UNIVERSITÀ CATTOLICA del Sacro Cuore

CONVEGNO MICROANGIOPATIE TROMBOTICHE UCSC 2016

Roma, 19 febbraio 2016
Fondazione Policlinico Universitario A. Gemelli

Le microangiopatie trombotiche
Inquadramento nosografico

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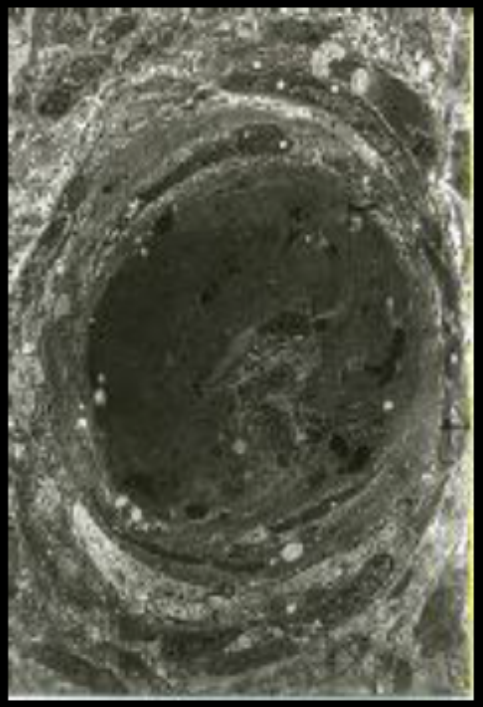
THROMBOTIC MICROANGIOPATHIES (TMAs)

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.

TMA and TTP

"Thrombotic microangiopathy and TTP are not synonymous terms".

- "TMA is not itself a diagnosis and is not an etiology for a specific disorder; it is a pathologic abnormality associated with diverse clinical syndromes"

George & Selby, BMT 2004

THROMBOTIC MICROANGIOPATHIES (TMAs)

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

TTP

- Acquired
- Congenital

4 cases/million/year

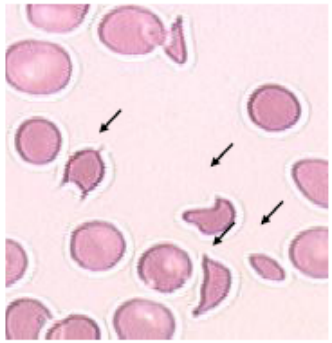
HUS

- Typical (STEC)
- Atypical

2–4 cases/million/year

Other entities

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



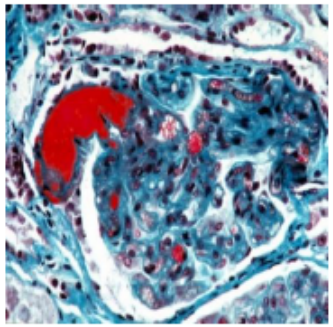


Table 3: Primary and secondary thrombotic microangiopathies

Primary TMA	Secondary TMA
- Hereditary TTP - Idiopathic TTP	Immune-mediated - Pregnancy - Autoimmune disorders - Infections - Medications (clopidogrel, ticlopidine)
- Hereditary (atypical) HUS - Sporadic (Shigatoxin-associated)	Non-immune mediated - Malignant hypertension - Solid organ transplantation - HCT - Metastatic tumors - Medications (cyclosporine, tacrolimus, IFN-α, Mitomycin C)

Stavrou & Lazarus, MJHID 2010

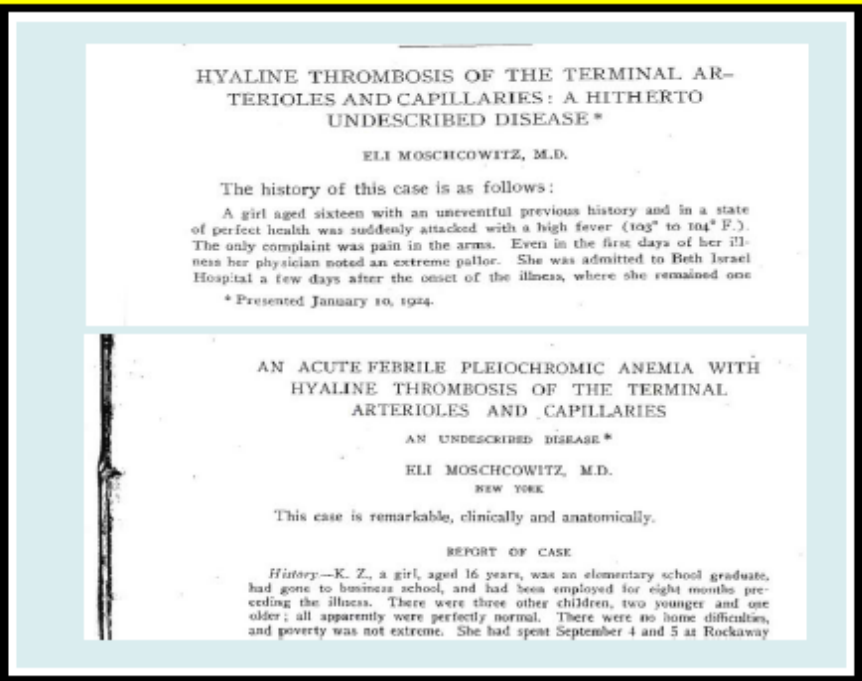
Table 4: Pathophysiologic classification of primary and secondary thrombotic microangiopathies.

Immune Mediated	Non Immune Mediated
Primary • Idiopathic TTP • Atypical HUS secondary to inhibitory antibodies to complement – regulating proteins	Primary • Hereditary TTP • Hereditary atypical HUS secondary to mutations in complement – regulating proteins
Secondary • Pregnancy • Autoimmune disorders • Infections • Medications (clopidogrel, ticlopidine)	Secondary • Malignant hypertension • Solid organ transplantation • HCT • Metastatic tumors • Medications (cyclosporine, tacrolimus, IFN-α, Mitomycin C)

Stavrou & Lazarus, MJHID 2010

PORPORA TROMBOTICA TROMBOCITOPENICA

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

AN UNDESCRIBED DISEASE *

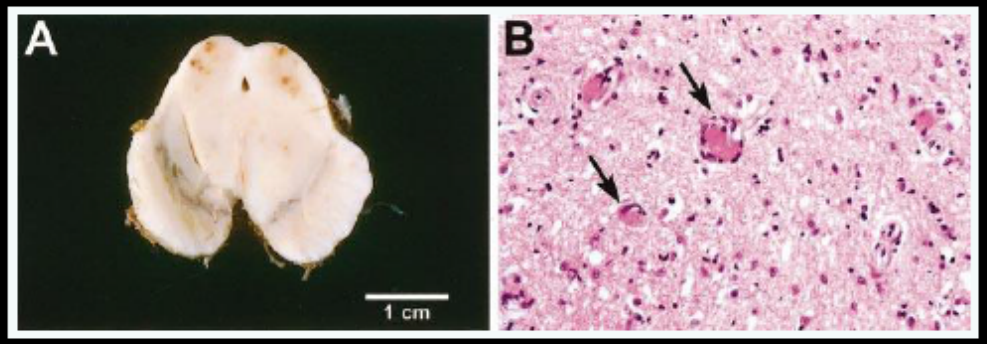
ELI MOSCHCOWITZ, M.D.
NEW YORK

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

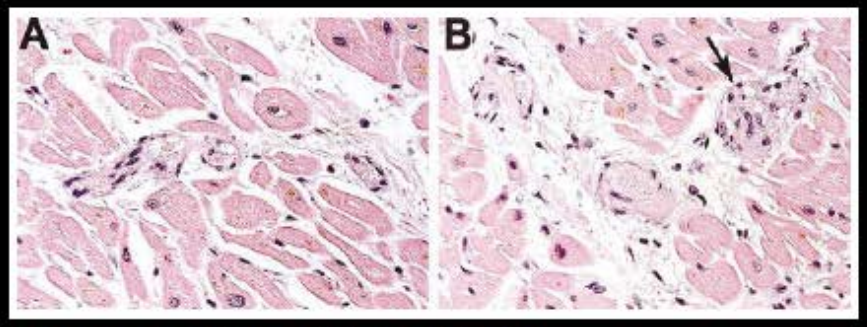
- 16-year-old girl
- Fever, cerebral manifestations
- Anemia, hemorrhage
- Heart failure
- Death to heart failure within 2 weeks



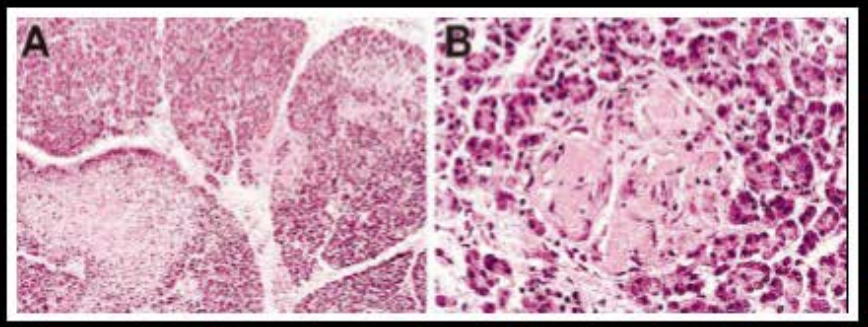
At autopsy: platelet-rich thrombi in arterioles and capillaries of multiples organs

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

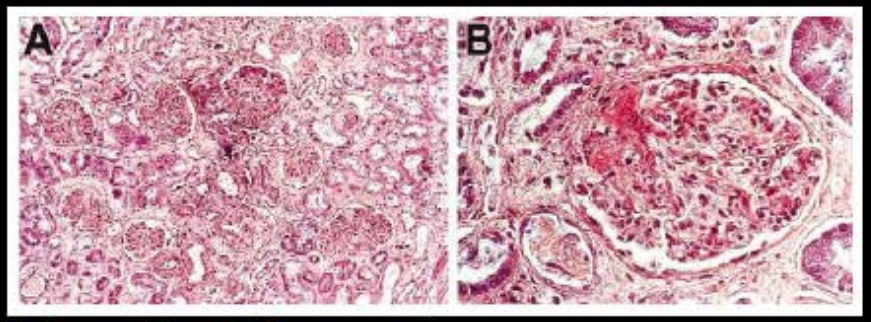
TTP: A MULTI-ORGAN DISEASE DUE TO INTRAVASCULAR PLATELET AGGREGATION



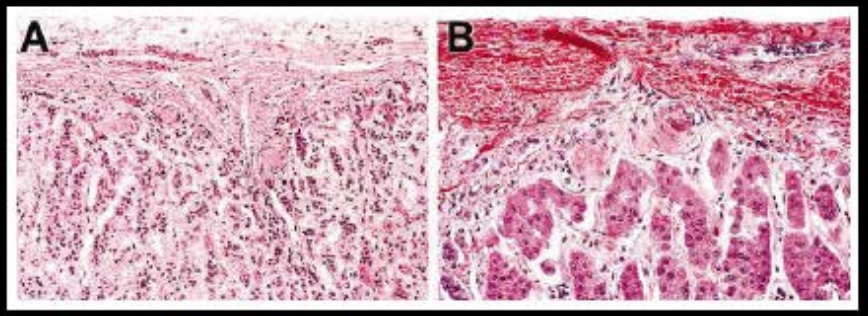
Myocardial involvement



Pancreas



Renal involvement



Adrenal glands

Common clinical and laboratory features of TTP.

- Thrombocytopenia (platelet count $<20\times10^9$/L in acute cases)
- Microangiopathic hemolytic anemia
- Neurologic abnormality or complaint
- Renal abnormalities
  - Proteinuria and microscopic hematuria
  - Peak BUN $\leq$ 0.4 g/L or Cr $\leq$ 0.03 g/L
- Fever $\geq$ 38.3°C
- Microthrombi on tissue biopsy
- Exclusion
  - Evidence of intravascular coagulation
  - Evidence of underlying condition associated with or producing microangiopathic syndrome
  - Positive antinuclear antibody, anti-DNA antibody, or LE preparation
  - Oliguria or anuria

Modified from Bukowski RM, 1982

Schistocytes

- RBC fragments *similar* to schistocytes can be found in non-TMA-related genetic or acquired RBC disorders (associated with anisopoikilocytosis and a wide range of additional RBC size and morphological changes):
- RBC membrane disorders
- thalassemia
- megaloblastic anemia
- primary myelofibrosis
- thermal injuries

International Journal of Laboratory Hematology
The Official journal of the International Society for Laboratory Hematology

ORIGINAL ARTICLE INTERNATIONAL JOURNAL OF LABORATORY HEMATOLOGY

Int J Lab Hematol. 2011 Nov 15

ICSH recommendations for identification, diagnostic value, and quantitation of schistocytes

G. ZINI*, G. D'ONOFRIO†, C. BRIGGS‡, W. ERBER§, J. M. JOU¶, S. H. LEE**, S. MCFADDEN††, J. L. VIVES-CORRONS¶, N. YUTAKA‡‡, J. F. LESESVE§§

Detailed goals of the ICSH Schistocyte Working Group were as follows:

- to define standardized morphological criteria for the recognition of schistocytes;
- to standardize the method for counting schistocytes;
- to indicate a consensus threshold value for the diagnosis of TMA;
- to evaluate the reliability and clinical utility of automated fragment count.

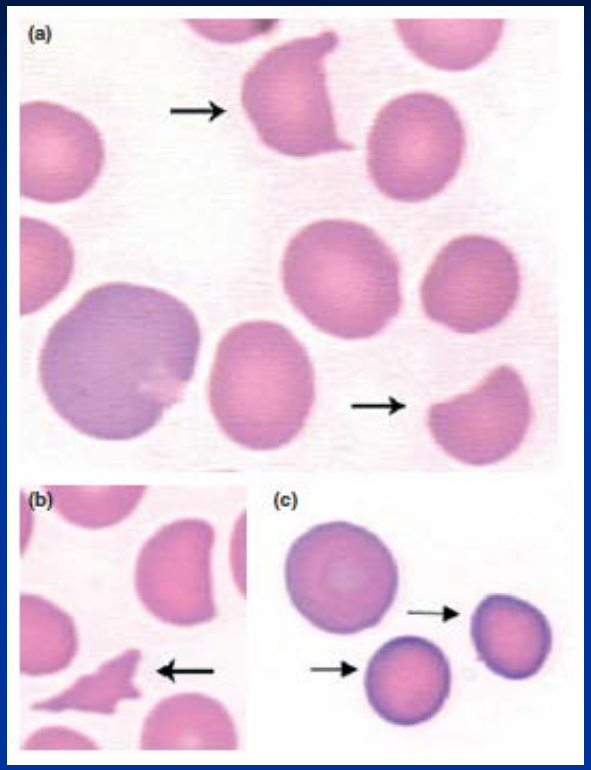
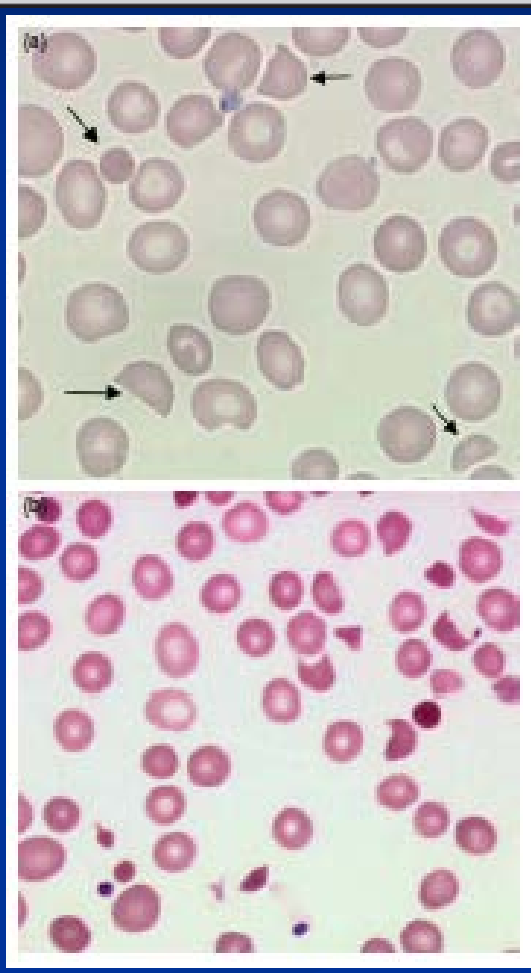


Figure 1. Typical shapes for specific identification of schistocytes. (a) keratocyte (upper arrow) and helmet cell (lower arrow), close to a polychromatophilic erythrocyte in the left lower corner; (b) a triangle schistocyte (arrow) with a helmet cell on the upper right; (c) two microspherocytes (arrows); they are derived, in a context of thrombotic microangiopathic anemia, from schistocytes.

Figure 2. Peripheral blood smear from a case of thrombotic thrombocytopenic purpura. (a) arrows indicate a helmet cells (lower left), a microspherocyte (upper left), a keratocyte (center top), and a microcrescent (lower right angle); (b)morphological abnormalities include microspherocytes, keratocytes, helmet cell, and several crescent and triangular schistocytes.



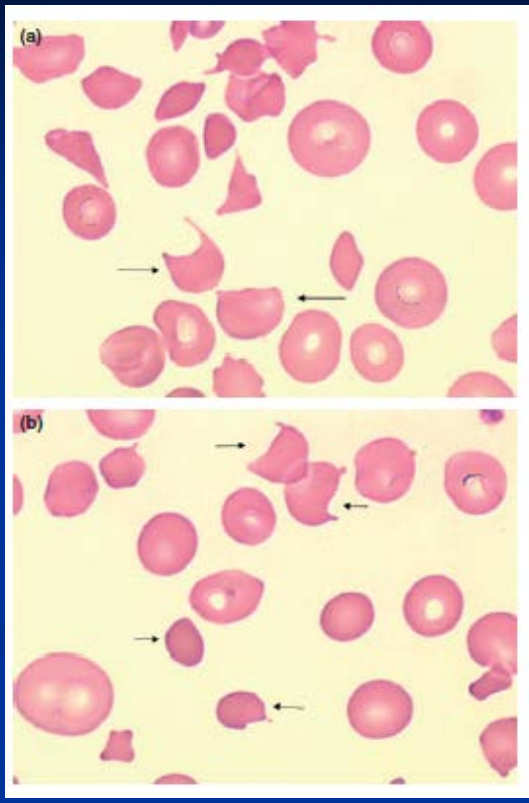


Figure 3. Peripheral blood smear from a case of post-transplant thrombotic microangiopathic anemia. (a) a keratocyte (left arrow), a helmet cell (right arrow), and several hyperchromatic triangular erythrocytes are present; (b) two keratocytes (upper arrow) and two deformed microspherocytes (lower arrow) are present, together with more bizarre red cell fragments.

American Journal of Hematology 75:18–21 (2004)

Morphologic Diagnosis of Thrombotic Thrombocytopenic Purpura

Edward R. Burns,[1,2]* Yenmay Lou,[2] and Anjali Pathak[2]
[1]Department of Pathology, Albert Einstein College of Medicine, Bronx, New York
[2]Department of Medicine, Albert Einstein College of Medicine, Bronx, New York

TABLE I. Incidence of Schistocytes on Peripheral Blood Smears

Patient groups	*N*	Prevalence (%)	Mean ± SD (%)	Range (%)
Normals	40	58	0.05 ± 0.03	0–0.27
Chronic renal disease	28	93	0.21 ± 0.18	0–0.6
Preeclampsia	5	80	0.25 ± 0.08	0–0.45
Mechanical valves	5	100	0.18 ± 0.15	0–0.48
TTP	6	100	8.35 ± 2.74	1.0–18.4

1. Br J Haematol. 1995 Mar;89(3):643-4.

Thrombotic thrombocytopenic purpura-like syndrome in the absence of schistocytes.

Fava S, Galizia AC.

Department of Medicine, St Luke's Hospital, G'Mangia, Malta.

Thrombotic thrombocytopenic purpura is an uncommon disorder that if left untreated has a very high mortality. Schistocytes are generally considered essential for the diagnosis. A patient is presented with a thrombotic thrombocytopenic purpura-like syndrome in whom schistocytes were persistently absent and who responded to plasmapheresis.

PMID: 7734369 [PubMed - indexed for MEDLINE]

1. South Med J. 2005 Mar;98(3):392-5.

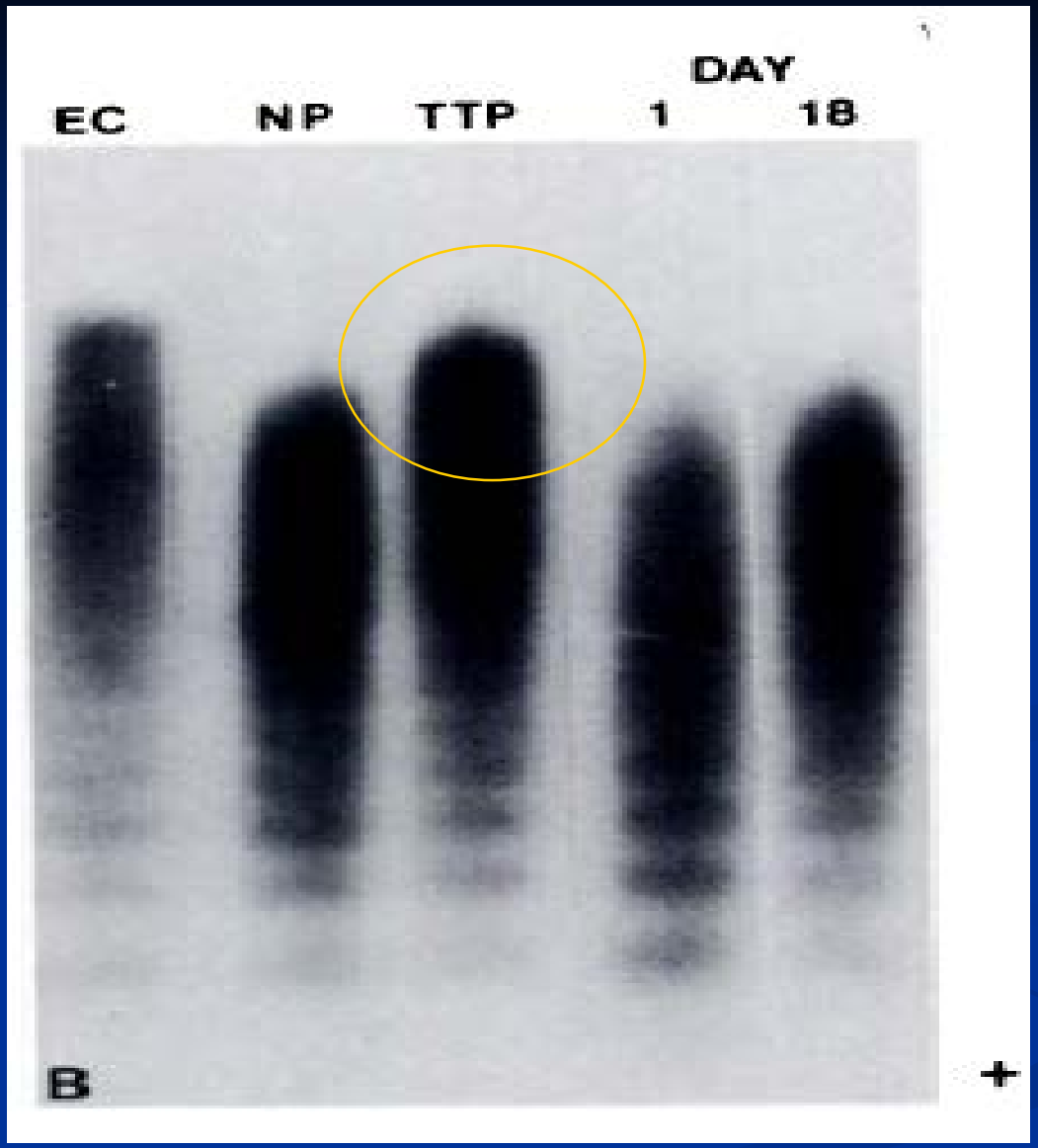
Thrombotic thrombocytopenic purpura without schistocytes on the peripheral blood smear.

Daram SR, Philipneri M, Puri N, Bastani B.

Division of Nephrology, Department of Internal Medicine, Saint Louis University School of Medicine, Saint Louis, MO 63110, USA.

A hallmark of the clinical syndrome of thrombotic thrombocytopenic purpura (TTP) is evidence of microangiopathic hemolytic anemia. The presence of schistocytes onthe peripheral blood smear, elevated plasma lactic dehydrogenase, and decreased haptoglobin concentration are used as evidence of microangiopathic hemolytic anemia to make a diagnosis of TTP. This report describes a case of recurrence of TTP in the absence of schistocytes in the peripheral blood smear during the recurrent episode. Although careful attention should be paid to microscopic examination of a blood smear in any patient presenting with acute renal failure and thrombocytopenia, this case emphasizes the need to consider TTP-hemolytic uremic syndrome in the differential diagnosis, even in the absence of peripheral schistocytosis.

PMID: 15813170 [PubMed - indexed for MEDLINE]



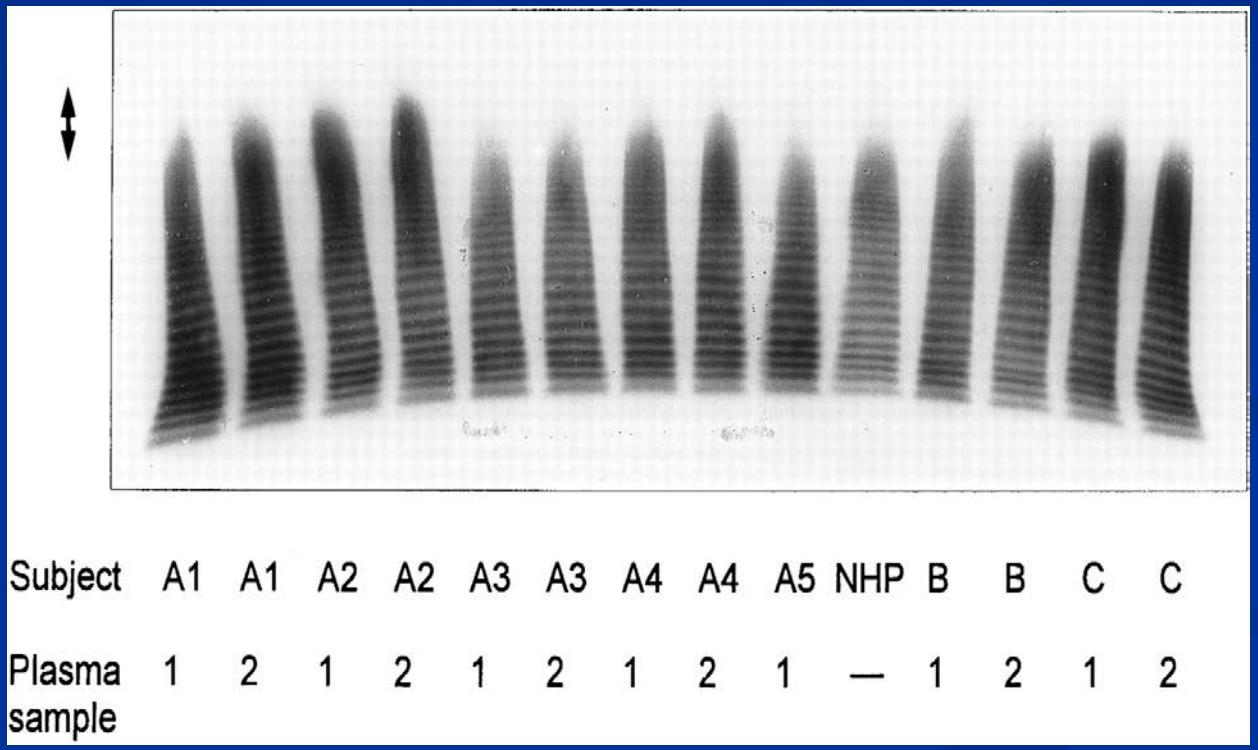
Moake JL et al, Unusually large plasma FVIII: von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. NEJM 1982

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

RAPID COMMUNICATION

Deficient Activity of von Willebrand Factor–Cleaving Protease in Chronic Relapsing Thrombotic Thrombocytopenic Purpura

By Miha Furlan, Rodolfo Robles, Max Solenthaler, Max Wassmer, Pierre Sandoz, and Bernhard Lämmle



Blood 1997;89:3097-3103

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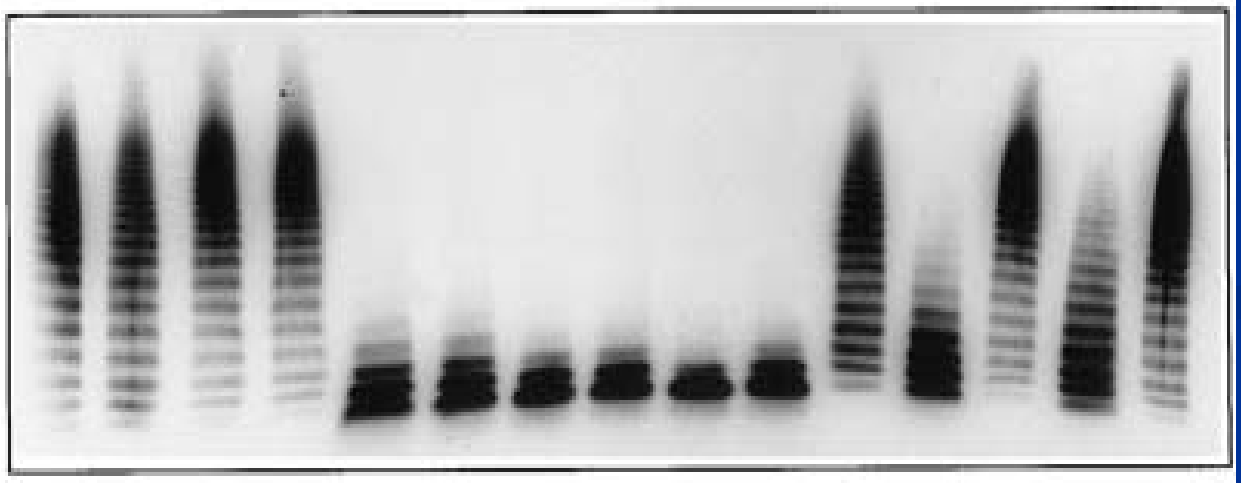
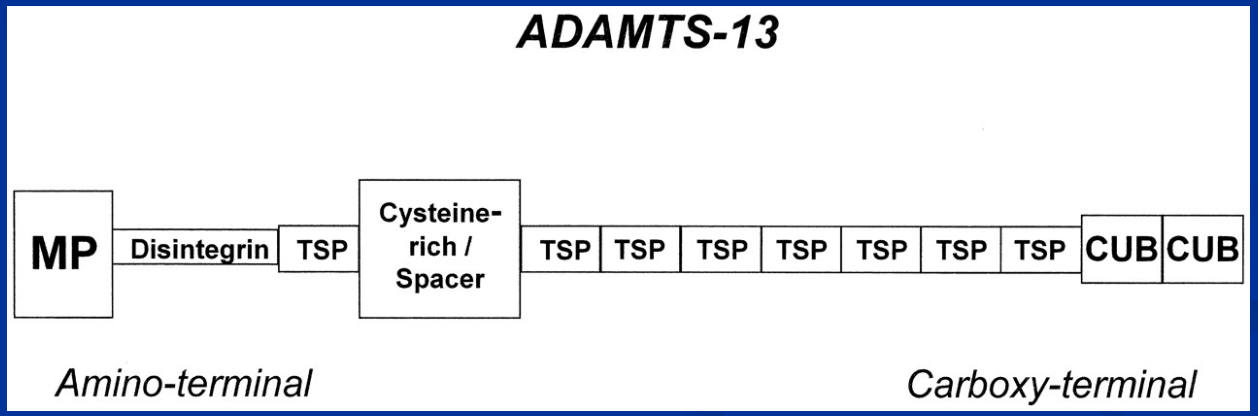


Subject	A1	A1	A2	A2	A3	A3	A4	A4	A5	NHP	B	B	C	C	TBS
Plasma sample	1	2	1	2	1	2	1	2	1	–	1	2	1	2	–

Blood 1997;89:3097-3103

HEMATOLOGY
ASH Education Program Book

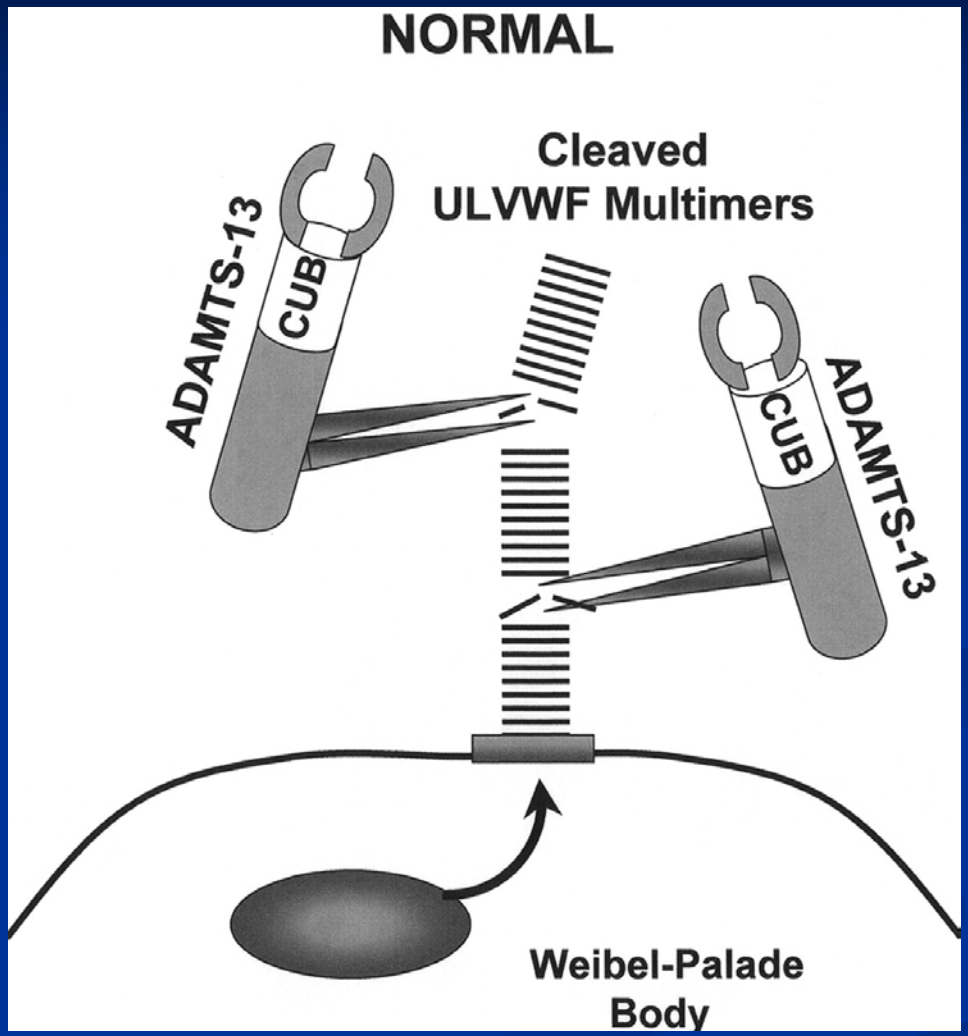
Figure 1. Domain structure of the plasma VWF-cleaving metalloprotease, ADAMTS13



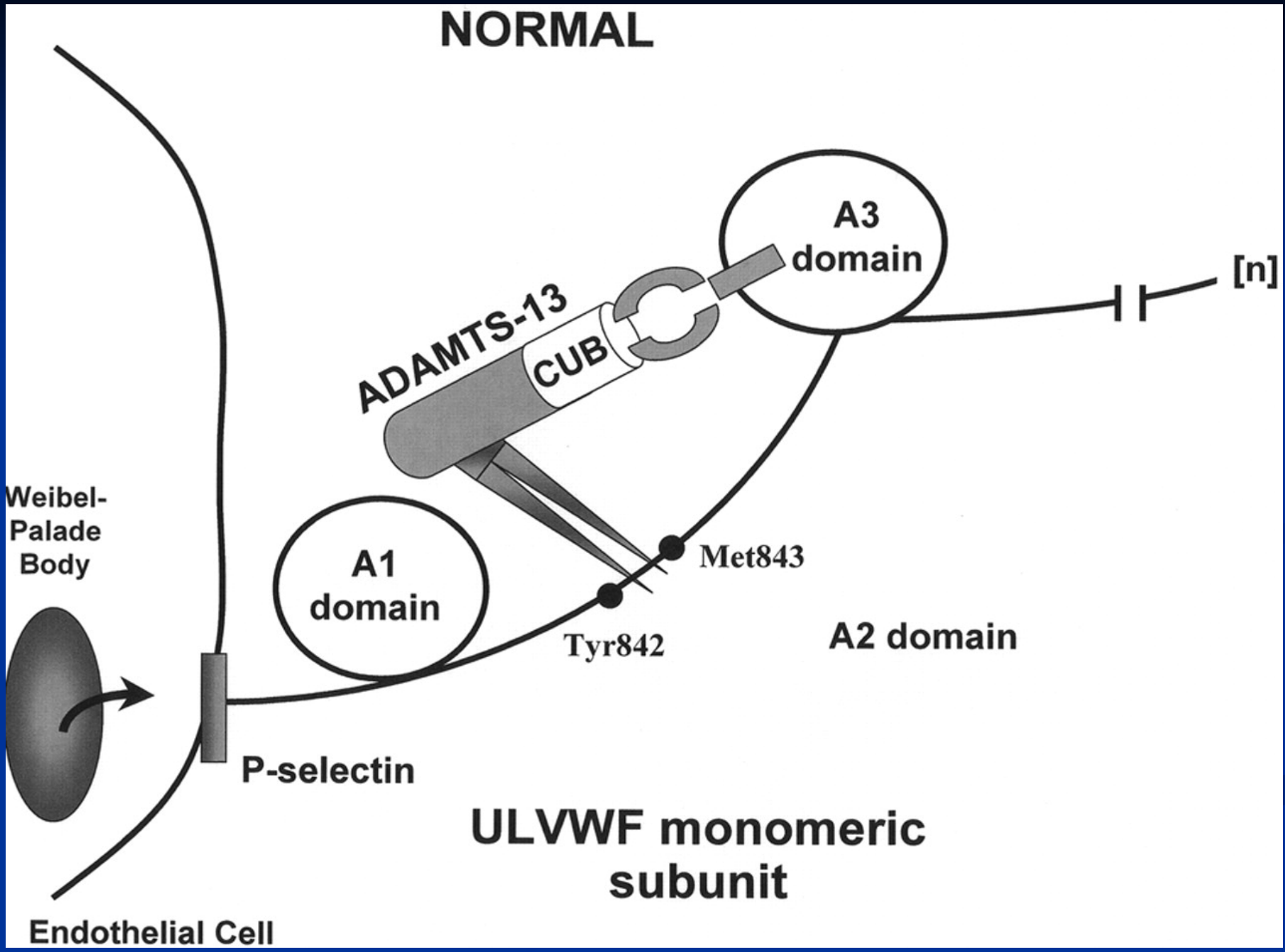
Sadler, J. E. et al. Hematology 2004;2004:407-423

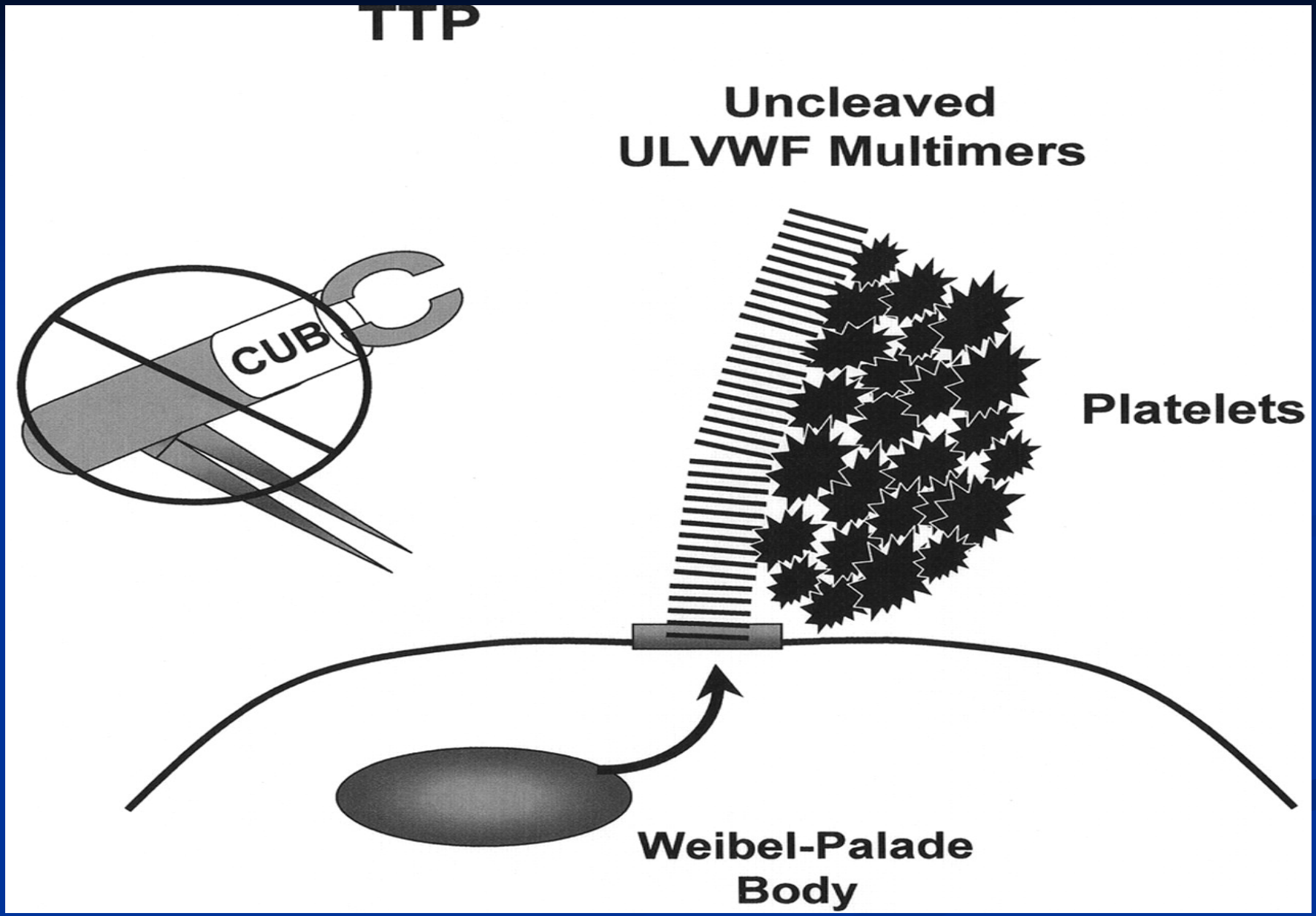
HEMATOLOGY
ASH Education Program Book

Figure 2. ADAMTS13 activity in normal and thrombotic thrombocytopenia purpura (TTP) plasma



Sadler, J. E. et al. Hematology 2004;2004:407-423


NORMAL
A3 domain
[n]
ADAMTS-13
CUB
Weibel-Palade Body
A1 domain
Met843
Tyr842
A2 domain
P-selectin
ULVWF monomeric subunit
Endothelial Cell


TTP
Uncleaved
ULVWF Multimers
CUB
Platelets
Weibel-Palade
Body

PTT: due differenti forme

PTT acquisita

- Circa il 90% di tutti i casi
- Femmine 70%
- Picco tra i 30 e 40 anni
- 30% di recidive
- Talora scatenata da infezioni o gravidanza (circa il 20%)
- Autoanticorpi vs ADAMTS 13

PTT ereditaria

- Meno del 10% del totale
- Maschi=femmine
- Tra i 0 e 4 anni
  - 20% tra i 20 e 30 anni
- Frequenti recidive
- Conosciuta come sindrome di Upshaw-Schulman
- Mutazioni del gene ADAMTS13 sul cromosoma 9q34

Anticorpi anti-ADAMTS-13

- Anticorpi inibitori
  - Inibiscono l'attività proteolitica di ADAMTS13 o ne accelerano la clearance dal plasma legandosi alla proteasi
- Anticorpi non inibitori
  - non neutralizzano l'attività in un test di inibizione
  - una moderata attività ADAMTS13 può essere correlata con un aumento di clearance dal plasma per opsonizzazione o altri meccanismi non noti
- Anticorpi inibitori e non inibitori possono essere simultaneamente presenti nei pazienti TTP
- Bassi livelli di attività(<5%-10%) ed alto titolo di anticorpi correlano con l'aumento di recidive [1]

1. Alvarez-Larran A., Ann. Hematol. 2009

Postrtransplantation TMA

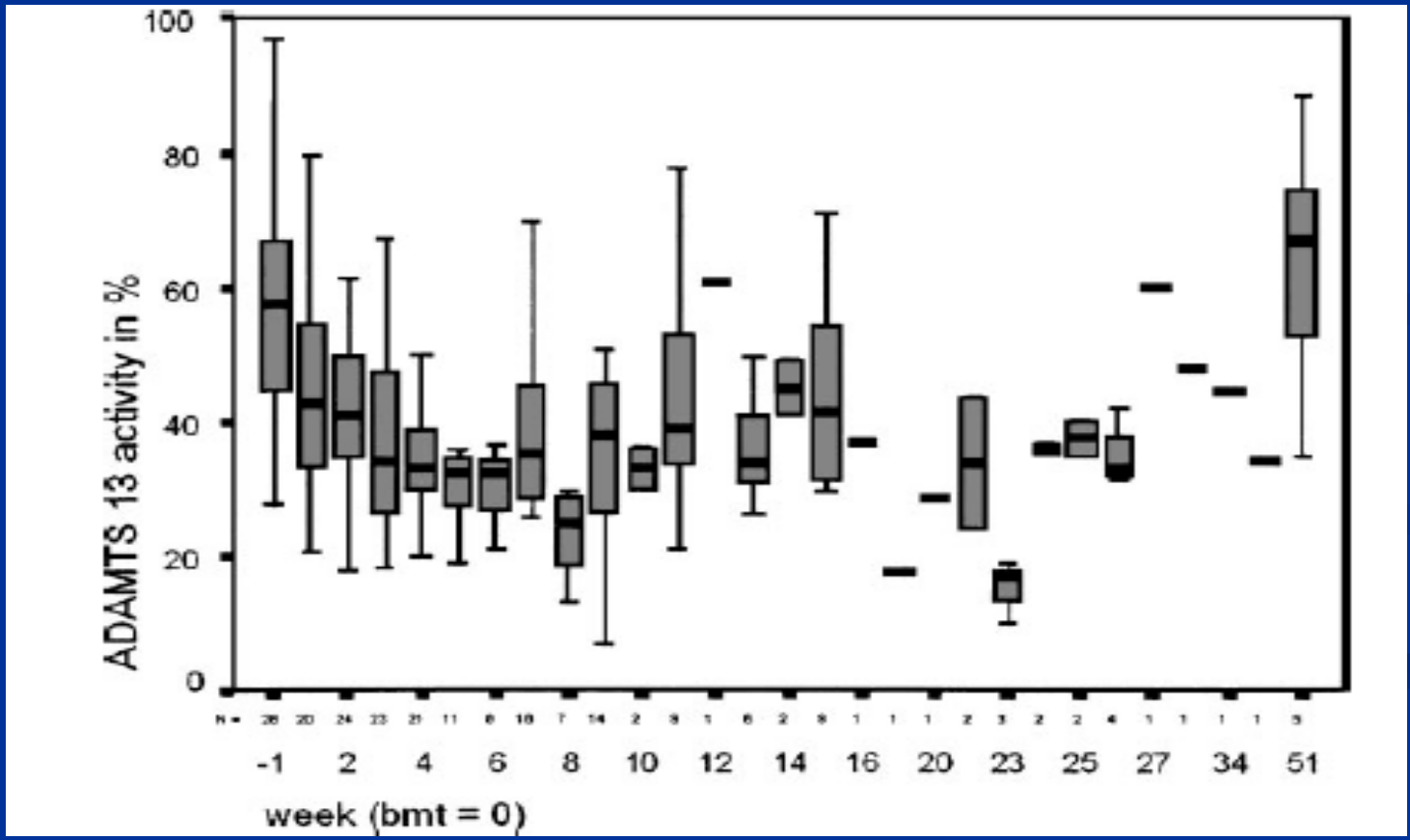
- Incidence quoted 7% (autoTx) to 14% (alloTx) or 0.5% (autoTx) to 0.13% (alloTx)

- Review of 6562 patients (Mayo Clin. Proc. 2003; 78: 421): 1.1% (range 0.28% - 4%)

von Willebrand Factor-Cleaving Protease (ADAMTS13) in the Course of Stem-Cell Transplantation

Karim Kentouche, M.D.,[1] Felix Zintl, M.D.,[1] Dorothea Angerhaus,[2]
Dietlinde Fuchs, M.D.,[1] Johann Hermann, M.D.,[1]
Reinhard Schneppenheim, M.D., Ph.D.,[3] and Ulrich Budde, M.D.[2]

Sem. Thromb. Hemostas. 2006; 32: 98



TMA in BMT

Endothelial cell injury due to

- toxic conditioning regimens,
- CMV infection,
- cyclosporine,
- a possible graft-vs-host effet on endothelium,
- decrease in ADAMTS 13

- mortality: 13-23%

Postrtransplantation TMA

- Intravascular hemolysis (absent haptoglobin)
- Red cell fragmentation
- Increased reticulocytes
- Elevation LDH
- Drop in platelet count (< 100,000)
- Negative Coomb's test
- (Absence of DIC)

Posttransplantation TMA

- In the Mayo Clinic series (10 patients) 80% of the patients had changes in mental status and 90% had renal insufficiency.

Table 1: Diagnostic criteria for transplantation-associated TMA

Blood and Marrow Transplant Clinical Trials Network (BMT CTN) toxicity committee consensus definition for TMA[18]	**International Working Group Definition for TMA[19] All of the following are present:**
1) RBC fragmentation and ≥ 2 schistocytes per high-power field on peripheral film	1) Increased percentage (> 4%) of schistocytes in the blood
2) Concurrent increased serum LDH above institutional baseline	2) *De novo*, prolonged or progressive thrombocytopenia (platelet count less than 5 x 109/l or a 50% or greater decrease from previous counts)
3) Concurrent renal[a] and/or neurologic dysfunction without other explanations	3) Sudden and persistent increase in LDH
4) Negative direct and indirect Coomb's test results	4) Decrease in hemoglobin concentration or increased red blood cell transfusion requirement
	5) Decrease in serum haptoglobin concentration

Stavrou & Lazarus, MJHID 2010

SINDROME EMOLITICO-UREMICA

HUS is defined by the triad

- non-immune haemolytic anaemia (hemoglobin < 10 g/dL) with schistocytes,
- thrombocytopenia (platelets <150 x10^3/mm^3)
- renal impairment (serum creatinine > upper limit of normal for age)

GASSER C, GAUTIER E, STECK A, SIEBENMANN RE, OECHSLIN R.

Hämolytisch-urämische Syndrome: bilaterale Nierenrindennekrosen bei akuten erworbenen hämolytischen Anämien.

[Hemolytic-uremic syndrome: bilateral necrosis of the renal cortex in acute acquired hemolytic anemia].

Schweiz Med Wochenschr. 1955 Sep 20; **85**(38-39):905–909

Sindrome Emolitico Uremica (SEU)

- Microangiopatia trombotica complemento-mediata con prevalente interessamento del parenchima renale
  - Insufficienza renale acuta
  - Emolisi intravascolare massiva
  - Insufficienza del microcircolo con interessamento multiorgano:
    - Cervello (frequente)
    - Polmoni
    - Apparato cardiovascolare (ipertensione, cardiopatia)

SEU tipica ed atipica

SEU tipica

- Più comune
- Indotta dalla tossina di Shiga (Stx) secreta da ceppi di E. Coli (0157:H7)
- Frequente anamnesi positiva per diarrea emorragica
- Significative sequele renali nel 25% dei casi
- Morte od ESRD nel 12% dei casi
- Non recidiva

SEU atipica

- Più rara
- Scatenata da stress *(infezioni, chirurgia...)* spesso nessun fattore è individuabile
- ESRD nel 50% dei casi
- Elevata mortalità (>25% a 5 anni)
- Recidive frequenti

[1]Upadhyaya K et al. *Pediatric*. 1980;65:115-20; [2]Stella Shin H et al. ASN 2011; abstract: TH-PO371; [3]Gallo EG et al. *Pediatr Nephrol*. 1995;9:117-9; [4]Palermo MS et al. *Expert Rev Anti Infect Ther*. 2009;7:697-707; [5]Stahl AL et al. *Blood* 2011;117:5503-13; [6]Mache C et al. International Conference on HUS-MPGN-PNH 2010; abstract ; [7]Thurman J. *CJASN.* 2009; 1920-4; [8]Orth D et al. *J Immunol* 2009;182:6394-40; [9]Morigi M et al. *J Immunol.* Epub 2011; [10]Chandler WL et al. *N Engl J Med.* 2002;346:23-32. [11]Frank C et al. *N Engl J Med.* Epub 2011; [12]Garg AX et al. *JAMA*. 2003;290:1360-70; 136. [13]Schlieper A. *Arch Dis Child.* 1999;80:214-20; [14]Schlieper A. *Archives of Disease in Childhood* 1992, 67:930-4; [15]Noris M et al. *J Am Soc Nephrol*. 2005; 16:1035-50; [16]Bitzan M et al. *Thromb Hemost*. 2010;36:594-610.

La sola manifestazione clinica non permette di differenziare la SEUa dalla STEC-SEU

- La diarrea è una caratteristica comune nella SEUa
  - Percezione: pazienti con storia di diarrea → "È la STEC-SEU"
  - Evidenze mediche: diarrea emorragica o senza sangue è riportata nel 30% dei pazienti affetti da SEUa [1]
- La terminologia D+ e D- non consente una differenziazione accurata fra STEC-SEU e SEUa
  - STEC-SEU precedentemente denominata SEU diarrea positiva/D+
  - SEUa precedentemente denominata SEU diarrea negativa/D- [2]

1. Zuber J et al. *Nat Rev Nephrol.* 2011;7:23-35.
2. Ohanian M et al. *Clin Pharmacol.* 2011;3:5-12.

37

Il complemento

- Il sistema del complemento rappresenta una componente del sistema immunitario[1]
- È costituito da proteine solubili e di membrana che interagiscono reciprocamente
- È composto da tre vie di attivazione con una sequenza effettrice finale comune
  - Classica
  - della Lectina
  - Alternativa

I componenti vengono indicati con la lettera C, seguita da un numero

I componenti specifici vengono indicati con le lettere maiuscole B e D

    - sempre attiva grazie all'idrolisi basale del C3 e legame con il Fattore B

1. Holers VM et al. *Immunol Rev.* 2008;223:300-316.

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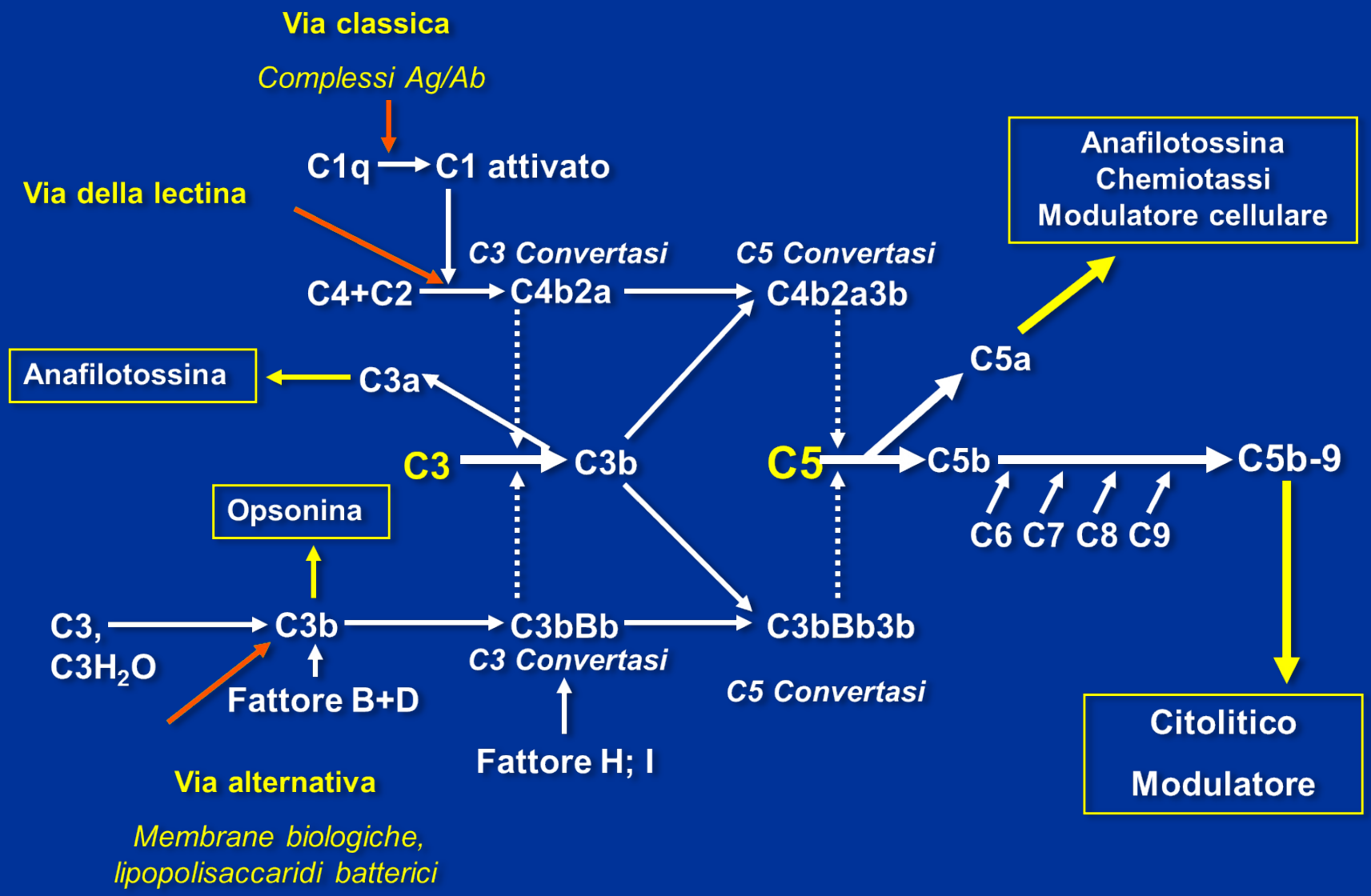
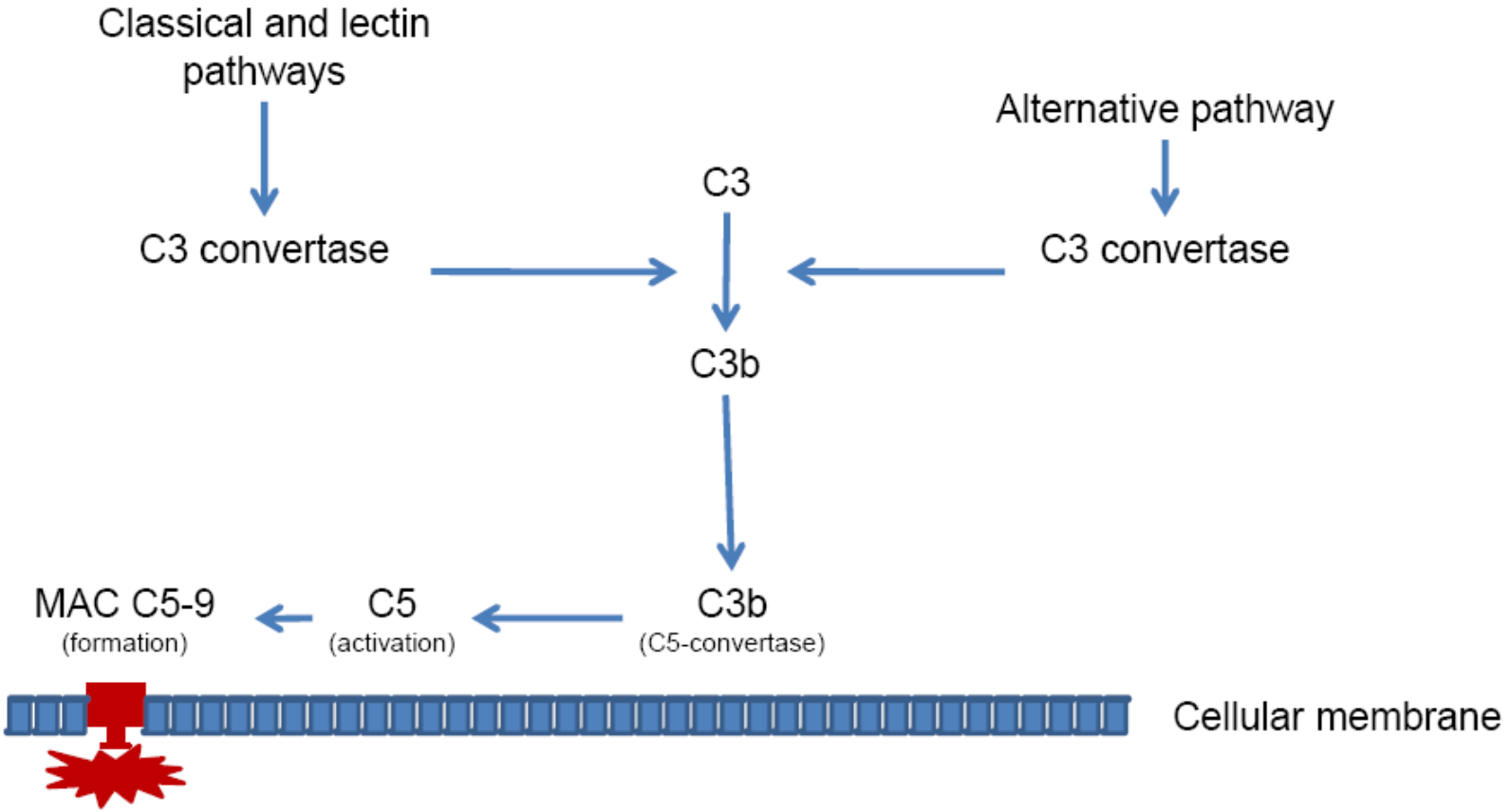
La cascata del complemento



SIMPLIFIED SCHEME OF THE COMPLEMENT SYSTEM

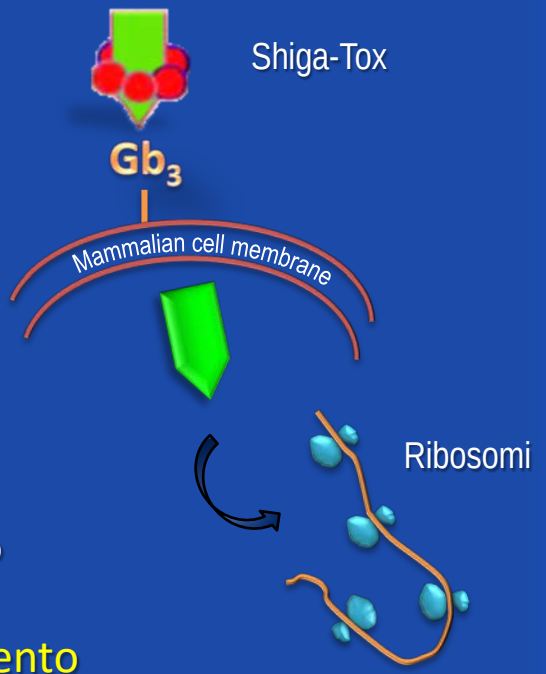


Noris M & Remuzzi G. *N Engl J Med* 2009; 361:1676-87.

Fisiopatologia

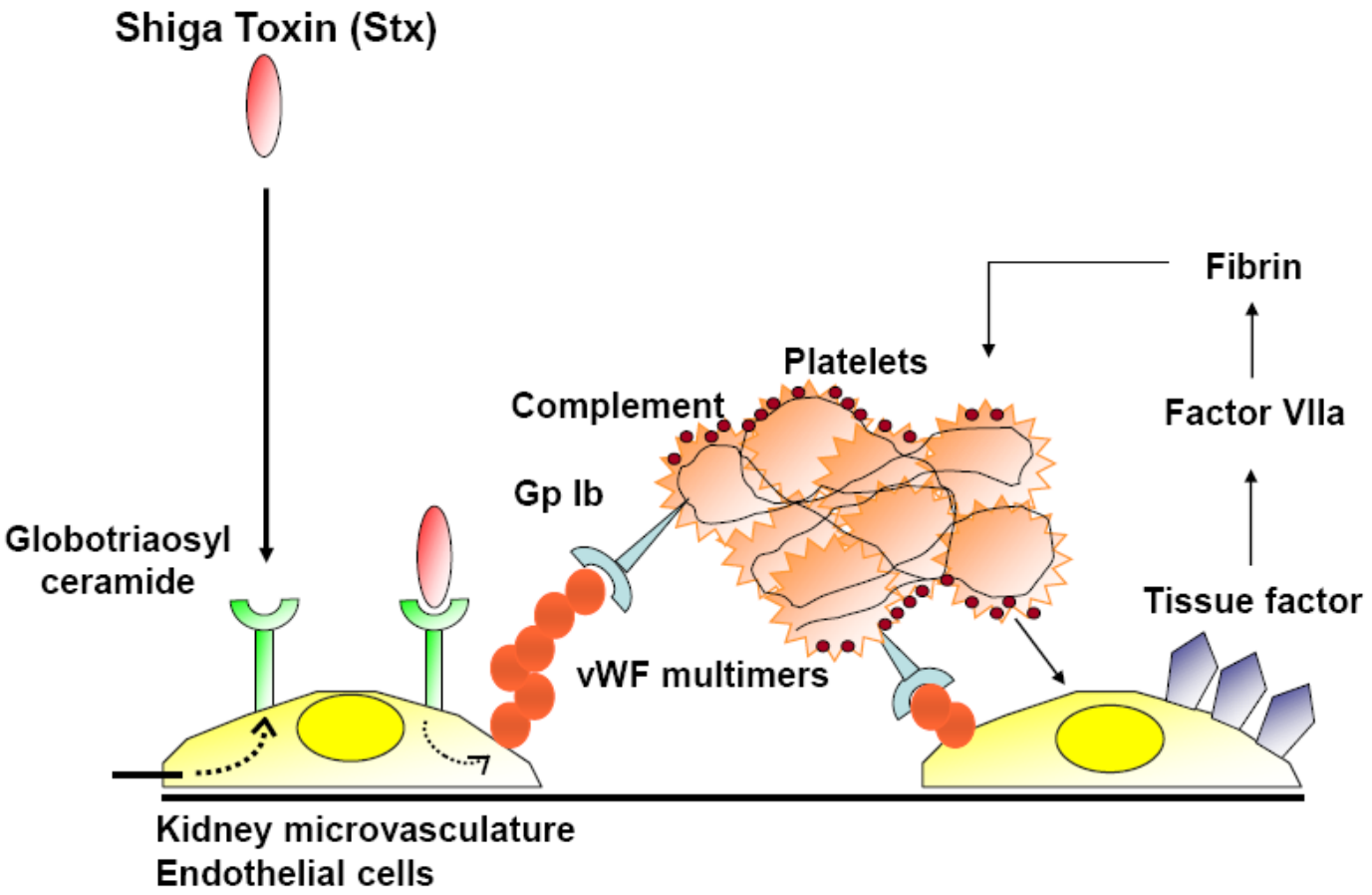
- Nella SEU tipica, la tossina batterica determina l'attivazione del complemento verso gli endoteli vascolari
  - La shiga toxin causa la morte delle cellule epiteliali intestinali bloccandone la sintesi proteica
    → Diarrea emorragica
  - Una volta penetrata in circolo la tox
    → Attiva il complemento come risposta all'infezione
    → Danneggia direttamente l'endotelio
      - al quale si lega tramite un recettere uguale a quello presente sull'epitelio intestinale

    attivando così la via alternativa del complemento



1. C. Loirat , J. Saland, M. Bitzan in Press 2012
2. del Conde I et al. J Exp Med 2005;201:871-879
3. D. Orth J. Immunol. 2009 182,6394-6400

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

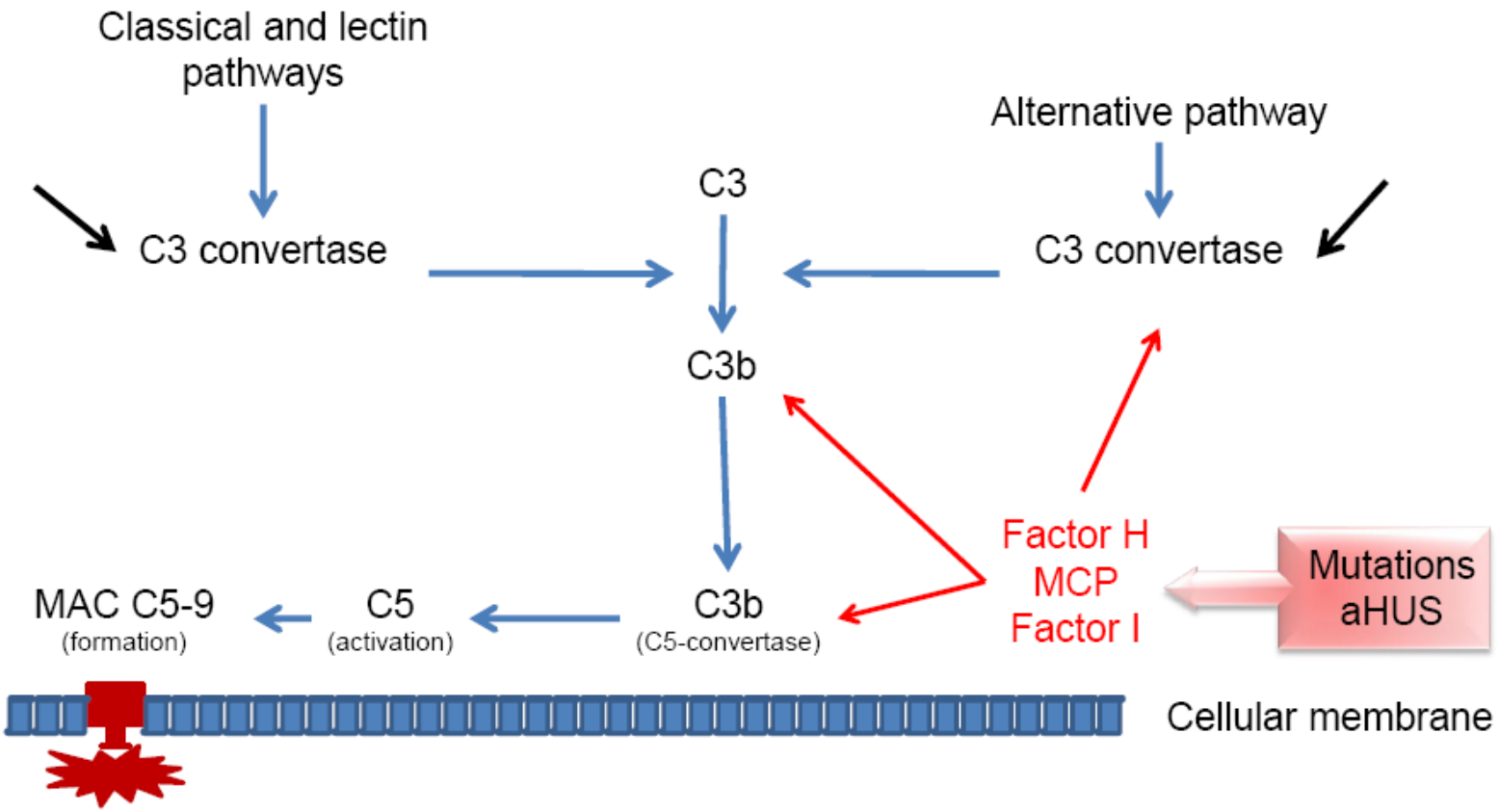


Fisiopatologia

- Nella SEU atipica, l'attivazione del complemento contro gli endoteli è provocata da
  - un deficit congenito di proteine di regolazione del complemento
  - produzione di anticorpi contro le proteine di regolazione del complemento

1. C. Loirat , J. Saland, M. Bitzan in Press 2012
2. del Conde I et al. J Exp Med 2005;201:871-879
3. D. Orth J. Immunol. 2009 182,6394-6400

GENETIC LOSS OF NATURAL REGULATORS LEADS TO UNCONTROLLED COMPLEMENT ACTIVATION



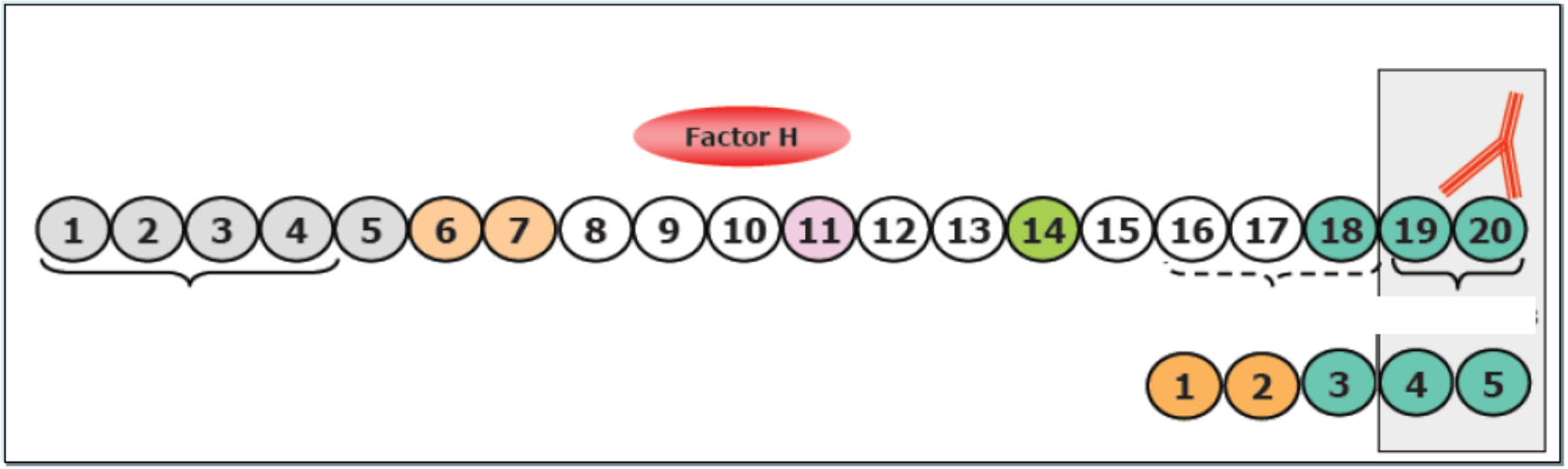
Noris M & Remuzzi G. *N Engl J Med* 2009; 361:1676-87.

SEUa: principali difetti genetici

Proteina	Effetto	%	Prognosi	Trapianto
Fattore H	Nessun legame sull'endotelio	25	Morte o ESRD 75%	Recidiva 80-90%
Fattore H (R1-R3)	Autoanticorpi anti-FH	6	ESRD 35%	Recidiva 20%
MCP	Assenza sulla membrana	12,5	Morte o ESRD <20%	Recidiva 15%
Fattore I, B	C3 convertasi stabilizzata	I: 7% B: 2%	Morte o ESRD 70%	Recidiva 75% (I)
C3	Resistenza all'inattivazione	7%	Morte o ESRD 60%	Recidiva 50%

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

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.

Dati epidemiologici

- L' incidenza della SEU atipica è stimata in 1-2 casi/milione/anno
  - 20% a carattere familiare
  - nel bambino sotto i 5 aa: 6,1 casi/milione/anno
- SEU tipica 10 volte più frequente
- TTP (diagnosi differenziale): 4 casi/milione/anno

Noris e Remuzzi, NEJM, 2009 361:1676-87

La diagnosi differenziale tra PTT e SEU

- PTT E SEUa, si presentano clinicamente in modo simile e sono state storicamente raggruppate come TTP/HUS
- Nel passato, il trattamento disponibile era lo stesso per entrambe le patologie e non richiedeva una diagnosi differenziale

1. Bianchi V et al. *Blood*. 2002;100:710-713.
2. Loirat C et al. *Semin Thromb Hemost*. 2010;36:673-681

La sola manifestazione clinica non permette di differenziare completamente la SEUa dalla TTP

- La SEUa colpisce i pazienti a tutte le età
  - Percezione: bambino → "si tratta di SEUa"; adulti → "si tratta di TTP"
  - Evidenza medica: il 40% dei pazienti affetti da SEUa sono adulti [1]
- I pazienti affetti da SEUa manifestano spesso interessamento del SNC
  - Percezione: il paziente manifesta sintomi neurologici →"è una TTP"
  - Evidenza medica: fino al 48% dei casi segnalati di SEUa mostrano disfunzione neurologica [2]
- L'attività di ADAMTS13 permette di differenziare la SEUa dalla TTP
  - Percezione: i sintomi clinici permettono la differenziazione tra SEUa e TTP
  - Evidenza medica: la ridottissima attività di ADAMTS13 differenzia la TTP (≤5 %) [3-5]

1. Noris M et al. *Clin J Am Soc Nephrol*. 2010;10:1844-1859.
2. Neuhaus TJ et al. *Arch Dis Childl*. 1997;76:518-521.
3. Tsai HM. *Int J Hematol*. 2010;91:1-19.
4. Sellier-Leclerc AL et al. *J Am Soc Nephrol*. 2007;18:2392-2400.
5. Bianchi V et al. *Blood*. 2002;110:710-713.

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TTP HUS: la diagnosi differenziale

"A single laboratory test may enable physicians to distinguish TTP from HUS"

ADAMTS 13

- Valore della determinazione dell'attività
- Riscontro di autoanticorpi

J. Moake et N. Engl J Med.1982;307:1432-5

Alta specificità nella diagnosi

- L'attività di ADAMTS 13 tra il 5% e il 10 % è sufficiente per prevenire la formazione di trombi piastrinici nel microcircolo [1]
- La specificità del deficit severo di ADAMTS 13 (attività <5%) nel discriminare tra la TTP acuta dalla HUS è di oltre il 90% [2]

1. Sasahara Y, et al. *Int J Hematol.* 2001;74:109-114
2. Bianchi et al, Blood. 2002;100:710-713

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…

Table 3: Primary and secondary thrombotic microangiopathies

Primary TMA	Secondary TMA
- Hereditary TTP - Idiopathic TTP	Immune-mediated - Pregnancy - Autoimmune disorders - Infections - Medications (clopidogrel, ticlopidine)
- Hereditary (atypical) HUS - Sporadic (Shigatoxin-associated)	Non-immune mediated - Malignant hypertension - Solid organ transplantation - HCT - Metastatic tumors - Medications (cyclosporine, tacrolimus, IFN-α, Mitomycin C)

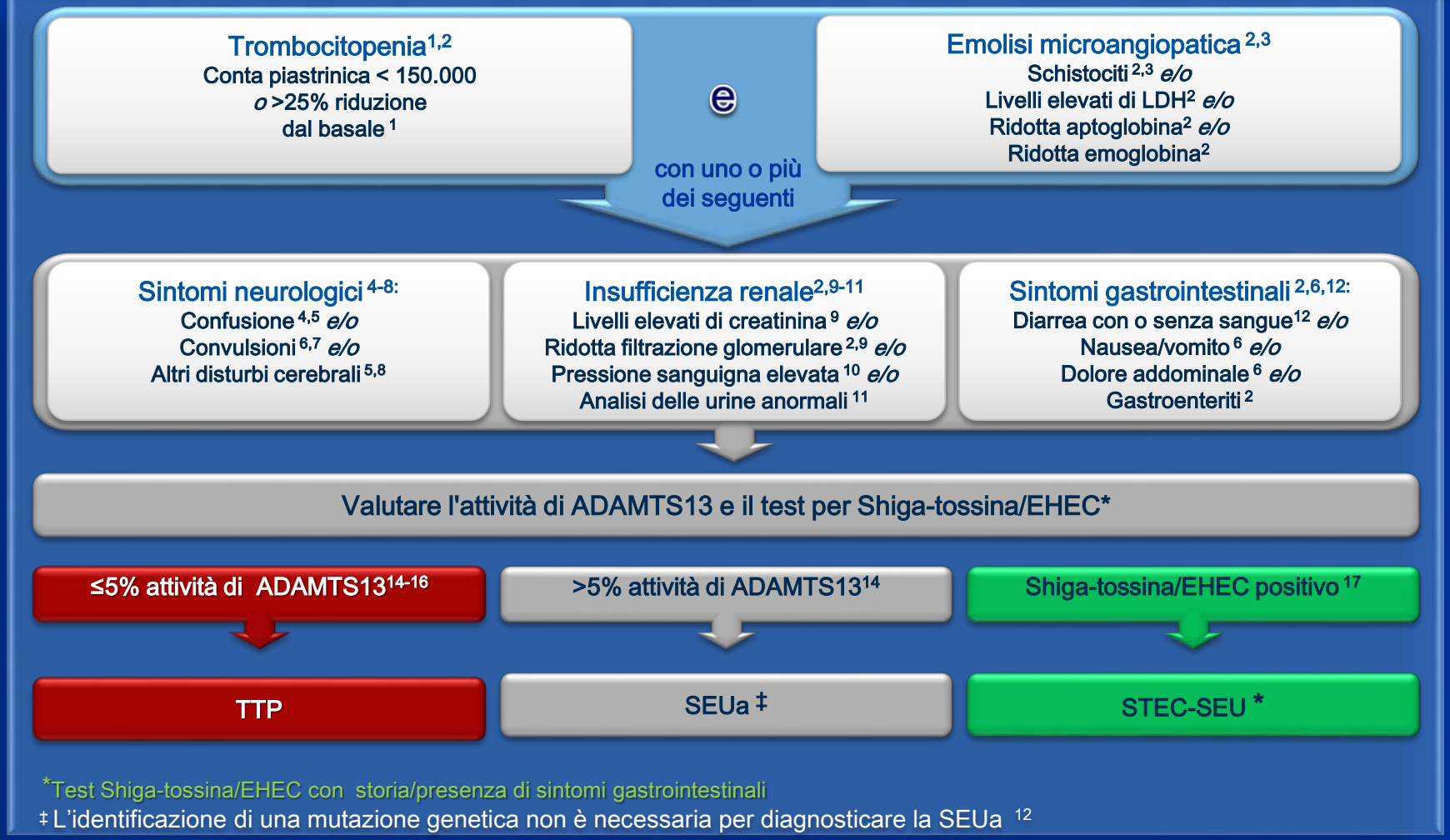
Stavrou & Lazarus, MJHID 2010

Table 4: Pathophysiologic classification of primary and secondary thrombotic microangiopathies.

Immune Mediated	Non Immune Mediated
Primary • Idiopathic TTP • Atypical HUS secondary to inhibitory antibodies to complement – regulating proteins	Primary • Hereditary TTP • Hereditary atypical HUS secondary to mutations in complement – regulating proteins
Secondary • Pregnancy • Autoimmune disorders • Infections • Medications (clopidogrel, ticlopidine)	Secondary • Malignant hypertension • Solid organ transplantation • HCT • Metastatic tumors • Medications (cyclosporine, tacrolimus, IFN-α, Mitomycin C)

Stavrou & Lazarus, MJHID 2010

Diagnosi differenziale tra PTT e SEU



*Test Shiga-tossina/EHEC con storia/presenza di sintomi gastrointestinali

‡ L'identificazione di una mutazione genetica non è necessaria per diagnosticare la SEUa [12]

1. Dati su file. Alexion Pharmaceuticals, Inc.; 2012.
2. Caprioli J et al. *Blood*. 2006;108:1267-1279.
3. Noris M et al. *N Engl J Med*. 2009;361:1676-1687.
4. Ohanian M et al. *Clin Pharmacol.* 2011;3:5-12.
5. Noris M et al. *J Am Soc Nephrol*. 2005;16:1177-1183.
6. Dragon-Durey MA et al. *J Am Soc Nephrol*.2010;21:2180-2187.
7. Neuhaus TJ et al. *Arch Dis Child*. 1997;76:518-521.
8. Davin JC et al. *Am J Kid Dis*. 2010;55:708-711.
9. Sellier-Leclerc AL et al. J Am Soc Nephrol. 2007;18:2392-2400.
10. Sallée M et al. Nephrol Dial Transplant. 2010;25:2028-2032.
11. Al-Akash SI et al. Pediatr Nephrol. 2011;26:613-619.
12. Noris M et al. Clin J Am Soc Nephrol. 2010;5:1844-1859.
13. Zuber J et al. Nat Rev Nephrol. 2012;8(11):643-657.
14. Bianchi V et al. Blood. 2002;100:710-713.
15. Tsai HM. Int J Hematol. 2010;91:1-19.
16. Barbot J et al. Br J Haematol. 2001;113(3):649-651.
17. Bitzan M et al. Semin Thromb Hemost. 2010;36:594-610.
18. Coppo P. et al 2010; 5:e10208

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