Thrombotic microangiopathies

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MICROANGIOPATIE TROMBOTICHE: PATOGENESI/TERAPIA

PERUGIA, 29 SETTEMBRE 2016

Financial disclosure

Nothing to declare

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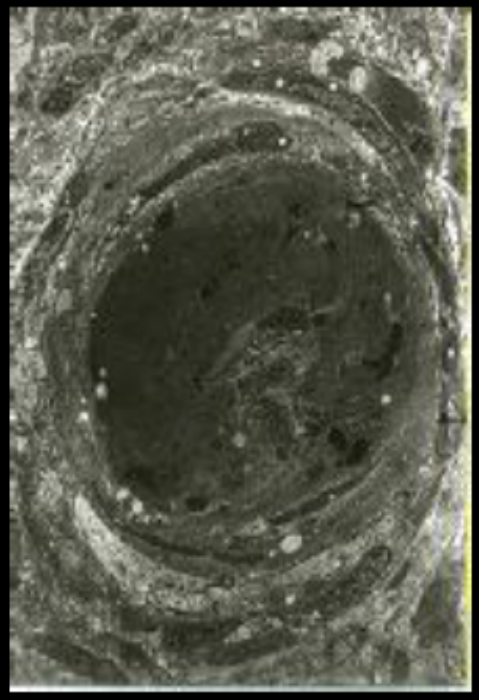
THROMBOTIC MICROANGIOPATHIES (TMAs)

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

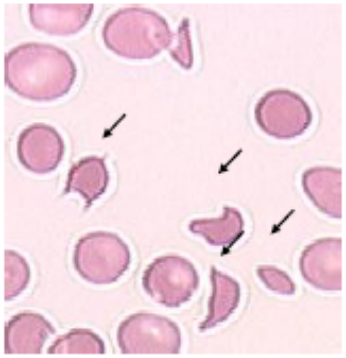


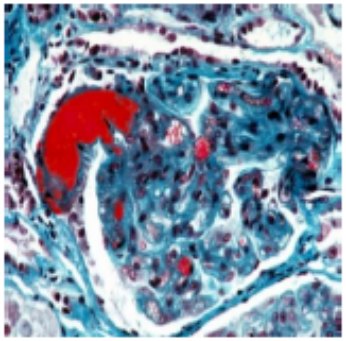
Definition

- Multisystem diseases, with predominant renal involvement in HUS and neurological and cardiac signs in TTP
- Characterized by microvascular endothelial damage and platelet-rich thrombus formation
- Consumption thrombocytopenia, mechanical hemolytic anemia with schystocytes and multiorgan dysfunction.

THROMBOTIC MICROANGIOPATHIES (TMAs)

- Microangiopathic hemolytic anemia *
- Peripheral thrombocytopenia
- Multiorgan failure of variable severity





TTP

- Acquired
- Congenital

4 cases/million/year

HUS

- Typical (STEC)
- Atypical

2–4 cases/million/year

Other entities

- HELLP syndrome
- Catastrophic antiphospholipid syndrome (CAPS)
- Malignant hypertension
- Cancer
- Transplantation

*** (Hb<12.5 gr/dl, ≥3 schistocytes/100x field, Coombs negative)**

OUTLINE OF THE PRESENTATION

1. Pathophysiology of TTP
2. Pathophysiology of HUS
3. More on treatment of congenital and cquired TTP

TTP - First described

AN ACUTE FEBRILE PLEIOCHROMIC ANEMIA WITH HYALINE THROMBOSIS OF THE TERMINAL ARTERIOLES AND CAPILLARIES

AN UNDESCRIBED DISEASE *

ELI MOSCHCOWITZ, M.D.
NEW YORK

This case is remarkable, clinically and anatomically.

REPORT OF CASE

History—K. Z., a girl, aged 16 years, was an elementary school graduate, had gone to business school, and had been employed for eight months preceding the illness. There were three other children, two younger and one older; all apparently were perfectly normal. There were no home difficulties, and poverty was not extreme. She had spent September 4 and 5 at Rockaway Beach, where she appeared in perfect health and spirits. She had returned home on the evening of September 5 and slept well. On the morning of September 6, she complained of weakness in the upper extremities and had pain on moving the wrists and elbows; she already had marked pallor and was slightly constipated. The symptoms increased in severity until she was admitted to the Beth Israel Hospital, September 15. While at home, she had a constant fever, the temperature rising once to 104 F. and staying at other times between 101 and 102. F.

Dr. Eli Moschcowitz

Arch Intern Med. 1925;36:89.

TTP: INITIAL DESCRIPTION

HYALINE THROMBOSIS OF THE TERMINAL ARTERIOLES AND CAPILLARIES: A HITHERTO UNDESCRIBED DISEASE *

ELI MOSCHCOWITZ, M.D.

The history of this case is as follows:

A girl aged sixteen with an uneventful previous history and in a state of perfect health was suddenly attacked with a high fever (103° to 104° F.). The only complaint was pain in the arms. Even in the first days of her illness her physician noted an extreme pallor. She was admitted to Beth Israel Hospital a few days after the onset of the illness, where she remained one

* Presented January 10, 1924.

AN ACUTE FEBRILE PLEIOCHROMIC ANEMIA WITH HYALINE THROMBOSIS OF THE TERMINAL ARTERIOLES AND CAPILLARIES

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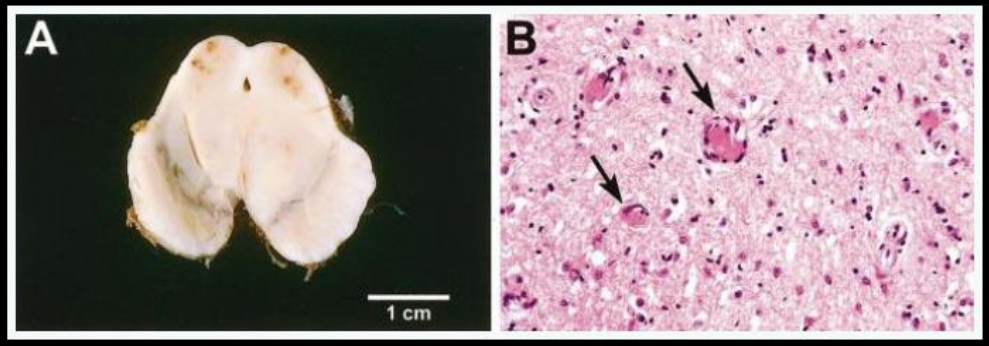
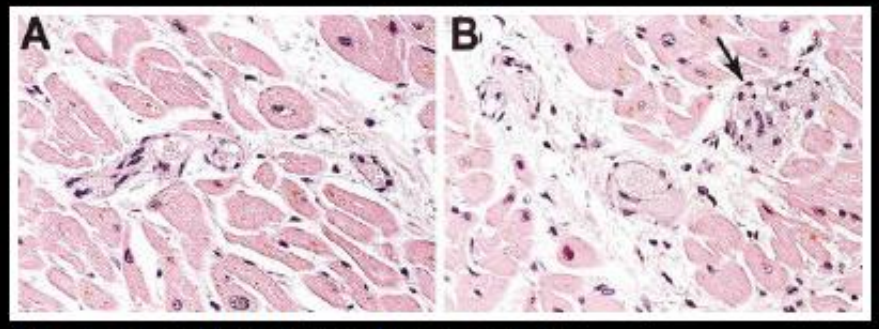
- 16-year-old girl
- Fever, cerebral manifestations
- Anemia, hemorrhage
- Heart failure
- Death to heart failure within 2 weeks



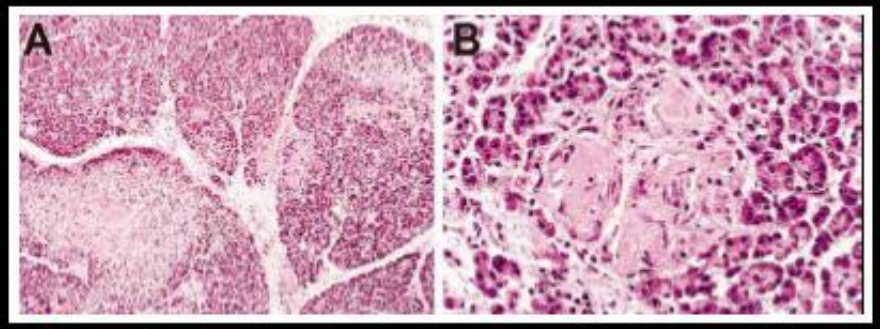
At autopsy: platelet-rich thrombi in arterioles and capillaries of multiples organs

Hemorrhagic / thrombotic lesions (A) resulting from platelet-rich microthrombi (B)

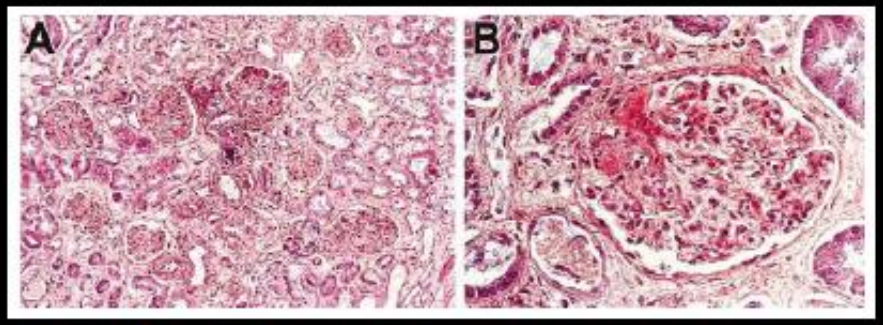
TTP: A MULTI-ORGAN DISEASE DUE TO INTRAVASCULAR PLATELET AGGREGATION



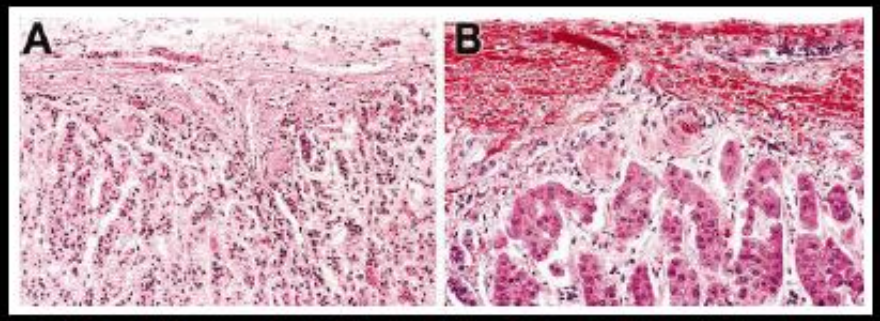
Myocardial involvement



Pancreas

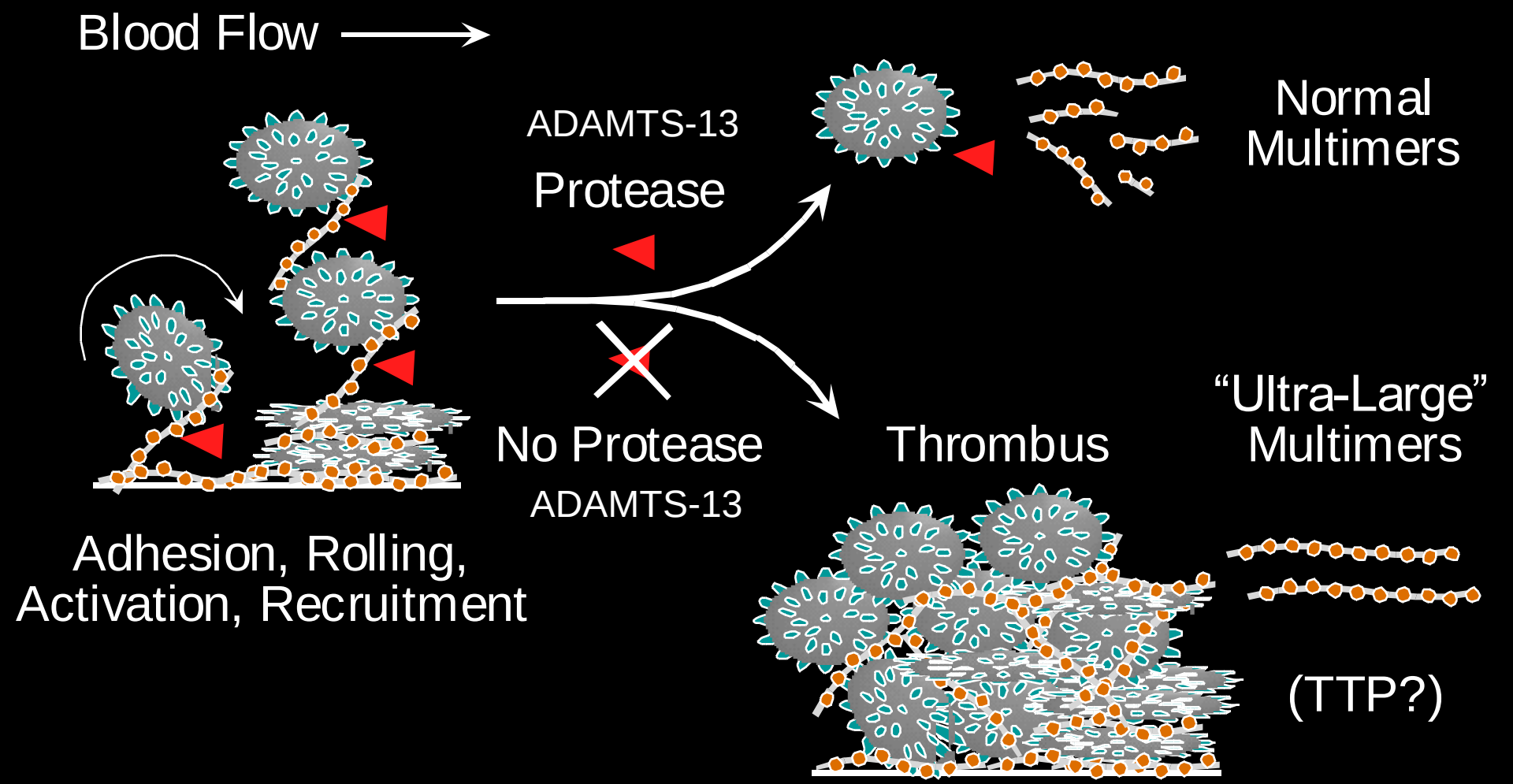


Renal involvement

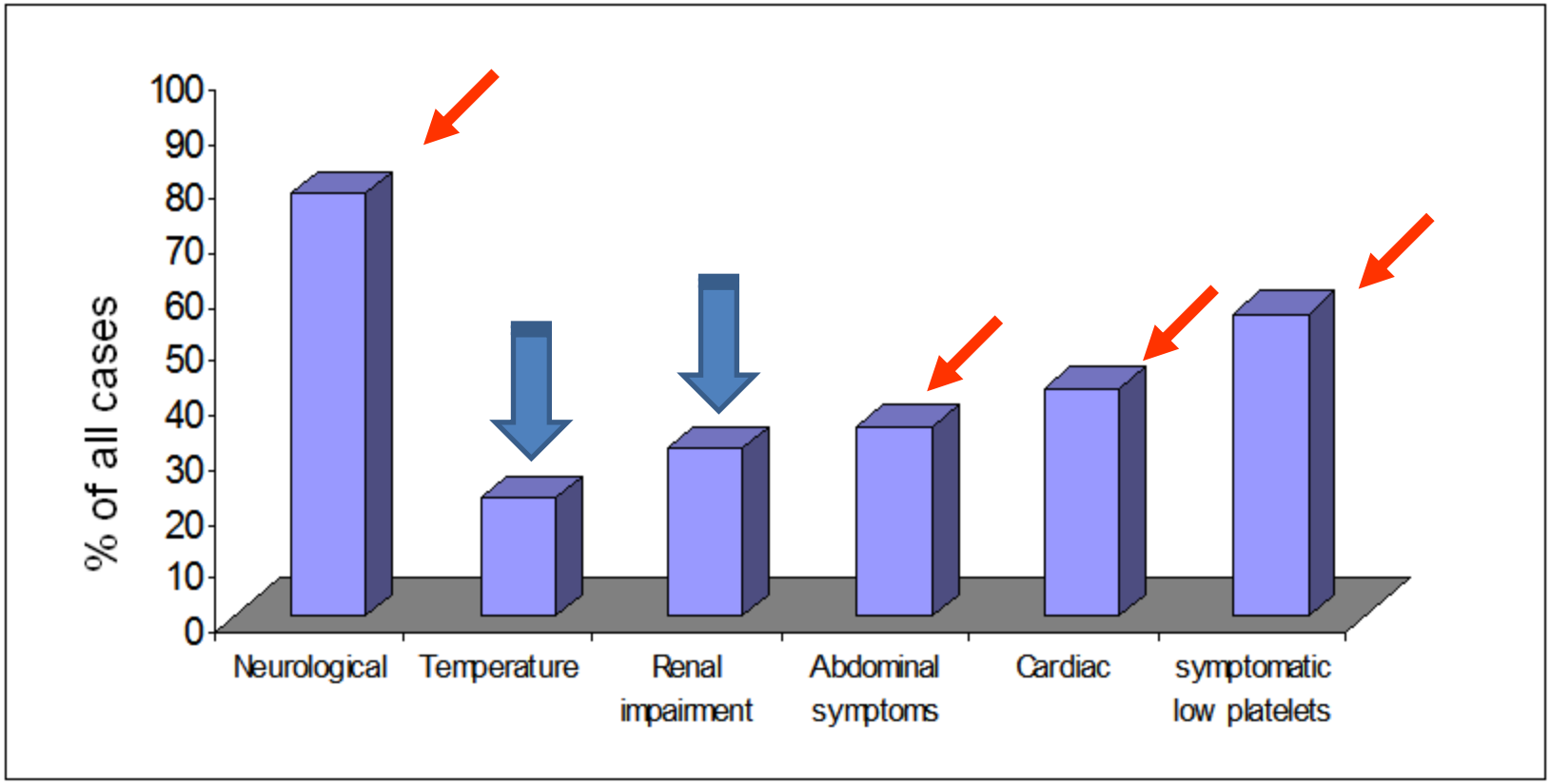


Adrenal glands

VWF, Proteolysis, and Platelet Adhesion



Presenting clinical features of acute TTP episodes-SE England TTP Registry



Scully, SSC ISTH, Liverpool 2012

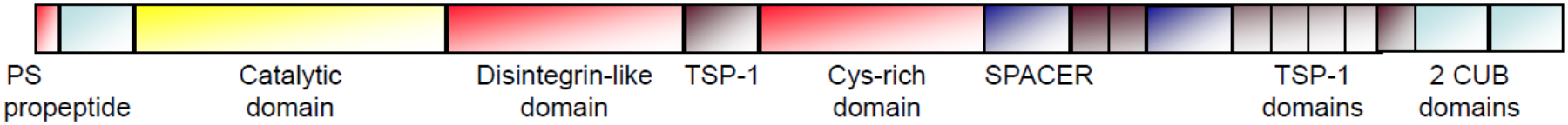
DIAGNOSIS-TTP

- FBC-Anaemia & Thrombocytopenia
- -Increased Reticulocytes
- MAHA-red cell fragmantation, polychromasia
- Normal coagulation
- -ve DAT
- Increased bilirubin
- Increased LDH
- Raised Troponin
- Renal impairment
- Virology-HIV, Hepatitis A, B & C
- Pregnancy Test

Scully, SSC ISTH, Liverpool 2012

ADAMTS13

- Metalloproteinase, ADAMTS family
- Monochain glycoprotein of 190 kDa (1427 aa)



- Gene: chromosome 9q34
- Synthesis: liver
- Plasma concentration = 1 µg/mL; half-life = 3 days

Mutations (hereditary TTP forms)

Autoantibodies (acquired TTP forms)

DIAGNOSIS-TTP

ADAMTS13 level and anti-ADAMTS13 Abs titer ?

↓

TTP diagnosis when ADAMTS13<5%

↓

Useful as exclusion criterion and for prognosis

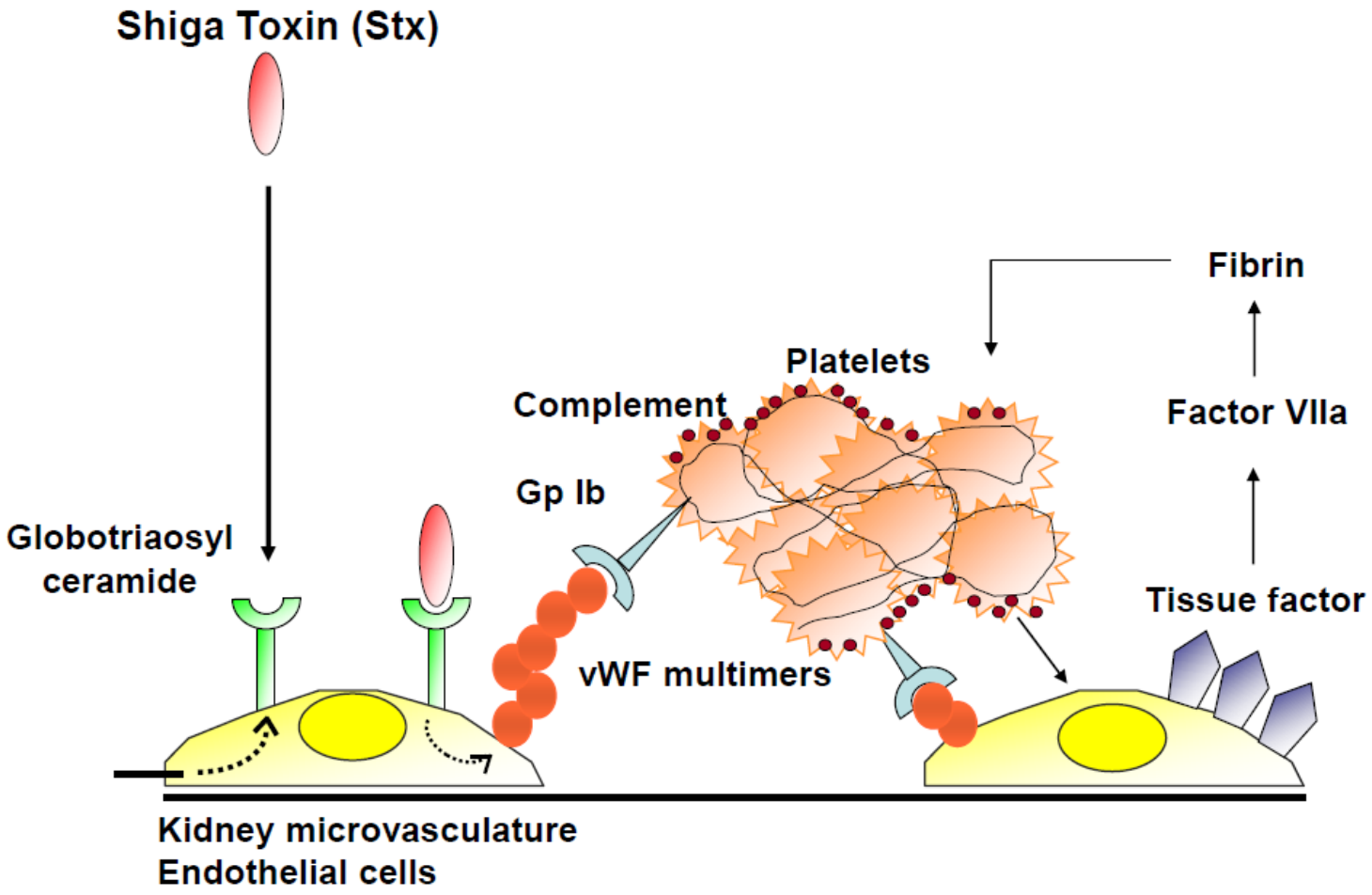
OUTLINE OF THE PRESENTATION

1. Pathophysiology of TTP

2. Pathophysiology of HUS [shiga-toxin E. Coli (STEC) and atypical HUS]

3. More on congenital and acquired TTP

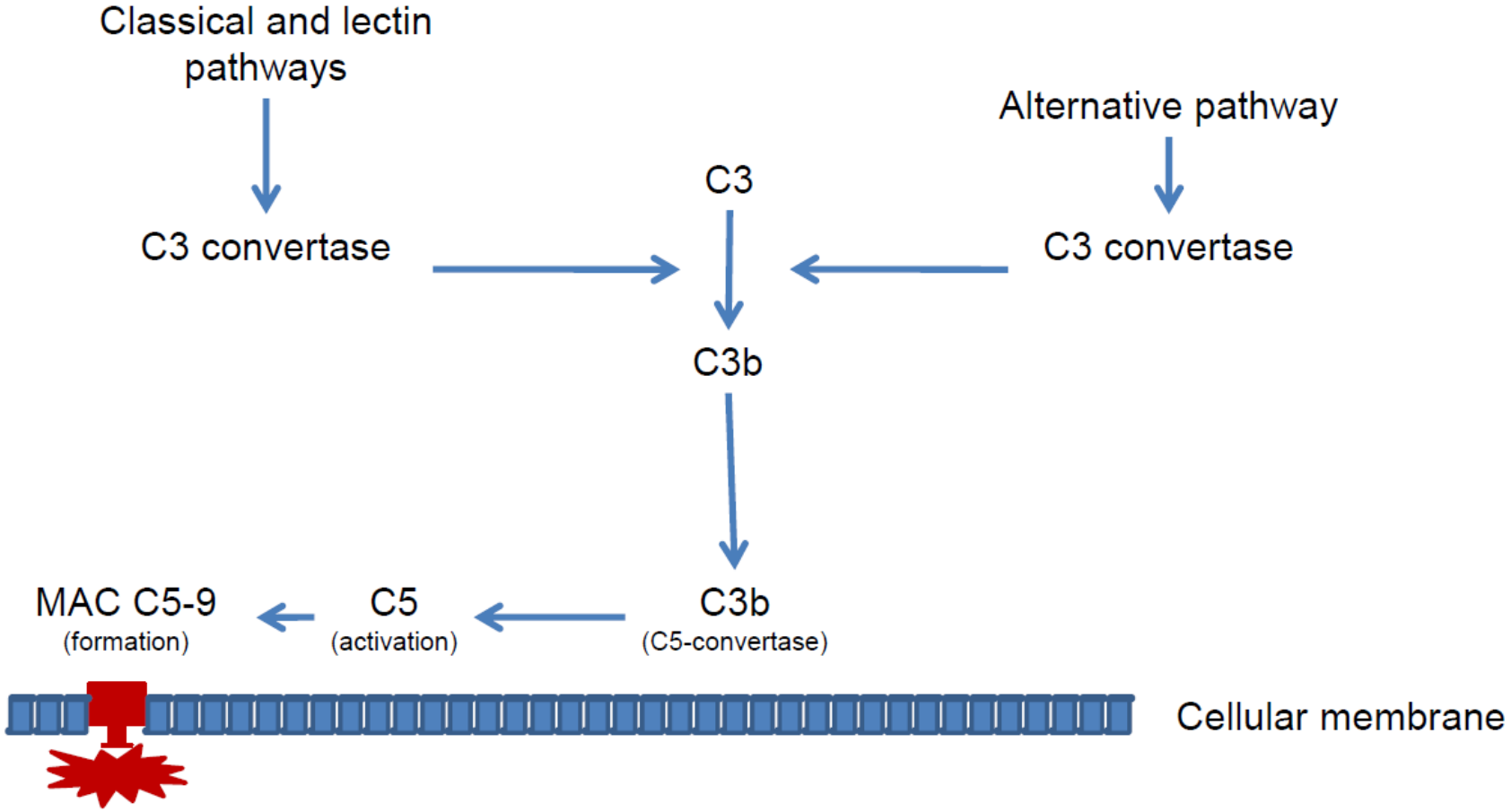
PATHOPHYSIOLOGY OF SHIGA TOXIN - E. COLI HUS (STEC-HUS)



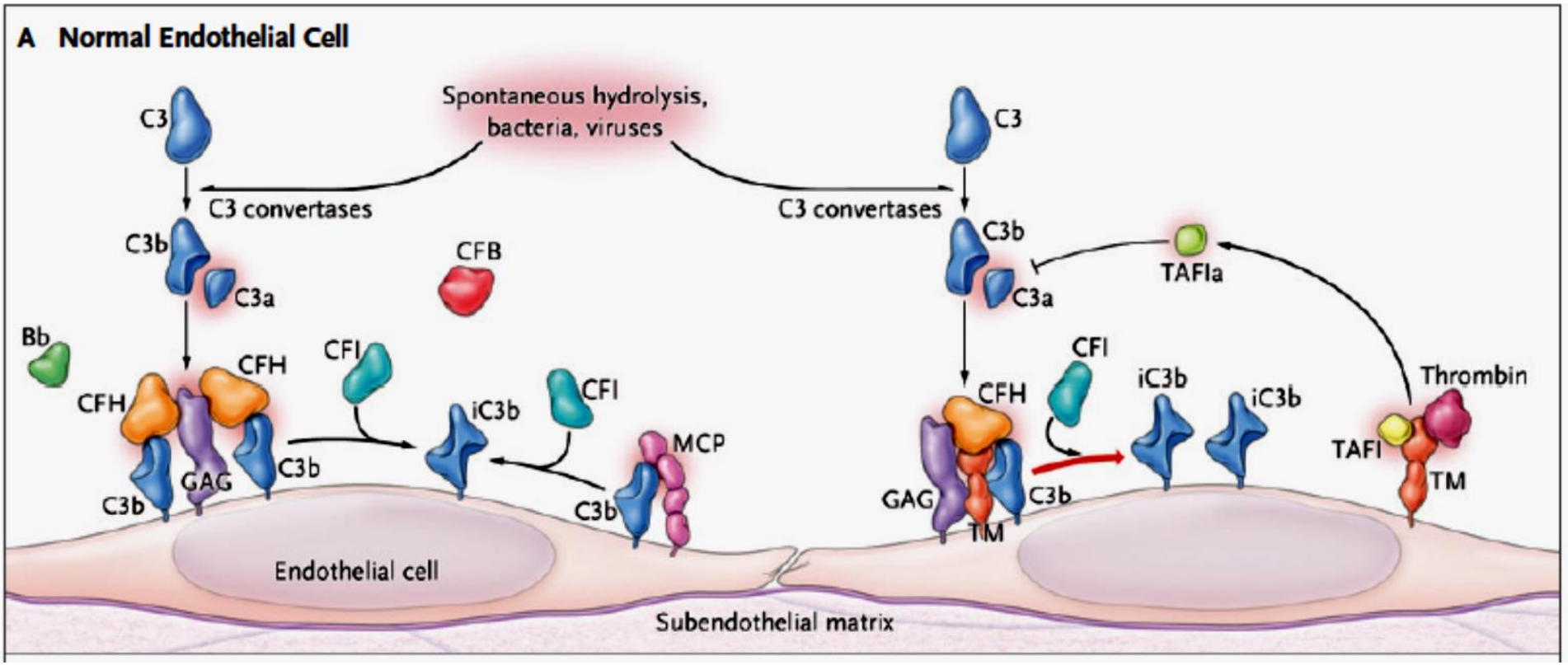
The relevance of a complete pathological anamnesis for an early diagnosis of typical HUS !

ATYPICAL HUS
(complement-related HUS)

SIMPLIFIED SCHEME OF THE COMPLEMENT SYSTEM

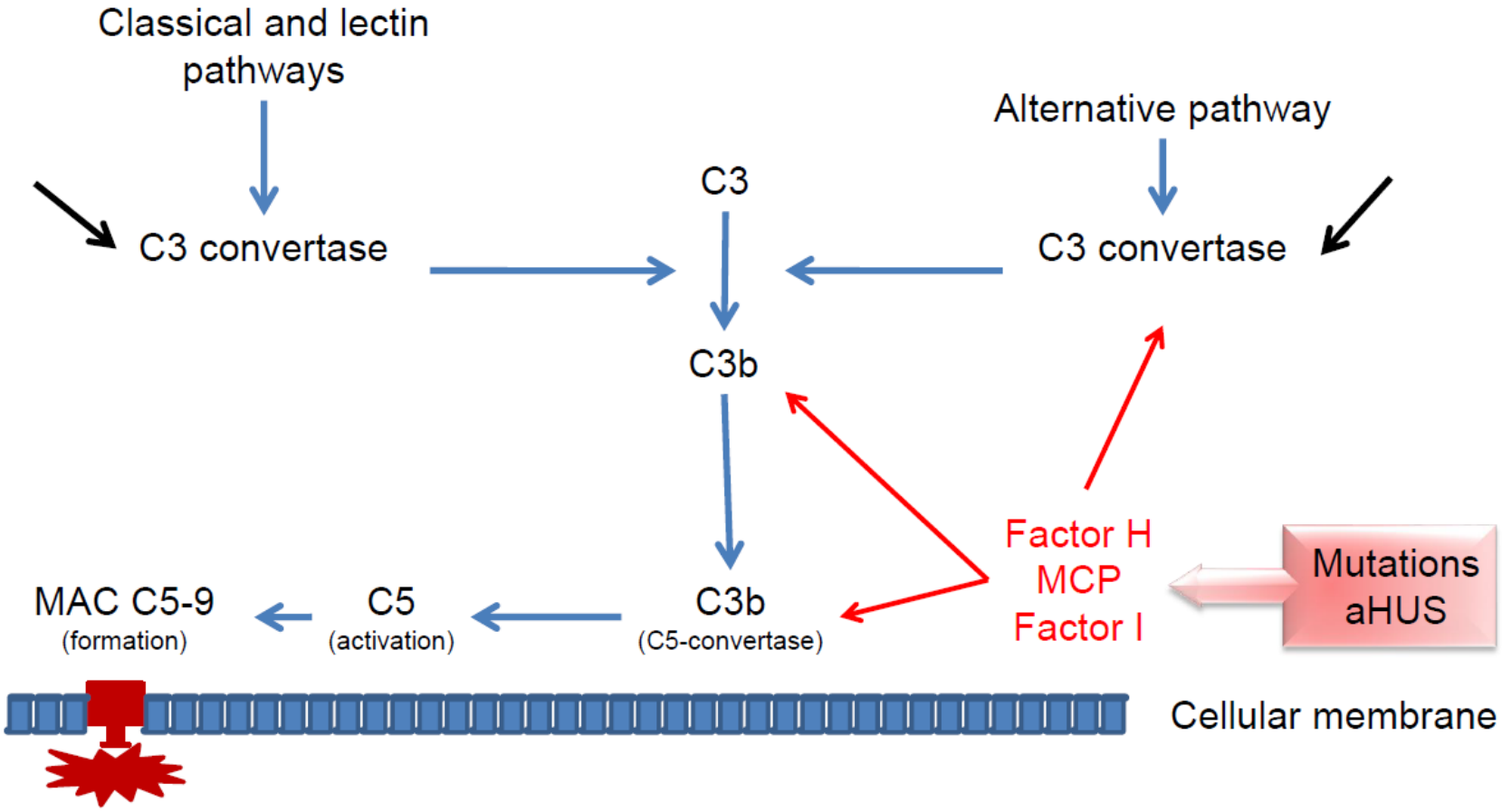


Noris M & Remuzzi G. *N Engl J Med* 2009; 361:1676-87.



Noris, M. et al. N Engl J Med 2009;361:1676-87.

GENETIC LOSS OF NATURAL REGULATORS LEADS TO UNCONTROLLED COMPLEMENT ACTIVATION



Noris M & Remuzzi G. *N Engl J Med* 2009; 361:1676-87.

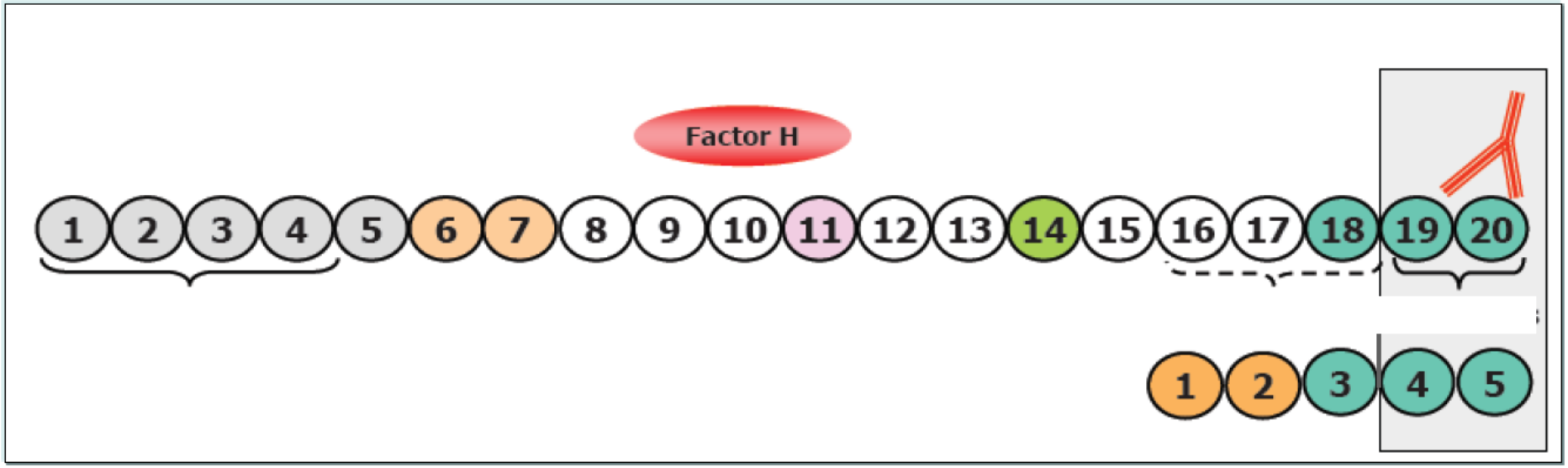
FREQUENCY OF LOSS-OF-FUNCTION AND GAIN-OF-FUNCTION GENE MUTATIONS (USUALLY HETEROZYGOUS)

Mutated gene	Frequency reported (%)
CFH	20-30
CFI	4-10
C3	5-10
Thrombomodulin	5
CFB	1-2
MCP	10-15

- No genetic mutation identified in ca. 30-40% of patients with atypical HUS
- Diagnosis does not require identification of a genetic mutation

Noris M, *et al. Clin J Am Soc Nephrol* 2010; 5:1844-59;
Fremeaux-Bacchi V, *et al. Clin J Am Soc Nephrol* 2013: 8:554-62.

ANTI-FACTOR H AUTOANTIBODIES



- 6-11% of cases in children (less in adults)
- Functional deficiency of factor H

Bresin, *et al. J Am Soc Nephrol* 2013; 24:475-86.

OTHER CAUSES OF ATYPICAL HUS OTHER THAN COMPLEMENT DYSFUNCTIONS

- 30 to 40% of HUS cases do no exhibit any complement alteration
- Loss-of-function mutations of DGKE (diacylglycerol kinase epsilon)
- VEGF inhibitors

COMPLEMENT ACTIVATION AND aHUS

- Dysregulated complement activity central to the pathophysiology of aHUS
- Eculizumab
  - Dramatic responses to therapy
  - Accurate and timely identification of aHUS patients
    - The key is the differentiation from TTP

THE DILEMMA OF TMA MANAGEMENT

Targeted, pathophysiology-based therapies are now available

Severe acquired (autoAb-mediated) ADAMTS13 deficiency (<10% activity)

→ Immunomodulating therapy (rituximab)

Detectable ADAMTS13 activity (≥10% activity)

→ Complement blockers (eculizumab)

So far however, tools aimed at differentiating one disease from the other are not available as routine assays in an emergency…

PREDICTION OF SEVERE A13 DEFICIENCY

Patient characteristics	Adjusted OR	95% CI	p value
Creatinine <200 µmol/L (<2.26 mg/L)	23.4	8.8, 62.5	<0.001
Platelets <30 x 10^9/L	9.1	3.4, 24.8	<0.0001

Prediction of severe ADAMTS13 deficiency

Sensitivity: 98.1%
Specificity: 48.1%

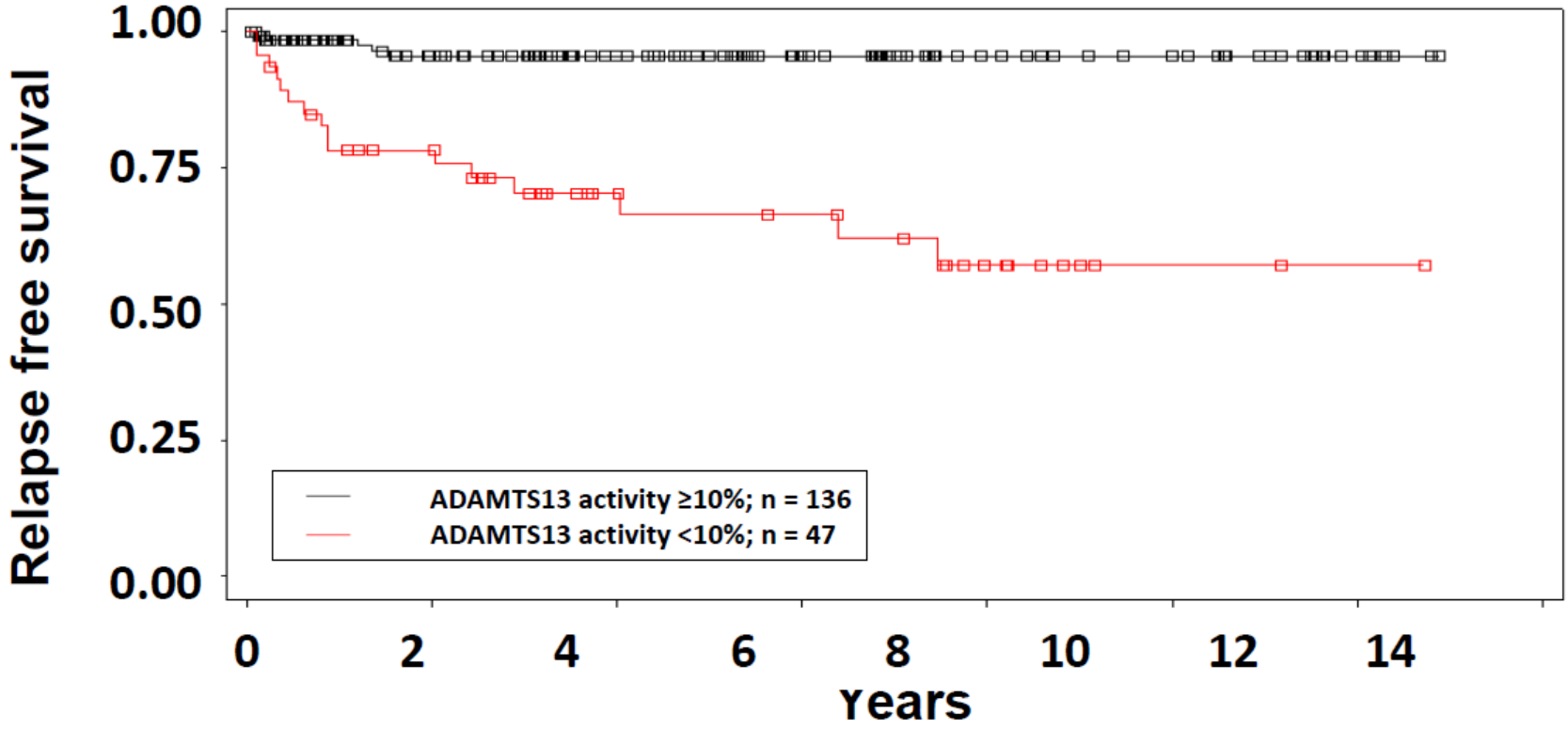
Positive predictive value: 85%
Negative predictive value: 93.3%

Coppo P *et al. Medicine (Baltimore)* 2004;83:233-44
Coppo P *et al. PLoS One* 2010;5:e10208

CLINICAL APPLICATIONS OF ADAMTS-13 ASSAY

Stage	ADAMTS-13 Deficiency (<5%)	Implication
Presentation	Yes	TTP
	No	Other TMA forms?
Remission	Yes	Risk of relapse

BASELINE ADAMTS13 LEVELS AND RISK OF RELAPSE IN ACQUIRED TTP



Kremer Hovinga, Vesely et al. Blood 2010; 115:1500f

The NEW ENGLAND JOURNAL of MEDICINE

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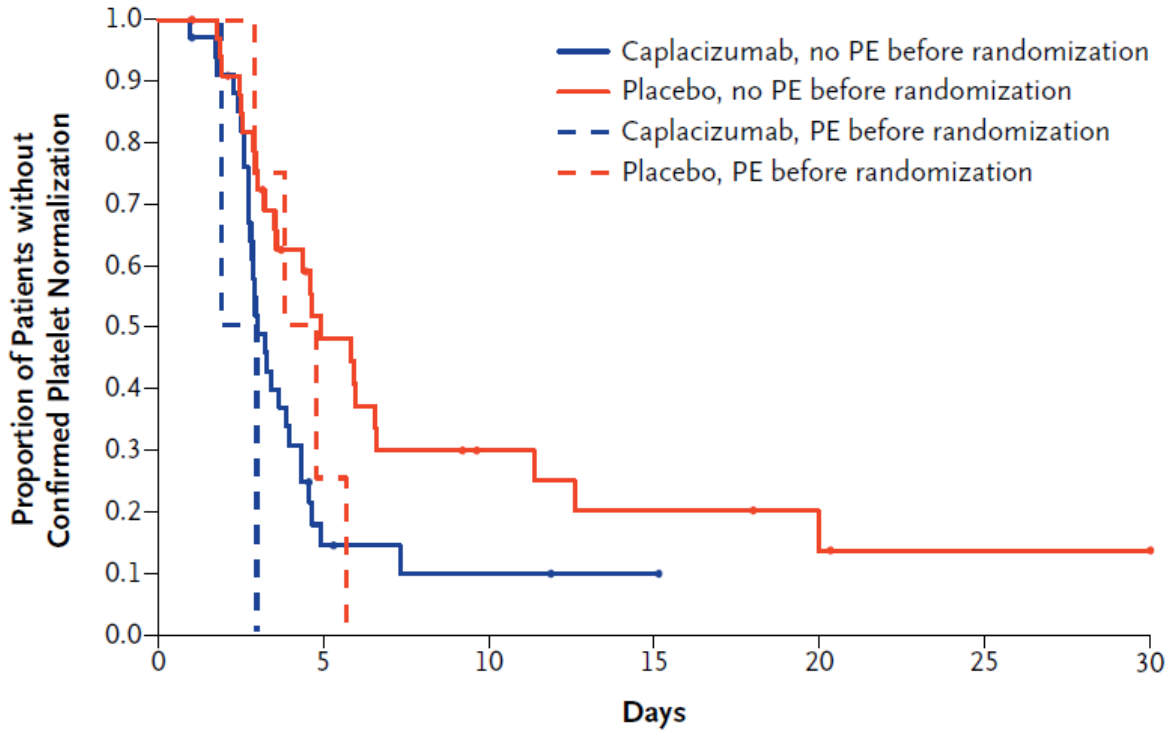
Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura

Flora Peyvandi, M.D., Ph.D., Marie Scully, M.D., Johanna A. Kremer Hovinga, M.D., Spero Cataland, M.D., Paul Knöbl, M.D., Haifeng Wu, M.D.,* Andrea Artoni, M.D., John-Paul Westwood, M.D., Magnus Mansouri Taleghani, M.D., Bernd Jilma, M.D., Filip Callewaert, Ph.D., Hans Ulrichts, Ph.D., Christian Duby, M.D., and Dominique Tersago, M.D., for the TITAN Investigators†



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.

RELAPSE IN ACQUIRED TTP

- Up to 40% of survivors have a persistently severe ADAMTS13 deficiency (< 10%) after complete remission through PEX
- Among them, at least one third experience a relapse within a 1-year period

Ferrari et al., Blood 2007

Relapse prevention is a major goal!!

OTHER CLINICAL ENTITIES ASSOCIATED WITH THROMBOTIC MICROANGIOPATHIES (TMA)

- HELLP syndrome
- Catastrophic antiphospholipid syndrome
- Metastatic cancer
- Bone marrow transplantation
- HIV infection
- Drug-related

CLINICAL AND LABORATORY FEATURES OF TMA OTHER THAN TTP

- Poor prognosis, poor response to plasma exchange (PEX)
- Low tendency to relapse (high mortality!)
- ADAMTS13 is normal or only slightly reduced in plasma
- Mechanism unknown

ELSEVIER

CrossMark

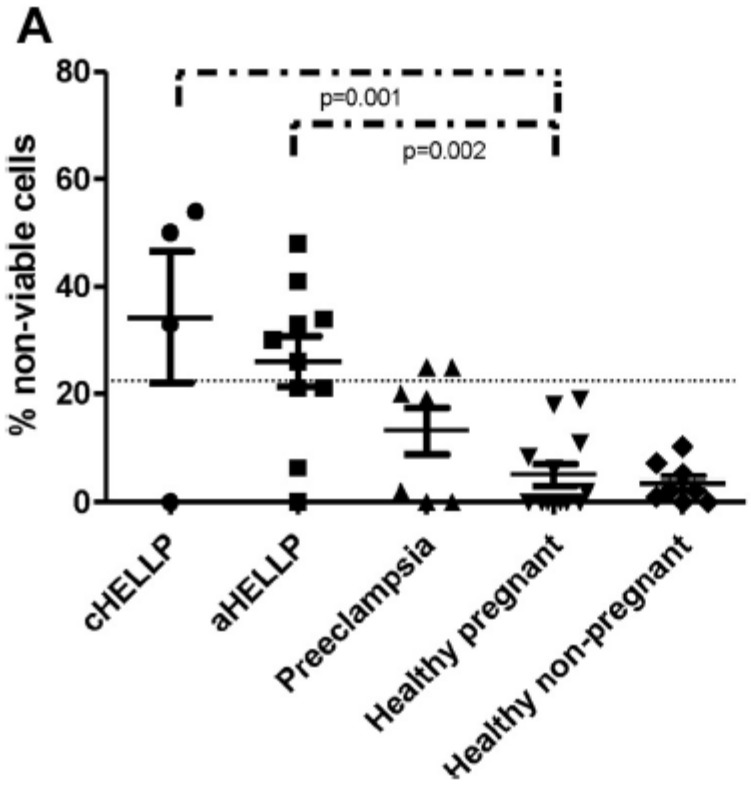
Experimental Hematology

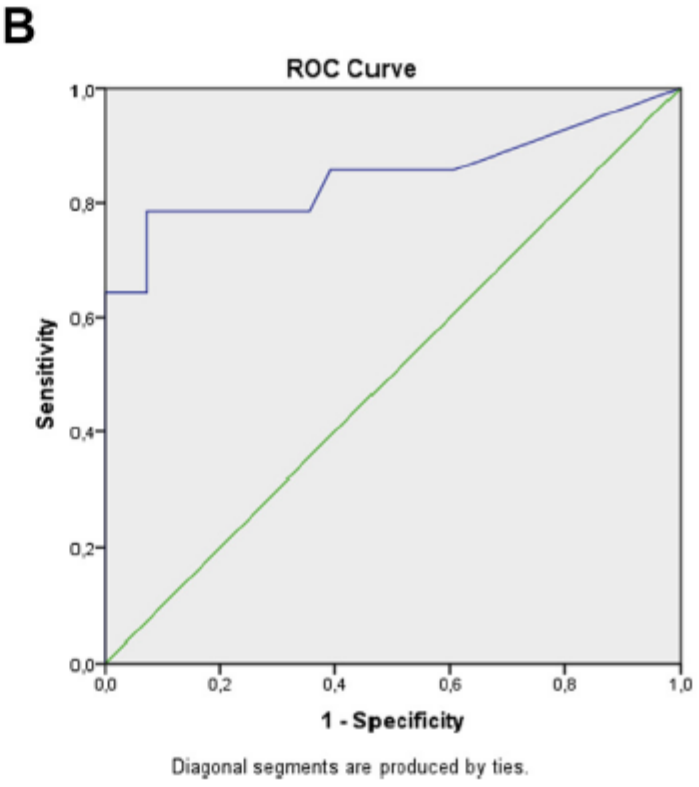
Experimental Hematology 2016;44:390–398

Direct evidence of complement activation in HELLP syndrome: A link to atypical hemolytic uremic syndrome

Arthur J. Vaught[a], Eleni Gavriilaki[b], Nancy Hueppchen[a], Karin Blakemore[a], Xuan Yuan[b], Sara M. Seifert[a], Sarah York[c], and Robert A. Brodsky[b]

[a]*Division of Maternal Fetal Medicine, Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, MD;* [b]*Division of Hematology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD;* [c]*Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD*





OUTLINE OF THE PRESENTATION

1. Pathophysiology of TTP

2. Pathophysiology of HUS

3. More on congenital and acquired TTP

CONGENITAL THROMBOTIC THROMBOCYTOPENIC PURPURA

- 5% of TTP cases are caused by mutations in the *ADAMTS13* gene

- Current treatment of choice: infusion of fresh frozen plasma
  - Reduced mortality (from 90 to 20%)
  - Inconvenient, risk of complications

- ADAMTS13 replacement as an alternative treatment option
  - Plasma products (VWF-FVIII concentrate containing ADAMTS13)
  - Recombinant products (rADAMTS13)

CONCLUSIONS: MOVING TOWARDS A CLASSIFICATION OF TMA

Severe ADAMTS13 deficiency (TTP)	Detectable ADAMTS13 activity (HUS)	Detectable ADAMTS13 activity
Congenital TTP: ADAMTS13 mutations	aHUS: complement dysfunction Mutations (30-40% of patients) Auto-Abs: • Anti-FH Abs	Other TMA syndromes: • Advanced HIV • Metastatic cancer • Bone marrow transplantation • Drugs
Autoimmune TTP: • Associated condition • Idiopathic	HUS: *E. Coli*	HELLP Syndrome CAPS

CONCLUSIONS: KEY MESSAGES

1. TMAs, either HUS or TTP, are severe diseases but their prognosis may be favorable provided early diagnosis and optimal treatment are implemented
2. To distinguish HUS from TTP remains mandatory in the era of targeted therapies (i.e. complement blockade, rituximab and other immunomodulators, ADAMTS13 replacement products)
3. Measurement of ADAMTS13 activity remains the most reliable tool to distinguish HUS from TTP
4. If ADAMTS13 activity is not available in emergency, platelet count and creatinine level can be used to predict (to some degree) ADAMTS13 activity (undetectable vs. detectable)

Thank you for listening