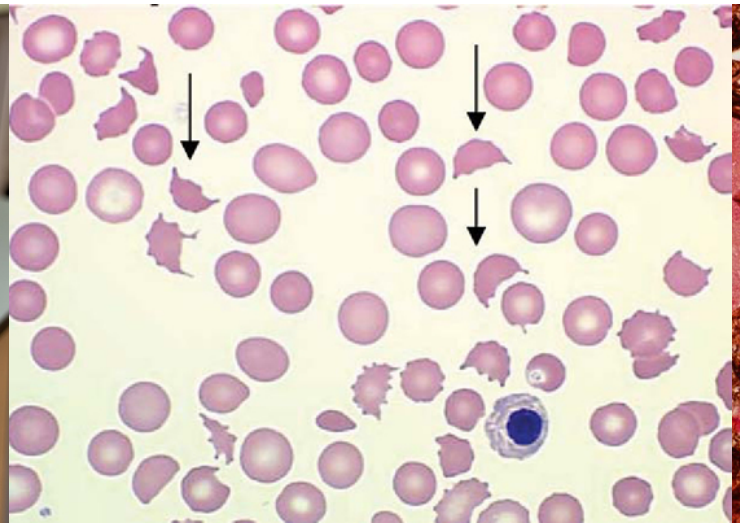
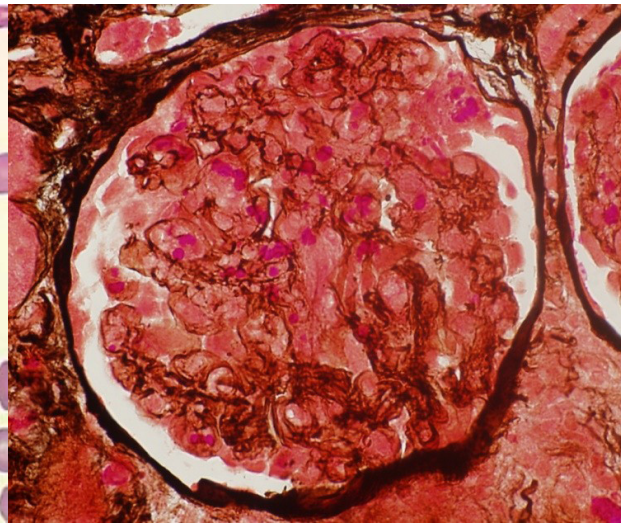
Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Thrombotic Microangiopathy

Assoc.Prof. Chanchai Traivaree M.D. Msc. (Clini Epi)

Chief, Division of Pediatric Hematology/Oncology
Phramongkutklao College of Medicines

Case Scenario

10-year-old girl who presented with drowsiness and fever last 5 days.

PH: No underlying disease

PE: Vital signs :**T 38 C** ,Tachycardia

Lung &CVS : clear

Abdomen : **No hepatosplenomegaly**

Ext. : No bruises over extremities

NS : **Drowsiness**

Sensory & motor : WNL

Lab investigations

Complete Blood Count

Hb 8.5 g/dL, Hct 26 %

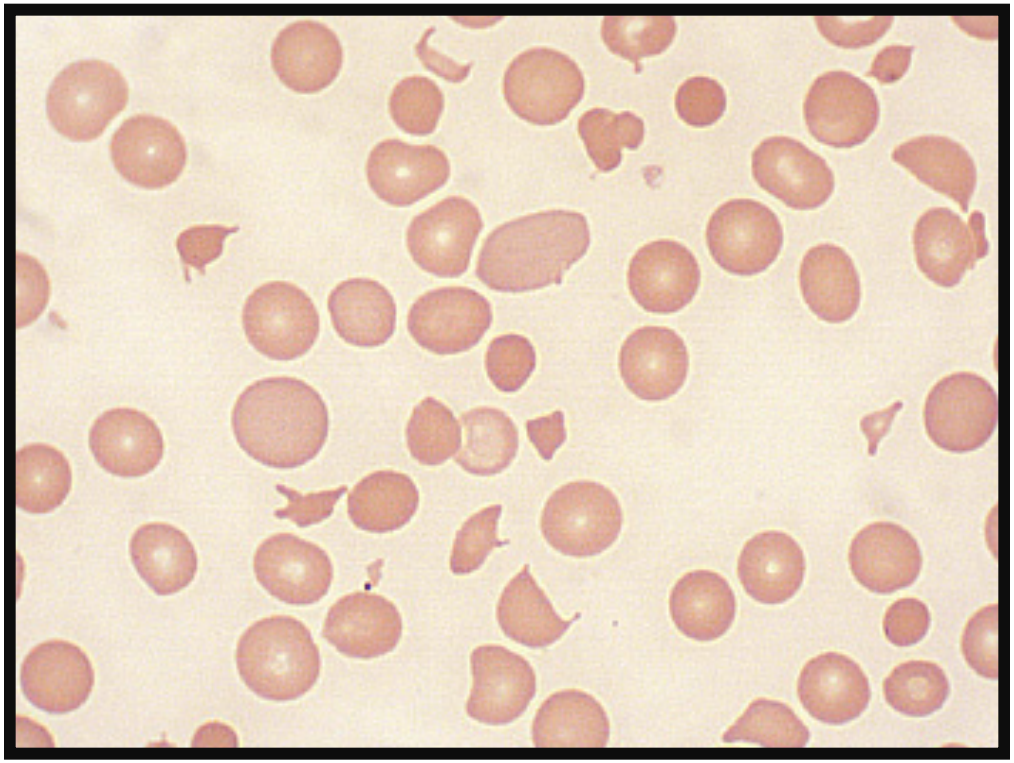
MCV 88 fL, MCH 28.9 pg,

MCHC 35.9 g/dL, RDW 14.5 %

WBC 13,000 (P66, L30, M4)

PLT 30,000

Coagulogram : Normal



Approach to TMA

Thrombotic Microangiopathies (TMA)

Hemolytic Uremic Syndrome

aHUS with dysregulation of the alternative complement pathway

- Mutations in CFH, CFI, MCP, C3, CFB, THBD, Anti-CFH antibodies
- CFH/CFHR1 hybrid gene
- CFHR1,3 deletion

Shigatoxin-induced *E.Coli* HUS (STEC-HUS)

TTP (ADAMTS13 deficiency)

- Acquired due to autoantibody to ADAMTS13
- Congenital due to homozygous ADAMTS13 mutations

Miscellaneous conditions

- **BM/ Solid organ transplantation**
- **Malignancy**
- **Sepsis/ DIC**
- **Autoimmune disorders**
- **Drugs (CNI, Gemcitabine)**
- **Malignant hypertension**
- **Pregnancy**
- **HELLP syndrome**
- **HIV infection, Influenza**

Ref : Dixon BP Pediatr Clin North Am2018

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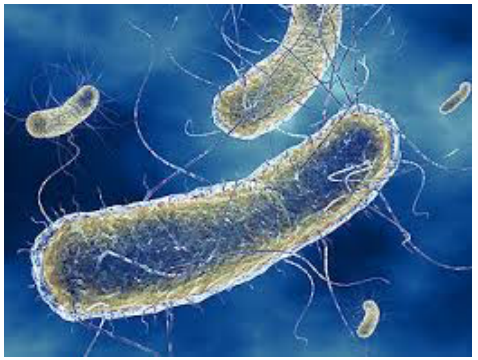
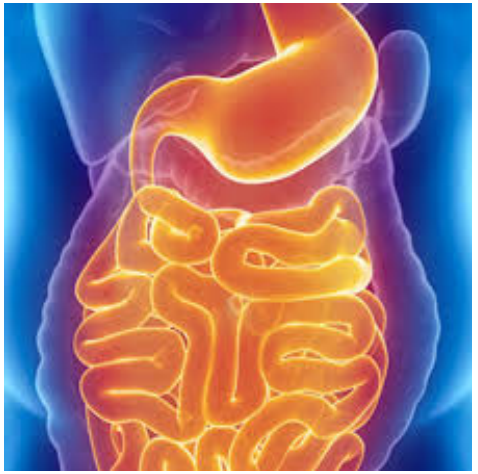
Ref : Dixon BP Pediatr Clin North Am2018

STEC-HUS

- Infants and young children
- Preceding GI symtoms with watery/bloody diarrhea
- Usually due to ***Shigatoxin-producing E.coli*** (serotype ***0157:H7***)
- Renal failure primary manifestation
- CNS and other organ involvement in some cases
- Normal levels of VWF-cleaving protease





Management

- Dialysis and other supportive care
- Plasmapheresis ***usually not required!!!***

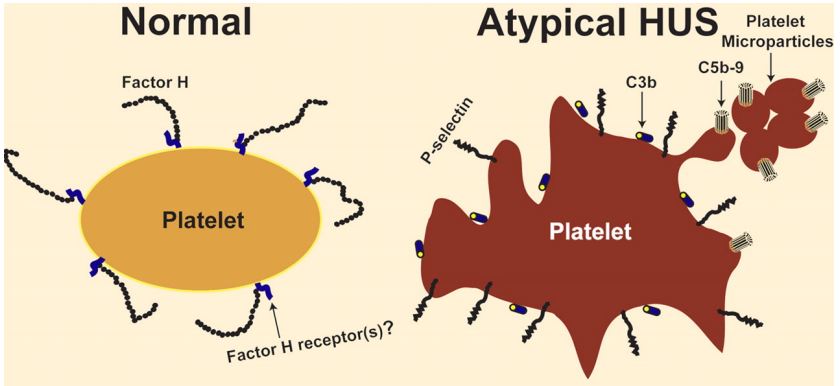
Ref : Dixon BP Pediatr Clin North Am2018

Atypical HUS

- 40%in children under 18 yrs of age
- Familial in 20% of cases
- Infections, inflammatory trigger complement activation
- ***A low level of C3 / Factor B with normal level of C4***
- Hypertension, renal failure, oliguria

Extrarenal manifestations (20%)

- Cardiac failure
- Seizures, drowsiness,coma
- Distal gangrene of fingers and toes
- Pulmonary hemorrhage



Ref : Dixon BP Pediatr Clin North Am2018

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

HUS

Clinical Taxonomy of HUS

Characteristics	STEC HUS	Atypical HUS Non-familial	Atypical HUS Familial
Cause	Shiga toxin	Infection Malignancy	Genetic defect in alternative complement cascade
Need for RRT	40%	30%	50-60%
Mortality	3-5%	Depends on U/D	25%
Recurrence	Rare	Rare	25-50%
ESRD	<10%	Depends on U/D	50-70%

Ref : Cheung V Front Med (Lausanne) 2014

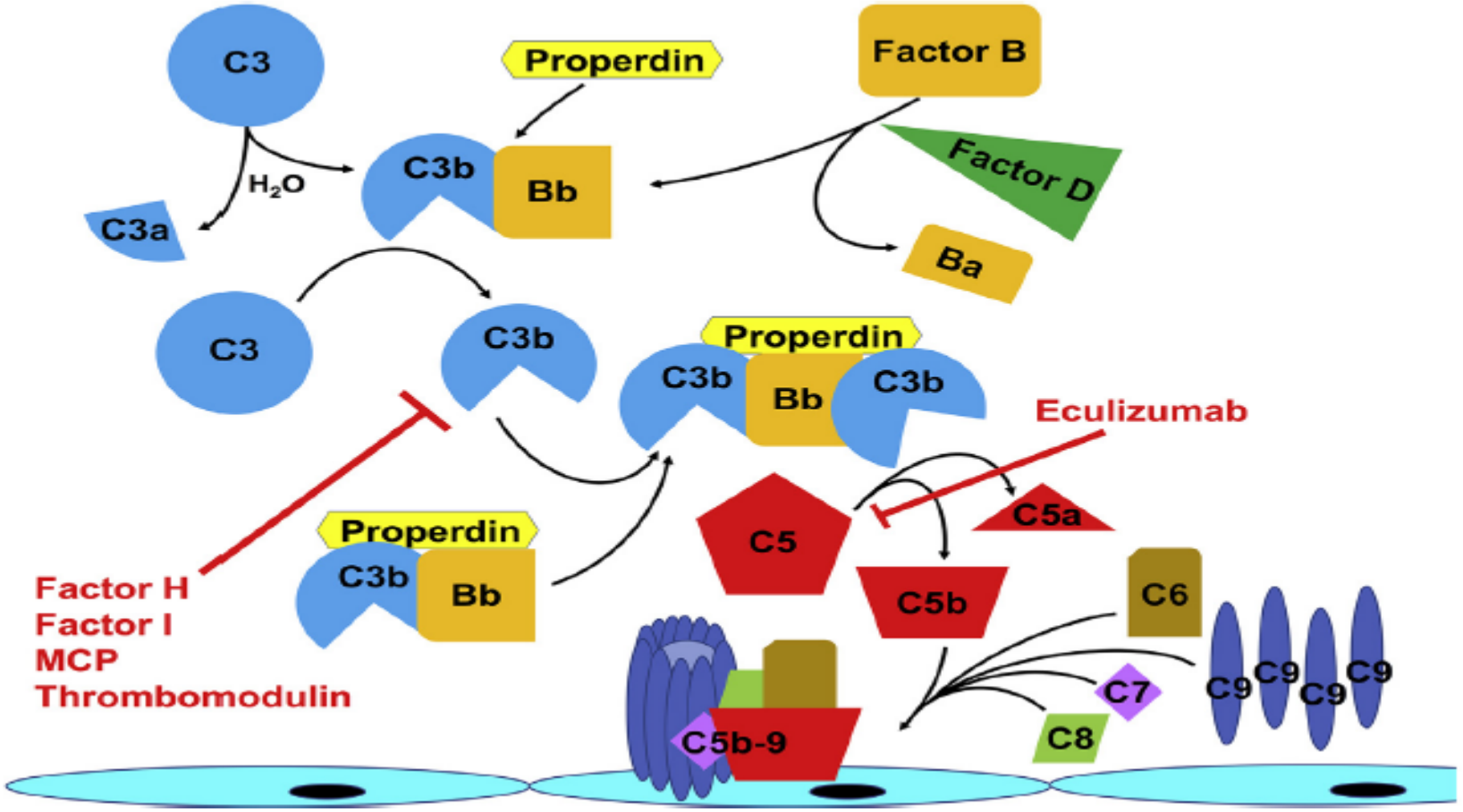
HUS

Inflammatory mediators in HUS

Characteristics	STEC HUS	Atypical HUS Non-familial	Atypical HUS Familial
Leucocytes	+++	+	None
Chemokines	IL-8 MCP-1 CXCR1 CXCR4/7- SDF-1	No data	None
Cytokines	IL-6	No data	Anti-IL-6 agents P38 Inhibitors
Complement	+	++++	Eculizumab

Ref : Cheung V Front Med (Lausanne) 2014

HUS



Ref : Dixon BP Pediatr Clin North Am2018

Genetic in Atypical HUS

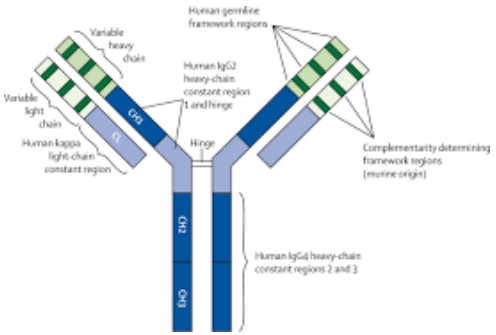
Table 1
Gene mutations associated with atypical hemolytic uremic syndrome

Gene Mutation	Inheritance	Type	Frequency (%)[a]
Factor H (*CFH*)	AD with IP	LOF	21–22
CFH/CFHR1 hybrid gene	AD with IP	Antagonist to CFH[b]	3–5
MCP (*CD46*)	AD with IP	LOF	5–9
Factor I (*CFI*)	AD with IP	LOF	4–8
C3 (*C3*)	AD with IP	GOF	2–8
Factor B (*CFB*)	AD with IP	GOF	12 individuals
Thrombomodulin (*THBD*)	AD with IP	LOF	5
CFHR1/CFHR3 deletion (associated with anti-Factor H autoantibodies)	AR	Loss of activity of Factor H	26
Diacylglycerol kinase ε	AR	Prothrombotic	27 (children presenting at age <1 y)
None identified			30–48

Ref : Loirat C Orphanet J Rare Dis 2011

Eculizumab

- Monoclonal humanized anti-C5 antibody prevent C5 cleavage
- ***Currently approved therapy for atypical HUS***
- Significant time-dependent ***improved in renal function and no plasma therapy*** in 26 wks of study
- TMA EFS in 95% of patients with or without mutations
- No infection-related adverse events
- ***Success 68%*** (20 of 29% pts) in associated diseases with a variety of TMA (SLE,acute humoral rejection)



Ref : Greenbaum LA Kidney Int 2016

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- **Malignant hypertension**
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- **HELLP syndrome**
- **HIV infection, Influenza**

Ref : Dixon BP Pediatr Clin North Am2018

TTP

TTP - Thrombotic Thrombocytopenic Purpura

Rare Disease 1:100,000

Mortality 20%

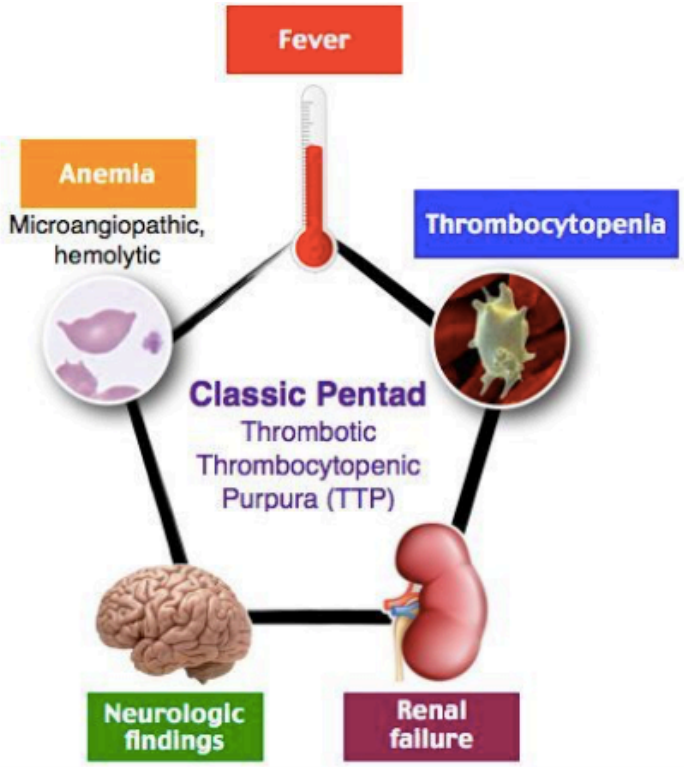
Classical Pentad

Thrombocytopenia, Anemia, fever

Neurological and Renal abnormalities

More Common:

- Microangiopathic hemolytic anemia,
- Thrombocytopenia
- In the absence of any other cause



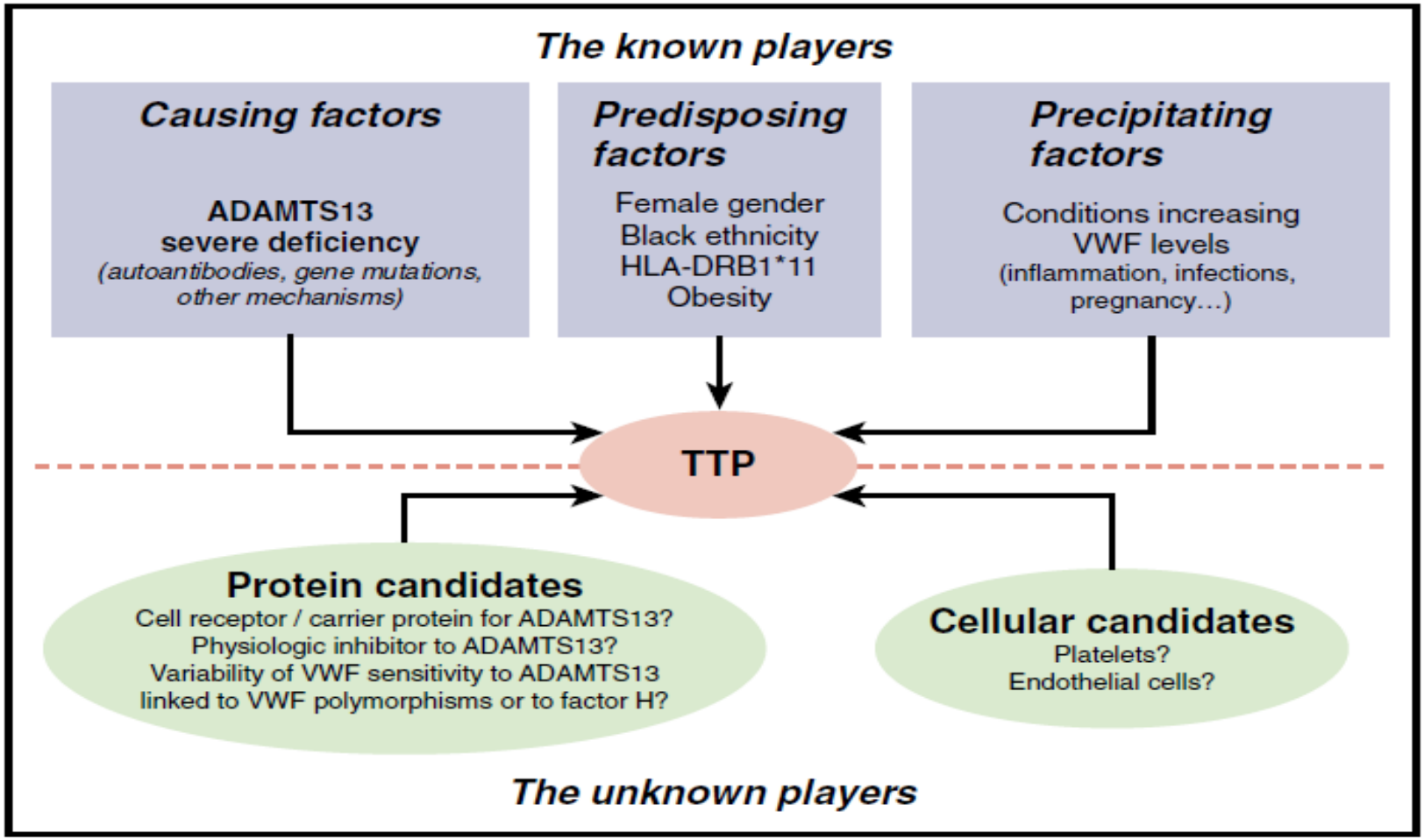
Ref : Masias C Blood 2017

TTP vs HUS

Characteristics	Chronic relapsing TTP	Acquired TTP	STEC HUS	Atypical HUS
Schistocyte	Yes	Yes	Yes	Yes
Thrombocytopenia	Yes	Yes	Yes	Yes
Hypofibrinogenemia	No	No	No	No
Neuro manifestration	Very common	Very common	Common	Common
Renal manifestration	Some	Some	Yes	Yes
Absent ADAMTS13	Yes	Yes	Rare	Occasional
Inhibitor to ADAMTS13	No	Most	No	Occasional

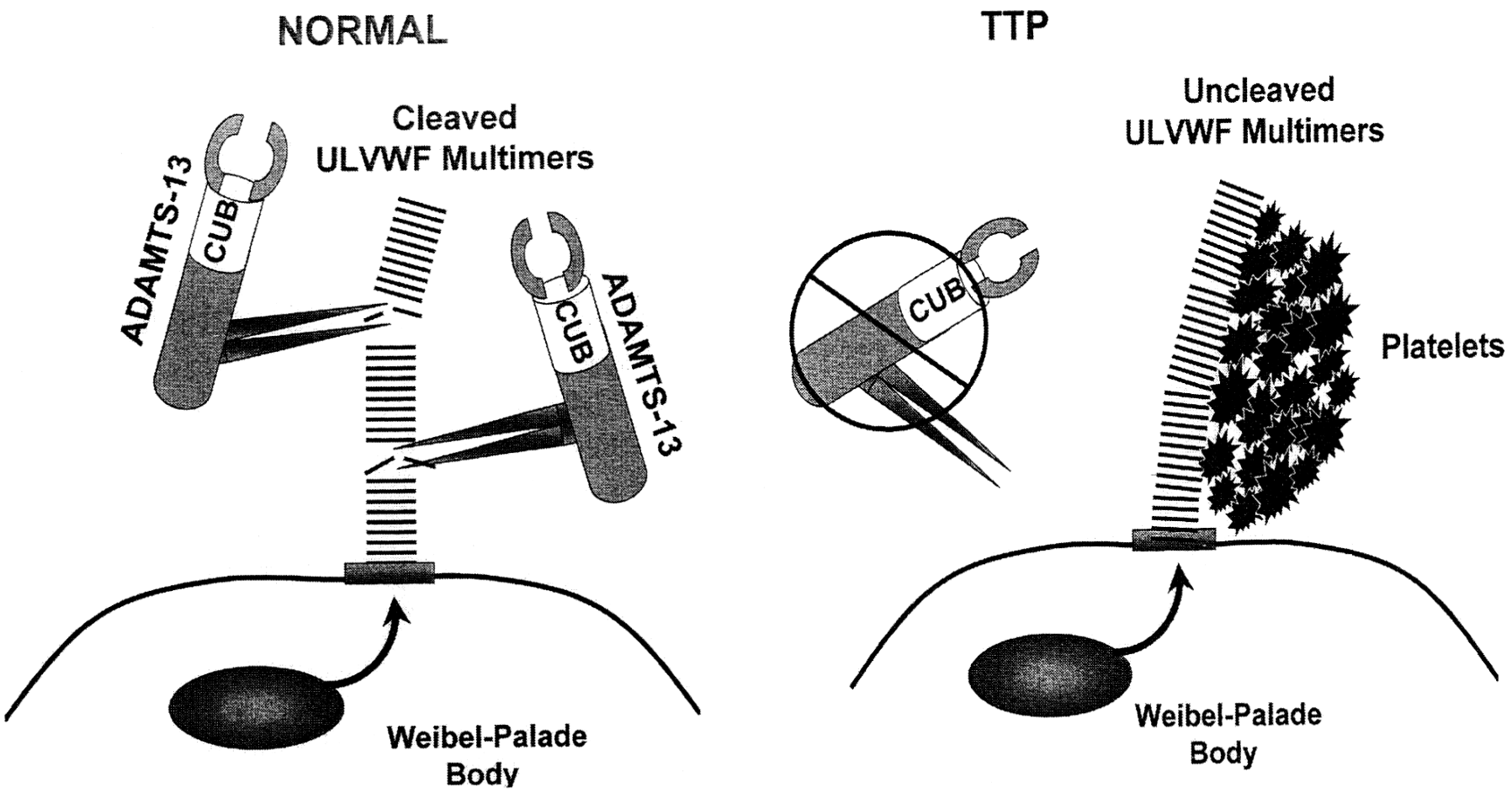
Ref : Masias C Blood 2017

Pathophysiology



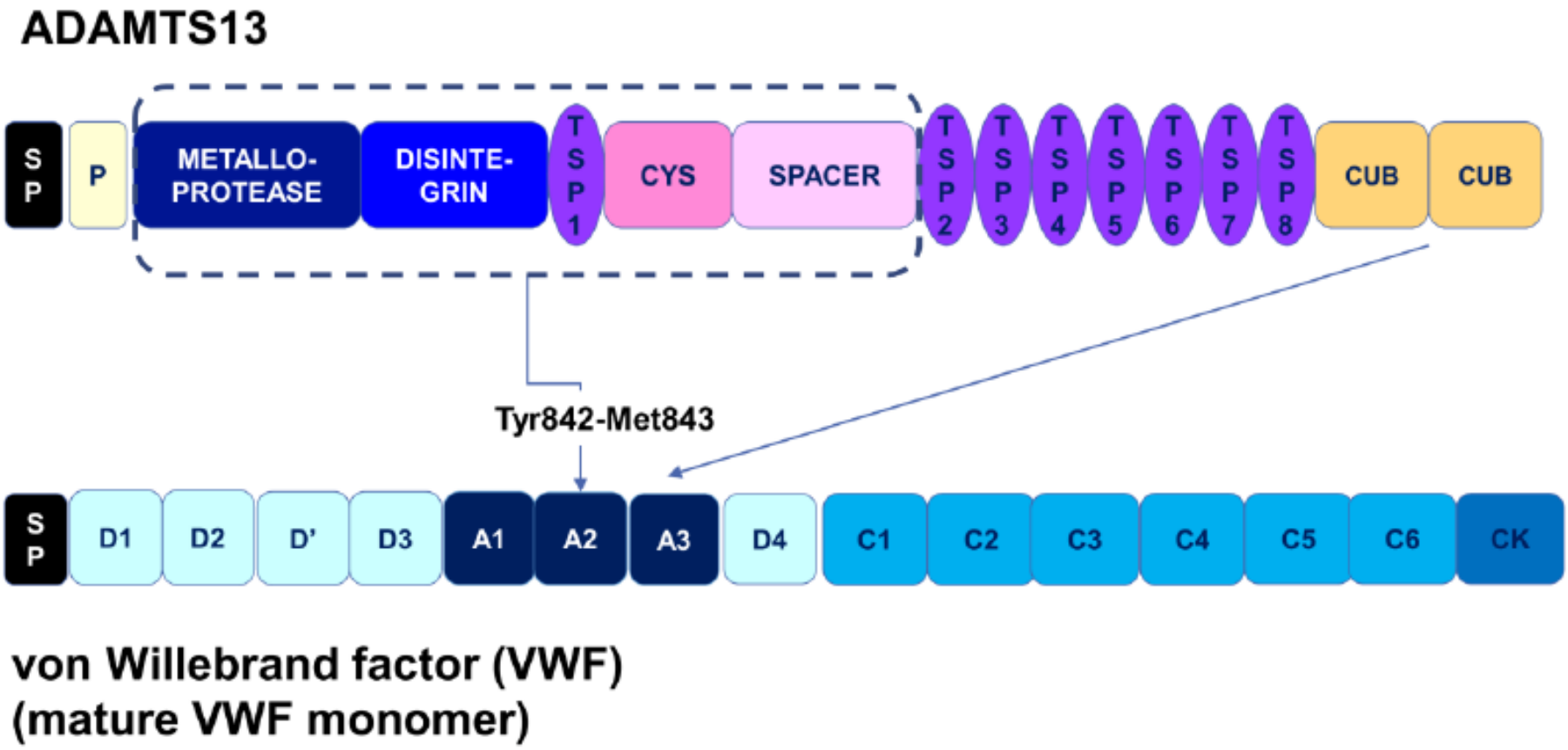
Ref : Joly BS Blood 2017

Pathophysiology



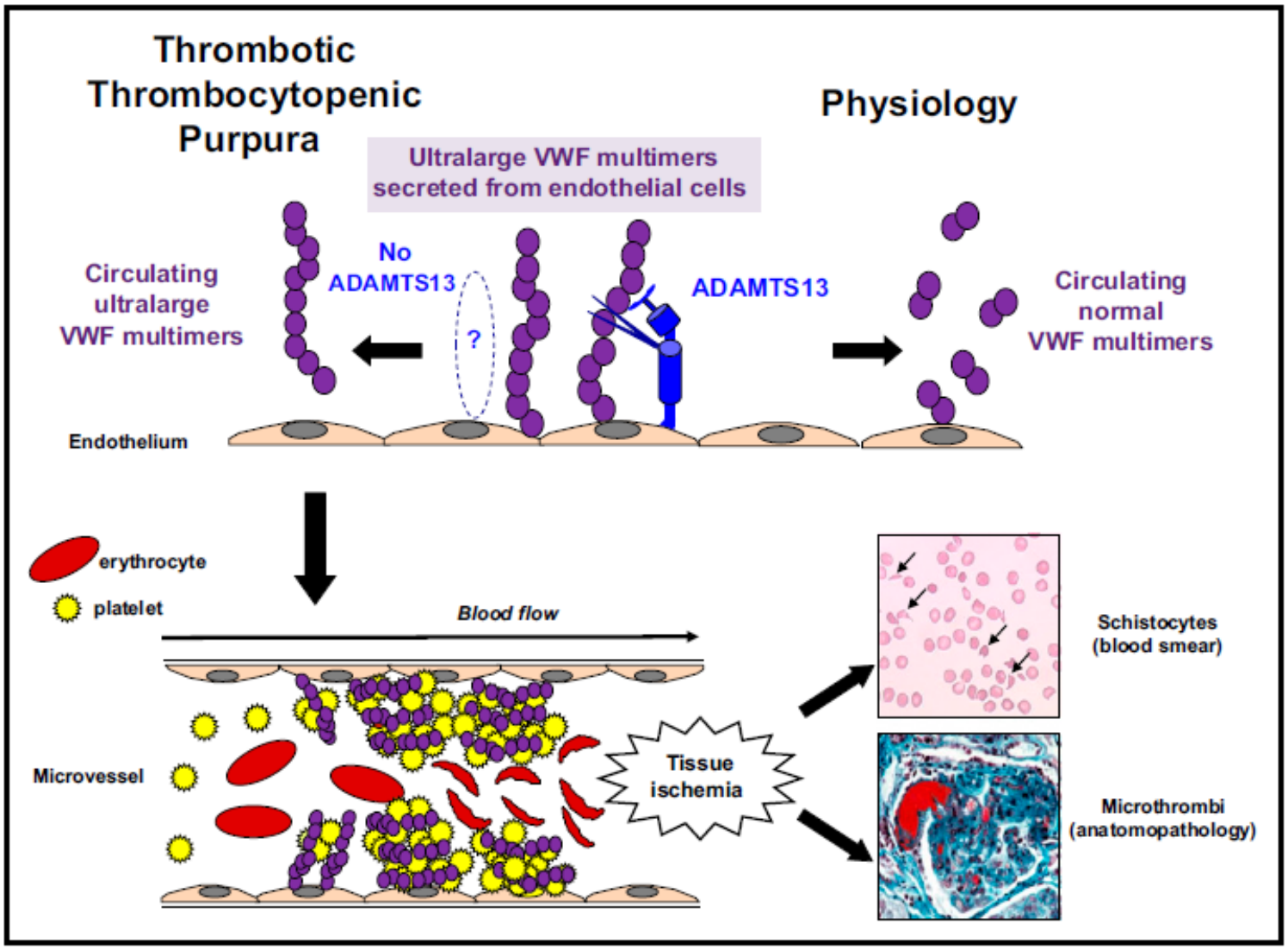
ADAMTS13 = a disintegrin and metalloprotease with eight thrombospondin-1-like domains

Von Willebrand Factor (VWF)



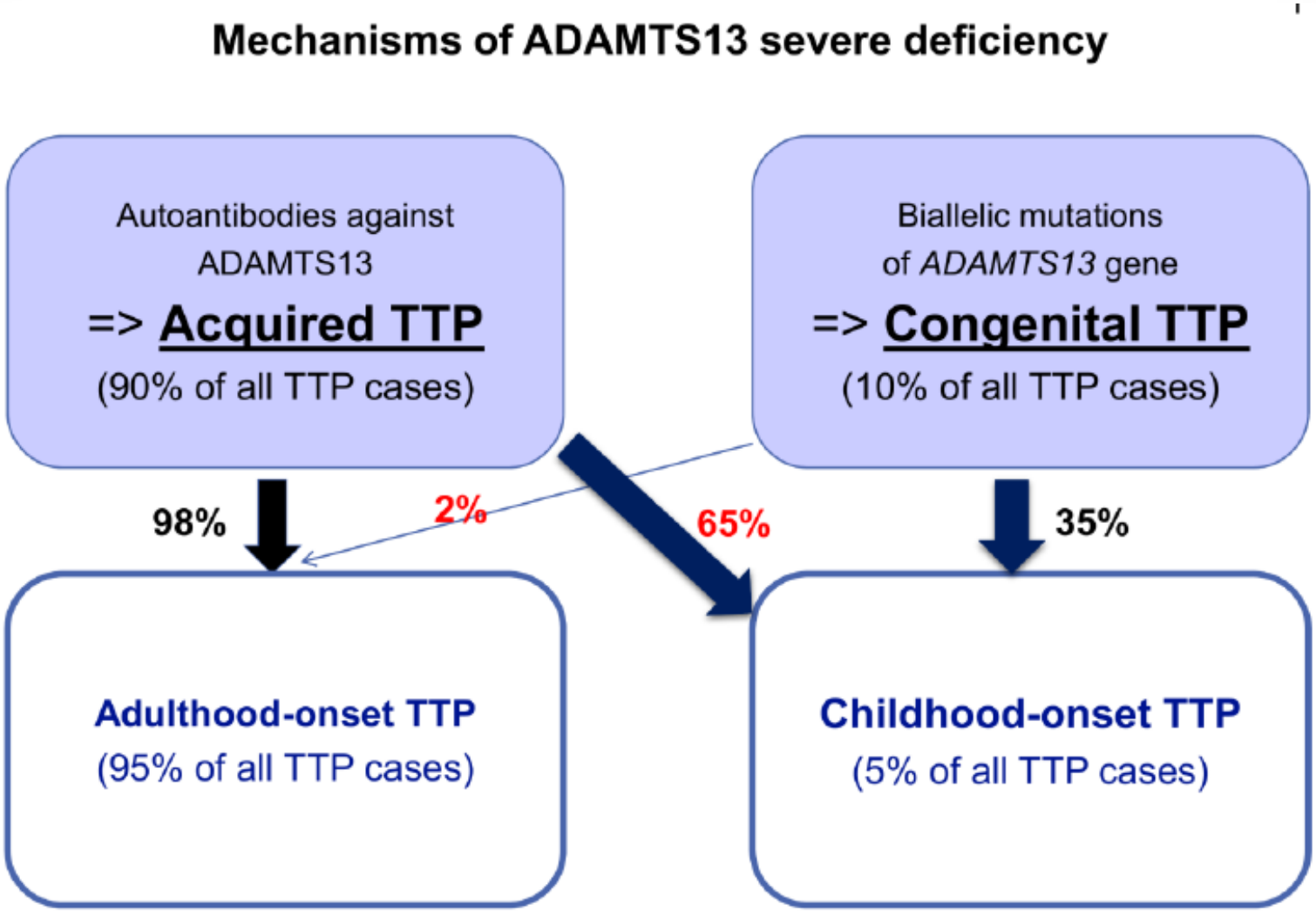
von Willebrand factor (VWF)
(mature VWF monomer)

TTP



Ref : Joly BS Blood 2017

Incidence



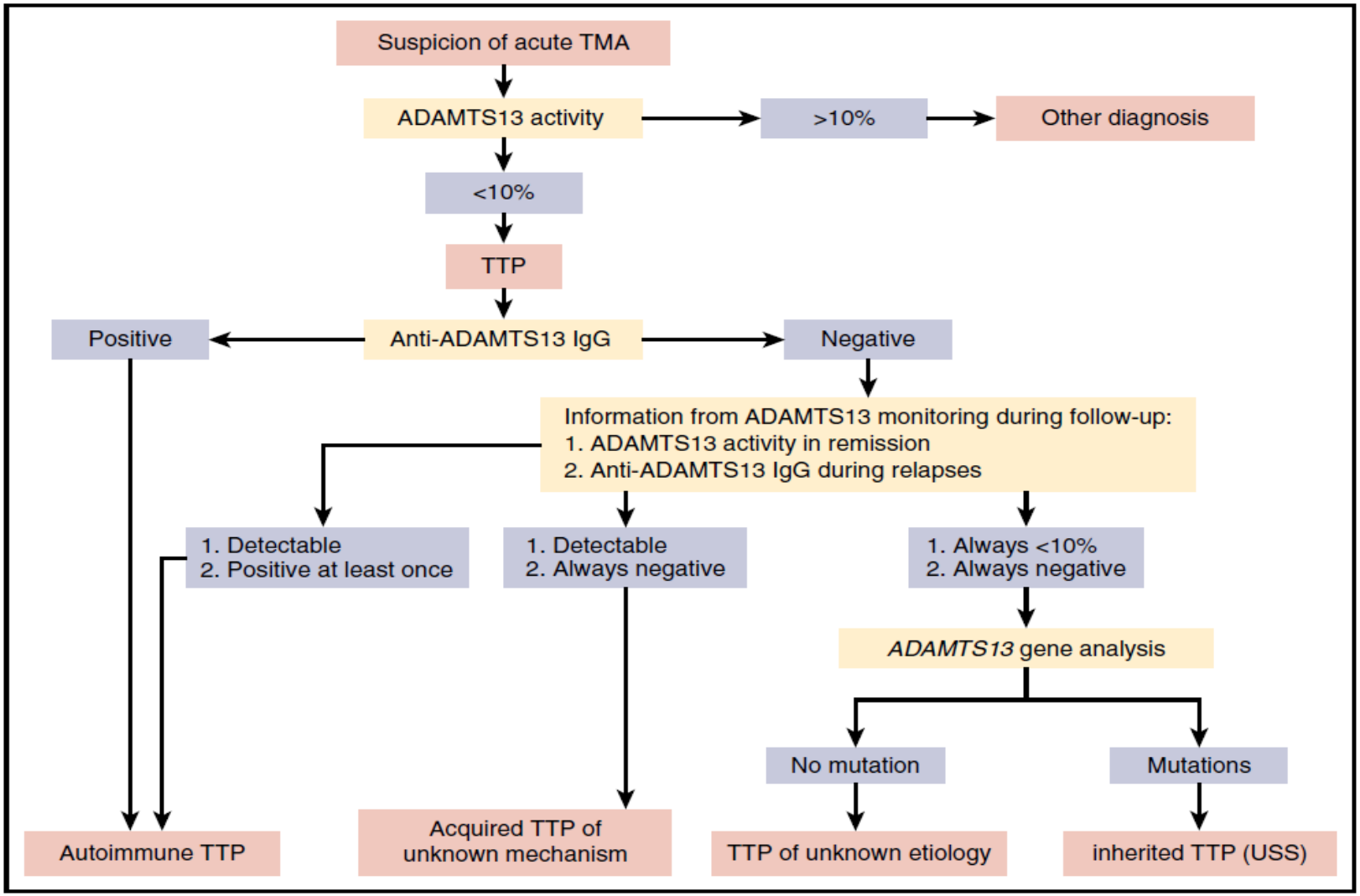
Ref : Joly BS Blood 2017

TTP

Acquired Immune-mediated TTP	Congenital Upshaw-Schulman syndrome
• ADAMTS-13 <10%,	• ADAMTS-13 <10%,
• anti-ADAMTS-13-Abs / inhibitor	• no Inhibitor
• ***ADAMTS-13 $t_{1/2}$ ↓***	• ***ADAMTS-13 ↑ f. Plasma infusion & $t_{1/2}$ 2-4 days***
• Spontaneous ADAMTS-13 in remission	• ADAMTS 13 mutations
• F:M ratio ~ 2.5-3.5:1	• ADAMTS-13~50% in "obligatory mutation carriers"
• ↑ association w. other autoimmune disorders (SLE)	

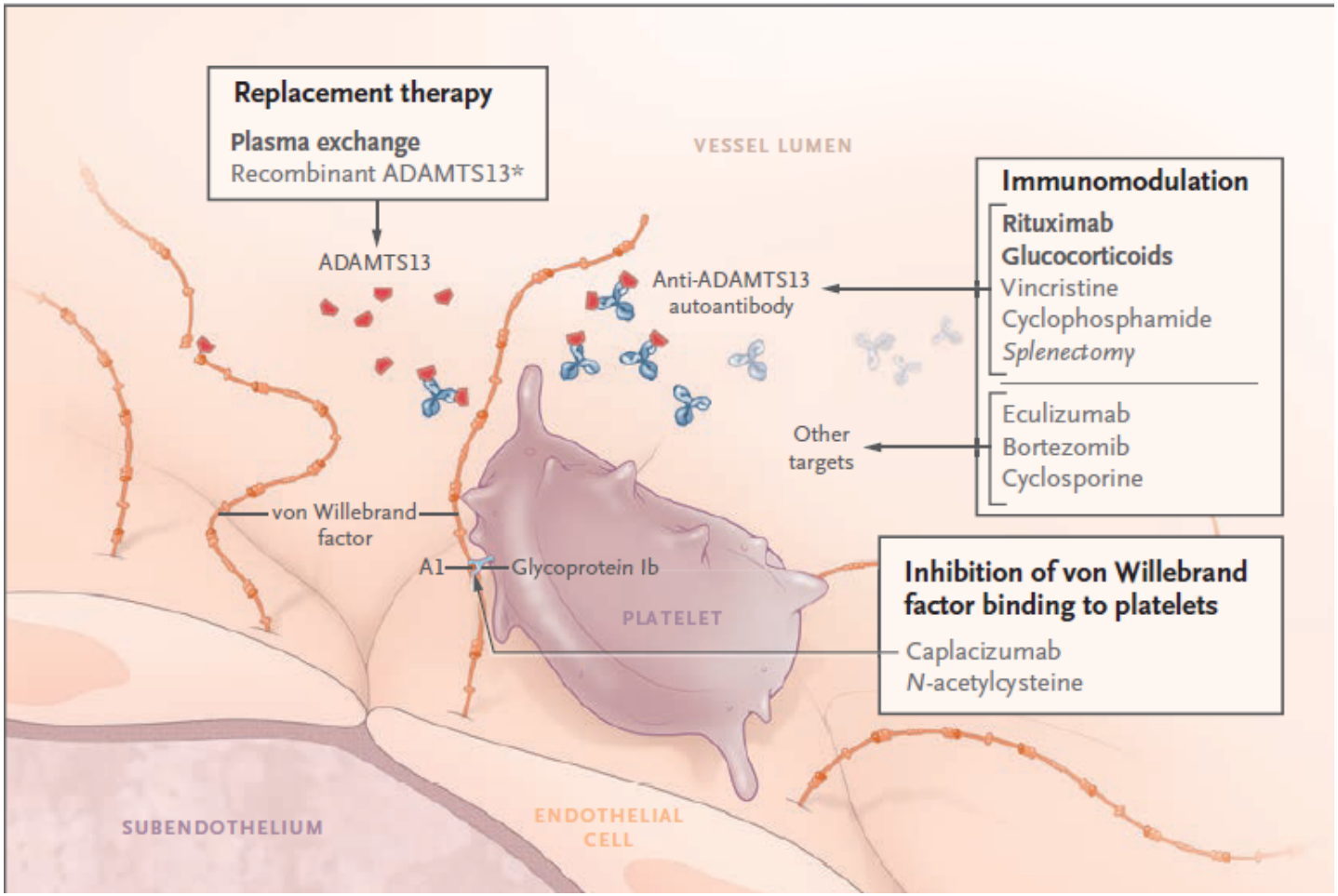
Ref : Moatti-Cohen M et al. Blood 2012

Summary



Ref : Joly BS Blood 2017

TTP Treatment



Von Willebrand Factor — A New Target for TTP Treatment?

Agnès Veyradier, M.D., Ph.D.

TTP Treatment

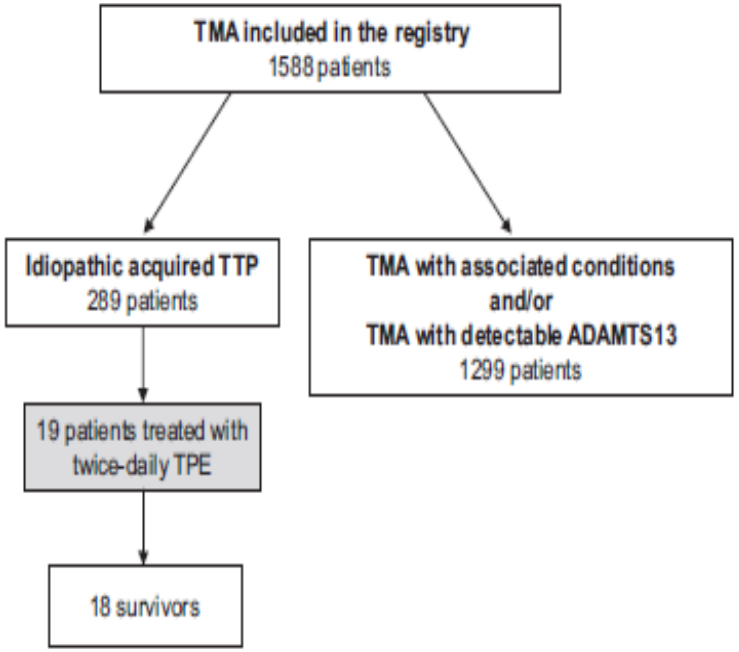
ORIGINAL ARTICLE

Twice-daily therapeutical plasma exchange-based salvage therapy in severe autoimmune thrombotic thrombocytopenic purpura: the French TMA Reference Center experience

Myriam Soucemarianadin[1,2], Ygal Benhamou[1,3,4], Yahsou Delmas[1,5], Claire Pichereau[6,7], Eric Maury[1,6,7], Frédéric Pène[1,8,9], Jean-Michel Halimi[1,10,11], Claire Presne[1,12], Jean-Marc Thouret[2], Agnès Veyradier[1,13,14], Paul Coppo[1,6,15,16]

Abstract

Background: Daily therapeutic plasma exchange (TPE) and rituximab improved thrombotic thrombocytopenic purpura (TTP) prognosis. In the more severe cases, salvage therapies including twice-daily TPE and/or cyclophosphamide may be proposed and require evaluation. *Methods:* TTP was defined as a thrombotic microangiopathy (TMA) with severe (<10%) acquired ADAMTS13 deficiency. Among patients included in the French Reference Center for TMA registry, we considered those with a severe disease (i.e., unresponsive to daily TPE and rituximab) who received twice-daily TPE. *Results:* Nineteen of 289 (6.6%) patients with TTP were treated by twice-daily TPE between 2008 and 2014. Twice-daily TPE was associated with rituximab in 16 cases. The median duration of twice-daily TPE treatment was 3 d (2–22 d). In 6 patients (31.6%), additional treatments (mainly pulses of cyclophosphamide) were performed because of a persistently refractory disease (4 cases) or an exacerbation (2 cases), despite twice-daily TPE. Only one patient (5.3%) died. The other 18 achieved a durable complete remission 25.5 d (13–68 d) after the first TPE. The median follow-up was 14.4 months (7 d–45 months). *Conclusions:* Twice-daily TPE may be an efficient strategy in the more severe TTP patients with a short-term life-threatening disease that could overcome their poor prognosis.



Ref : Soucemarianadin M Eur J Haematol 2016

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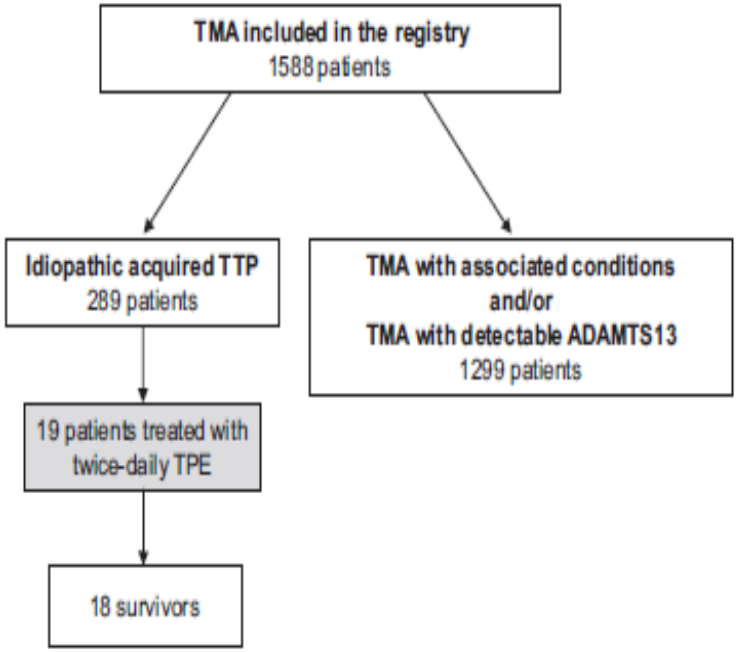
- 19/289 pts were treated by twice-daily TPE
- ***Only 1 pt died!!!*** Others 18 achieved CR 25.5 days
- ***Twice-daily TPE may efficient in more severe TTP patients with short-term life-threatening disease that could overcome poor prognosis***



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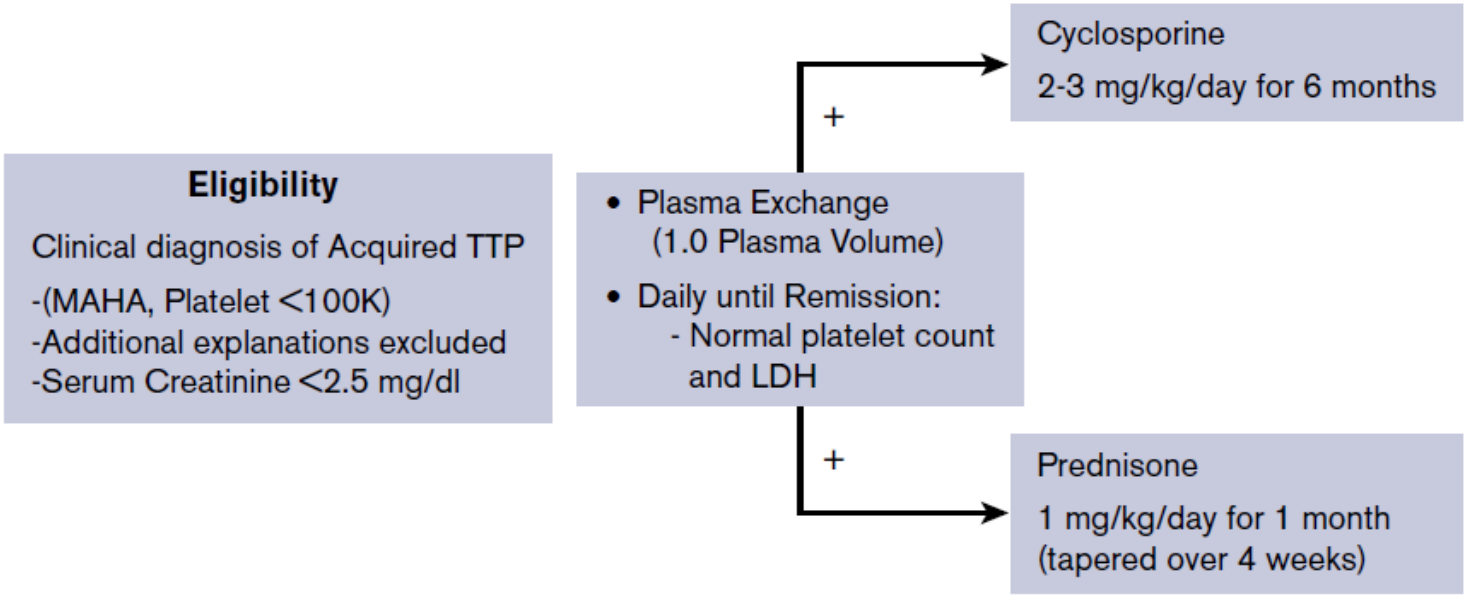
TTP Treatment

Cyclosporine or steroids as an adjunct to plasma exchange in the treatment of immune-mediated thrombotic thrombocytopenic purpura

Spero R. Cataland,[1] Peter J. Kourlas,[2] Shangbin Yang,[3] Susan Geyer,[4] Leslie Witkoff,[1] Haiwa Wu,[3] Camila Masias,[1] James N. George,[5] and Haifeng M. Wu[3]

[1]Department of Medicine, The Ohio State University, Columbus, OH; [2]Columbus Oncology and Hematology Associates, Columbus, OH; [3]Department of Pathology, The Ohio State University, Columbus, OH; [4]Department of Pediatrics, University of South Florida, Tampa, FL; and [5]Department of Epidemiology and Biostatistics, University of Oklahoma Health Sciences Center, Oklahoma City, OK



Ref : Cataland SR. Blood Adv. 2017

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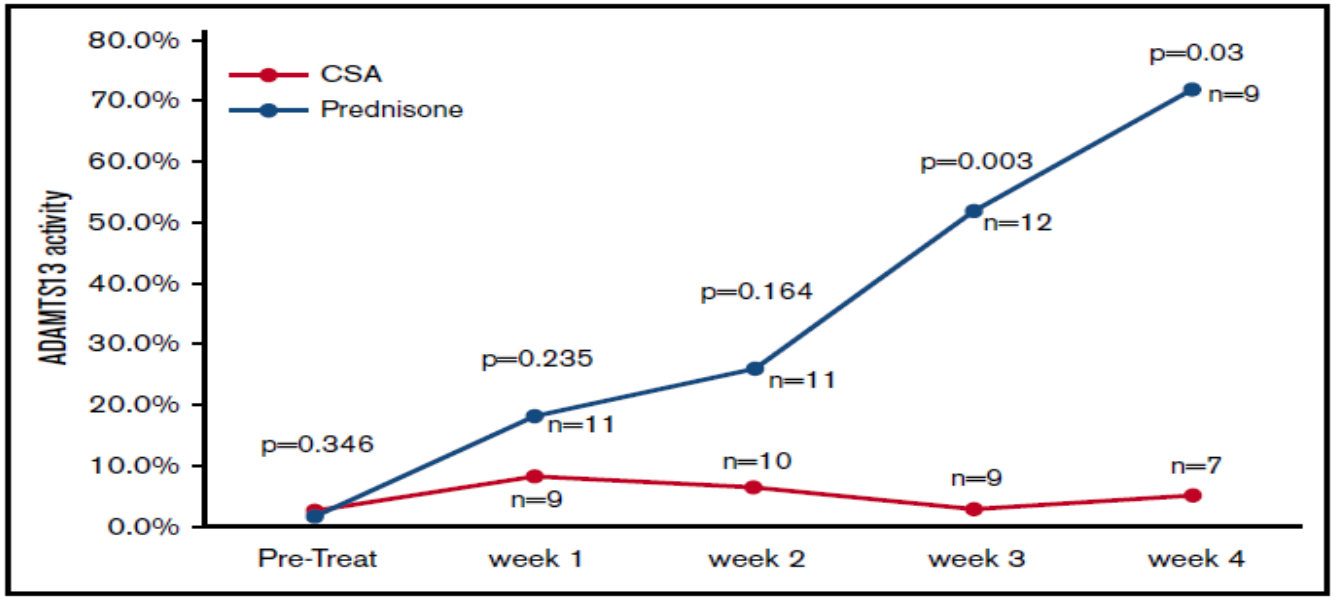


Ref : Cataland SR. Blood Adv. 2017

TTP Treatment

Recombinant ADAMTS13 Protease

Pre-clinical models

- Prophylactic administration of rADMATS13 was protective in mouse model[1]

In Vitro studies of human plasma samples[2]

- Linear relationshi[between inhibitor titer and rADAMTS13 concentration necessary to reconstitute VWF-Cleaving activity

SUGGESTED ROLE OF rADAMTS13 IN BOTH CONGENITAL AND ACQUIRED TTP

Ref : Schiviz et al. Blood,2012;v. 119 p. 6128-35
Ref : Plaimauer et al. JTH,2011;v. 9 p. 936-44

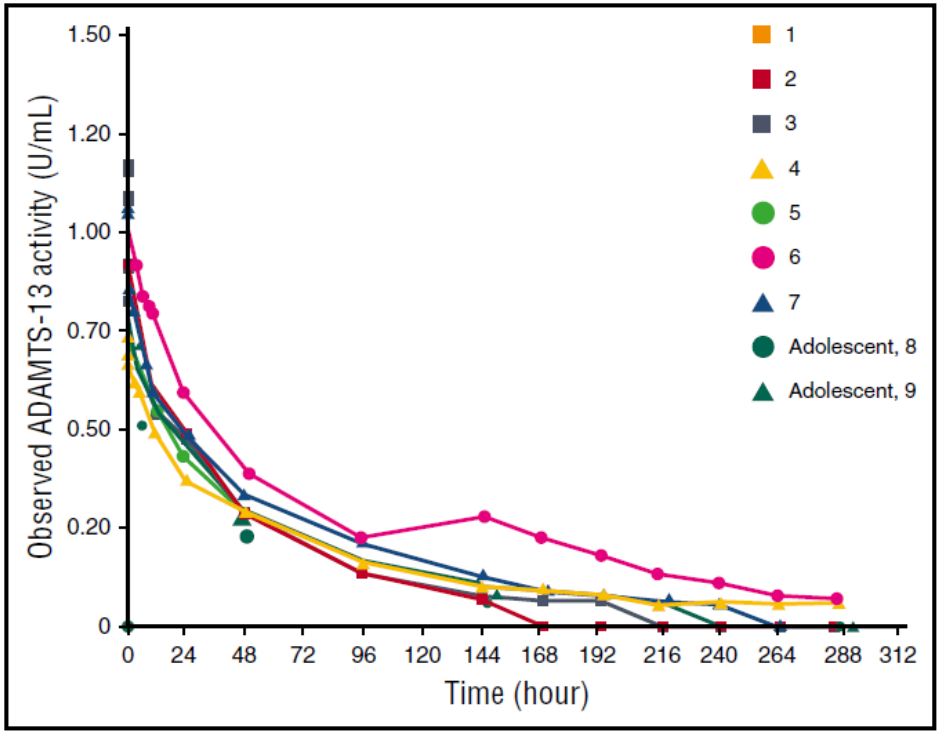
Recombinant ADAMTS13

CLINICAL TRIALS AND OBSERVATIONS

Recombinant ADAMTS-13: first-in-human pharmacokinetics and safety in congenital thrombotic thrombocytopenic purpura

Marie Scully,[1] Paul Knöbl,[2] Karim Kentouche,[3] Lawrence Rice,[4] Jerzy Windyga,[5] Reinhard Schneppenheim,[6] Johanna A. Kremer Hovinga,[7] Michiko Kajiwara,[8] Yoshihiro Fujimura,[9] Caterina Maggiore,[10] Jennifer Doralt,[11] Christopher Hibbard,[12] Leah Martell,[12] and Bruce Ewenstein[12]

- First-in-human, phase 1 study, recombinant ADAMTS-13 was safe, nonimmunogenic, and tolerated in congenital thrombotic thrombocytopenic purpura.
- Recombinant ADAMTS-13 pharmacokinetic profile was comparable to plasma infusion studies, with evidence of pharmacodynamic activity.



Rituximab

Indication for acquired TTP	Grade of recommendation and evidence by Lim et al*	Japanese guidelines
Initial treatment	2C	-
Refractory and relapsing episodes	1C	1B**
For prophylactic in asymptomatic patients with severe ADAMTS13 activity	1C (against the use)	-

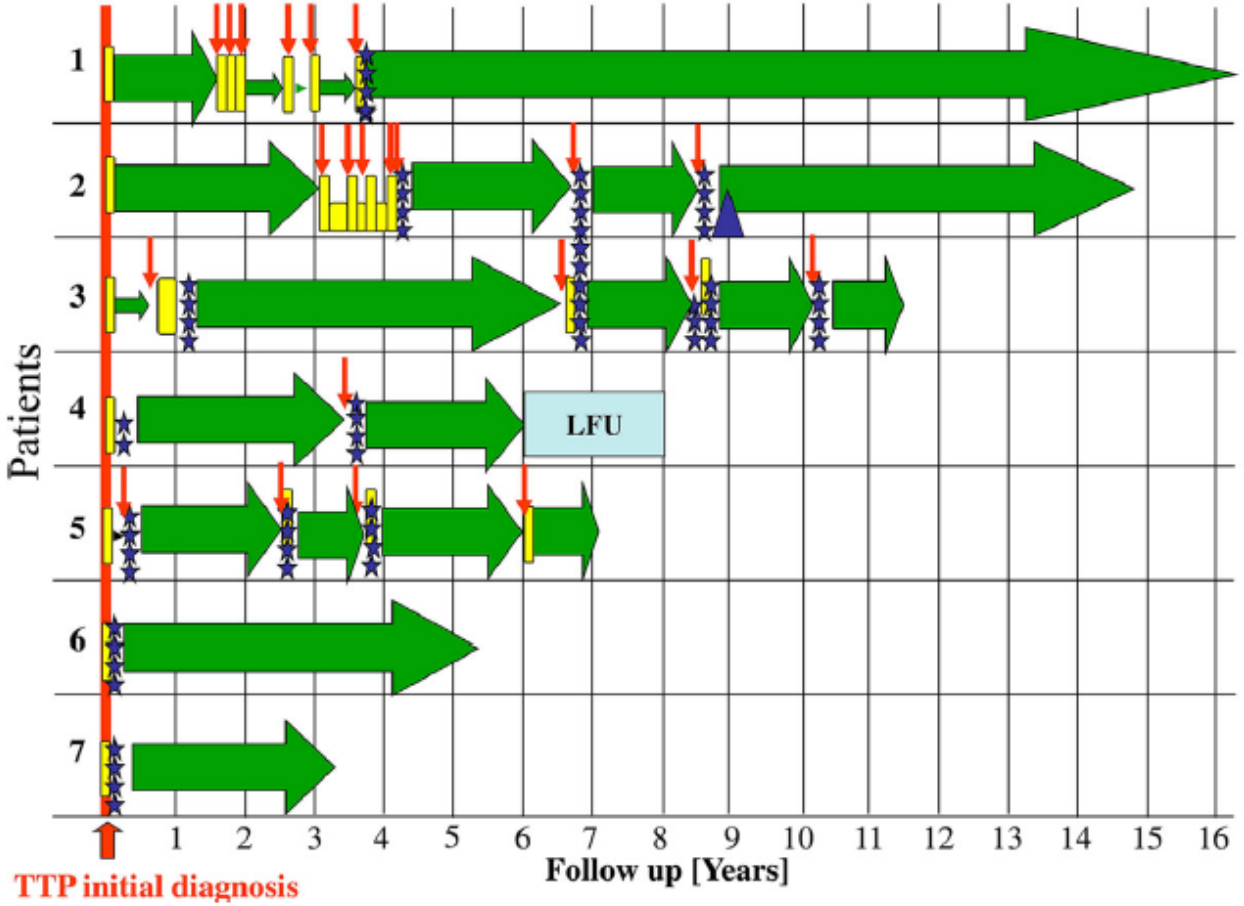
The indication of rituximab in acquired TTP at acute phase is still debated

* *Lim, W et al. Blood 2015; 125: 1526-1531*

** *Not covered by Japanese goverment*

Rituximab

Long-term Remission of Recurrent Thrombotic Thrombocytopenic Purpura (TTP) After Rituximab in Children and Young Adults



Ref : Wieland I. PediatrBlood Cancer 2015

Caplacizumab

Table 1. Baseline Characteristics and Therapy in the Intention-to-Treat Population.*

Characteristic	Caplacizumab (N=36)	Placebo (N=39)	Total (N=75)
Mean age (range) — yr	41 (19–72)	42 (21–67)	42 (19–72)
Female sex — no. (%)	24 (67)	20 (51)	44 (59)
Race — no. (%)†			
White	32 (89)	34 (87)	66 (88)
Black	4 (11)	5 (13)	9 (12)
Presenting episode of TTP — no. (%)			
Initial	24 (67)	27 (69)	51 (68)
Recurrent	12 (33)	12 (31)	24 (32)
Mean platelet count (range) — per mm^3‡	21,100 (2000–70,000)	28,000 (5000–84,000)	24,600 (2000–84,000)
Mean LDH (range) — U/liter§	1277 (240–3874)	1270 (247–4703)	1274 (240–4703)
ADAMTS13 activity — no. (%)			
<10%	28 (78)	30 (77)	58 (77)
≥10%	2 (6)	6 (15)	8 (11)
Missing data	6 (17)	3 (8)	9 (12)
PE tapering — no. (%)	11 (31)	11 (28)	22 (29)
Glucocorticoids during daily PE — no. (%)	32 (89)	36 (92)	68 (91)
Rituximab during daily PE — no. (%)¶	2 (6)	9 (23)	11 (15)

Ref : Peyvandi F, NEJM 2016

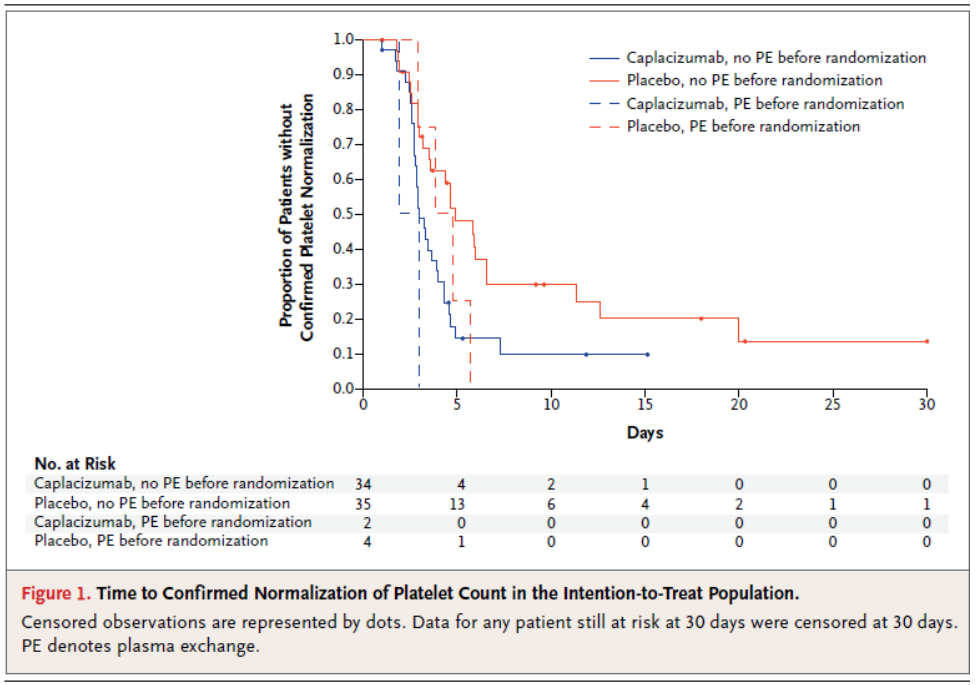
Caplacizumab

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 11, 2016 VOL. 374 NO. 6

Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura

- Single variable domain immunoglobulin (nanobody) ***directed to the VWF A1 domain***
- Reduced the ***time to plt. count normal***
- Reduced ***acute the mortality and morbidity***



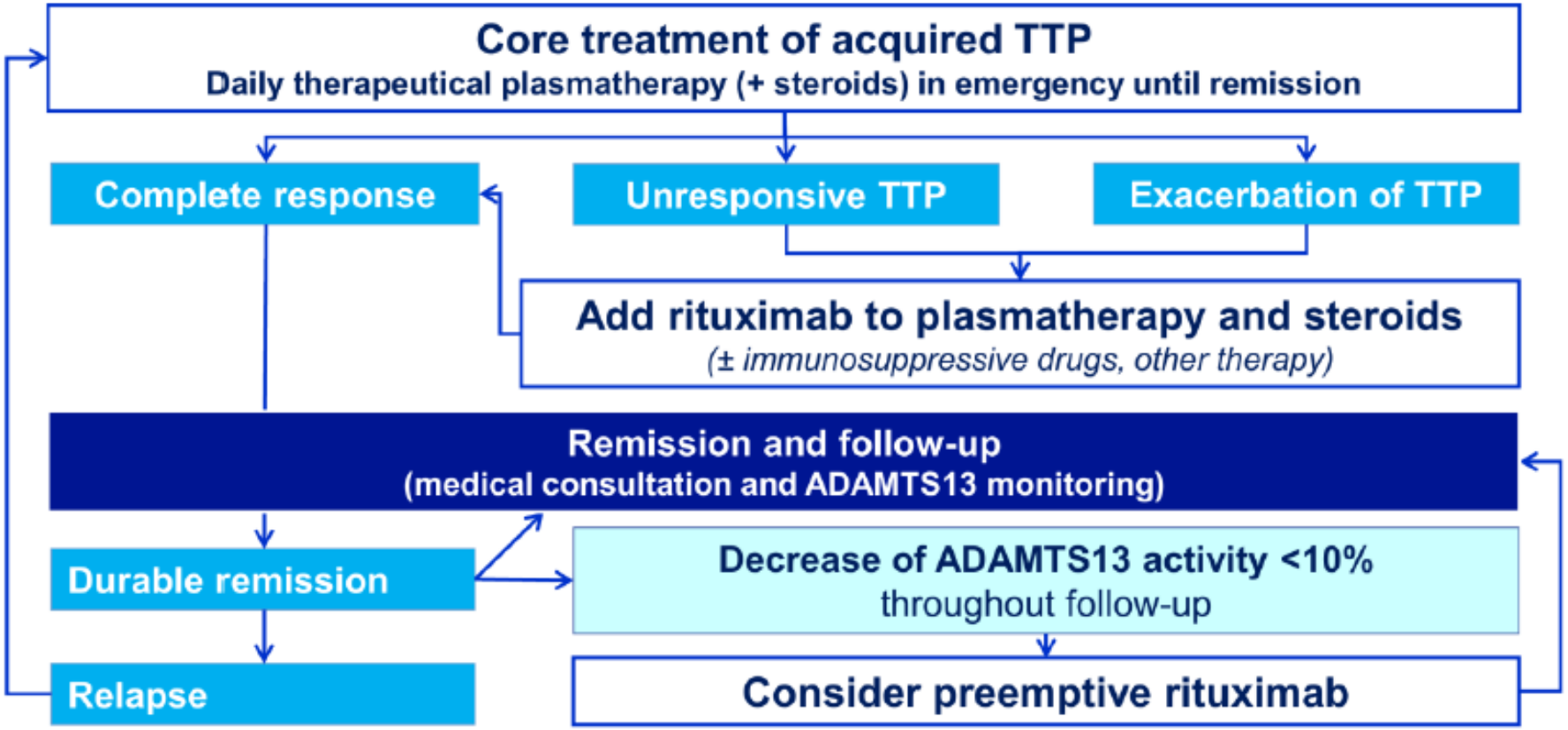
No. at Risk

Caplacizumab, no PE before randomization	34	4	2	1	0	0	0
Placebo, no PE before randomization	35	13	6	4	2	1	1
Caplacizumab, PE before randomization	2	0	0	0	0	0	0
Placebo, PE before randomization	4	1	0	0	0	0	0

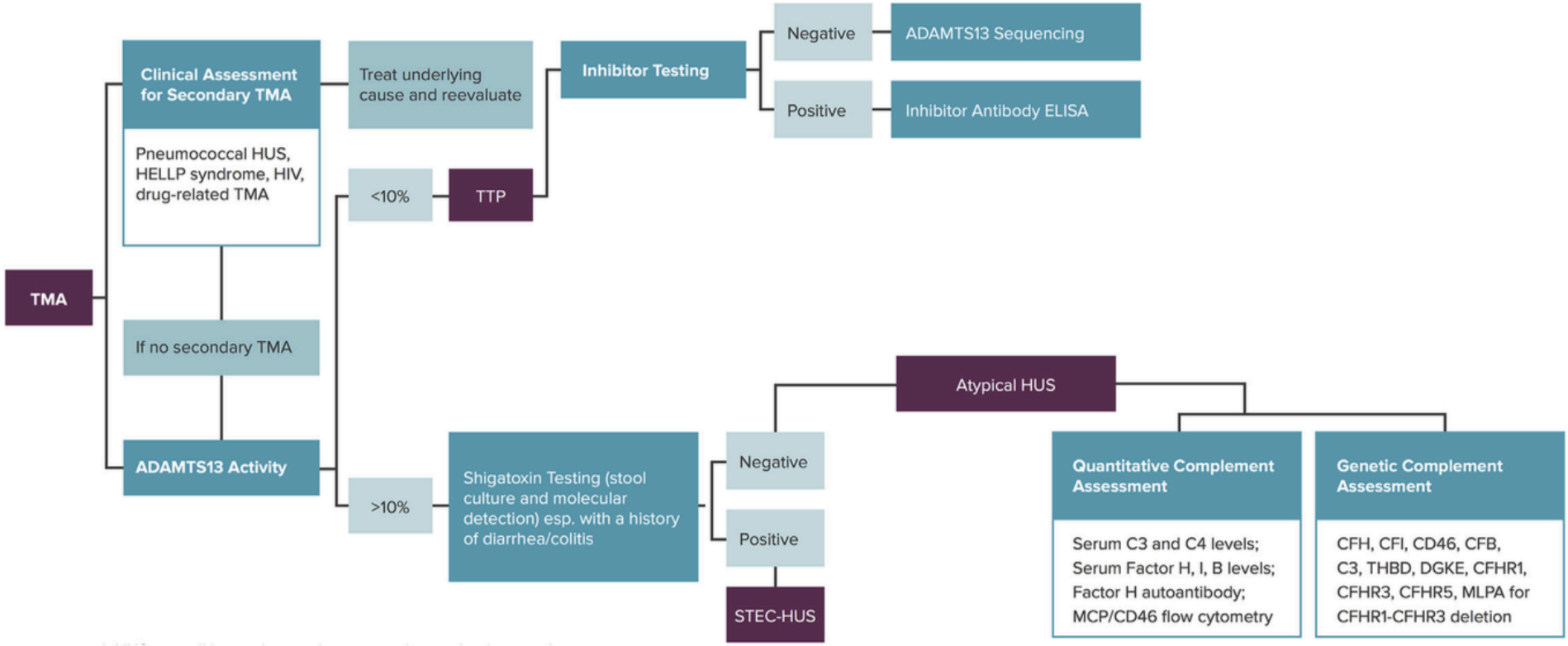
Figure 1. Time to Confirmed Normalization of Platelet Count in the Intention-to-Treat Population.
Censored observations are represented by dots. Data for any patient still at risk at 30 days were censored at 30 days. PE denotes plasma exchange.

Ref : Peyvandi F, NEJM 2016

TTP Treatment



Conclusions



Ref : Dixon BP Pediatr Clin North Am2018

Conclusions

- ***Thrombotic microangiopathy is a histopathological lesion*** that is present in all patients with HUS or TTP.

- HUS is usually caused by infection with ***Shiga toxin producing bacteria.*** Less than 25% develop ***chronic kidney injury***.

- Familial forms of atypical HUS are linked to genetic mutations in proteins that regulate the activity of the alternative pathway of complement.
- ***Eculizumab***, a monoclonal antibody to C5 is the standard of care for these patients.

- TTP is rare in children and responds well to treatment with plasmapheresis.

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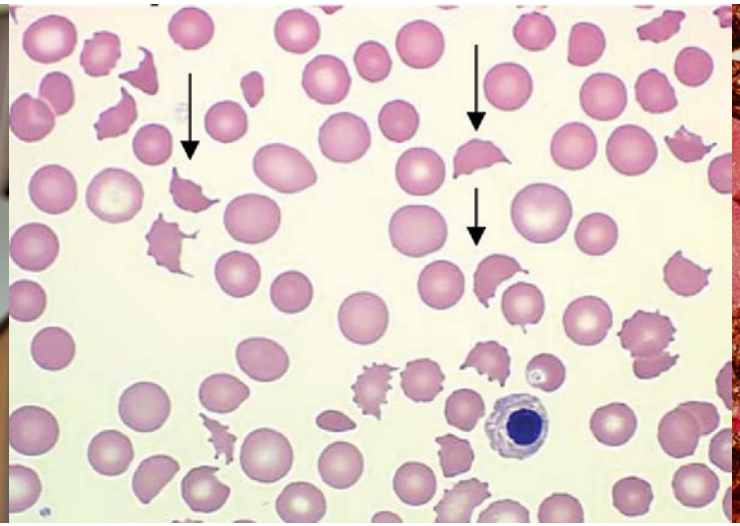
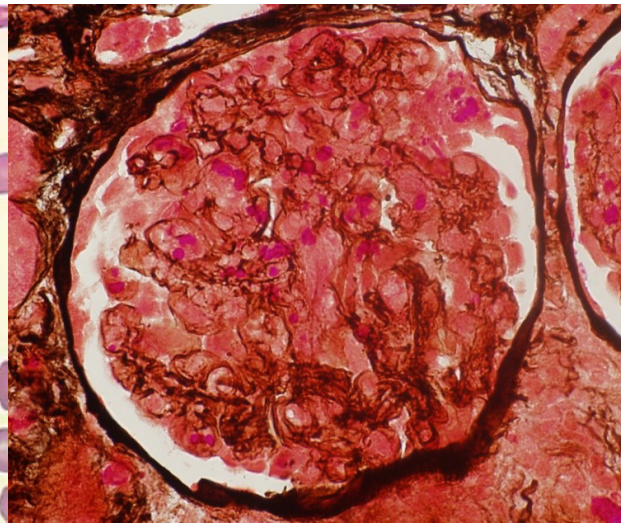
PedHemOnc-PMK

Thrombotic Microangiopathy





Thank you for your kind attention