Hemolytic-uremic Syndrome

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PO/SOL-aHUS/17/0030

Clinical Case

28-year-old woman after cesarean childbirth (pregnancy 31th week, preeclampsia) admitted to Dept. of Nephrology because of lower legs oedema, hypertension, sadden elevation of creatinine level and proteinuria (1-2 g/day) with hematuria. Laboratory: anemia (HGB 8.7 g/dl) and lower platelets count (PLT 75 000/ul).

Since 2 years the patient has been effectively treated with methyldopa and Ca-blocker because of hypertension. The first pregnancy and childbirth without any complications.

<u>Question:</u>

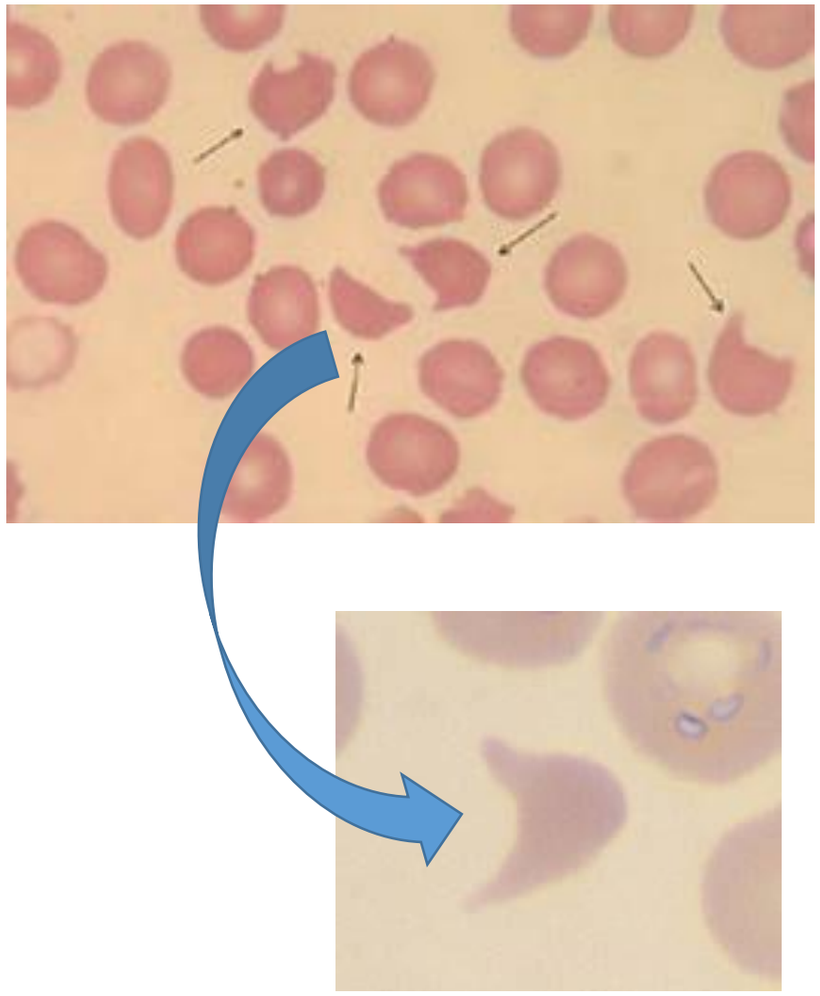
What additional laboratory analysis/es do you propose?

a. Coagulation parameters
b. LDH (lactate dehydrogenase) and bilirubin (fraction) concentration
c. Blood smear and the percentage of reticulocytes
d. Haptoglobin and free hemoglobin levels in blood
e. All the above

Clinical Case

Laboratory findings:

retikulocytes	5.12%
LDH	574 j/l
haptoglobin	0.08 g/l
bilirubin conjugated	increased
clotting parameters	normal
blood smear	5% *schistocytes*

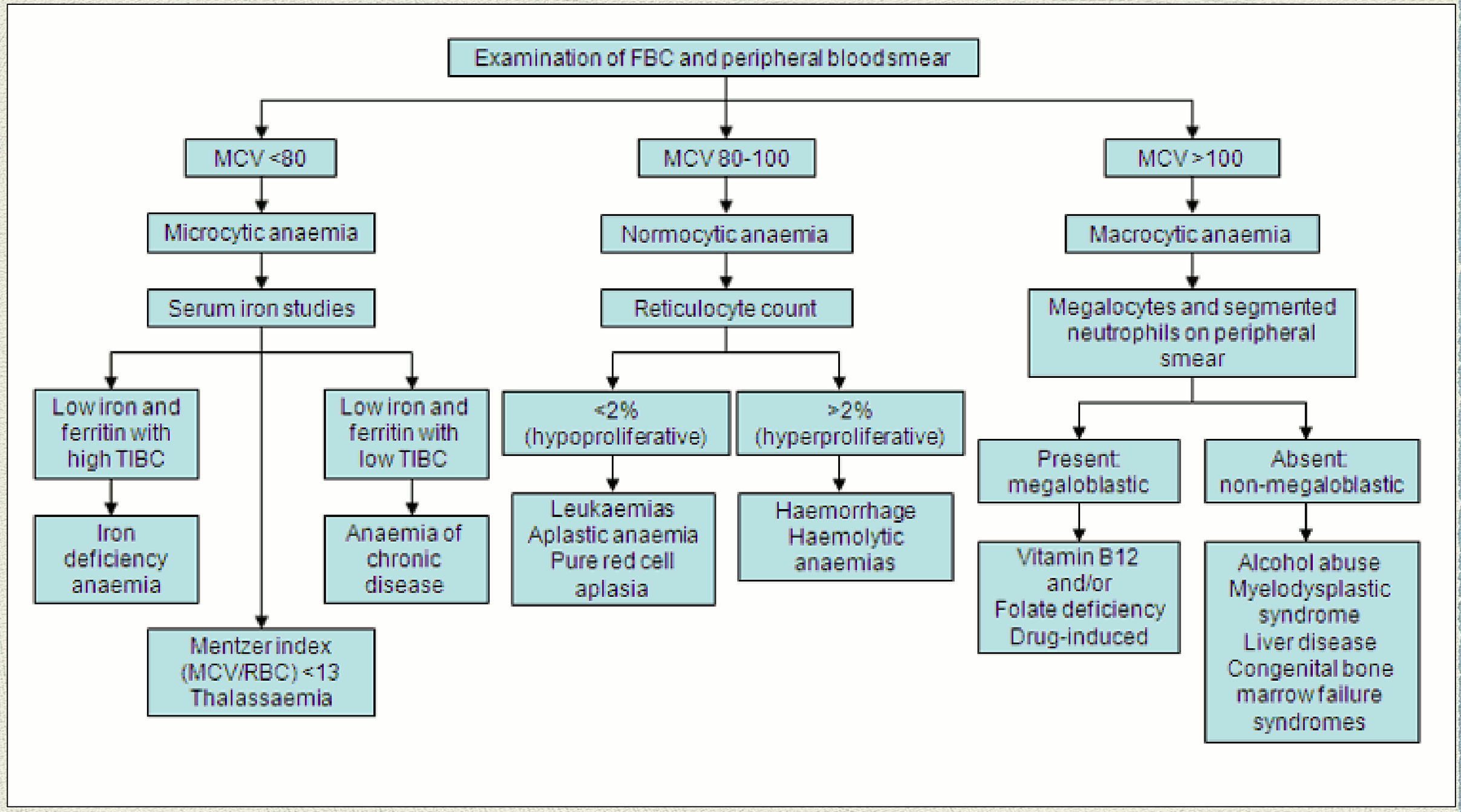


Question:

What will be your preliminary diagnosis?

a. Glomerulonephritis
b. Hypertensive nephropathy
c. Childbirth sepsis
d. Acute prerenal kidney injury
e. Hemolytic-uremic Syndrome

ANEMIA

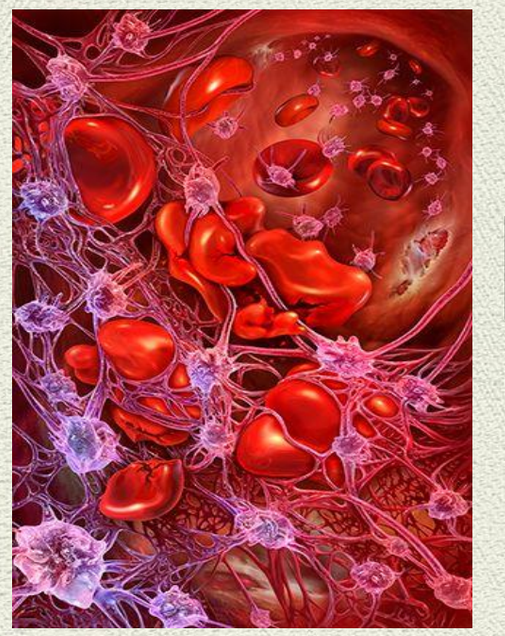

Examination of FBC and peripheral blood smear
MCV <80
MCV 80-100
MCV >100
Microcytic anaemia
Normocytic anaemia
Macrocytic anaemia
Serum iron studies
Reticulocyte count
Megalocytes and segmented neutrophils on peripheral smear
Low iron and ferritin with high TIBC
Low iron and ferritin with low TIBC
<2% (hypoproliferative)
>2% (hyperproliferative)
Present: megaloblastic
Absent: non-megaloblastic
Iron deficiency anaemia
Anaemia of chronic disease
Leukaemias
Aplastic anaemia
Pure red cell aplasia
Haemorrhage
Haemolytic anaemias
Vitamin B12 and/or Folate deficiency
Drug-induced
Alcohol abuse
Myelodysplastic syndrome
Liver disease
Congenital bone marrow failure syndromes
Mentzer index (MCV/RBC) <13
Thalassaemia

Anemia

↓HGB

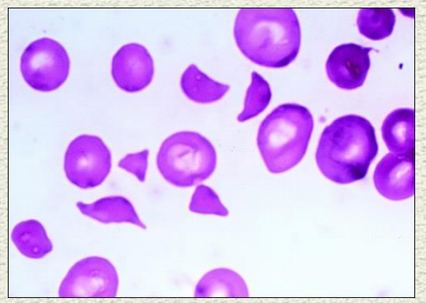
HEMOLYSIS
↑LDH, ↑conj. bil, ↑free HGB, ↓haptoglobin
(-) Coombs

HEMOLYTIC ANEMIA



↓PLT

SCHISTOCYTES



Microangiopathic Hemolytic Anemia and Thrombocytopenia (MAHAT)

Thrombotic Microangiopathy (TMA)

+ renal injury (↑Crea) diarrhoea

PLT <15o ooo

Hemolytic Uremic Syndrome (HUS) – 90% of al cases

Other (aHUS) complement depended TMA

+ neurological symptoms fever?

PLT < 35 ooo

Thrombotic thrombocytopenic purpura (TTP)

Different TMAs Have Different Etiologies and Require Different Management Approaches

- **aHUS associated with a complement-amplifying condition**
  - Infection, autoimmune disorders (ie, SLE)[a-c]
  - Malignant hypertension[d]
  - Pregnancy-associated
  - Drug-mediated[a]
- **aHUS without a complement-amplifying condition[f-h,k]**
- **TTP (severe ADAMTS13 deficiency)[f,j]**
- **HUS (*E coli* Shiga-toxin-induced)[i]**

a. George JN. *Kidney Int*. 2009;75:S8-S10; b. Zipfel PF, et al. *Curr Opin Nephrol Hypertens*. 2010;19:372-378; c. Ornstein BW. *Curr Opin Rheumatol*. 2012;24:522-529; d. Zhang B. *Hypertens Res*. 2008;31:479-483; e. Fakhouri F. *J Am Soc Nephrol*. 2010;21:859-867; f. Noris M, et al. *Nat Rev Nephrol*. 2012;8:622-633; g. Totina A, et al. *Clin Pediatr (Phila)*. 2011;52:183-186; h. Kavanagh D, et al. *Br Med Bull*. 2006;77-78:5-22; i. Bitzan M. *Semin Thromb Hemost*. 2010;36:594-610; j. Tsai HM. *Int J Hematol*. 2010;91:1-19; k. Noris M, Remuzzi G. *N Engl J Med*. 2009;361:1676-1687.

Thrombotic Microangiopaty (TMA) - causes

TMA Diseases

Primary

Infection-induced (HUS)
- *E coli* Shiga-toxin
- *S pneumoniae*

aHUS
- Complement dysregulation
  - Inherited
  - Acquired
- Metabolic mutations
- Unknown etiology?

Severe ADAMTS13 deficiency (TTP)
- Acquired
- Inherited

Cobalamin defect :
- deficiency
- mutation *MMACHC*

Secondary

Malignant hypertension

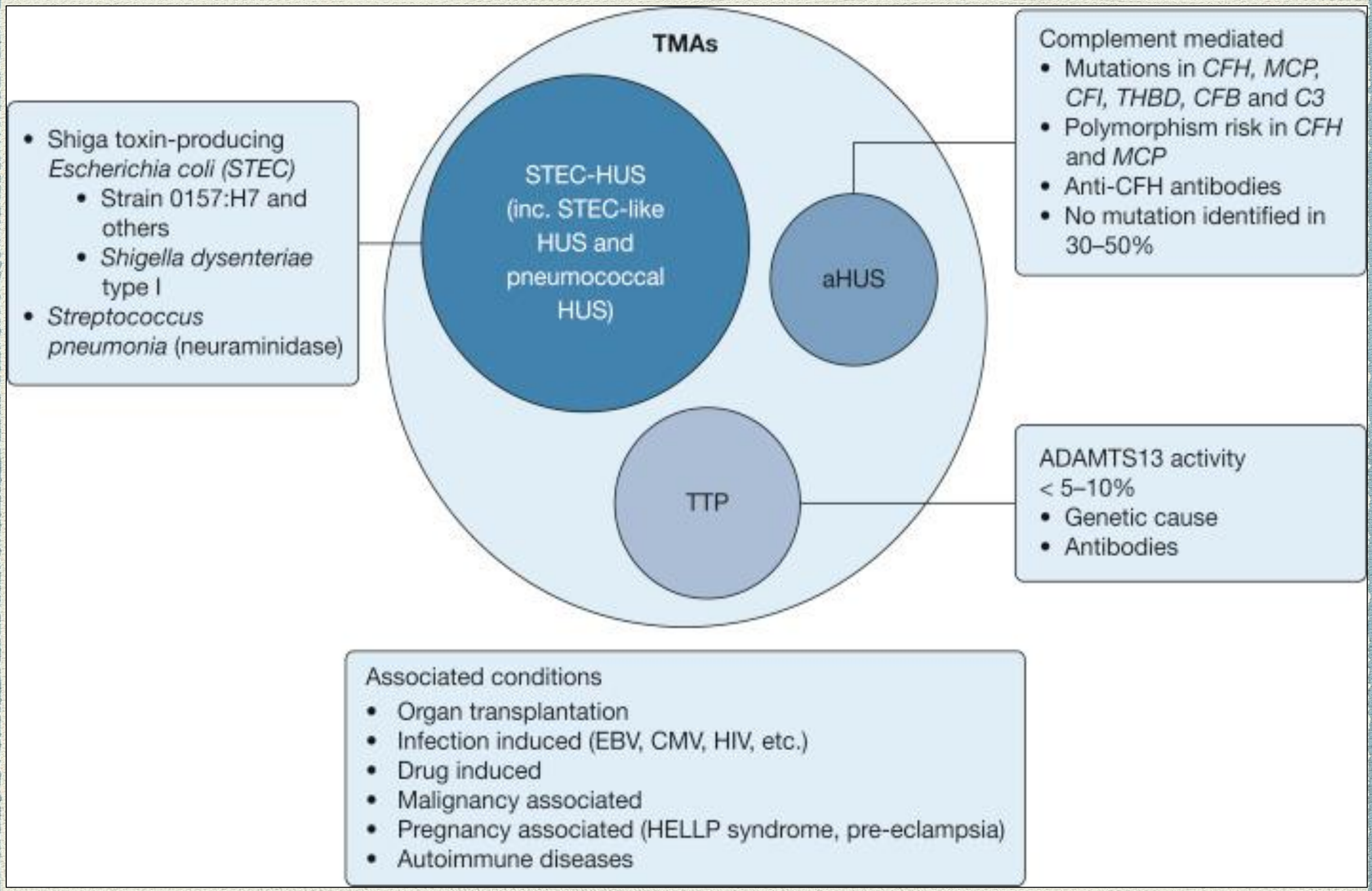
Drug-induced
- Chemotherapy
- CNIs
- Cocaine
- **Chinine**

Pregnancy
- HELLP syndrome
- Preeclampsia?

Miscellaneous
- DIC
- BMT
- Malignancy
- HIV

Connective tissue disorders
- SLE
- CREST
- **APS**

UpToDate


TMAs
STEC-HUS (inc. STEC-like HUS and pneumococcal HUS)
aHUS
TTP
• Shiga toxin-producing *Escherichia coli (STEC)*
  • Strain 0157:H7 and others
  • *Shigella dysenteriae* type I
• *Streptococcus pneumonia* (neuraminidase)
Complement mediated
• Mutations in *CFH, MCP, CFI, THBD, CFB* and *C3*
• Polymorphism risk in *CFH* and *MCP*
• Anti-CFH antibodies
• No mutation identified in 30–50%
ADAMTS13 activity < 5–10%
• Genetic cause
• Antibodies
Associated conditions
• Organ transplantation
• Infection induced (EBV, CMV, HIV, etc.)
• Drug induced
• Malignancy associated
• Pregnancy associated (HELLP syndrome, pre-eclampsia)
• Autoimmune diseases

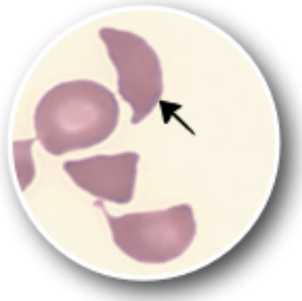
Hemolytic Uremic Syndrome (HUS)

Most common cause of acute renal failure in children

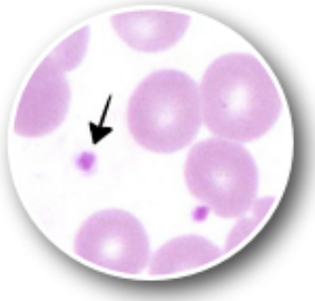
E. coli H7:0157

Shiga-like toxin (Verotoxin)

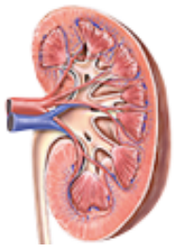
Abdominal Pain
Bloody Diarrhea
Fever
Seizures
Lethargy



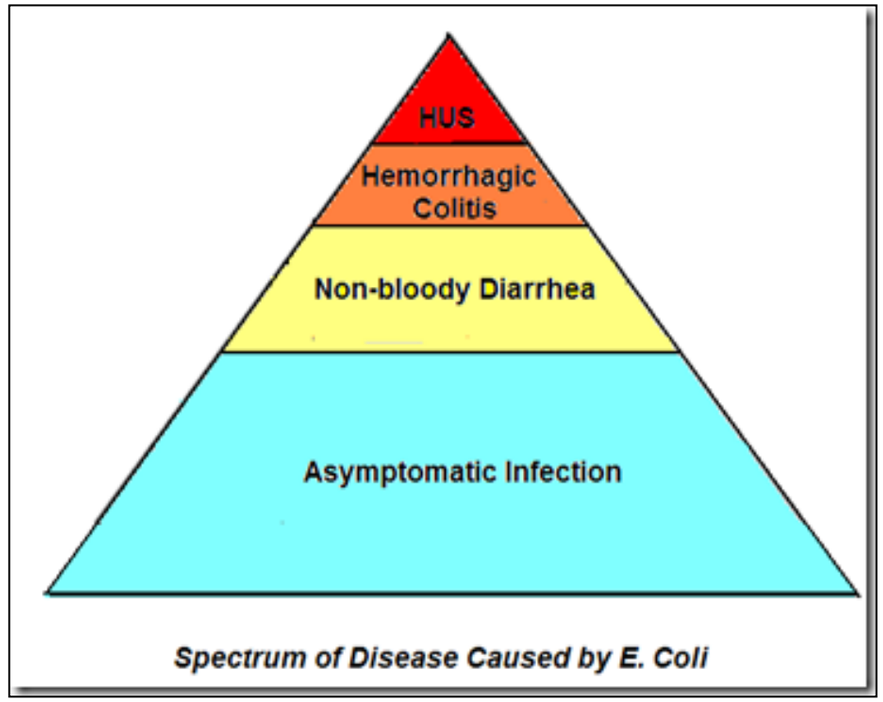
Microangiopathic hemolytic anemia (schistocytes)



Thrombocytopenia

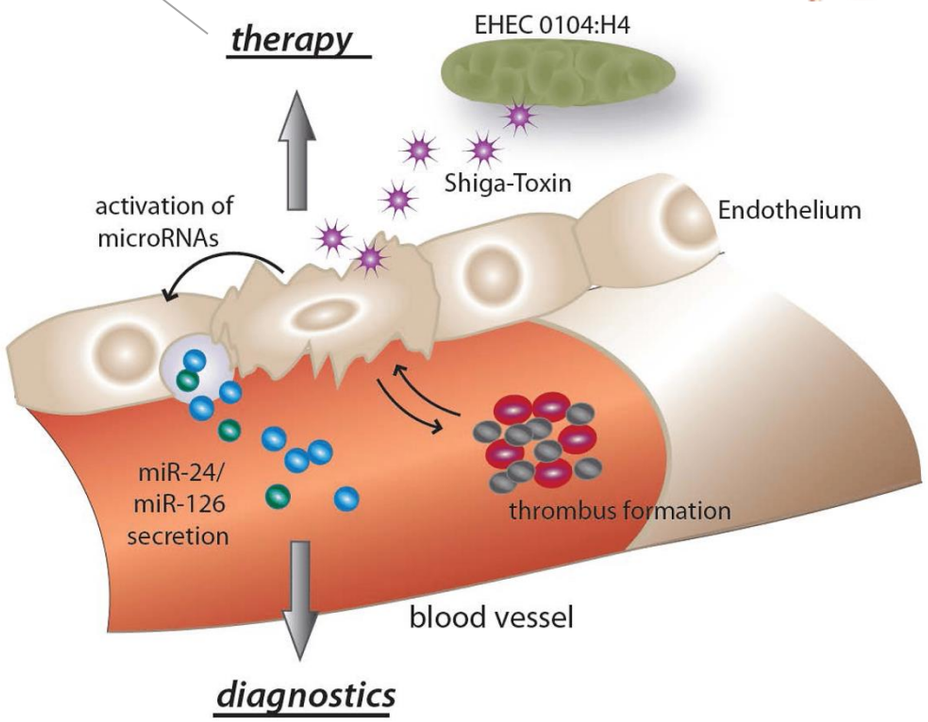


Renal insufficiency



Spectrum of Disease Caused by E. Coli

Treatment
- Mainly supportive
- Dialysis
- No Antibiotics
- Plasmapharesis/IVIG

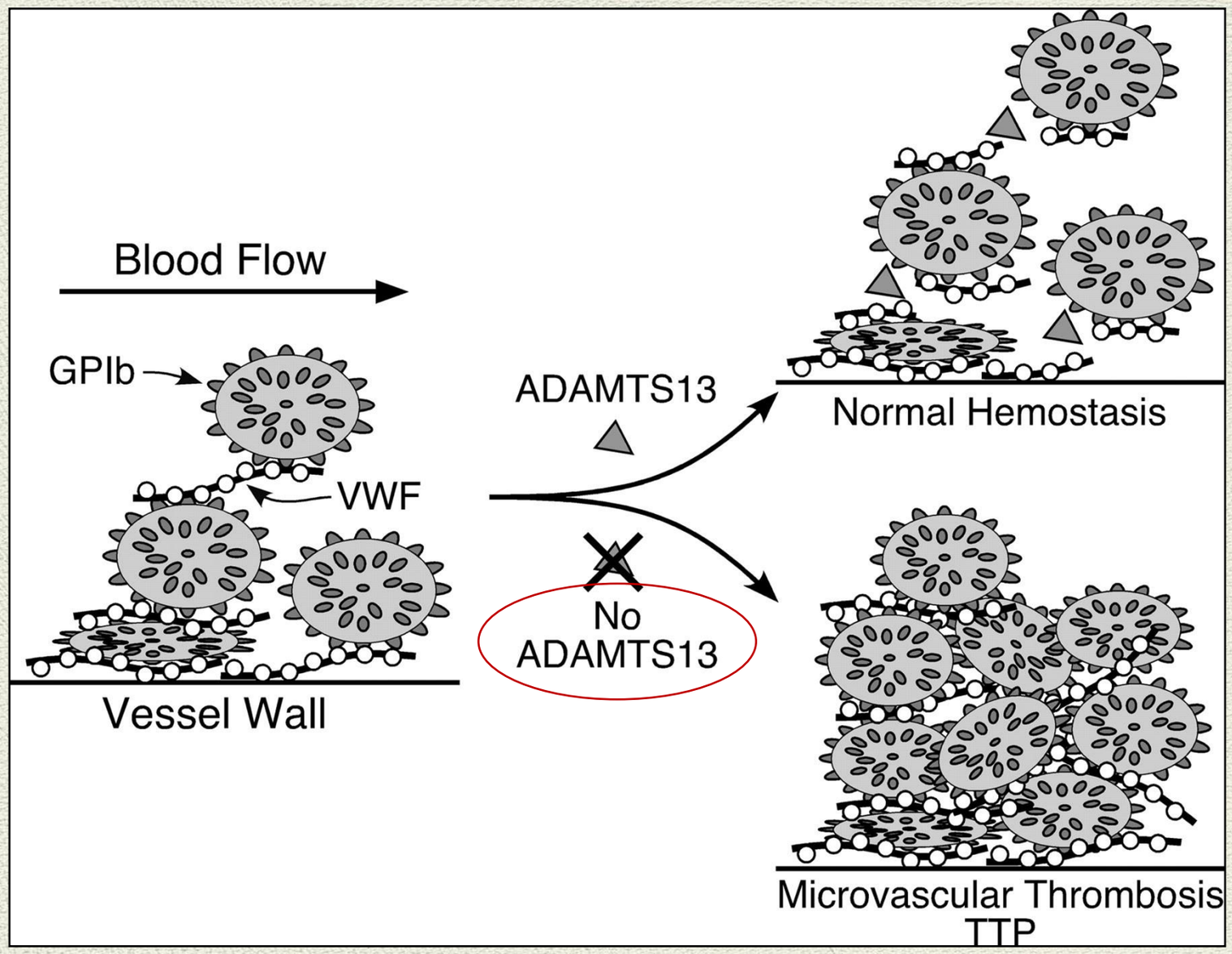


DIAGNOSTICS

- Stool/rectal swab for culture
  (STEC only E. coli H7:O157)
  E. coli non-O157 (O104:H4)! 50% of cases
  +
- Stool/rectal swab for Shiga toxin presence (EIA)
  wszystkie toksyny *Shiga*

- PCR for gen of Shiga 1 toxin (stx1)
  gen of Shiga 2 toxin (stx2)

Thrombotic Thrombocytopenic Purpura (TTP) - pathogenesis



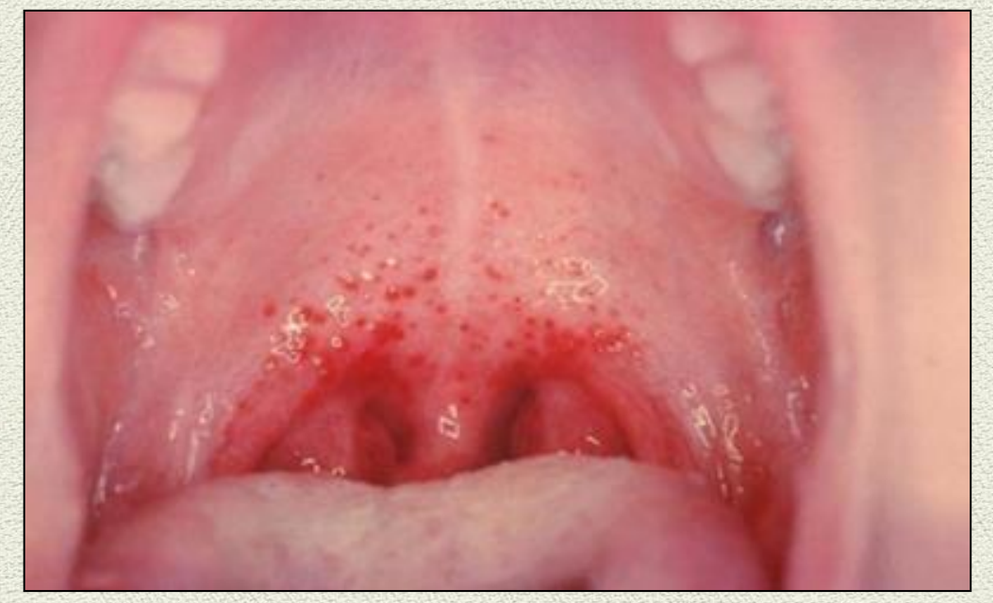
Variations:

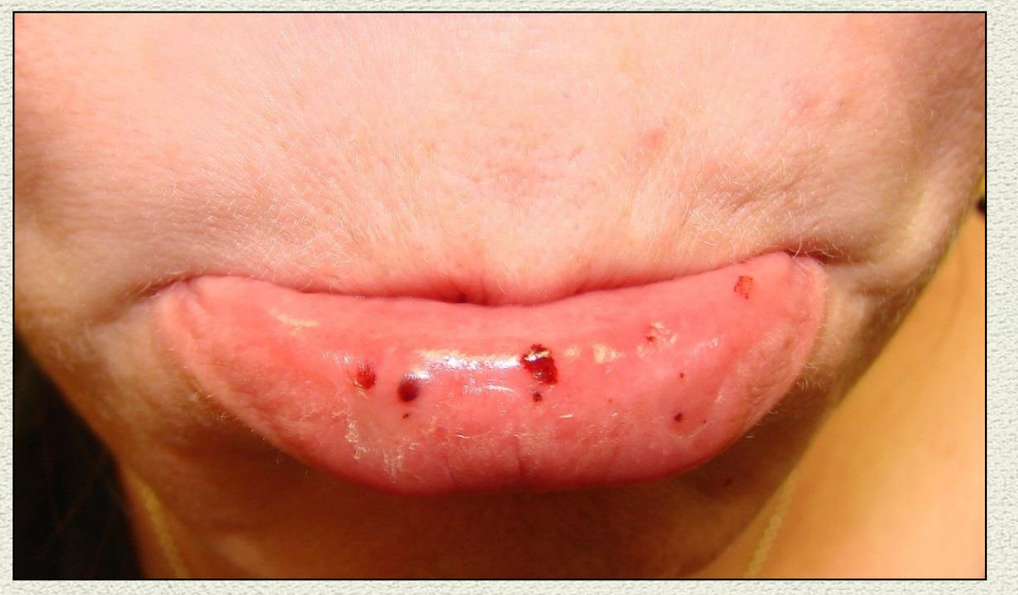
- congestive (Upshaw-Shulman Syndrome)
- acquired (auto a-b)

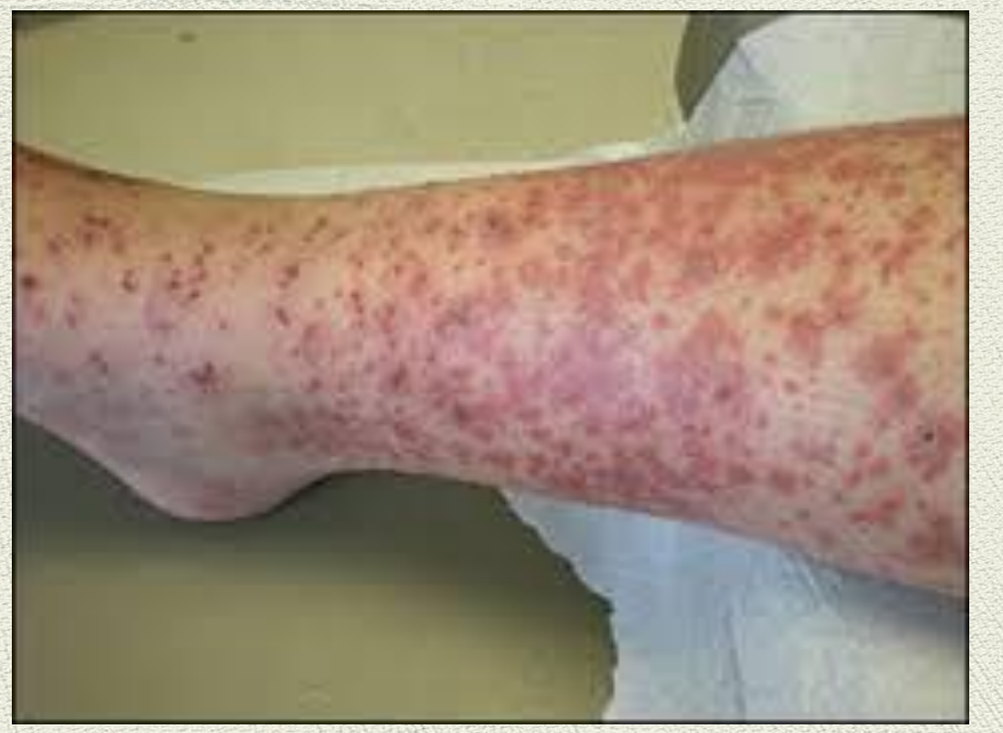
ADAMTS13 defficiency

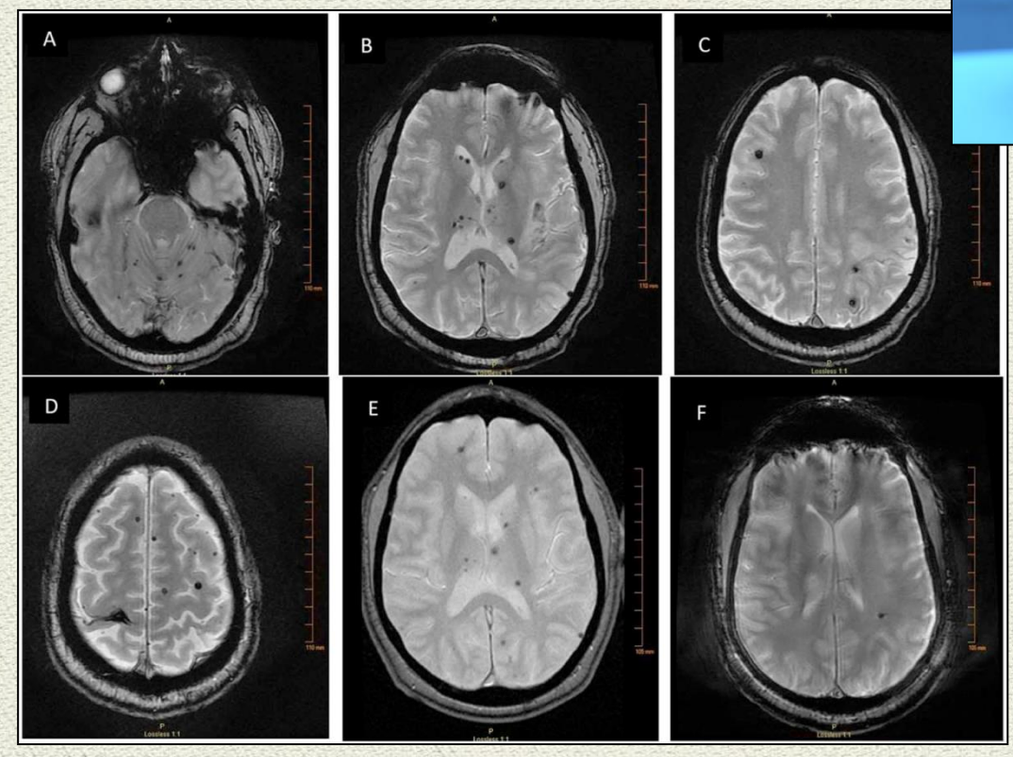
- < 10 % (UpToDate)
- ≤ 5 %

Thrombotic Thrombocytopenic Purpura (TTP) - symptomps

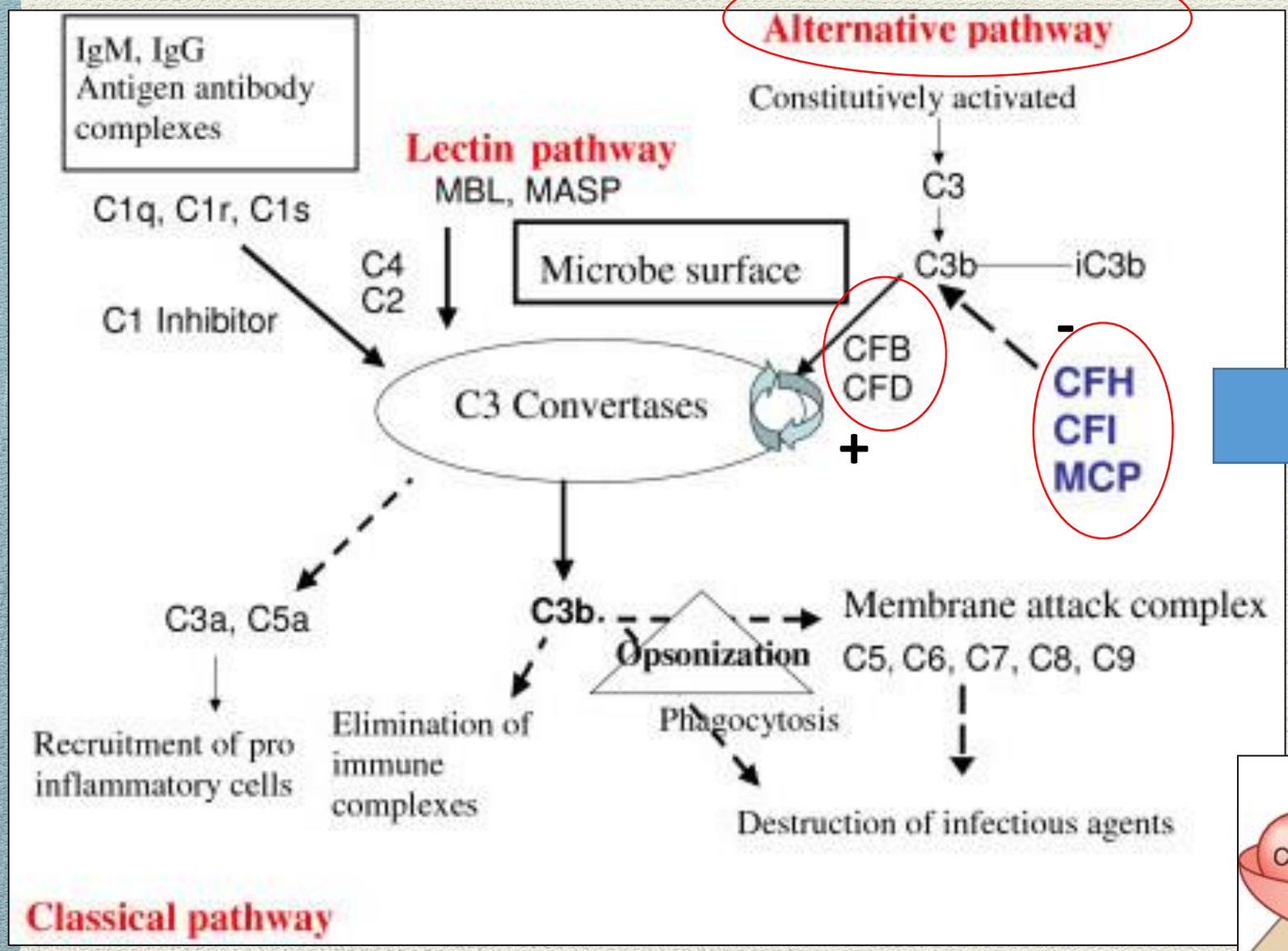








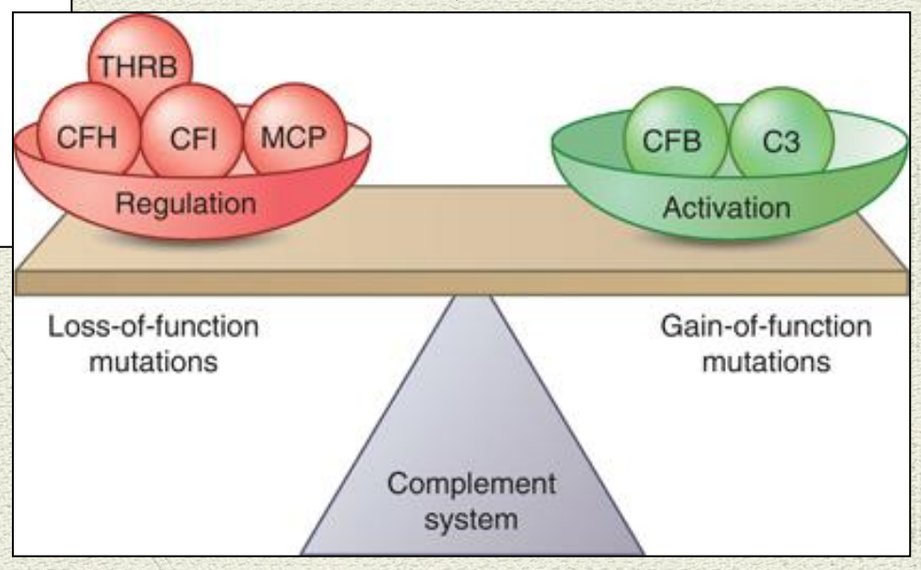
Complement depended TMA - pathogenesis



Within 3 years after the first episode of TMA 79% of patients will die

Irreversible renal injury:

The first flare – 33-40% cases
Next relapse – 80% cases



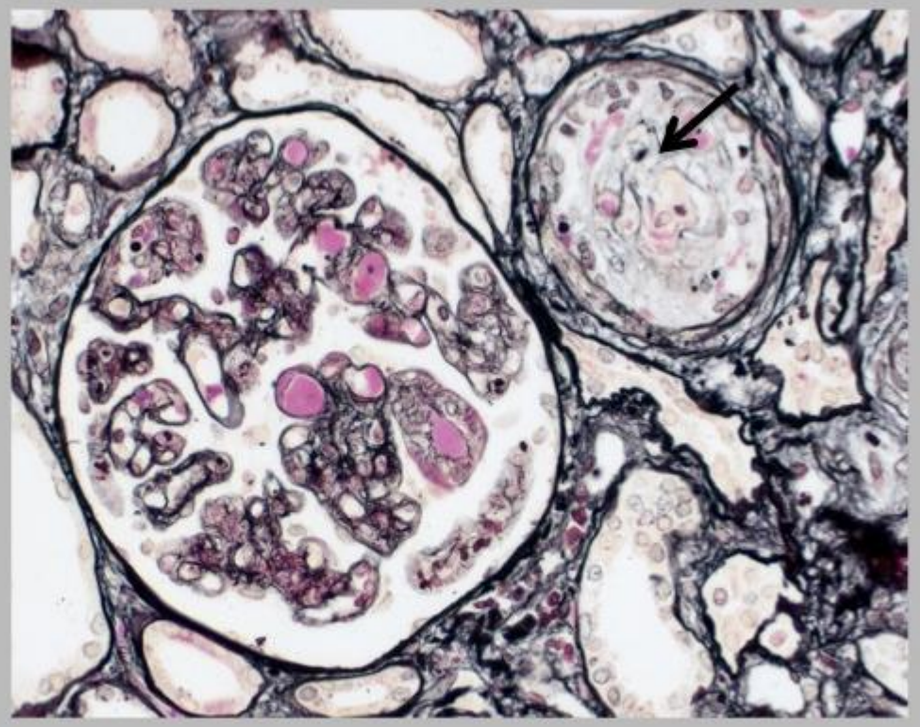
Variations:

- Congenital (gene mutations: MCP, CFH, CFB, CFI)
- Acquired (auto antibodies against CFH, CFI)

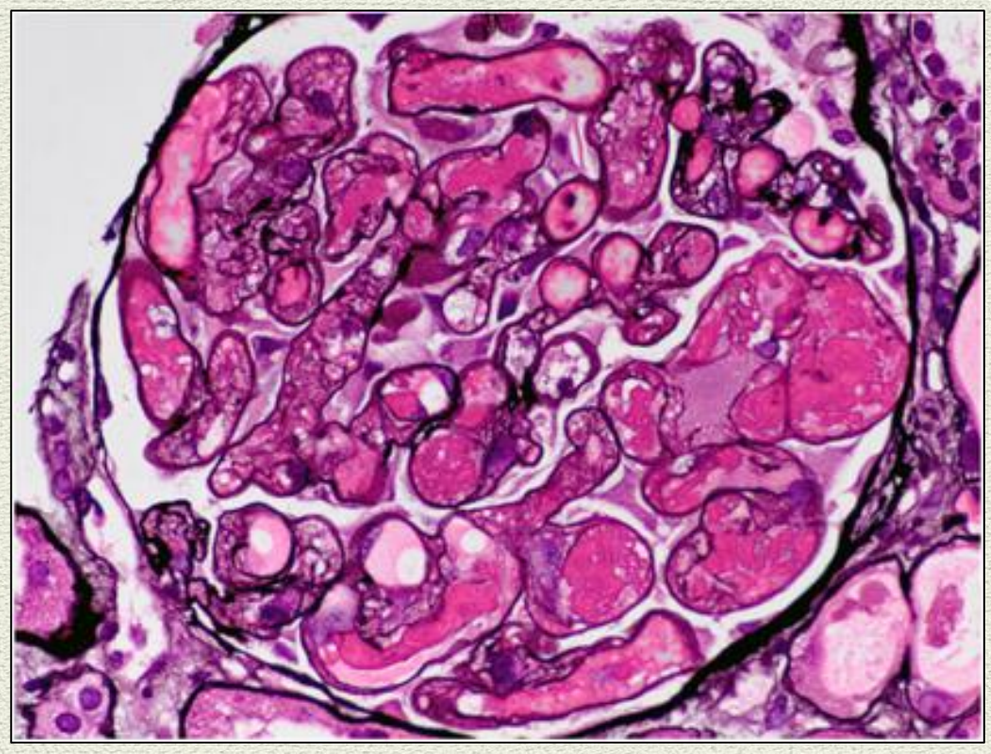
TMA – kidney biopsy

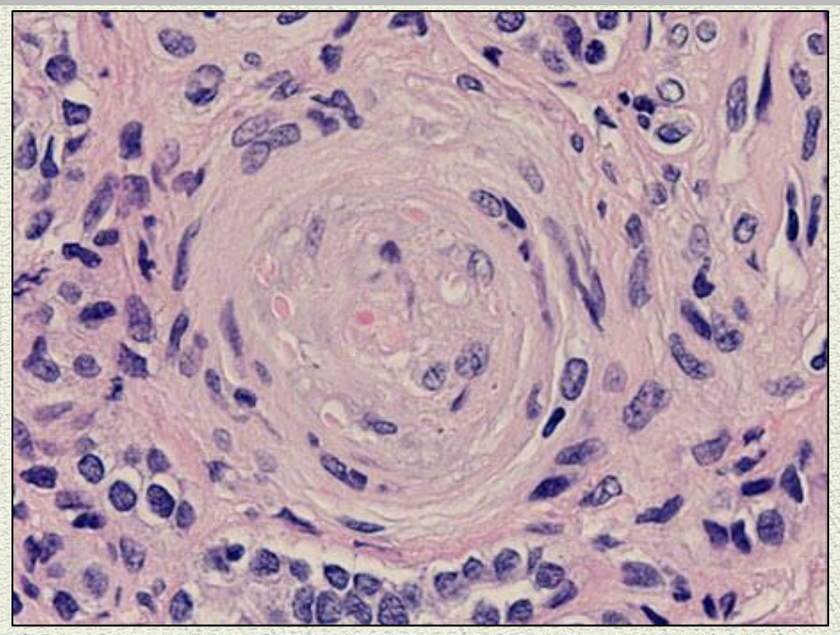
Thrombotic Microangiopathy TMA

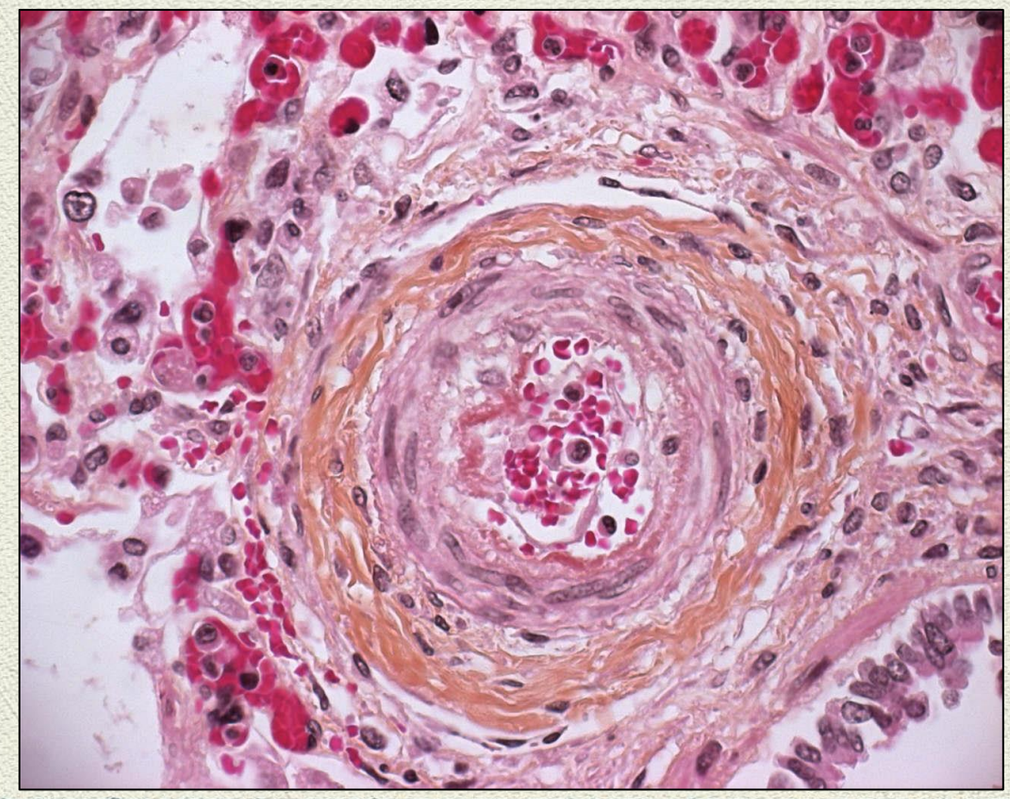
Glomerulus and arteriole



Glomerulus with fibrin thrombi (red) and basement membrane irregularities. Arteriole with wall thickening and cellular intimal infiltrates (remnant lumen arrow)







An importance of TMA differentiation:

	STEC–HUS	Atypical HUS non-familial	Atypical HUS familial
Cause	Shiga toxin producing bacteria	Infections Medications Malignancy	Genetic defects in regulation of alternative complement cascade
Incidence	1–3/10^5 population	Unknown	1–3/10^6 population
Need for RRT	40%	30%	50–60%
Mortality	3–5%	Depends on underlying disease	25%
Recurrence	Rare	Rare	25–50%
Progression to ESKD	<10%	Depends on underlying disease	50–70%

The Problem with Names: Why do we care anyway?

- Morbidity and mortality are significant in untreated patients
- Early effective therapy can minimize long-term morbidity and organ damage
- Therapeutic implications of diagnostic certainty
  - Plasmapheresis vs. eculizumab
- Prognostic implications of diagnostic certainty
  - aHUS and TTP likely to recur, whereas STEC-HUS is not

aspho

Differential Diagnosis for TMAs: aHUS, TTP and STEC-HUS

Thrombocytopenia
<150,000 or >25% deterioration

±

Microangiopathic haemolysis
Elevated LDH and/or decreased haptoglobin, and/or schistocytes, and/or decreased haemoglobin[a]

More than one of the following:

Neurological symptoms:
Confusion and/or convulsions

Renal involvement:
elevated creatinine levels and/or decreased glomerular filtration rate and/or urine abnormalities

Gastrointestinal involvement:
Diarrhoea and/or nausea/vomiting, abdominal pain, gastroenteritis

Evaluate ADAMTS13 activity and shiga toxin/STEC test[b]

≤5% ADAMTS13 activity → TTP

>5% ADAMTS13 activity → aHUS; Secondary TMA

Shiga toxin/STEC positive → STEC-HUS[c]

TTP treatment

TREATMENT

- Plasma exchange
  - Mechanism :
    - Removes autoantibodies against ADAMTS13
    - Restores ADAMTS13 levels
- Not effective for Transplant associated TMA

Table 3. *Response and Mortality for Post-HSCT TMA Treated with Plasma Exchange (PE)*

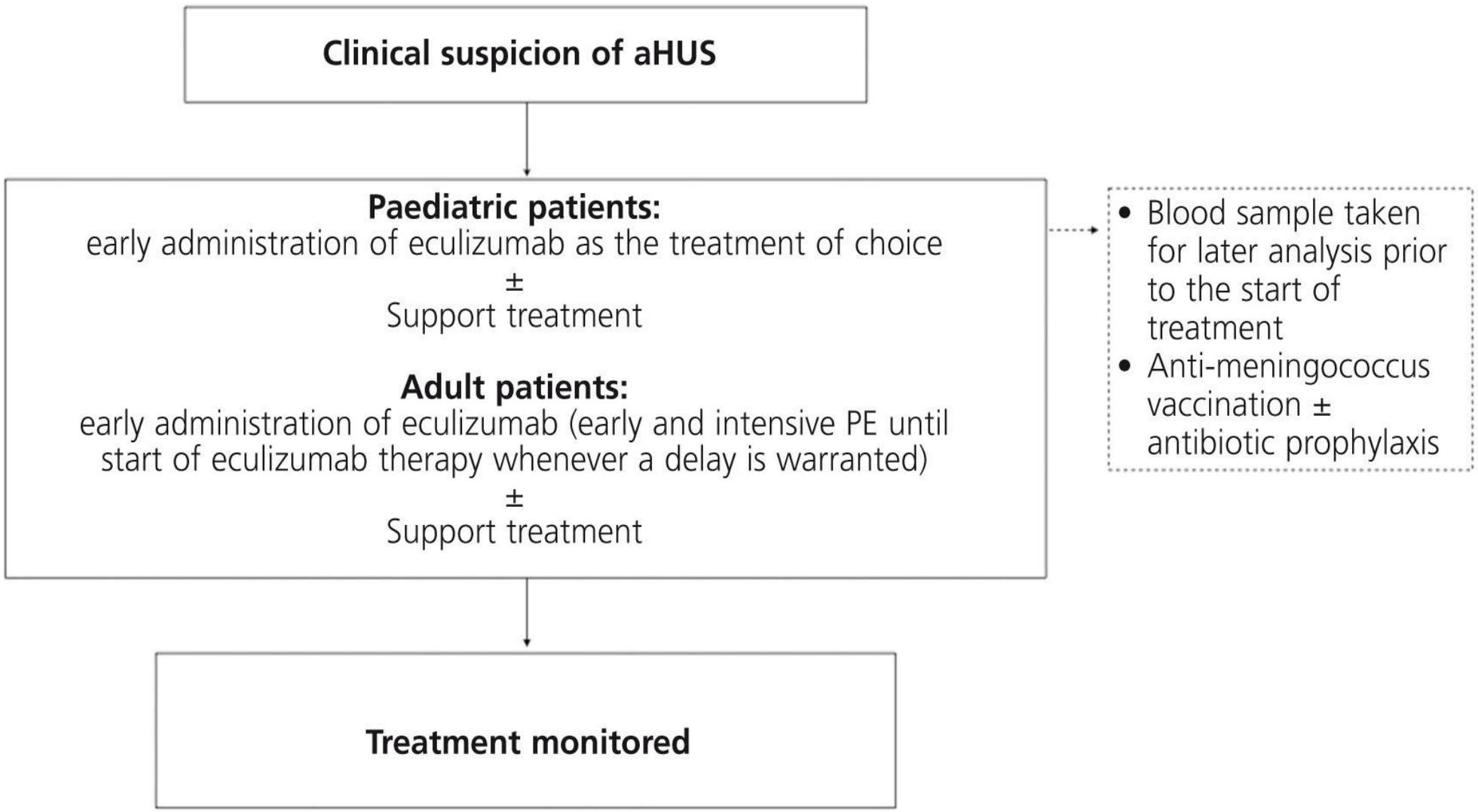
Study	No. Treated with PE	Response	Mortality
Silva et al. [17]	8	4 (50%)	7 (88%)
Sarode et al. [18]	8	3 (38%)	6 (75%)
Dua et al. [19]	16	8 (50)%	12 (80%)
Llamas et al. [20]	10	8 (80%)	7 (70%)
Paquette et al. [21]	7	0 (0%)	7 (100%)
Iacopino et al. [3]	6	1 (17%)	5 (83%)
Uderzo et al. [16]	16 (pediatric)	NA	7 (44%)
Roy et al. [22]	17	3 (18%)	16 (94%)
Fuge et al. [5]	17	6 (35%)	16 (94%)
Ruutu et al. [4]	5	4 (75%)	4 (80%)
Sarkodee-Adoo et al. [23]	11	2 (18%)	9 (82%)

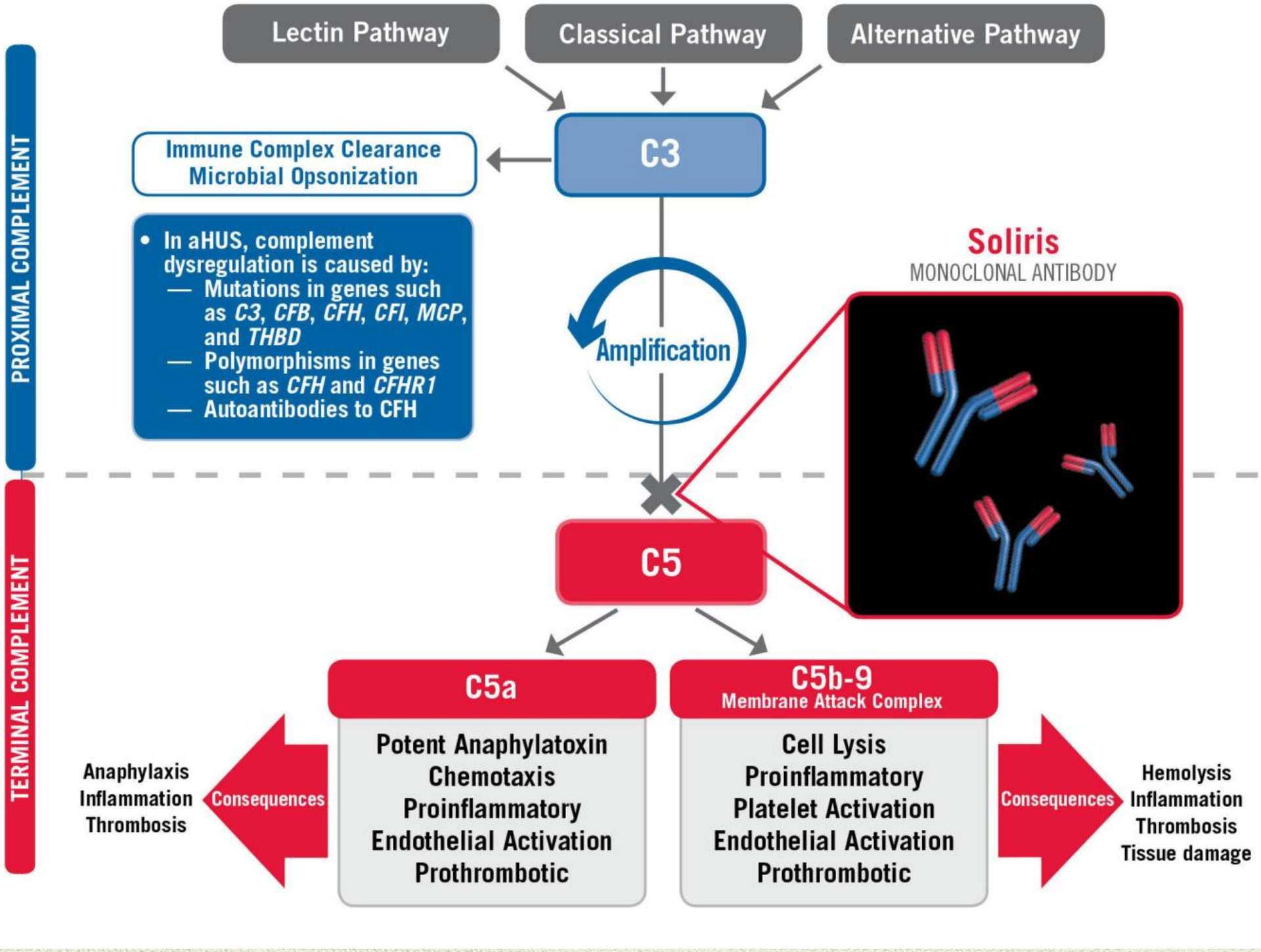
NA indicates not available.

Ho, Vincent T., et al. "Blood and marrow transplant clinical trials network toxicity committee consensus summary: thrombotic microangiopathy after hematopoietic stem cell transplantation." *Biology of Blood and Marrow Transplantation* 11.8 (2005): 571-575.

By Dr. JAGJIT KHOSLA

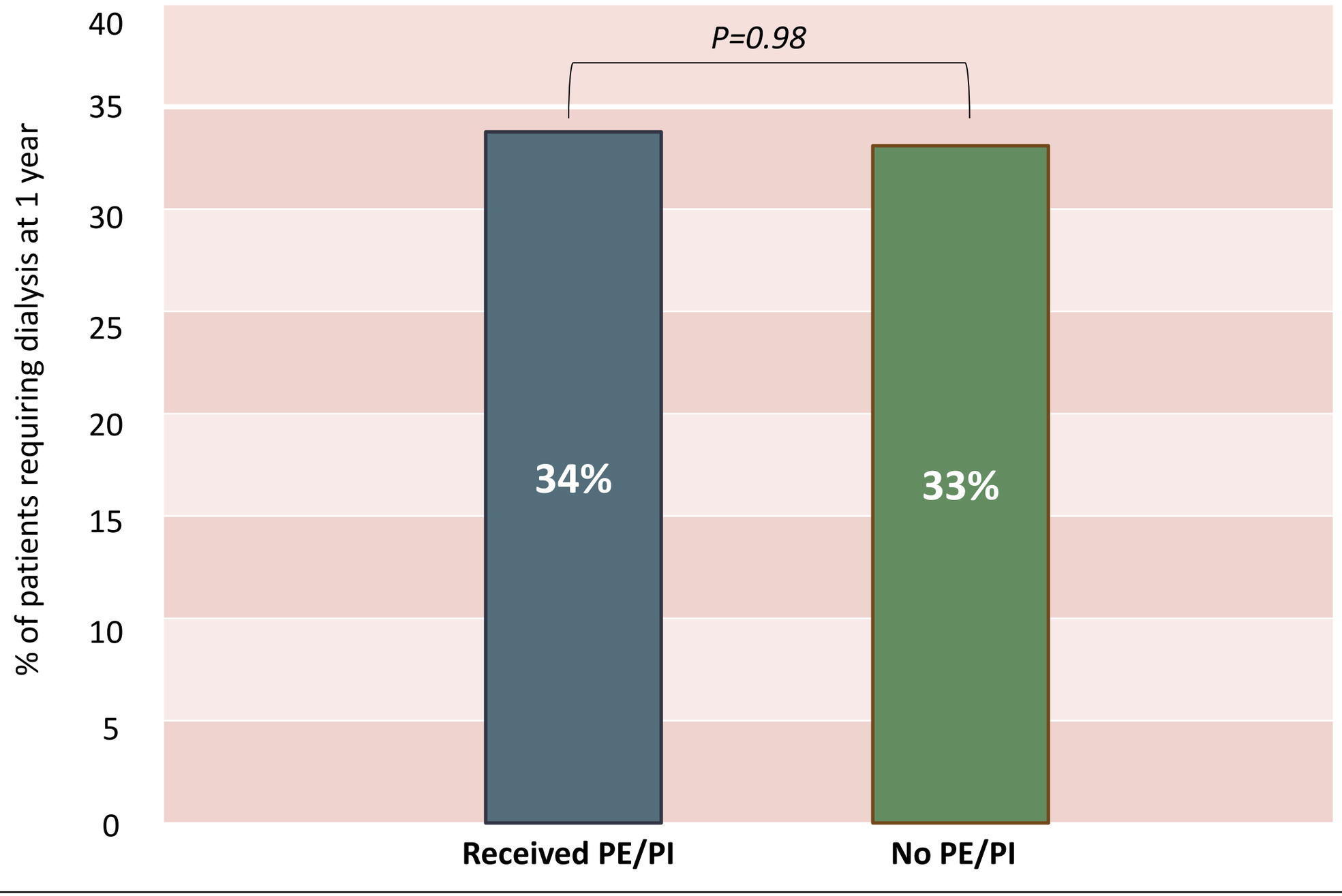
aHUS treatment





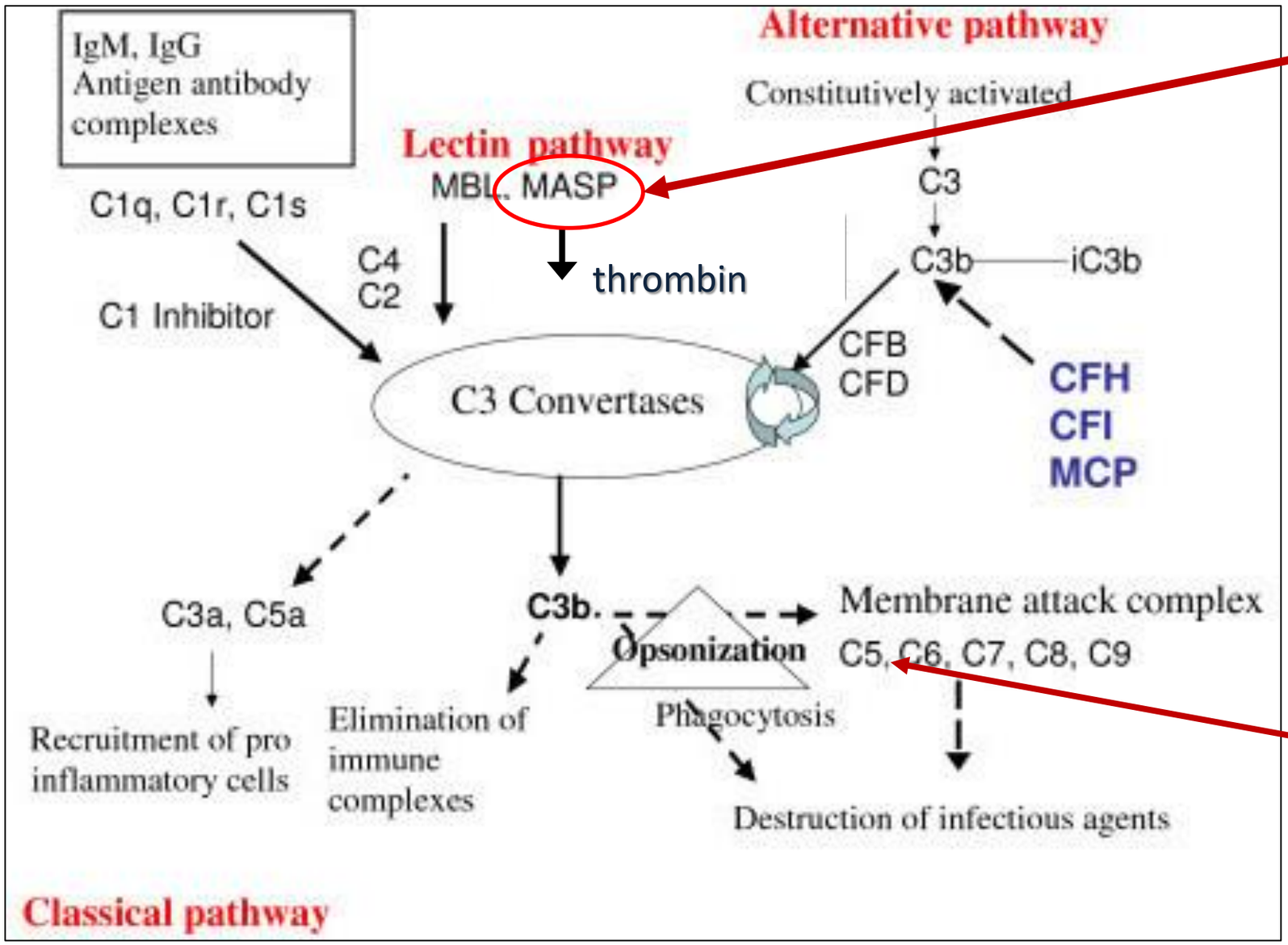
Duration of therapy? Cost !!!!

PE/PI do not decrease the risk of ESRD in aHUS (N=99)



Riedl M, Hofer J, Rosales A, et. al. Initiale plasmatherapie bei patient mit antypischem HUS: kein negative Vorhersagewert für das outcome nach einem jahr. *Klin Padiatr.* 2011; 223-P031 DOI: 1055/s-0031-1273832

Omeros: OMS721, monoclonal human IgG4 anty MASP-2



OMS721

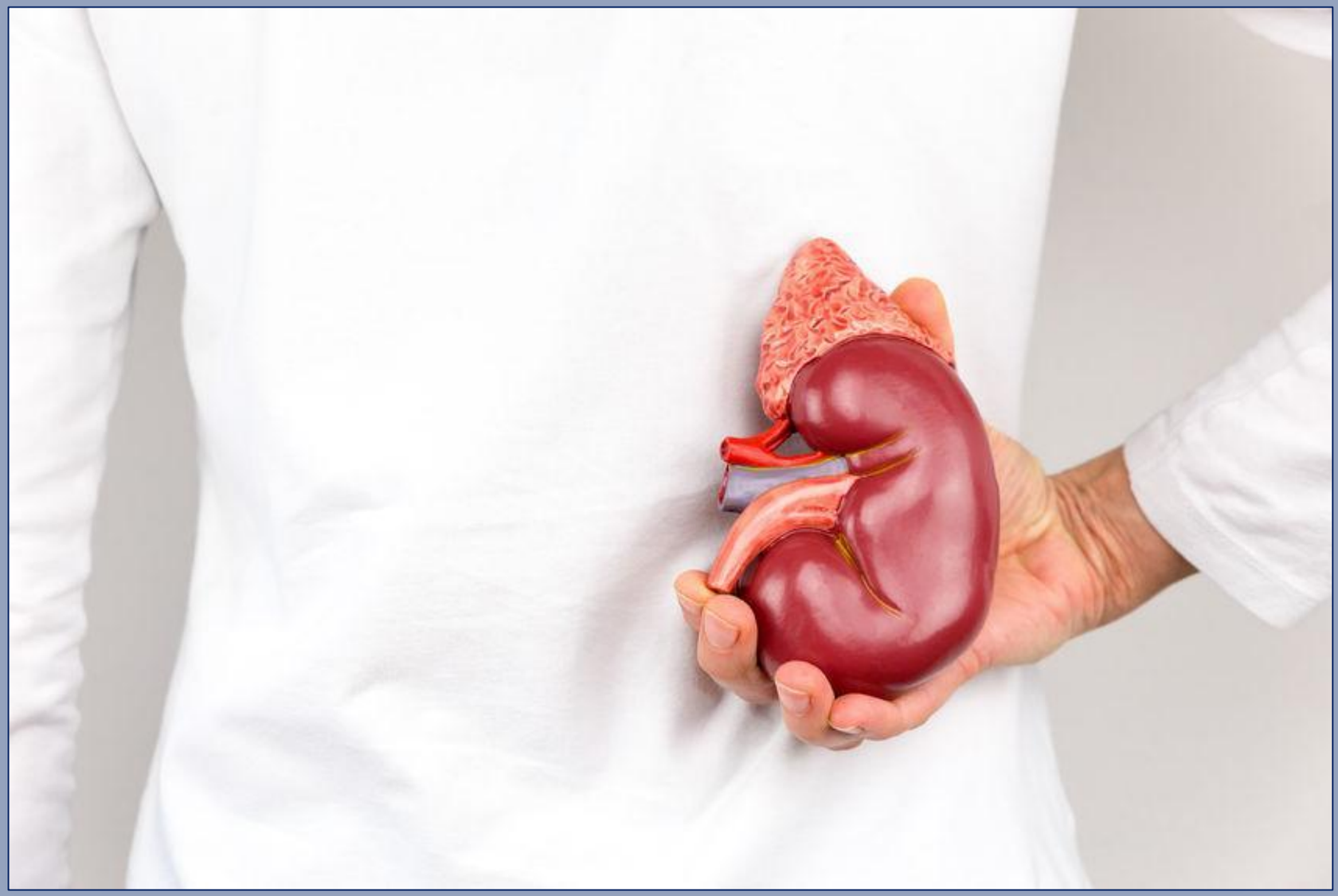
eculizumab

Benefit:

- **OMS721 does not interfere with classical complement pathway so it does not influence the response for bacteriae such as *meningococcus, pneumococcus, Haemophilus influenzae*,**

- **OMS721 is given subcutaneously**

Which one is better?



THANK YOU!

Conclusion:

- Niedokrwistość normocytarna z retikulocytozą bez cech krwawienia – **pomyśl o HEMOLIZIE!**
- Sprawdź ilość płytek i rozmaz krwi obwodowej – **MIKROANGIOPATIA**!
- Wyklucz wtórne przyczyny mikroangiopatii i rozważ konieczność pilnego wdrożenia **PLAZMAFEREZY**!
- W przypadku **biegunki** – wykonaj posiew/wymaz z odbytu w kierunku STEC i sprawdź obecność toksyny *Shiga*, w przypadku potwierdzenia infekcji - nie stosuj antybiotyku!
- Pamiętaj o odstawieniu wszystkich leków mogących powodować hemolizę!
- Zwróć uwagę na wykładniki uszkodzenia nerek – skontaktuj się z **NEFROLOGIEM (DIALIZA?)**
- **W PRZYPADKU PODEJRZENIA HUS ZALEŻNEGO OD KOMPLEMENTU – SKONTAKTUJ SIĘ z I KLINIKĄ NEFROLOGII w Białymstoku**

DIAGNOSTYKA TMA W POLSCE

Jeżeli:
aktywność ADAMTS13 ≥ 10% i
posiew stolca na EHEC (-), EIA toksyny Shiga (-) i brak genu toksyn (stx 1 i 2)

to obowiązuje:
wykluczenie TMA zależnego od niedoboru kobalaminy (wit. B12)

- stężenie w surowicy homocysteiny i kwasu metylomalonowego (MMA)
- *bad. genetyczne - mutacja MMACHC (rzadko?)*

↑ stężeń

Terapia: hydroksykobalamina + betaina