Le sindromi trombotiche microangiopatiche: il ruolo del laboratorio

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Microangiopatie trombotiche: patogenesi/terapia
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Thrombotic Microangiopathy

Describes a process comprising:

1) Consumptive Thrombocytopenia

2) Microangiopathic Haemolytic Anaemia

3) Microvascular Thrombosis

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Clinical Spectrum of TMA

- Haemolytic uremic syndrome
- Thrombotic thrombocytopenic purpura
- Malignant hypertension
- Preeclampsia – eclampsia
- Systemic lupus erythematosus
- Antiphospholipid antibody syndrome
- Systemic sclerosis
- Transplant associated
- Radiation therapy associated
- Drug induced
- Infection associated

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TTP: Epidemiology

- Acquired: annual incidence rate 4-6 per 1,000,000
  - Rare in children
  - More frequent in females (3:1) and blacks (7:1)
- Hereditary (Upshaw – Schulman Syndrome): prevalence unknown (very rare, <5% of all TTP)

TTP: Pathophysiology

- Increased ultralarge VWF – multimers with formation of platelet rich thrombi in the microvasculature
- Severe deficiency of the VWF-cleaving protease ADAMTS-13 (inherited, autoimmune)

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TTP: the classic PENTAD

- Microangiopathic anemia
- Thrombocytopenia
- Acute renal failure
- Fever
- Fluctuating neurologic abnormalities

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Presenting clinical features of 70 consecutive patients with severe ADAMTS-13 deficiency (activity <10%)

Clinical feature	Frequency
Thrombocytopenia	70 (100%)
Microangiopathic hemolytic anemia	70 (100%)
Neurologic abnormalities	
Severe	25 (36%)
Minimal	21 (30%)
None	24 (34%)
Kidney function abnormalities	
Acute renal failure	6 (9%)
Renal insufficiency	29 (41%)
None (normal renal function)	35 (50%)
Fever	15 (21%)
Complete pentad of clinical features	3 (4%)

George JN et al., Hematology 2012: 604

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Presenting clinical features and signs in acute TTP

Thrombocytopenia	Epistaxis, bruising, petechiae, gingival bleeding, haematuria, menorrhagia, gastrointestinal bleeding, retinal haemorrhage and haemoptysis
Central neurological often flitting and variable 70-80%	Confusion, headache, paresis, aphasia, dystarthria, visual problems, encephalopathy, coma (10%)
Fever (>37.5%) Non-specific symptoms	Pallor, jaundice, fatigue, arthralgia or myalgia
Jaundice	Resulting from microangiopathic hemolytic anaemia
Renal impairment	Proteinuria, microhaematuria
Cardiac	Chest pain, heart failure, hypotension
Gastro-intestinal tract	Abdominal pain

Scully M et al., Br J Hematol 2012;158:323

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HUS: Epidemiology

HUS Shiga Toxin-associated

- Shiga Toxin producing E. Coli (STEC) contributes 90% of cases worldwide
- Can be sporadic or epidemic
- Prevalence: 2-6 per 100,000 persons per year (peaks in children <5 yrs old)

'Atypical' HUS: non-STEC, non-Pneumococcal

- Much rarer (~1-2 per 1,000,000 persons in registry data from Europe/US)

HUS: Pathophysiology

HUS:

- Shiga toxin leads to endothelial damage

'Atypical' HUS:

- Genetic and acquired factors leading to dysregulation of the alternative complement pathway
- Uncontrolled complement activation results in microvascular injury

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HUS: the classic TRIAD

- Microangiopathic anemia
- Thrombocytopenia
- Acute renal failure

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Diagnostic approach to acute TMA

Microangiopathic anemia

Symptoms	Diagnostic tools
Haemolysis	Haemoglobin ↓ red blood cells ↓
	Reticulocytes ↑
	Lactate dehydrogenase ↑
	Haptoglobin ↓ free serum haemoglobin ↑
	Direct antiglobulin test (Coombs test): negative
	Schystocytes ↑

adapted from Knobl P et al., Hemostaseologie 2013;2:149

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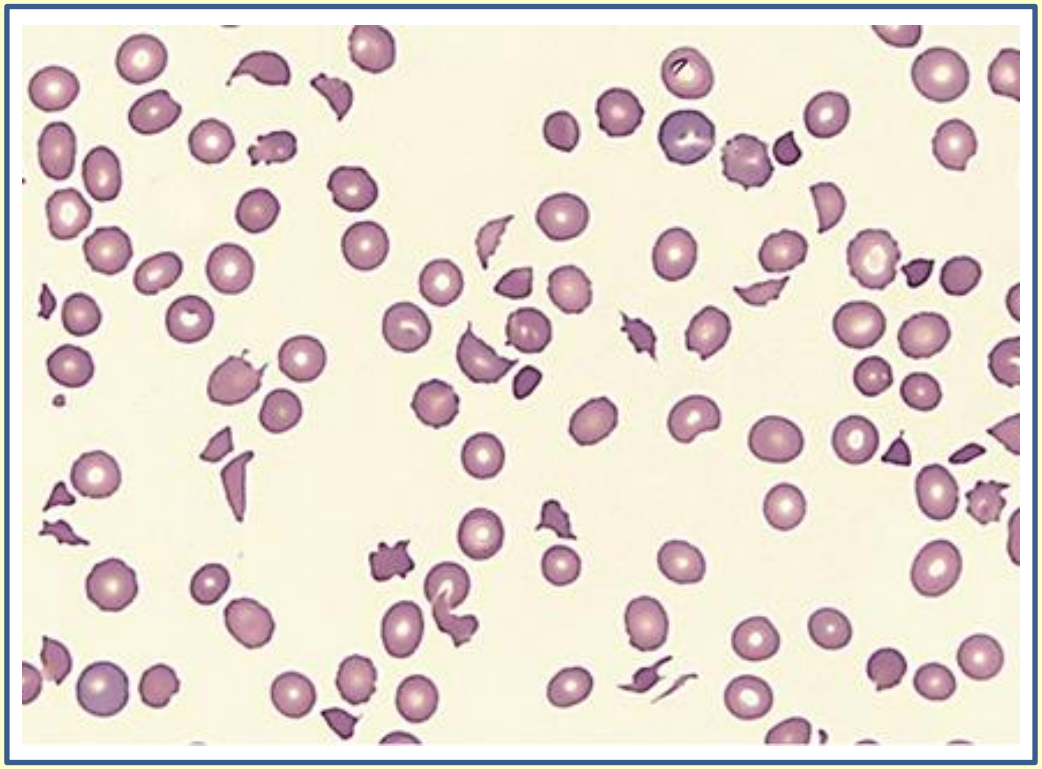
Peripheral blood smear of microagiopathic hemolytic anemia and thrombocytopenia



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Recommendations for schistocyte counting

International council for standardization in hematology

- Should be evaluated on peripheral blood smears; optical microscope; percentage after counting at least 1000 red blood cells
- Identified by specific positive morphological criteria; always smaller than intact red cells; shape of fragments with sharp angles and straight borders; small crescents; helmet cells; keratocytes or microspherocytes
- Meaningful if schistocytes represent the main morphological red blood cells abnormality in the smear
- Indication for diagnosis: above 1%

Zini G et al., Int J Lab Hem 2011;34:107

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Diagnostic approach to acute TMA

Consumption thrombocytopenia

Symptoms	Diagnostic tools
Thrombocytopenia	Platelet count ↓
	Immature platelet fraction ↑

adapted from Knobl P et al., Hemostaseologie 2013;2:149

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TTP coagulation laboratory findings

- **Coagulation tests**:
  - Prothrombin time/INR – usually normal
  - Activated partial thromboplastin time – usually normal
  - Fibrinogen – usually normal
  - VWF multimers – excessive levels of ultra large molecular weight multimers by Western blot analysis

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Diagnostic approach to acute thrombotic microangiopathy – organ damage

Symptoms		Diagnostic tools
Organ damage	Brain	CT scan Perfusion MRT (electroencephalogram) (neurocognitive testing)
	Kidneys	Serum creatinine Glomerular filtration rate Urinalysis-proteinuria Urine output
	Heart	Electrocardiogram Troponin, NT-proBNP Echocardiography
	Lung	Oxygen saturation, gas exchange Chest x-ray High-resolution lung CT scan
	Pancreas	Blood glucose Serum amylase and lipase

adapted from Knobl P et al., Hemostaseologie 2013;2:149

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Additional laboratory testing of potential help for TTP

For diagnosis	
Liver function tests	Usually normal
Calcium	May reduce with PEX
Blood group and antibody screen	To allow provision of blood products
Hepatitis A/B/C and human immunodeficiency virus testing	Pre-blood products and to exclude an underlying viral precipitant
For possible underlying cause	
Thyroid function tests	To exclude Graves Disease
Auto-antibody screen (ANA/RF/ LA/ACLA), including lupus anticoagulant	Exclude associated autoimmune disease
Stool culture	For pathogenic Escherichia coli (if diarrhoea)
CT Chest/abdomen/pelvis (if indicated) ± tumour markers	To look for underlying malignancy

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Adapted from Scully M et al., Br J Hematol 2012;158:323

ADAMTS-13 activity and ADAMTS-13 inhibitor in different thrombotic microangiopathies

Type of TMA	ADAMTS-13 level during acute episode	
	Activity	Anti-ADAMTS-13 antibodies
Congenital TTP	< 5 %	Absent
Acquired TTP	< 10 %	Very high
Shiga-HUS	>20 %	Absent
aHUS	>20 %	Absent
HELLP syndrome and preeclampsia	>20 %	Absent
Transplant and malignancy-associated TMAs	>20 %	Absent
DIC	>20 %	Absent
Catastrophic antiphospholipid syndrome	>20 %	Absent

adapted from Sarig G, 2014

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The PLASMIC Scoring System to predict the likelihood of ADAMTS-13 less than 10%

Criteria	Point
1. Platelet count <30x10^9/L	1
2. MCV <90fL	1
3. Creatinine <2.0 mg/dL	1
4. INR <1.5	1
5. Evidence of hemolysis based on any of the following : Reticulocyte count > 2.5% Indirect bilirubin > 2.0 mg/dL Undetectable haptoglobin	1
6. No active cancer	1
7. No history of bone marrow or solid organ transplantation	1
Total score	
Low likelihood	1-4
Intermediate	5-6
high	7

Bendapudi PK et al., Blood 2014,124:21

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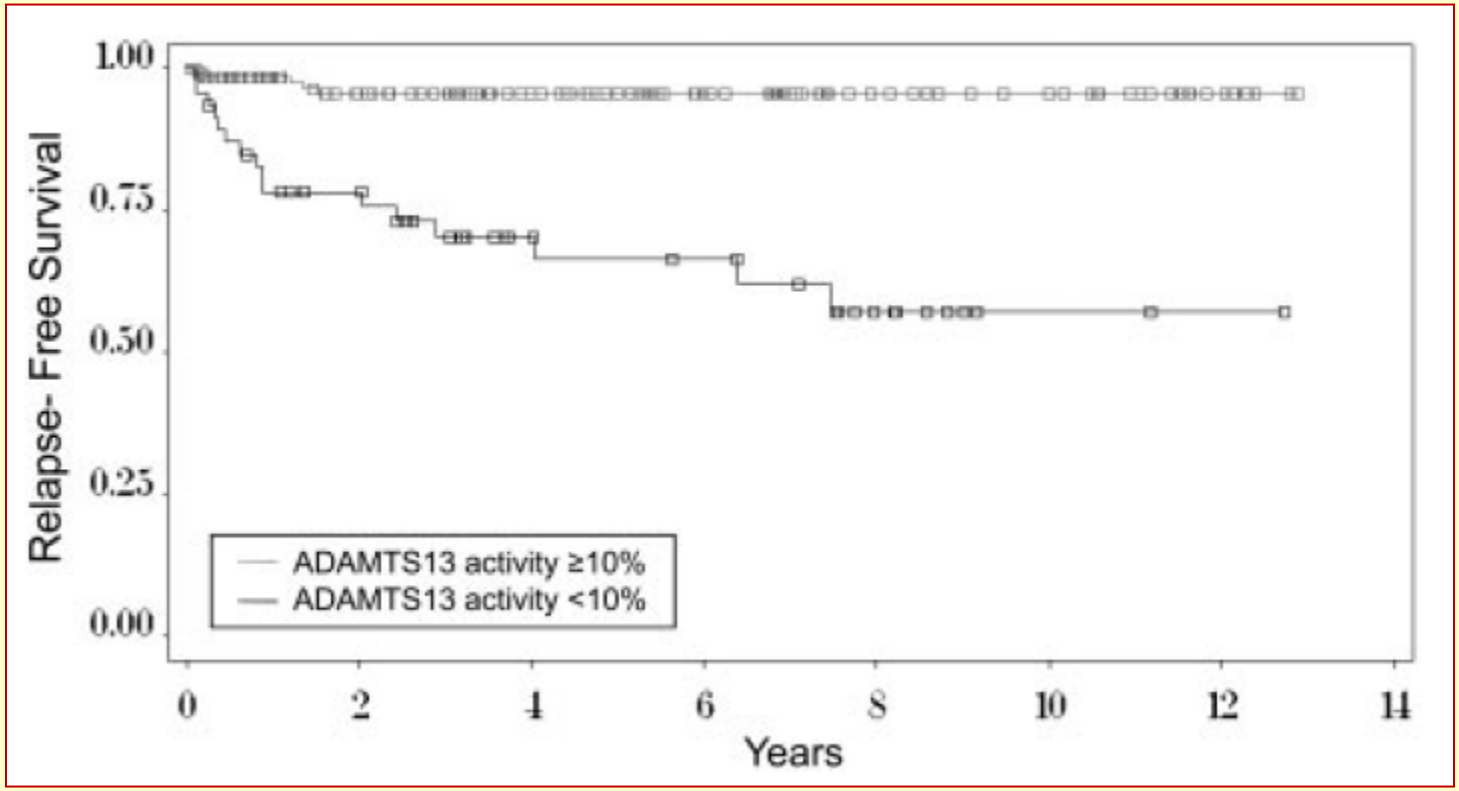
ADAMTS-13 activity at remission predicts recurrence risk



Kremer-Howinga JA et al., Blood 2010;115:1500

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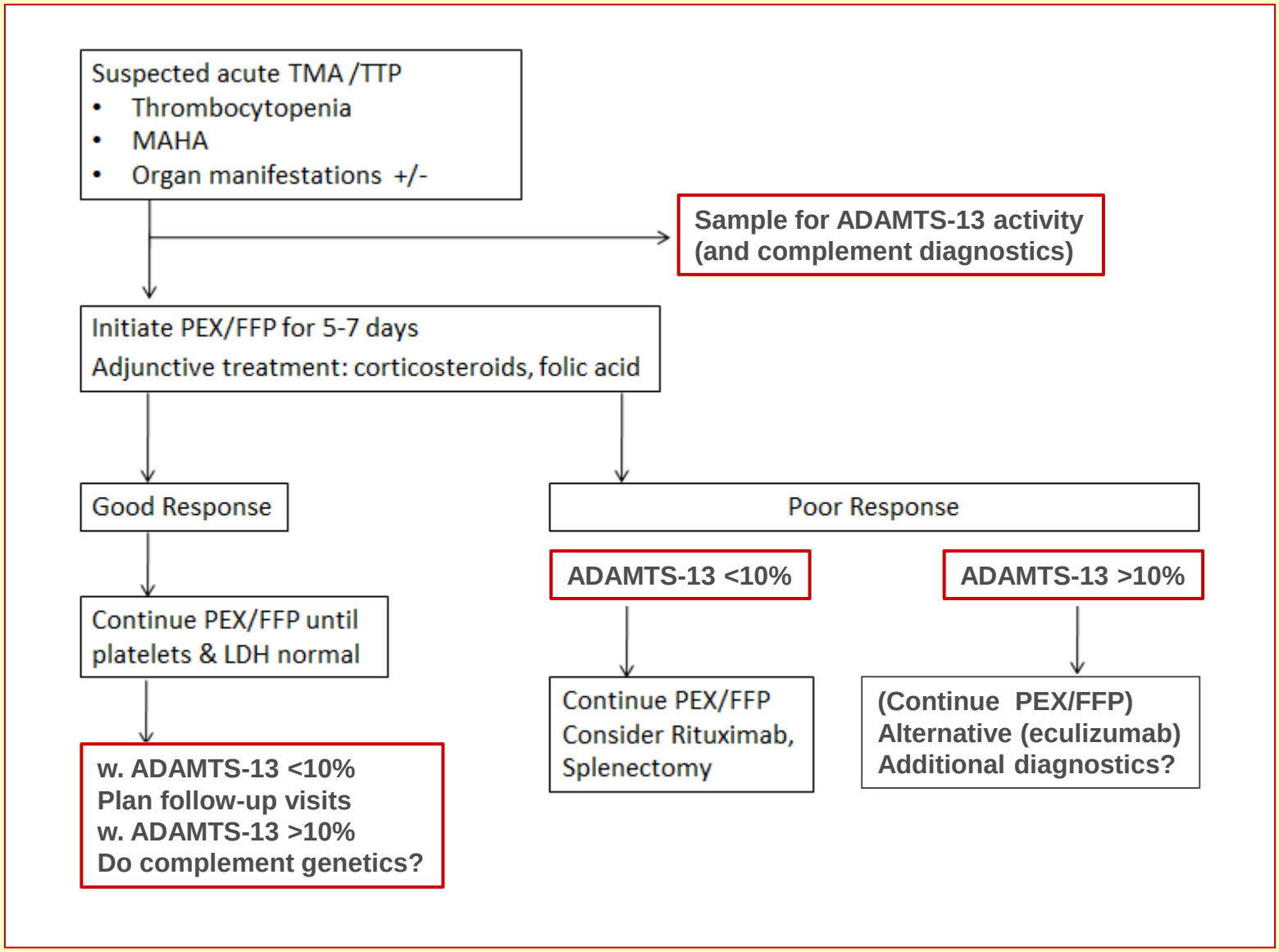
TMA treatment algorithm



Kremer-Hovinga JA, «Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome» in *Gresele P et al. eds, Platelets in Thrombotic and non Thrombotic Disorders – an update*, Springer, 2016

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Conclusions

- Thrombotic microangiopathies represent a diagnostic and therapeutic challenge
- A prompt diagnosis and appropriate treatment are of paramount importance to reduce mortality and/or permanent organ failure
- Clinical features are quite polymorphous and not sufficient for diagnosis
- An appropriate use of laboratory tests may greatly help in TMA differential diagnosis
- A striking reduction of ADAMTS-13 activity and/or the presence of ADAMTS-13 inhibitors proves the diagnosis of TTP and identifies patients at risk of relapse

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ADAMTS-13 measurements

Several different types of assays are available for the measurement of ADAMTS-13.

1) ANTIGEN: ELISA to monitor plasma antigen levels

2) ACTIVITY: Functional assays based on the ability of the patient plasma to degrade VWF multimers (first generation assays) or synthetic VWF peptides

3) anti-ADAMTS-13 antibodies: classical mixing studies or ELISA

Pre-analytical Variables of ADAMTS-13 Measurement Assays

Blood samples should be drawn prior to treatment initiation

Samples should be collected into buffered sodium citrate anticoagulant tubes and should be centrifuged within 2 hours after collection.

If plasma is not tested within 4 hours of collection, it should be separated into a secondary aliquot tube for storage at below –30°C for up to 3 months or below –70°C for a longer period of time.

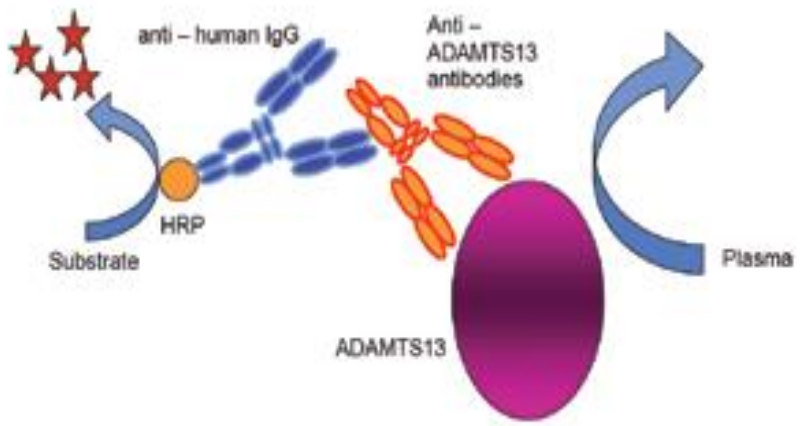
Chromogenic Autoantibody ELISA

Two types of anti-ADAMTS-13 antibodies have been described: one inhibiting (neutralizing) ADAMTS-13 proteolytic activity and the other (less frequent) binding to the protease and accelerating its clearance from plasma.

Neutralizing ADAMTS-13 autoantibodies (inhibitor) can be titrated *in vitro* using classic mixing studies of heat-inactivated patient and normal plasmas at a 1:1 dilution or several dilutions. However Bethesda assays are complex, far from being optimized and generally lack sensitivity.

New assays use recombinant ADAMTS-13 for the measurement of anti-ADAMTS-13 antibodies (neutralizing and non-neutralizing) in a simplified ELISA.

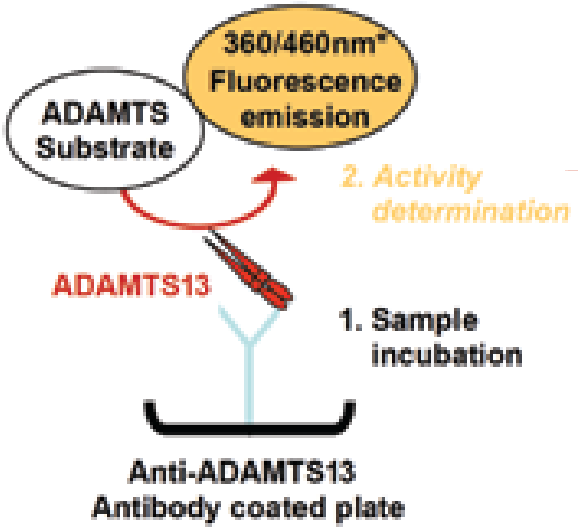
The time for results with this method using the Technozyme ADAMTS-13 INH kit, (Technoclone, Vienna, Austria) is **2 hours 15 minutes.**

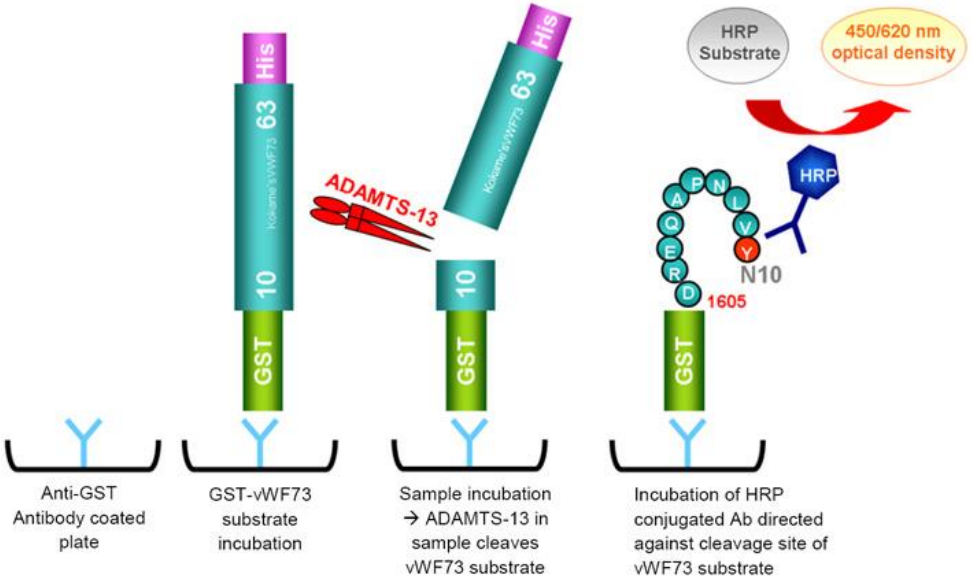


Chromogenic and Fluorogenic Activity Assays

Current commercially available tests utilize peptide substrates based on the ADAMTS-13 cleavage site of VWF.

Patient plasma is incubated with the peptide substrate and the residual cleavage product is measured by **fluorescence resonance energy transfer** (FRET) technique or **immunoassay**.





Chromogenic Activity ELISA

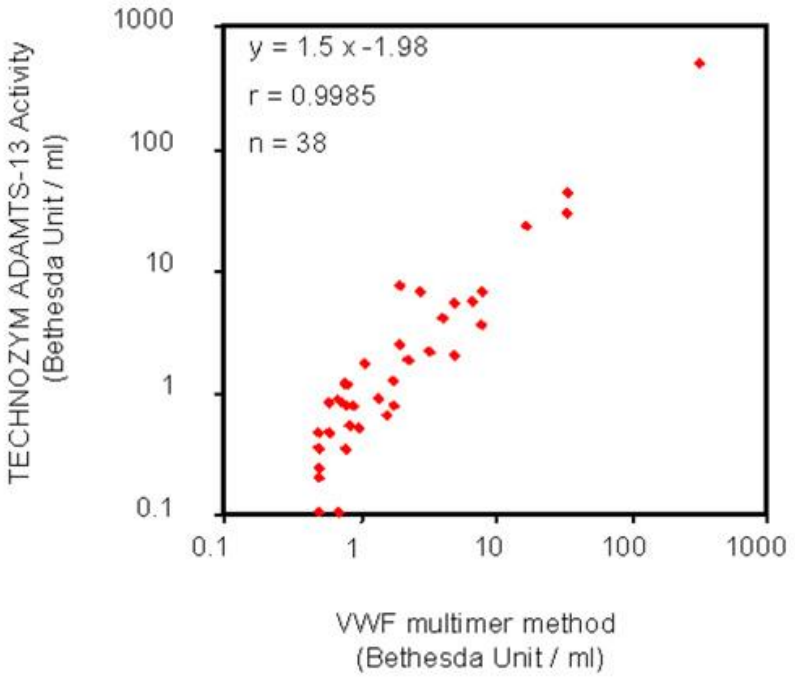
+ Sensitivity down to 0.5%

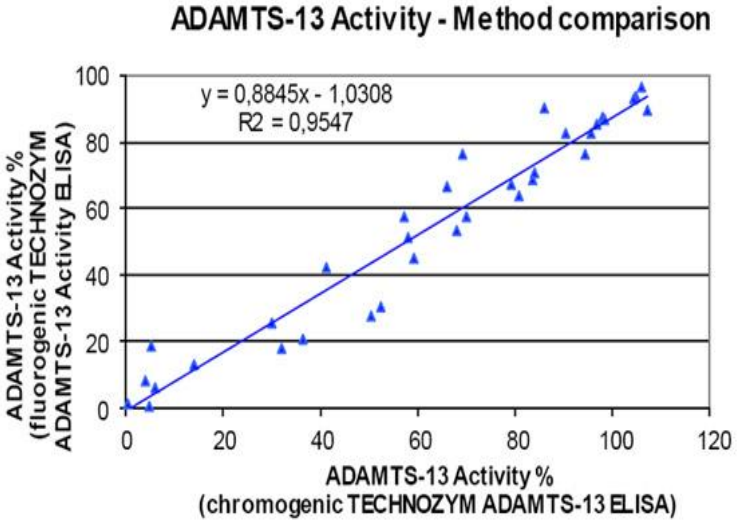
+ Short assay time (3h), results in 3.5h

+ No interferences from bilirubin, hemoglobin or elastase

+ High precision with less than 10%CV (inter and intra-assay)

+ It shows a 13% coefficient of variation (CV) inter-laboratory vs a 34% CV of the FRET method *(2014-2 survey report. ECAT Foundation. July 30, 2014. http://www.ecat.nl/)*





ADAMTS-13 measurements

Istituto di Medicina Interna e Cardiovascolare - Università degli Studi di Perugia
Direttore: Prof. G. Agnelli

CENTRO PER LO STUDIO DELLA EMOSTASI E DELLA TROMBOSI
Responsabile: Prof. P. Gresele

Data esame: _____

Paziente: _____

Data di nascita: _____

Provenienza: _____

ADAMTS-13

		VN
Attività (%)		40-130%

Il Responsabile

Prof. Paolo Gresele

Istituto di Medicina Interna e Cardiovascolare - Università degli Studi di Perugia
Direttore: Prof. G. Agnelli

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Data esame: _____

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ADAMTS-13

		VN
Inibitori (unità/ml)		<12U/ml negativo
		12-15 U/ml soglia
		>15 U/ml positivo

Commento:

Il Responsabile

Prof. Paolo Gresele

Accettazione prelievi: **dal lunedì al venerdi, 8:00-14:00**
Referenti in laboratorio: **Dr.ssa Mezzasoma Anna Maria, Dr.ssa Emanuela Falcinelli**
Recapito telefonico: **075783399**

Frequency odf severe ADAMTS-13 deficiency (<10%) in TTP versus microangiopathy due to other causes in published studies

Study reference	Patients (*n*)	TTP, %	Non-TTP, %	Patient source
Tsai and Lian (1998)	91	100	0	Single Centre
Furlan *et al* (1998)	53	100*	0	Referral
Veyradier *et al* (2001)	111	89	13	Referral
Remuzzi *et al* (2002)	49	100†	56	Referral
Mori *et al* (2002)	27	72	0	Single Centre
Vesely *et al* (2003)	142	41	5	Referral
Zheng *et al* (2004)	37	80	0	Single Centre
Peyvandi *et al* (2004)	100	48	NA	Referral
Kremer-Hovinga *et al* (2004)	396	68	2	Referral
Scully *et al* (2008)	176	74	NA	Referral
Shah *et al* (2008)	60	100	0	Single Centre Prospective

«…referred centers…may have incorrect assignment to disease entities
…variability in early ADAMTS-13 assays…
…severe ADAMTS-13 deficiency could be included as a diagnostic criteria for TTP in addition to clinical criteria…

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Shan N et al., Br J Hematol 2013;163:514

Long-term outcomes following recovery from TTP associated with ADAMTS-13 activity <10%

Outcome	Comments
Cognitive abnormalities	Problems with memory, concentration, and fatigue are common and persistent but rarely impair normal activities and careers.
Relapse	Estimated risk at 7.5 years—41%. Most relapses occur in the first year after recovery. ADAMTS13 deficiency during remission may not predict risk for relapse. Although pregnancy is recognized as a risk factor for acute episodes of TTP, most subsequent pregnancies are not associated with relapse.
Other autoimmune disorders	Serologic abnormalities characteristic of SLE are common; risk for development of overt SLE or other autoimmune disorders may be increased.

George JN. The Thrombotic Thrombocytopenic Purpura and Hemolytic uremic Syndrome. In: Hemostasis and Thrombosis: Basic Principles and Clinical Practice, Sixth Edition, Marder JV et al, Eds. Pg. 1196

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Nomenclature of the TTP and HUS syndrome

Name	Definition
Pathologic Descriptive Term	
TMA	The characteristic histologic abnormality of both TTP and HUS. Describes the microvascular features (swelling of endothelial cells and the subendothelial space) associated with thrombosis. TMA may also occur in many other disorders, such as malignant hypertension, antiphospholipid antibody syndrome, systemic lupus erythematosus, and preeclampsia.
Acquired Clinical Syndromes	
TTP	The appropriate term for all adults with microangiopathic hemolytic anemia and thrombocytopenia with or without renal failure or neurologic abnormalities and without an alternative etiology. Children without renal failure are also described as TTP. Includes but is not limited to patients with severe ADAMTS13 deficiency (<10%). In some adults with predominant acute renal failure, such as with quinine sensitivity or *E. coli* O157:H7 infection, the comprehensive term, TTP–HUS, is often used.
Typical HUS	Children with a syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure with a diarrhea prodrome caused by enteric infection with *E. coli* O157:H7 or other Shiga toxin–producing bacteria.
aHUS	A syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure without a diarrhea prodrome. May be caused by pneumococcal infections or acquired disorders of complement regulation.
Congenital Clinical Syndromes	
Upshaw-Shulman syndrome	Caused by congenital deficiency of ADAMTS13.
aHUS	Associated with congenital deficiencies of complement regulatory factors, resulting in unrestrained complement activation.

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Thrombotic thrombocytopenic purpura vs Hemolytic uremic syndrome

	Thrombotic thrombocytopenic purpura	Hemolytic-uremic syndrome
Ischemia, tissue injury	Multiorgan	Renal
Presentation in children	Few cases (early onset of congenital TTP)	Most cases; usually accompanied by bloody diarrhea (except in atypical hemolytic-uremic syndrome)
ADAMTS13 activity	Markedly reduced	Normal or mildly reduced in almost all cases
Recurrence	Common	Rare
Therapeutic plasma exchange	Good response	Poor response when associated with *Escherichia coli* infection May help in atypical hemolytic-uremic syndrome
Sequelae	Approximately 80% of patients showing complete response without sequelae	Permanent renal damage in 30% (rate higher in atypical hemolytic-uremic syndrome)

Rogers HJ et al., Cleve Clin J 2016;83:597

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ADAMTS-13 related parameters in TMAs

	Congenital TTP	Acquired TTP	Other TMAs
Antigen	Very low or absent	Low or variable	Normal or moderately decreased
Activity	≤5%	≤5% or variable	30–100%
Inhibitor	No	Mostly yes	No

Shenkman B et al., Autoimmun Rev 2014;13:584

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Complete pentad of clinical features	3 (4%)

George JN et al., Hematology 2012: 604

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Laboratory parameters in a cohort of TMA patients with or w/o ADAMTS-13 deficiency

	Deficiency group ($n=160$)	Detectable group ($n=54$)	*P* Value
Hemoglobin level, g/dL	8.1 (2.2)	8.7 (2.1)	.06
Reticulocyte count, x10^9/L	**185(118)**	**106(80.1)**	**<.0001**
LDH level, U/L	6.0 (4.6)	5.8 (3.5)	.70
Platelet count, x10^9/L	**17.4(14.2)**	**66.6(49.3)**	**<.0001**
Creatinine level, µmol/L mg/dl	**114(68.4) 1.29(0.77)**	**4546(326) 5.13(3.68)**	**<.0001**
Estimated GFR, ml/min	**80.6(33.3)**	**35.0(59.2)**	**<.0001**
ANA	**85(53%)**	**13(24%)**	**<.001**
Anti-dsDNA antibodies	9 (7%)[3]	0 (0%)[4]	.21
Anticardiolipin antibodies	14 (11%)[3]	9 (20%)[5]	.11

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Coppo P et al., PLOs ONE 2010;5:e10208

Cox regression analysis of hazard of recurrence in relation to biomarkers levels at previous remission observation

	No. patients	No. patients with recurrences	Hazard Ratio	95% CI	*P*-value*
ADAMTS13 activity (%)					
≥ 10	71	18	1.00	(ref)	0.001
< 10	19	9	4.89	2.00–11.99	
ADAMTS13 antigen (%)					
≥ 10	77	19	1.00	(ref)	0.001
< 10	5	3	5.66	2.10–15.24	
Inhibitor (U mL^{-1})					
Absent	43	9	1.00	(ref)	< 0.001
Present	13	9	4.30	2.00–9.21	

Bettoni G et al., JTH 2012;10:1556

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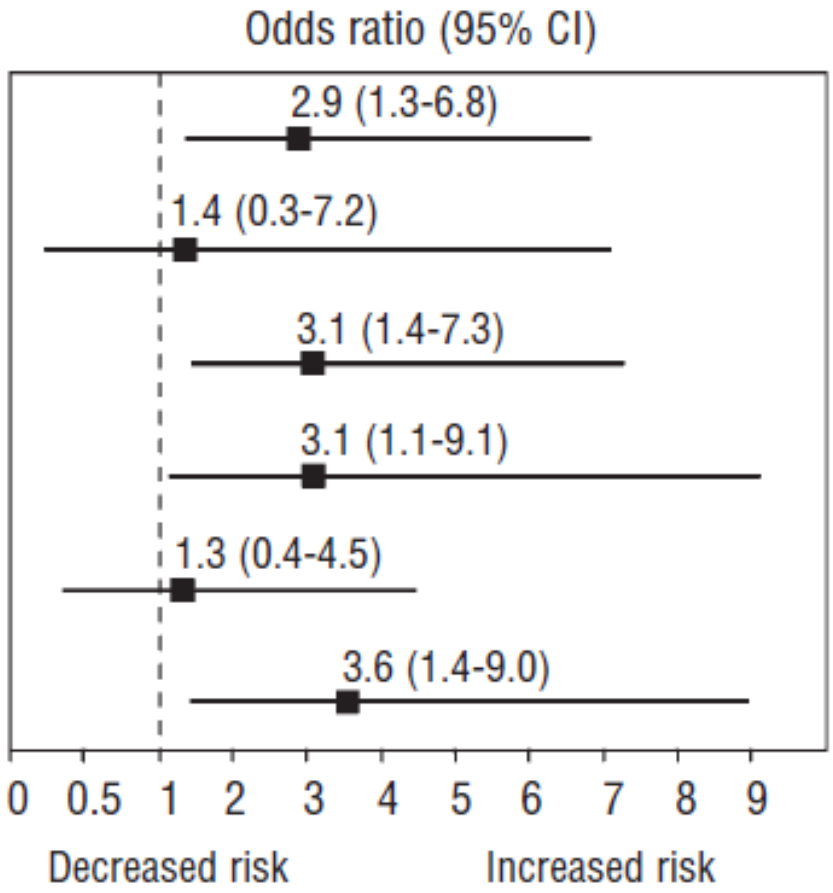
Markers of TTP recurrence

Risk factor	TTP Recurrence NO (n=63)	Yes (n=46)
ADAMTS13 activity < 10%	14/63 (22%)	21/46 (46%)
ADAMTS13 antigen < 10%	3/44 (7%)	3/33 (9%)
Any anti-ADAMTS13 antibody	20/55 (36%)	27/42 (64%)
Anti-ADAMTS13 inhibitor	10/28 (36%)	19/30 (63%)
ULVWF multimers	6/44 (14%)	6/35 (17%)
ADAMTS13 activity < 10% and any anti-ADAMT13 antibodies	13/48/ (27%)	20/35 (57%)



Peyvandi F et al., Hematologica 2008;93:232

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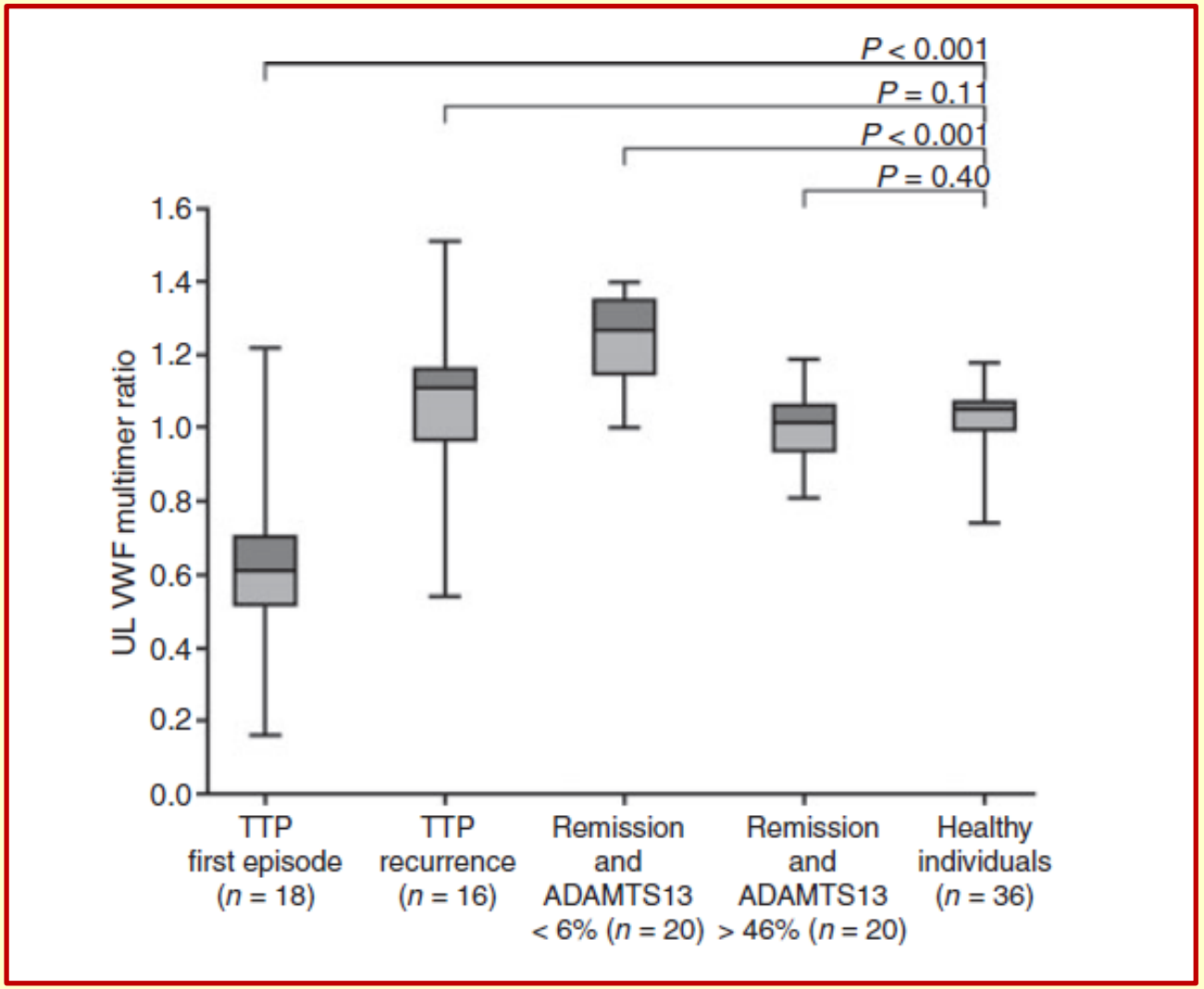
UL-VWF multimers ratio in TTP at various stages



Lotta LA et al., JTH 2011;9:1744

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Testing and expected resullts for patients with suspected diagnosis of TTP

For diagnosis	
Full blood count and blood film	Anaemia, thrombocytopenia, fragments on film
Reticulocyte count	Raised
Haptoglobin	Reduced
Clotting screen including fibrinogen	Normal
Urea and electrolytes	Renal impairment
Troponin T/Troponin I	For cardiac involvement
Liver function tests	Usually normal
Calcium	May reduce with PEX
Lactate dehydrogenase	Raised due to haemolysis
Urinalysis	For protein
Direct antiglobulin test	Negative
Blood group and antibody screen	To allow provision of blood products
Hepatitis A/B/C and human immunodeficiency virus testing	Pre-blood products and to exclude an underlying viral precipitant
Pregnancy test (in women of child-bearing age)	
ADAMTS 13 assay (activity/ antigen and inhibitor/antibody in specialized laboratory)	Do not wait for result before starting treatment in suspected TTP
Electrocardiogram/Echocardiogram	To document/monitor cardiac damage
CT/MRI brain	To determine neurological involvement*

Scully M et al., Br J Hematol 2012;158:323

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Testing and expected resullts for patients with suspected diagnosis of TTP

For possible underlying cause	
Thyroid function tests	To exclude Graves Disease
Auto-antibody screen (ANA/RF/ LA/ACLA), including lupus anticoagulant	Exclude associated autoimmune disease
Stool culture	For pathogenic *Escherichia coli* (if diarrhoea)
CT Chest/abdomen/pelvis (if indicated) ± tumour markers	To look for underlying malignancy

Scully M et al., Br J Hematol 2012;158:323

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International council for standardization in hematology recommendations for schistocyte counting

- Should be evaluated on peripheral blood smears; optical microscope; percentage after counting at least 1000 red blood cells
- Identified by specific positive morphological criteria; always smaller than intact red cells; shape of fragments with sharp angles and straight borders; small crescents; helmet cells; keratocytes or microspherocytes.
- Meaningful if schistocytes represent the main morphological red blood cells abnormality in the smear
- Indication for diagnosis: above 1%

Zini G et al., Int J Lab Hem 2011;34:107

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Thrombotic thrombocytopenic purpura vs Hemolytic uremic syndrome

	Thrombotic thrombocytopenic purpura	Hemolytic-uremic syndrome
Ischemia, tissue injury	Multiorgan	Renal
Presentation in children	Few cases (early onset of congenital TTP)	Most cases; usually accompanied by bloody diarrhea (except in atypical hemolytic-uremic syndrome)
Recurrence	Common	Rare
Therapeutic plasma exchange	Good response	Poor response when associated with *Escherichia coli* infection May help in atypical hemolytic-uremic syndrome
Sequelae	Approximately 80% of patients showing complete response without sequelae	Permanent renal damage in 30% (rate higher in atypical hemolytic-uremic syndrome)

Rogers HJ et al., Cleve Clin J 2016;83:597

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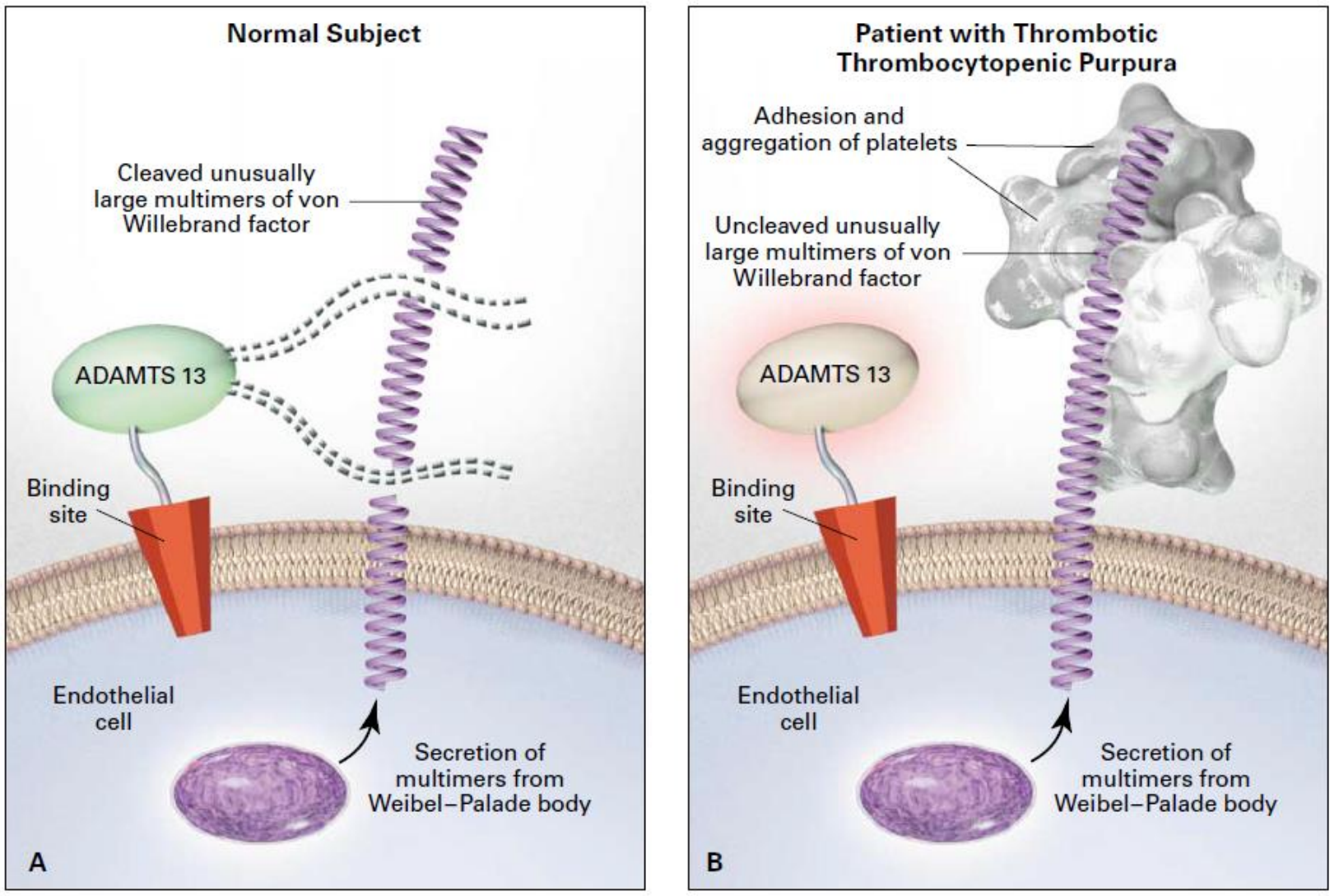
Role of ADAMTS-13 in TTP



Moake JL. NEJM 2002;347:587

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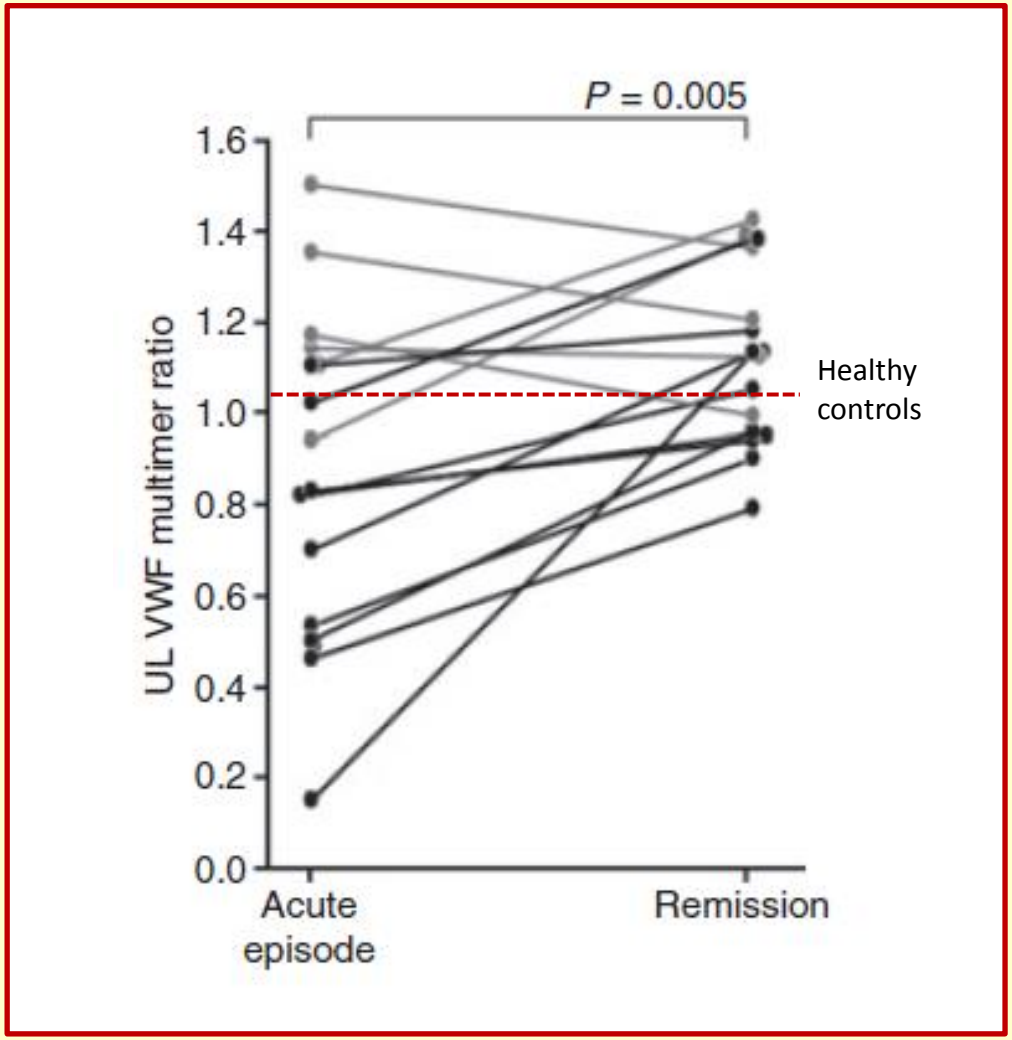
UL-VWF multimers ratio in TTP at various stages



Lotta LA et al., JTH 2011;9:1744

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ADAMTS-13 activity and ADAMTS-13 inhibitor in different thrombotic microangiopathies

Type of TMA	Pathophysiology	ADAMTS-13 level during acute episode	
		Activity	Anti-ADAMTS-13 antibodies
Congenital TTP	ADAMTS-13 deficiency	< 5 %	Absent
Acquired TTP	Antibodies against ADAMTS-13	< 10 %	Very high
Shiga-HUS	Shiga toxin causes secretion of UL-VWF and the formation of VWF-platele thrombi in the glomerular microvasculature which lead to acute renal failure	>20 %	Absent
aHUS	Dysregulation of the complement system, mostly due to complement factor H deficiency, leads to VWF-platelet thrombi in the glomerular microvasculature	>20 %	Absent
HELLP syndrome and preeclampsia	Abnormal and hypoxic placenta activates the complement and coagulation cascades which lead to thrombotic microangiopathy	>20 %	Absent
Transplant and malignancy-associated TMAs	Endothelial toxicity causes thrombotic microangiopathy	>20 %	Absent
DIC	Disseminated intravascular coagulation activation leads to thrombotic microangiopathy and multi-organ ischemic failure	>20 %	Absent
Catastrophic antiphospholipid syndrome	Antiphospholipid antibodies cause endothelial damage, thrombotic microangiopathy and multiorgan ischemic syndrome	>20 %	Absent

adapted from Sarig G, Rambam Main Med J 2014;5:e0026

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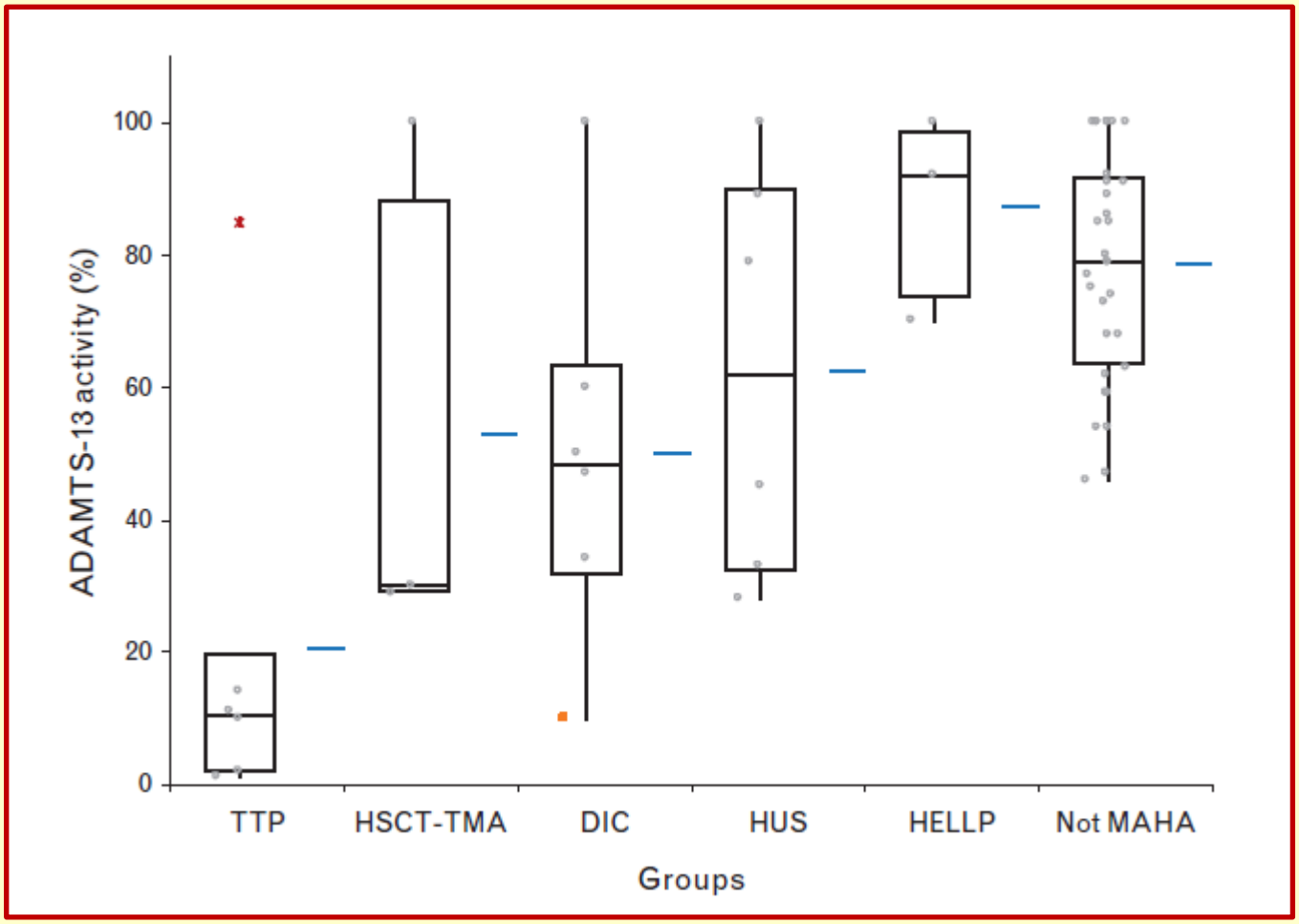
ADAMTS-13 activity in suspected thrombotic microangiopathies



Severely reduced ADAMTS-13 in one patients with fulminant hepatic failure

Garizio DG et al, Pathology 2012

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Association between some laboratory alterations and ADAMTS-13 deficiency in a TMA cohort

Multivariate analysis

Patient Characteristics	Adjusted Odds Ratio	95% CI	*P* Value
Creatinine level ≤200 µmol/L (2.26 mg/dL)	23.4	8.8–62.5	<.001
Platelet count ≤30×10^9/L	9.1	3.4–24.2	<.001
Positive ANA	2.8	1.0–8.0	<.05

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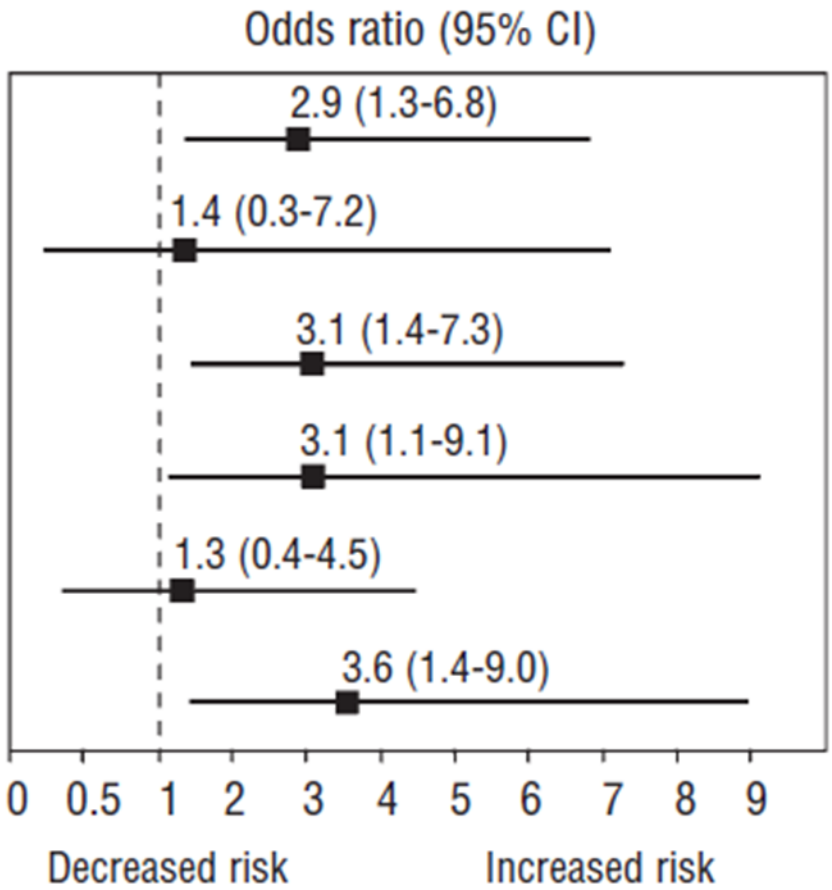
Coppo P et al., PLOs ONE 2010;5:e10208

Markers of TTP recurrence

Risk factor	TTP Recurrence NO (n=63)	Yes (n=46)
ADAMTS13 activity < 10%	14/63 (22%)	21/46 (46%)
ADAMTS13 antigen < 10%	3/44 (7%)	3/33 (9%)
Any anti-ADAMTS13 antibody	20/55 (36%)	27/42 (64%)
Anti-ADAMTS13 inhibitor	10/28 (36%)	19/30 (63%)
ULVWF multimers	6/44 (14%)	6/35 (17%)
ADAMTS13 activity < 10% and any anti-ADAMT13 antibodies	13/48/ (27%)	20/35 (57%)



Peyvandi F et al., Hematologica 2008;93:232

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