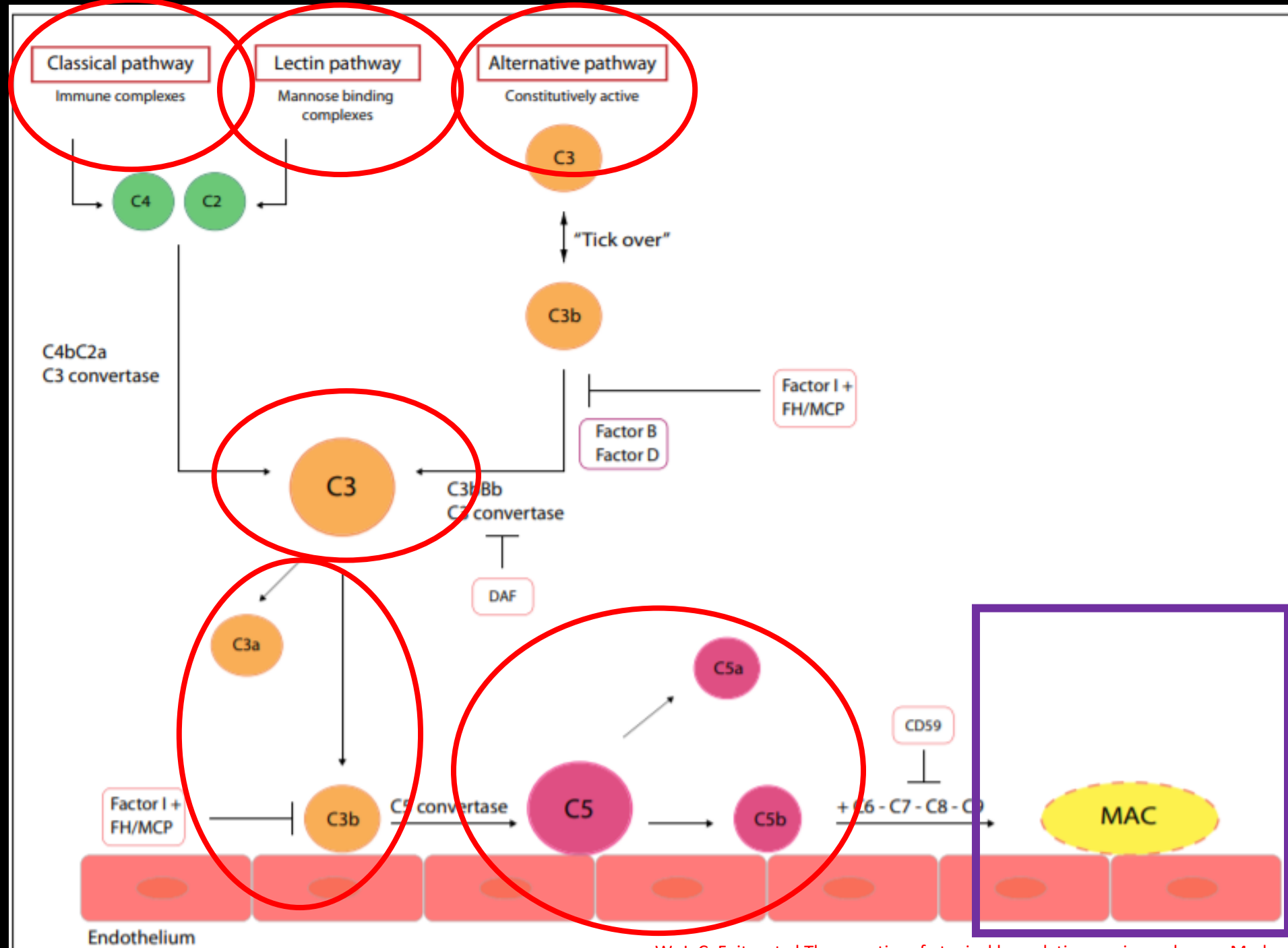


## Atipik HUS

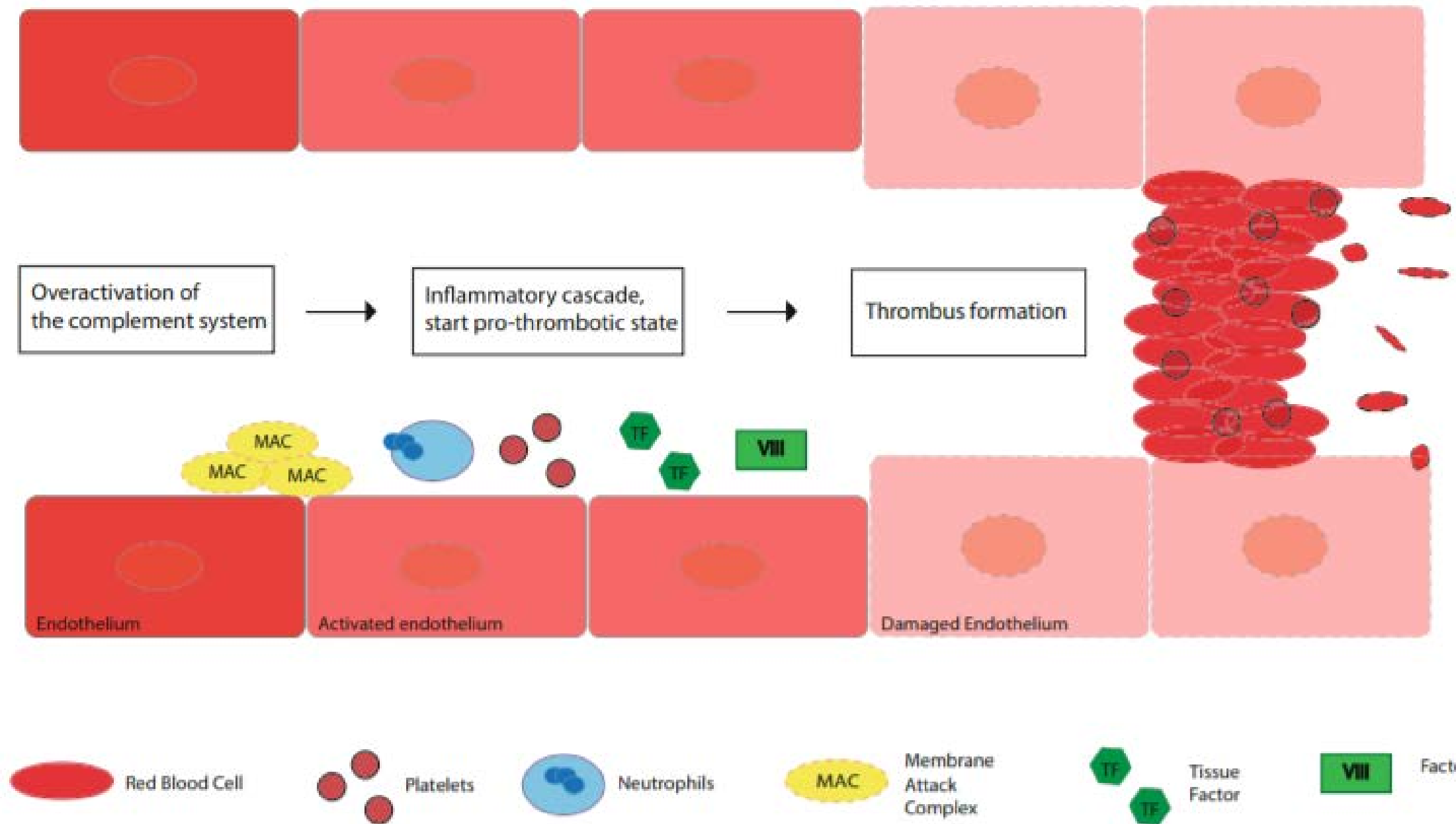
- Enfeksiyonlar : STECØ
- Gebelik
- Kanser- kemoterapi
- Solid organ transplantasyonu veya HKHN
- Otoimmün hastalıklar

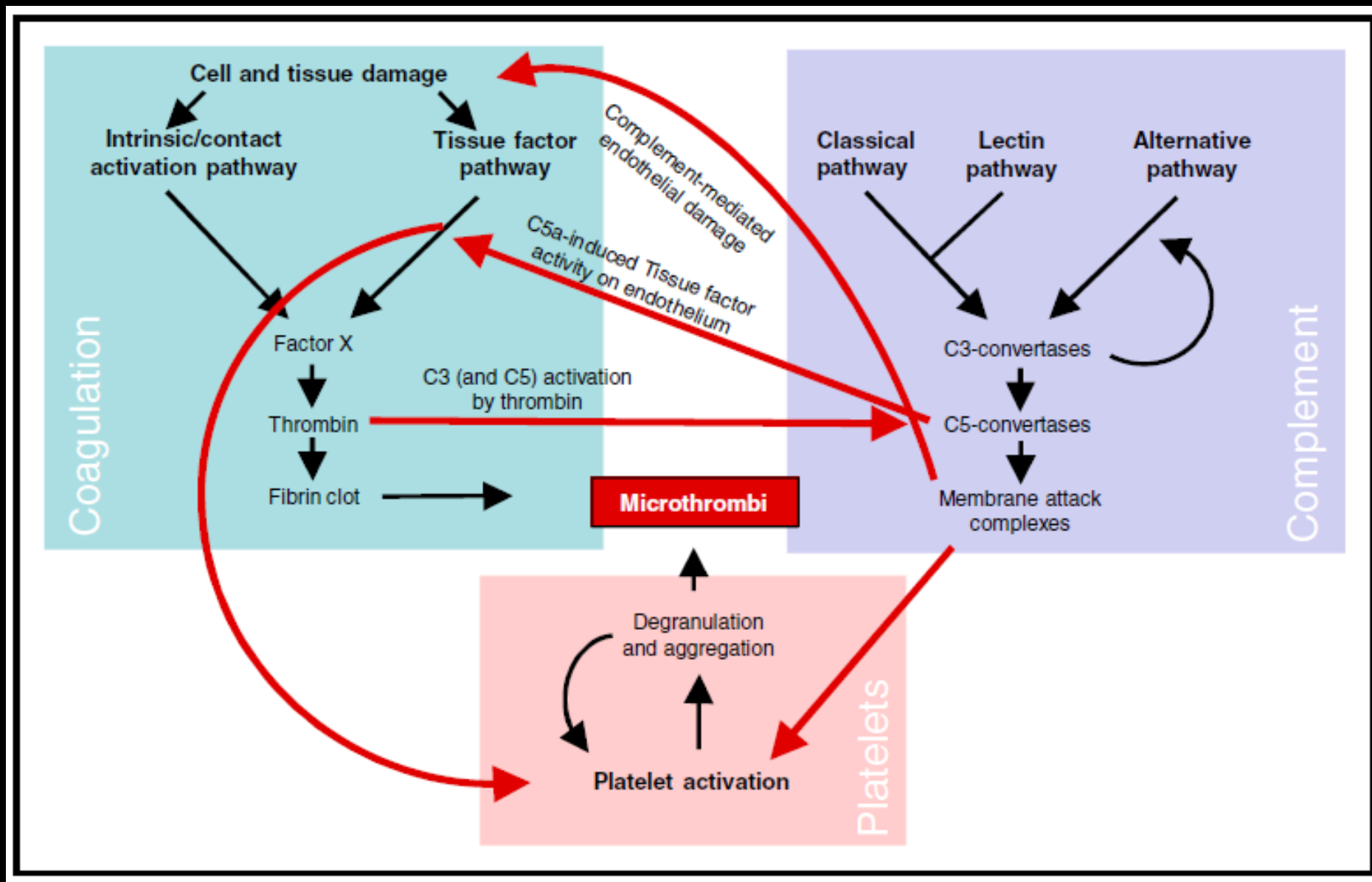
- Genetik mutasyonlar
- Otoantikor oluşumu

- Alternatif Kompleman yolağı aktive hale gelir









**Table 1** Complement-related genetic mutations in aHUS. Various clinical outcomes and the relationship with the different complement-related genetic mutations involved in aHUS

		Function in complement system	Frequency in aHUS (%)	ESRD after 5 years (%)	Recurrence (%)	Recurrence after kidney transplantation (%)	References
FH	Factor H	Co-factor for factor I	21–25	70–80	30–50	68–90	[5, 8, 10–14, 19, 25, 28–31]
MCP/CD46	Membrane co-factor protein	Membrane-bound complement regulator	5–22.8	10–50	58–90	11–20	[5, 8, 10–13, 29–31]
FI	Factor I	Inactivation of C3b and C4b	6–16.6	45–60	10–30	70–80	[5, 8, 10, 12, 13, 29–31]
FB	Factor B	Allows the formation of C3 and C5 convertases	1.9–4	70	Rare	Rare	[5, 8, 10, 13]
C3	Complement C3	Necessary for complement cascade activation	6–9	45–65	50	40–50	[5, 8, 10, 12, 13]
FHRs	Factor H-related proteins	Circulating proteins similar to factor H associated with autoantibodies against FH	4.5–35	30–63	23–60	20	[8, 10, 12, 13, 30]
FHR hybrid genes	Factor H, Factor H-related proteins	See function FH and FHRs	1–5	–	–	–	[8, 10]
THBD/CD141	Thrombomodulin	Degradation C3b	2–5	53–60	23–30	Rare	[5, 8, 10, 13]

**FH** factor H, **MCP/CD46** membrane cofactor protein, **FI** factor I, **FB** factor B, **FHR** factor H-related proteins, **THBD/CD141** thrombomodulin, **aHUS** atypical hemolytic uremic syndrome, **ESRD** end-stage renal disease

# Klinik Bulgular

## Tanı

- Klinik bulgular mikrovasküler hasar ve tromboza bağlıdır.
- Tüm organlarda iskemik hasar gelişebilir.
- Mikroanjiopatik hemolitik anemi
- Trombositopeni
- Böbrek hasarı ( proteinuri, hematüri, hipertansiyon, azotemi)
- Son organ hasarı bulguları



**Extra-renal  
manifestations of  
aHUS**

**Central Nervous  
System**

%10-48

Irritability, drowsiness,  
convulsions, encephalopathy,  
diplopia, cortical blindness,  
hemiparesis, hemiplegia,  
stupor, and/or coma

Is it aHUS?

Is it aHUS?

Is it aHUS?

Atypical HUS

TMAAs

STEC-HUS

Thrombotic Microangiopathy

TTP

*Perhaps it*

**Ayırıcı Tanı**

*TMA*

TTP

TMAAs

angiopathy

Is it aHUS?

Is it aHUS?

Is it aHUS?

Thrombotic Microangiopathy

Atypical HUS

STEC-HUS

TTP

TMAAs

STEC-HUS

TTP

Thrombotic Microangiopathy

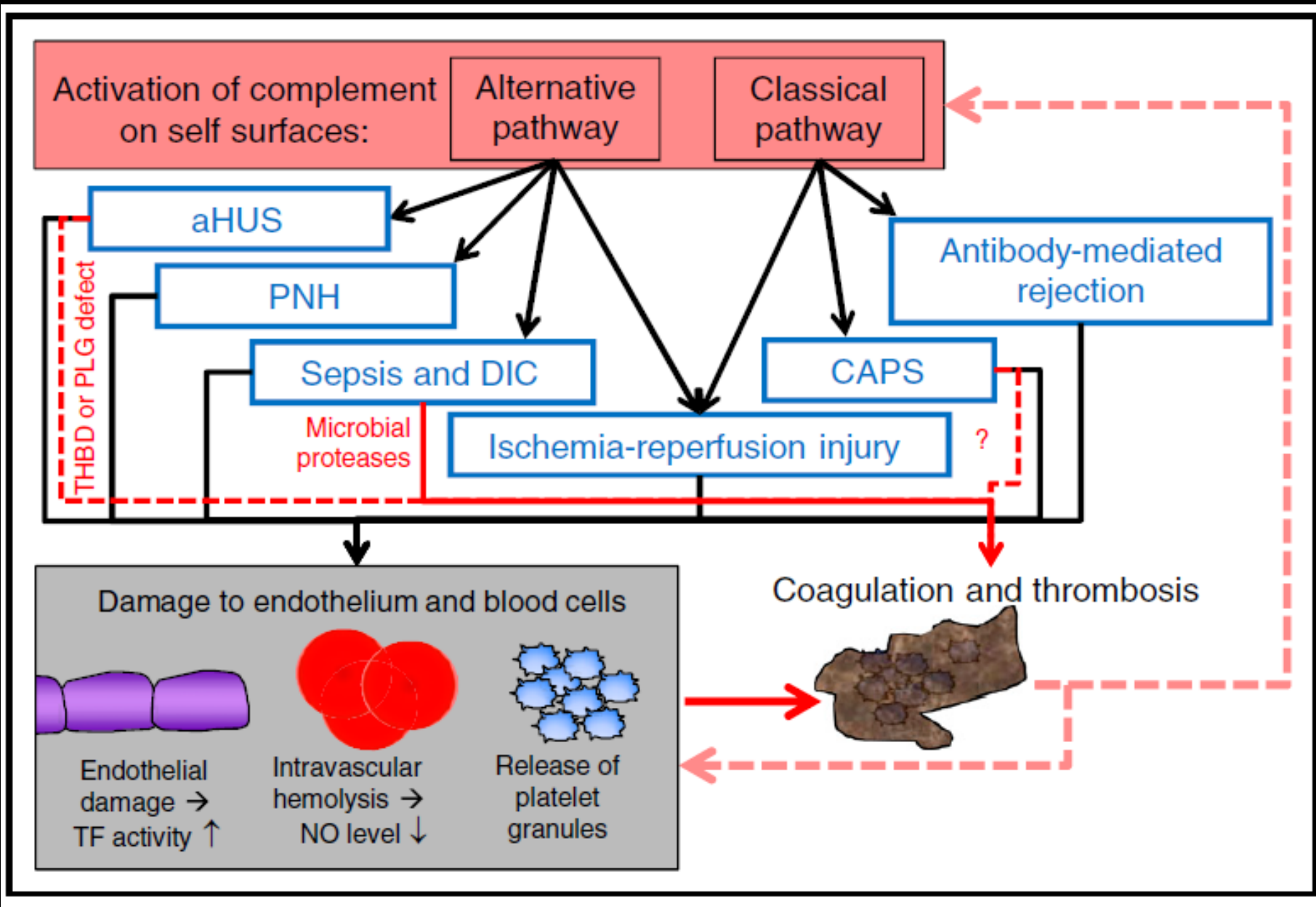
TMAAs

Atypical HUS

Is it aHUS?

Is it aHUS?

Is it aHUS?



- Malignant hypertension
- Pregnancy-associated
  - Preeclampsia and eclampsia
  - HELLP syndrome
- Autoimmune diseases
  - SLE
  - Scleroderma
  - APLS
  - Vasculitis
- Glomerulonephritis
  - C3GN
  - IgA nephropathy
- Infection
- Malignancy
- Surgery or trauma
- Drug therapy
  - Immunosuppressive agents
  - mTOR inhibitors
  - Chemotherapy
  - Antitumor agents
  - Antimalarial agents
  - Antiplatelet therapies
  - Antiviral agents
  - Oral contraceptives
  - Illicit drugs
- Solid organ/bone marrow transplant

# Ayırıcı Tanı

## 1. Aşama

### Thrombocytopenia

Platelet count  $<150,000/\text{mm}^3$   
or  $>25\%$  decrease from baseline

*sine qua non*

AND

### Microangiopathic hemolysis

Schistocytes and/or  
Elevated LDH and/or  
Decreased haptoglobin and/or  
Decreased hemoglobin

DIC açısından  
değerlendirmek gerekir  
PT-aPTT  
Fibrinojen seviyesi

Genellikle 2 katı kadar artar

# Ayırıcı Tanı

## 2. Aşama

STEC-HUS ün ekartasyonu  
Kanlı Diare+TMA



# Ayırıcı Tanı

## 3. Aşama

### Thrombocytopenia

Platelet count  $<150,000/\text{mm}^3$   
or  $>25\%$  decrease from baseline

AND

### Microangiopathic hemolysis

Schistocytes and/or  
Elevated LDH and/or  
Decreased haptoglobin and/or  
Decreased hemoglobin

DIC açısından  
değerlendirmek gerekir  
PT-aPTT  
Fibrinojen seviyesi

Plus 1 or more of the following:

### Neurologic symptoms

Confusion and/or  
Seizures and/or  
Stroke and/or  
Other cerebral abnormalities

### Renal impairment

Elevated creatinine and/or  
Decreased eGFR and/or  
Elevated blood pressure and/or  
Abnormal urinalysis

### Gastrointestinal symptoms

Diarrhea  $\pm$  blood and/or  
Nausea/vomiting and/or  
Abdominal pain and/or  
Gastroenteritis/pancreatitis

### Cardiovascular symptoms

Myocardial infarction and/or  
Hypertension and/or  
Arterial stenosis and/or  
Peripheral gangrene

### Pulmonary symptoms

Dyspnea and/or  
Pulmonary hemorrhage and/or  
Pulmonary edema

### Visual symptoms

Pain and blurred vision  
Retinal vessel occlusion  
Ocular hemorrhage

# Ayırıcı Tanı

## 4. Aşama

Trombositopeninin seviyesi  
Kreatinin seviyesi

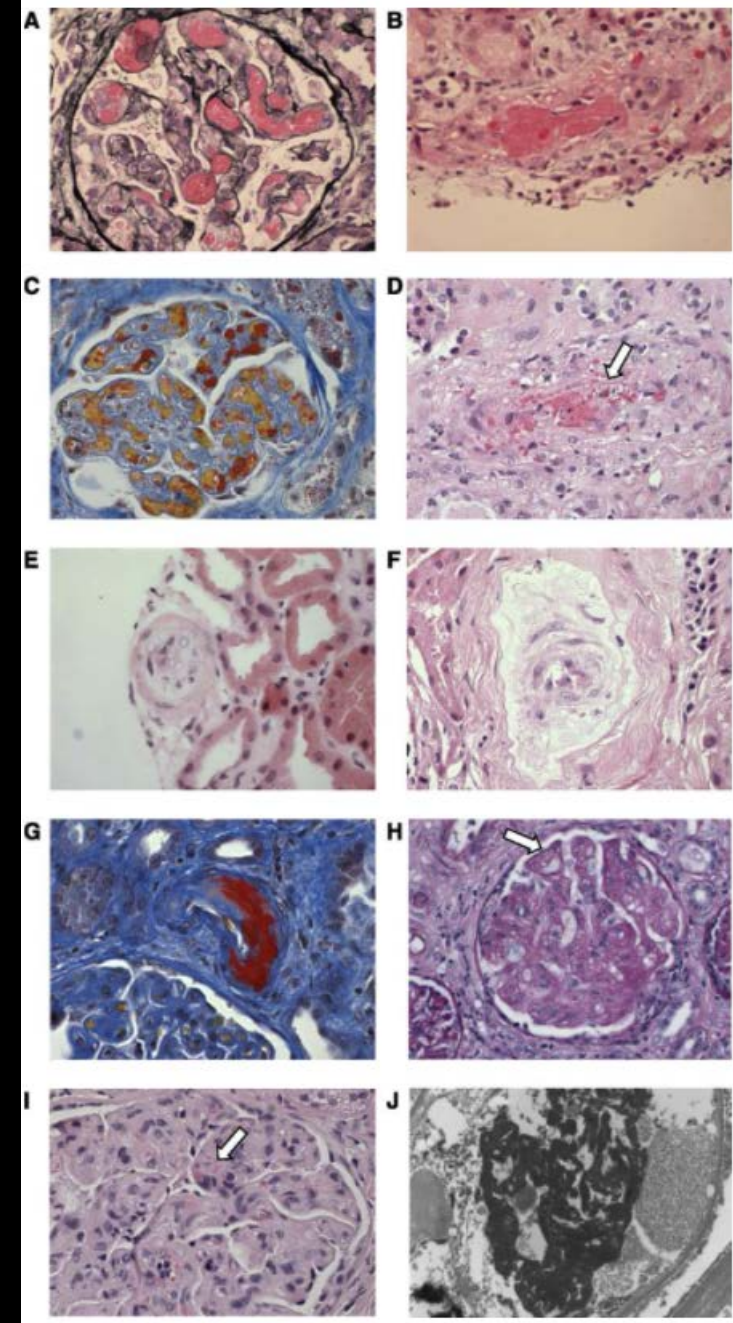
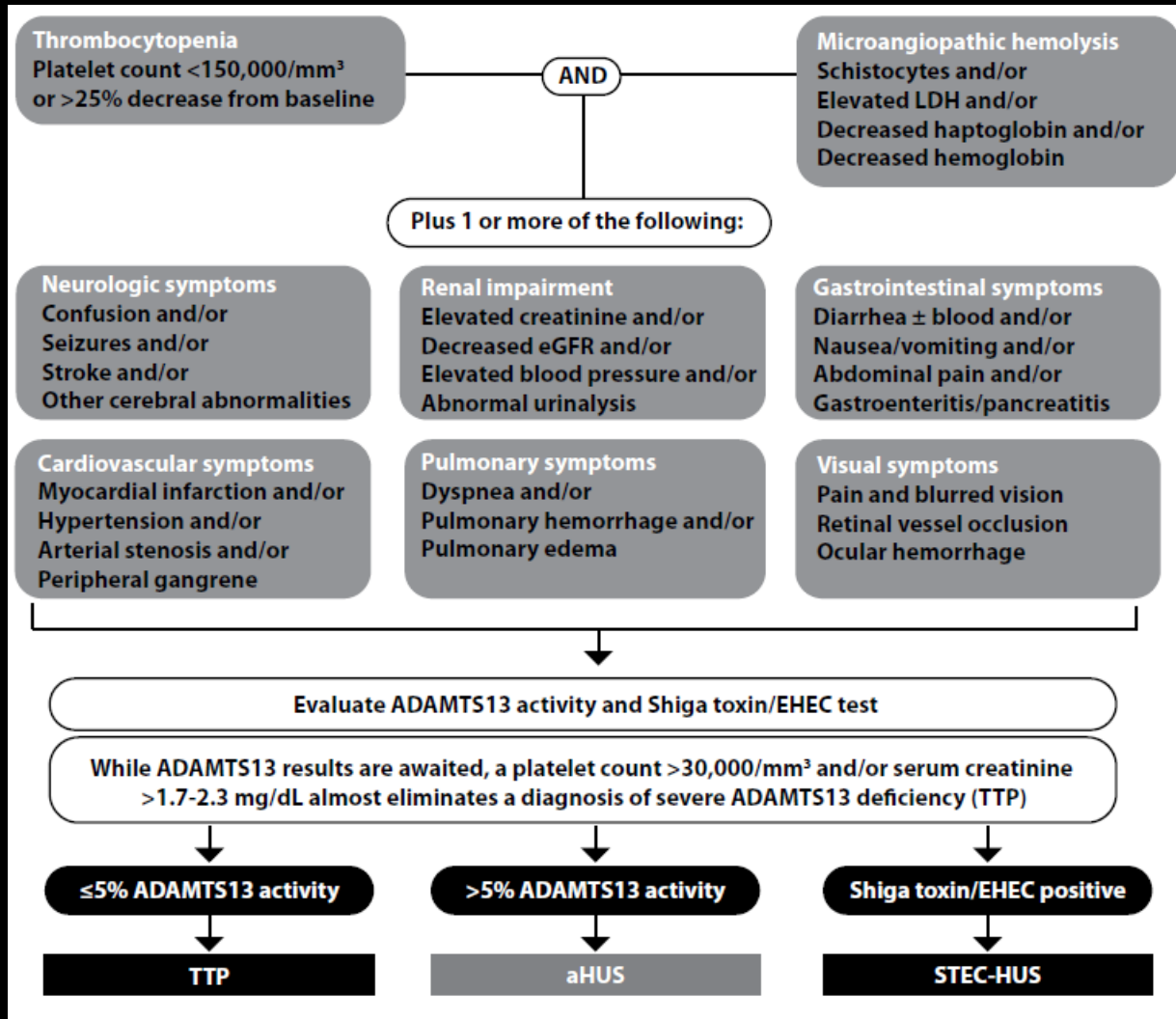
Trombosit > 30000 → aHUS  
Trombosit < 30000 → TTP

Kreatinin > 2.3 → aHUS  
Kreatinin < 2.3 → TTP

# Ayırıcı Tanı

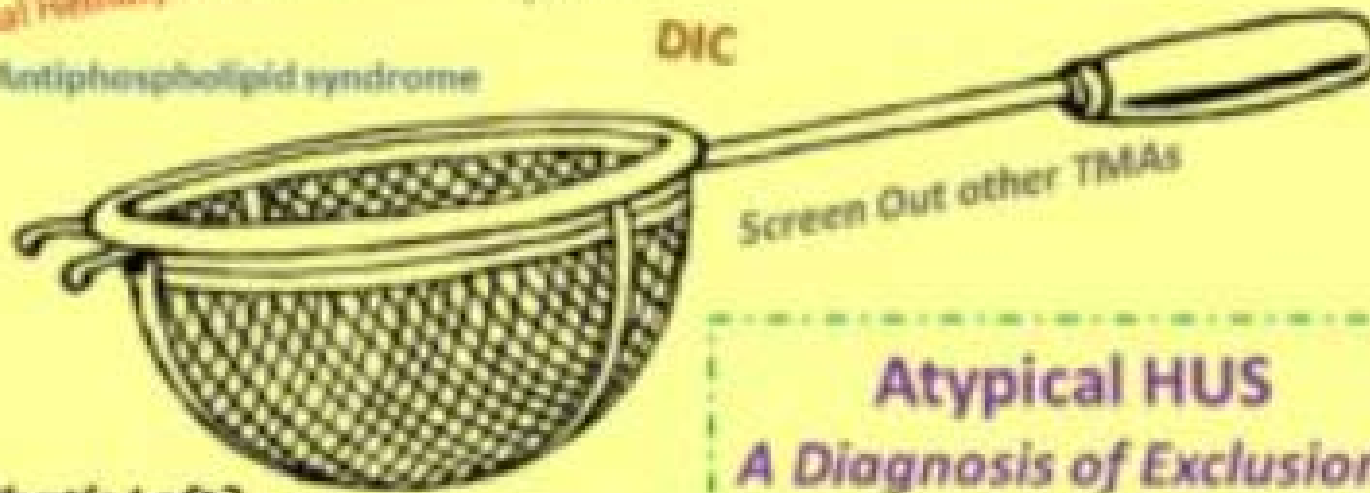
## 5. Aşama

Kobalamin eksikliği  
de ekarte edilmeli



# Thrombotic Microangiopathy

Disseminated intravascular coagulation  
HUS  
TTP  
APLS  
Atypical Hemolytic Uremic Syndrome  
Thrombotic Thrombocytopenic Purpura  
Antiphospholipid syndrome  
DIC



What's Left?

aHUS

**Atypical HUS**  
**A Diagnosis of Exclusion**

**Tedavi**



# Plazma tedavisi -I: plazma infüzyonu veya değişimi

- Plazma içerisinde FH, FI, FB ve C3 bulunur.
- Plazma MCP(membran-core protein) and THBD(trombomodulin) içermez.

**2 ana rasyoneli vardır**

- 1. mutasyon dışı etkenlerin uzaklaştırılmasını sağlar**
- 2. mutasyonlu faktörlerin uzaklaştırılmasını sağlar.**

# Plazma tedavisi-II

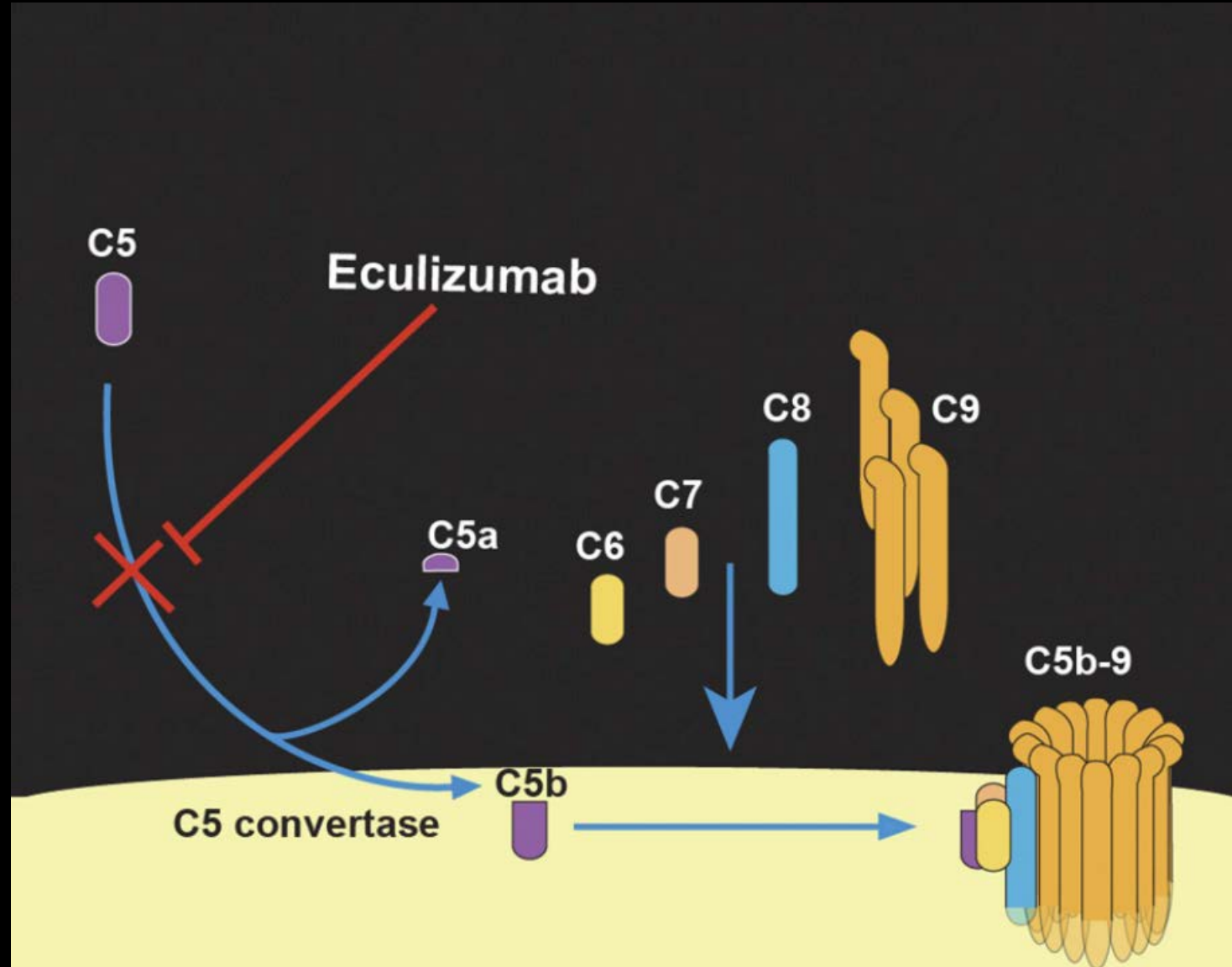
- PE tedavisi ile hematolojik parametrelerde ~ %50 hastada düzelme görülmektedir.
- Son dönem böbrek yetersizliği veya ölüm %67 hastada görülmektedir.
- C3 veya trombomodulin mutasyonu ve anti-FH antikoru olanlar PE'den belirgin fayda görebilir.
- FH ve FI mutasyonu olanlar daha az yanıt verir.
- Anti-FH antikoru olan hastalara PE tedavisine immunsupresifler eklenmeli.
- MCP (membran core protein) mutasyonu olanlarda PE tedavisi etkili değildir.

# Plazma tedavisi-III

- TMA Şüphesi olan tüm hastalara çok hızlı bir şekilde PE tedavisi başlanmalı
- PE tedavisi 1.5- 2 volüm plazma veya 20-30ml/kg TDP infüzyonu ile yapılmalı
- PE tedavisi en az 5 gün devam edilmeli
- ADAMTS13 ve stx sonuçları geldiği zaman kesin tanıya vararak tedaviye nasıl devam edileceğine karar verilir.
- Eğer 5 gün içerisinde hemoliz ve trombositopenide düzelme olmazsa antikompleman tedavi düşünülmelidir.

# Anti kompleman tedavi

## Eculizumab



# Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

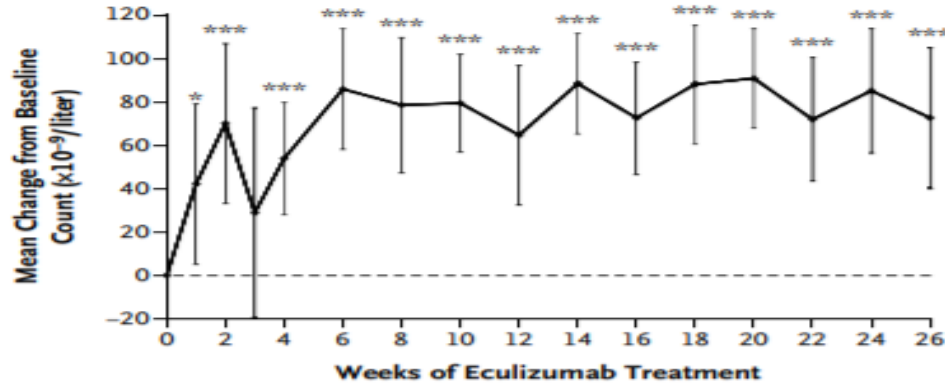
C.M. Legendre, C. Licht, P. Muus, L.A. Greenbaum, S. Babu, C. Bedrosian,

The NEW ENGLAND JOURNAL of MEDICINE

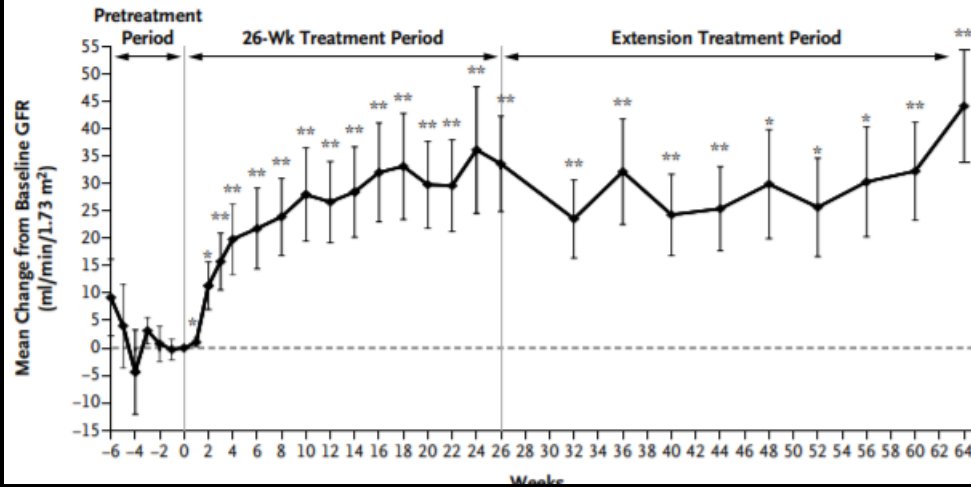
N Engl J Med 2013;368:2169-81

ORIGINAL ARTICLE

**A Platelet Count, Trial 1**



**B Estimated GFR, Trial 1**



TMA yanıtı 26 haftada elde edildi  
%50 hastada 1 haftada %90 hastada 26 haftada trombosit sayısı normale döndü.  
LDH %90 hastada normal  
GFR %76-80 hastada 26 haftada düzeldi.  
QoL >%70 hastada düzeldi.  
Meningokokal enfeksiyonlar açısından aşılama !!

**Güvenli ve Etkin bir tedavi**



# Eculizumab Safety: Five-Year Experience From the Global Atypical Hemolytic Uremic Syndrome Registry

Eric Rondeau<sup>1</sup>, Spero R. Cataland<sup>2</sup>, Imad Al-Dakkak<sup>3</sup>, Benjamin Miller<sup>3</sup>,  
 Adult patients (n = 842)



Variable	Ever treated with eculizumab (n = 535)	Never treated with eculizumab (n = 307)
Patients with evaluable data, n	529	272
<b>Meningococcal infections</b>		
Patients with event (n)	2	0
Events (n)	2	0
Events/100 patient-yr <sup>c</sup>	0.17	0.00
95% CI	0.02–0.43	0.00–0.71
<b>Serious infection</b>		
Patients with event (n)	46	14
Events (n)	86	26
Events/100 patient-yr <sup>c</sup>	7.48	6.17
95% CI	5.98–9.24	4.03–9.04
<b>Sepsis</b>		
Patients with event (n)	14	8
Events (n)	19	12
Events/100 patient-yr <sup>c</sup>	1.65	2.85
95% CI	0.99–2.58	1.47–4.98
<b>Malignancy</b>		
Patients with event (n)	3	5
Events (n)	4	6
Events/100 patient-yr <sup>c</sup>	0.35	1.42
95% CI	0.09–0.89	0.52–3.10
<b>Hepatic impairment</b>		
Patients with event (n)	6	1
Events (n)	7	1
Events/100 patient-yr <sup>c</sup>	0.61	0.24
95% CI	0.24–1.25	0.01–1.32
<b>Infusion reaction</b>		
Patients with event (n)	4	0
Events (n)	6	0
Events/100 patient-yr <sup>c</sup>	0.52	0.00
95% CI	0.19–1.14	0.00–0.71
Deaths, n (%)	25 (4.7)	27 (9.9)

Meningokok enfeksiyonu açısından aşılama programı !!  
 Ciddi enfeksiyon ve Sepsis !!!

Daha önce yapılmış olan çalışmalardan etkinlik ve güvenlik anlamında bir fark yoktur

# Asıl sorulacak sorular

- Eculizimab'ı
- Kim almalıdır?
- Ne zaman başlanmalıdır?
- Nasıl takip etmek gereklidir?
- Ne zaman kesilmelidir?

# Eculizumabı Kim Almalıdır? Almamalıdır?

- Ailesel aHUS ve relaps aHUS (transplant yapılan veya diğerleri)
  - ADAMTS13 aktivitesi normal olan ve Stx negatif olan TMA'lı hastalar.
  - Plazma tedavisine bağımlı olan veya rezistan olan TMA hastaları
  - Renal transplantasyon yapılacak olan ve mutasyonlarından dolayı rekurrens riski olan hastalar profilaktik olarak
- 
- Kompleman protein mutasyonları olduğu göstermediği sürece TTPde kompleman aktivasyonu olmasına rağmen plazma tedavisi ile eş zamanlı eculizumab tedavisi verilmesi için yeterli kanıt yoktur.
  - Cbl eksikliği veya DGKE mutasyonunda kullanılmaz
  - STEC-HUS'te nadir vakalar dışında etkinliği yoktur.
  - Sekonder aHUS (kanser, ilaca bağlı vb) te kanıtlanmamıştır. Sadece çalışmalarda...

# Eculizumabı ne zaman başlanmalıdır?

- aHUS 'den şüphelenildiği anda tedaviye başlanmalıdır
  - İndüksiyon tedavisi : 900 mg/hafta 4 hafta
  - İdame tedavisi : 1200mg/ 2 haftada bir
  - Eş zamanlı plazmaferez yapılan hastalar da her plazmaferezden sonra ek doz 600 mg uygulanmalıdır
- 
- Tüm hastalara Neisseria meningitides e karşı tetraavalan aşısı (konjuge) yapılmalıdır.
  - Aşılama en az 2 hafta önce yapılmalıdır eğer yapılamazsa profilaktik antibiyotik verilmelidir.

# Eculizumab yanıtı nasıl takip etmek gereklidir?

- aHUS aktivite belirteçleri: Trombosit sayısı, LDH, Haptoglobin ve kreatinin düzeyleri
- Aktivite belirteçlerinde düzelme olmuyorsa kompleman aktivite belirteçlerine bakılabilir.
- Eculizumabın kan konsantrasyonu takip için kullanılmaz ( $\geq 100$ mg/ml terapötik seviye)

# Eculizumab ne zaman kesilmelidir?

- Net bir öneri yok .
- Son dönem böbrek yetmezliğinin gelişme olasılığı ve relaps riski yüksek olan FH,C3,FB ve FI mutasyonu olan hastalarda
- aHUS başlangıcında şiddetli ekstra-renal bulguları olan hastalar
- Renal transplantasyonlu ve yüksek riskli genotipli olan hastalarda düşünmemeli.

Anti-FH antikor seviyesi  $\leq 2.5$  x üstnormal + KBY olan hastalarda idame tedavisinin kesilmesi düşünülebilir. Eculizumab tedavisi kesilen tüm hastalar relaps bulgularını yakın takip gereklidir.

# The long-acting C5 inhibitor, Ravulizumab, is effective and safe in adult patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment



see commentary on page 1106  
OPEN

Eric Rondeau<sup>1</sup>, Marie Scully<sup>2</sup>, Gema Ariceta<sup>3</sup>, Tom Barbour<sup>4</sup>, Spero Cataland<sup>5</sup>, Nils Heyne<sup>6</sup>, Yoshitaka Miyakawa<sup>7</sup>, Stephan Ortiz<sup>8</sup>, Eugene Swenson<sup>9</sup>, Marc Vallee<sup>10</sup>, Sung-Soo Yoon<sup>11</sup>, David Kavanagh<sup>12</sup> and Hermann Haller<sup>13</sup>; on behalf of the 311 Study Group<sup>14</sup>

## Antikompleman tedavi yenilikler

**Table 2 | Complete TMA response, individual components, and hematologic normalization through initial evaluation period of 26 weeks**

Variable	Overall (N = 56)
Complete TMA response	30 (53.6)
95% CI	39.6–67.5
Hematologic normalization <sup>a</sup>	41 (73.2)
95% CI	60.7–85.7
Platelet count normalization	47 (83.9)
95% CI	73.4–94.4
LDH normalization	43 (76.8)
95% CI	64.8–88.7
≥25% improvement in serum creatinine from baseline	33 (58.9)
95% CI	45.2–72.7

CI, confidence interval; LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy.

<sup>a</sup>Defined as normalization of both LDH and platelet count.

Data shown as n (%). 95% CIs for the proportion are based on the asymptotic

Category	Overall (N = 58)	
	n (%)	Events
Any AE	58 (100.0)	818
Treatment-related	20 (34.5)	58
Not treatment-related	58 (100.0)	760
Any SAE	30 (51.7)	71
Fatal TEAE	3 (5.2)	3
Fatal pretreatment SAE	1 (1.7)	1
Meningococcal infection	0 (0.0)	0
AE severity		
Grade 1	54 (93.1)	454
Grade 2	46 (79.3)	223
Grade 3	31 (53.4)	116
Grade 4	14 (24.1)	22
Grade 5	3 (5.2)	3



Built on the foundation  
of Soliris<sup>®</sup> (eculizumab),  
**ULTOMIRIS** has an ~4x longer half  
life<sup>2,3,c,d</sup>



## For patients with atypical-HUS

ULTOMIRIS is administered based on weight

### ULTOMIRIS WEIGHT-BASED DOSING REGIMEN<sup>1</sup>

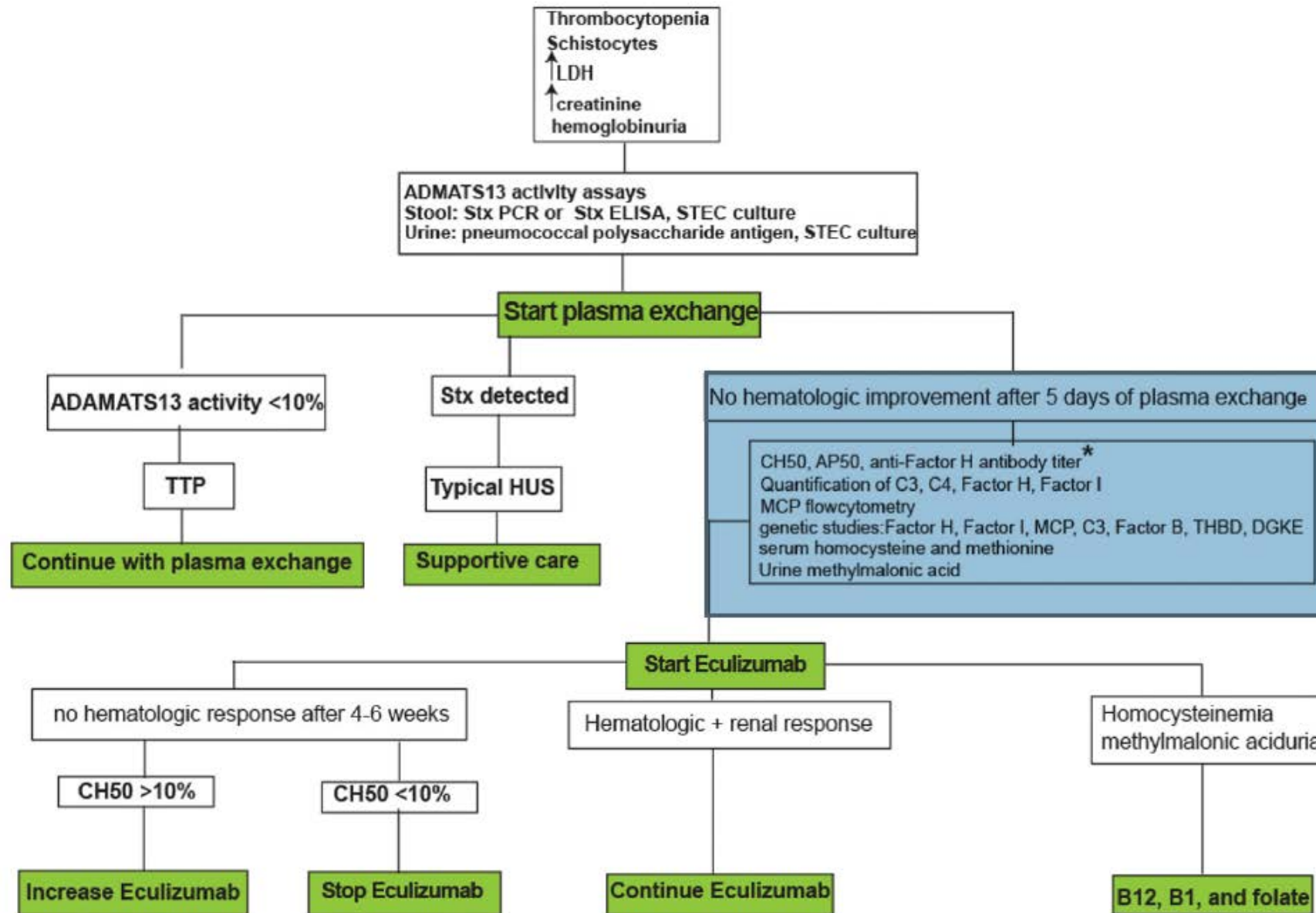
Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg) and Dosing Interval	
5 to <10	600	300	Every 4 weeks
10 to <20	600	600	
20 to <30	900	2,100	Every 8 weeks
30 to <40	1,200	2,700	
40 to <60	2,400	3,000	
60 to <100	2,700	3,300	
100 or greater	3,000	3,600	

With ULTOMIRIS, atypical-HUS patients can experience up to 8 weeks of freedom between infusions.<sup>1,e</sup> Uncover more about ULTOMIRIS dosing and find out how you can widen their world.

<sup>e</sup>Starting 2 weeks after the loading dose, maintenance doses are administered once every 4 or 8 weeks (depending on body weight).<sup>1</sup>

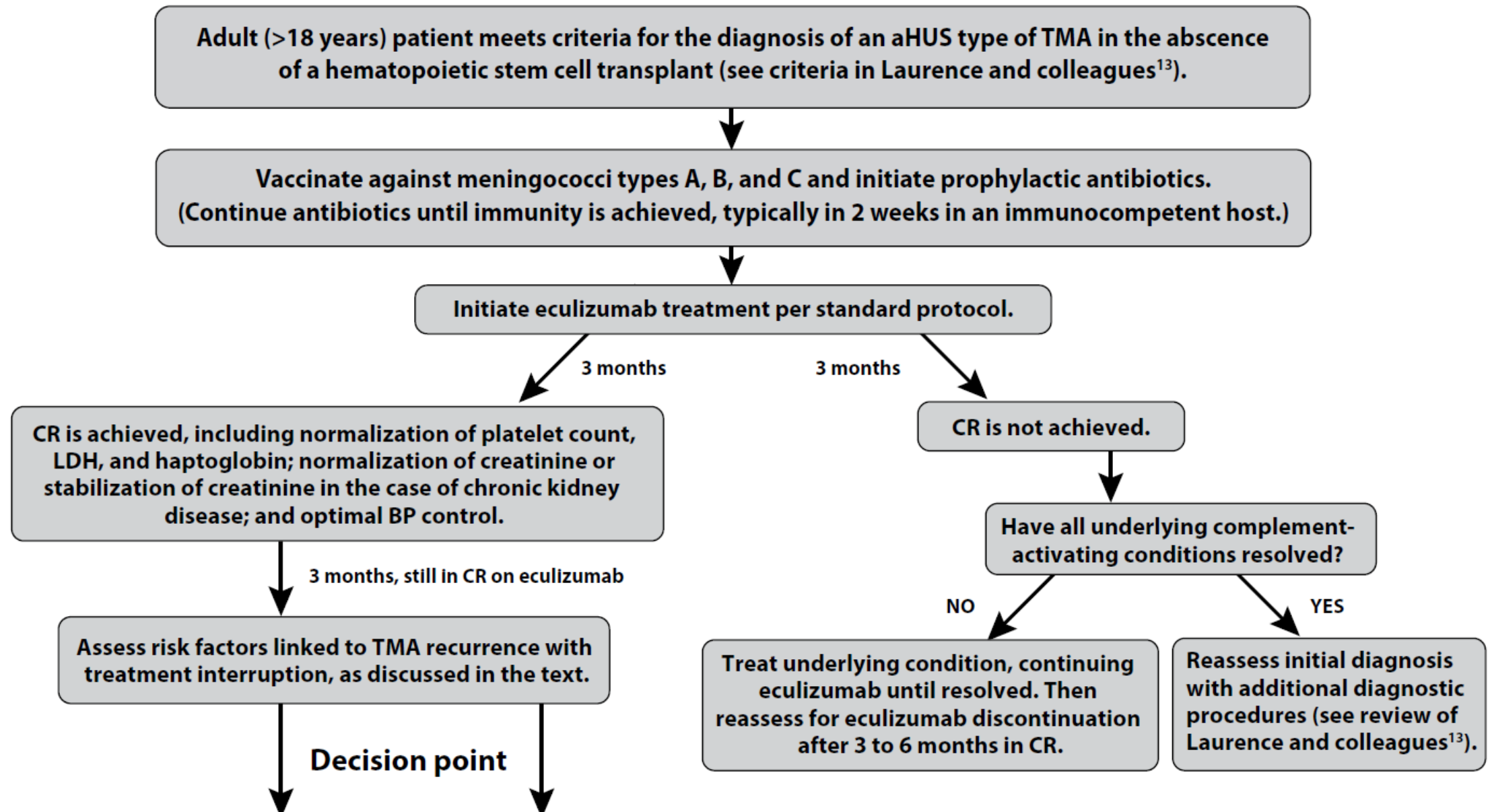


# Tedavi Algoritması



# Defining Treatment Duration in Atypical Hemolytic Uremic Syndrome in Adults: A Clinical and Pathological Approach

2020



**Prior renal allograft  
Prior TMA  
Extrarenal manifestations  
Anti-CFH autoantibodies  
Mutation in gene coding for CFH  
(especially in exon 17, 19, or 20),  
C3, CFB, or CFI, or hybrid gene**

Continue eculizumab for an  
additional 3 to 6 mo

If patient still in CR, consider withdrawal  
of therapy with close, controlled monitoring  
for 24 months. Consider continued use of  
eculizumab if the eGFR persists  
<30 mL/min/1.73 m<sup>2</sup>.

24 months in CR off eculizumab

Routine clinical care. Close monitoring if a potent  
complement-activating condition is encountered.

**No history of renal allograft  
No prior TMA  
No extrarenal manifestations  
No anti-CFH autoantibodies  
No complement gene mutation  
except for isolated *MCP* mutation  
*CFH* mutations restricted to exons 9 and 15**

Consider withdrawal of  
therapy with close,  
controlled monitoring  
for 24 months.

Relapse off eculizumab

Reinstitute eculizumab.

First relapse

Repeat course of eculizumab,  
as outlined above.

Second or later relapse

Consider lifelong treatment  
with eculizumab.



*Basic Discovery*

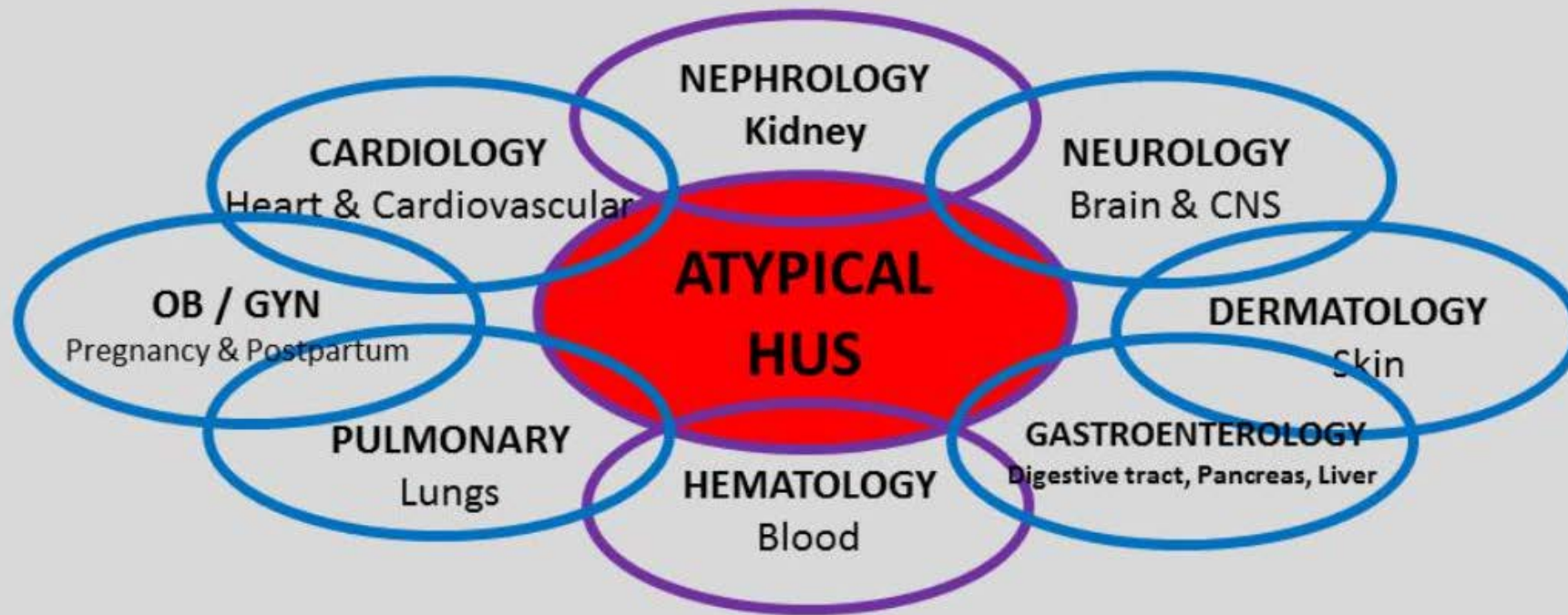
*Epidemiology & Community Research*

*Clinical Research*

*Policy & Regulations*

*Patient Centered Research*

*Translation to Patient Care*



### **Collaboration among Specialists Yields Better aHUS Patient Outcomes**

*Basic Discovery*

*Epidemiology & Community Research*

*Clinical Research*

*Policy & Regulations*

*Patient Centered Research*

*Translation to Patient Care*



[www.aHUSallianceAction.org](http://www.aHUSallianceAction.org)

*Global Advocacy for aHUS Patients*



*Sabrınız için teşekkür ederim...*