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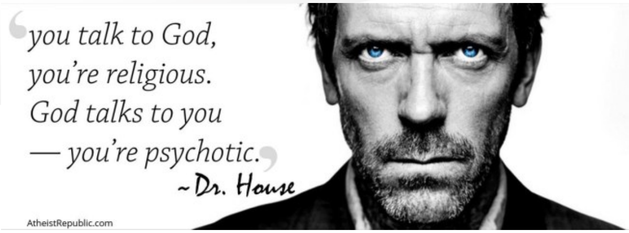

"you talk to God,
you're religious.
God talks to you
— you're psychotic."
~Dr. House

AtheistRepublic.com

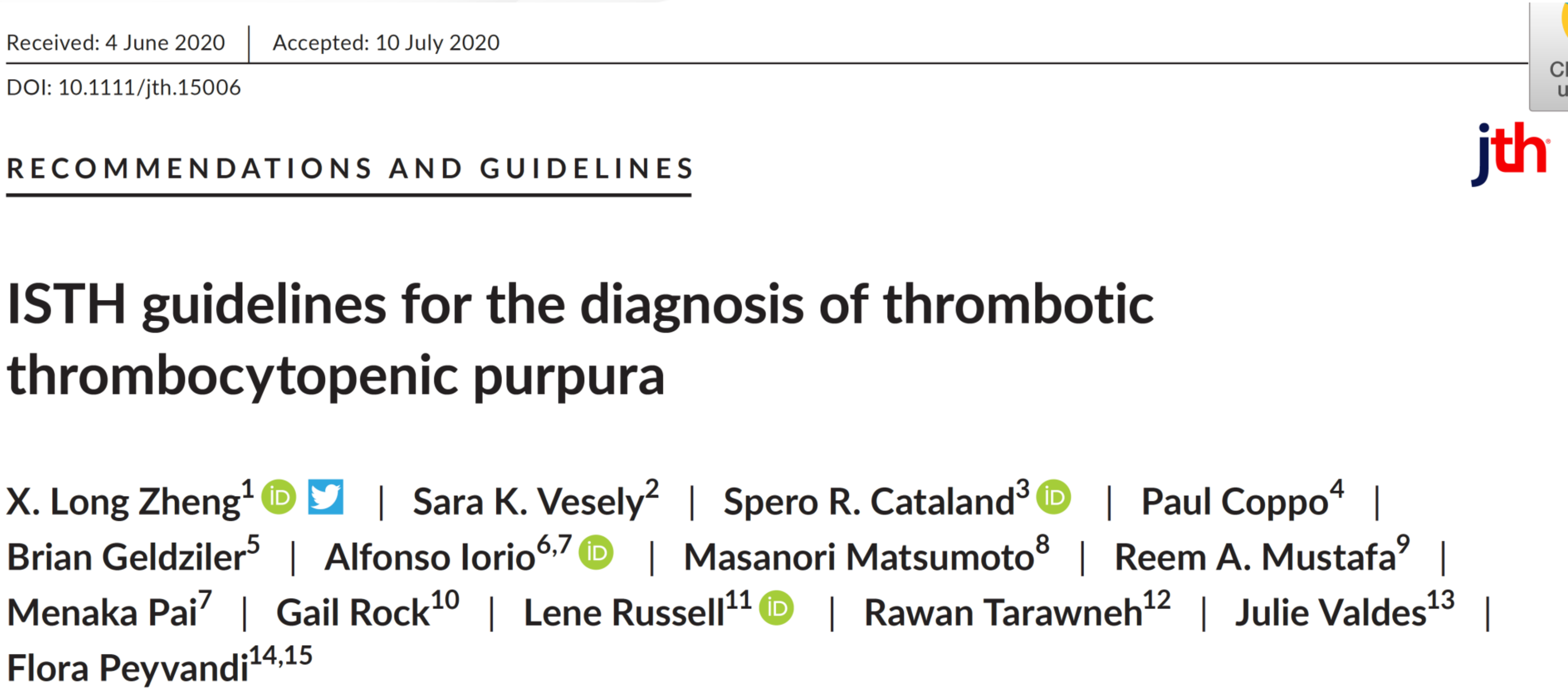
Diagnostik der TTP

Ralph Wendt
Abteilung Nephrologie
Klinik für Infektiologie/Tropenmedizin, Nephrologie und Rheumatologie

NOTAUFNAHME
NOTAUFNAHME
NOTAUFNAHME

06.11.2020

www.sanktgeorg.de



Received: 4 June 2020 | Accepted: 10 July 2020

DOI: 10.1111/jth.15006

RECOMMENDATIONS AND GUIDELINES

jth

ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura

X. Long Zheng[1] | Sara K. Vesely[2] | Spero R. Cataland[3] | Paul Coppo[4] | Brian Geldziler[5] | Alfonso Iorio[6,7] | Masanori Matsumoto[8] | Reem A. Mustafa[9] | Menaka Pai[7] | Gail Rock[10] | Lene Russell[11] | Rawan Tarawneh[12] | Julie Valdes[13] | Flora Peyvandi[14,15]

Long Zheng et al., J Thromb Haemost. 2020;18:2486–2495

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I SEE YOU WERE WITH A BIG PHARMACEUTICAL COMPANY-- OH! THE COST OF GETTING INTO HEAVEN SUDDENLY JUMPED UP BY 450 %-- NOTHING PERSONAL! IT'S JUST BUSINESS--
9-26

COI

lecture fees / advisory board honaria / traval grants:

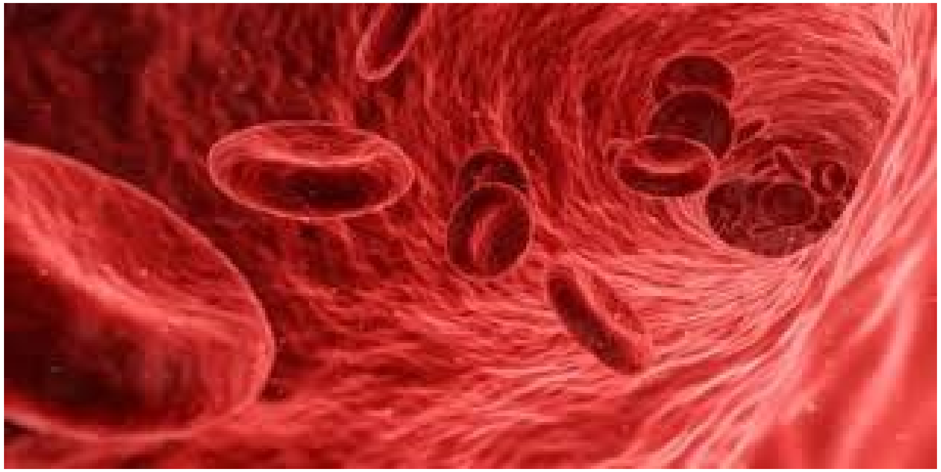
Fresenius Medical Care, Vifor Fresenius Pharma, Amgen, Shire, Novartis, Alexion, Otsuka, Cellpharm, **Ablynx,** Daiichi Sankyo, **Sanofi**, AstraZeneca

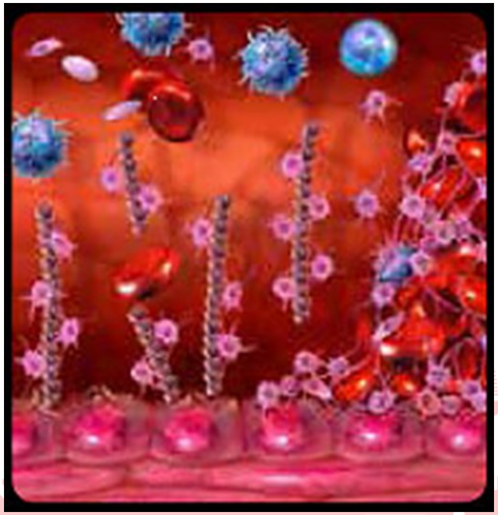
Agenda

YOU MEAN TO TELL ME
WHAT WE ARE DOING TODAY IS WRITTEN ON THE BOARD?
SpanishPlans.org/memes

1) Thrombotische Mikroangiopathie – What‘s that?
2) Diagnose der TTP
3) Was sagen die ISTH Leitlinien?
4) Zusammenfassung

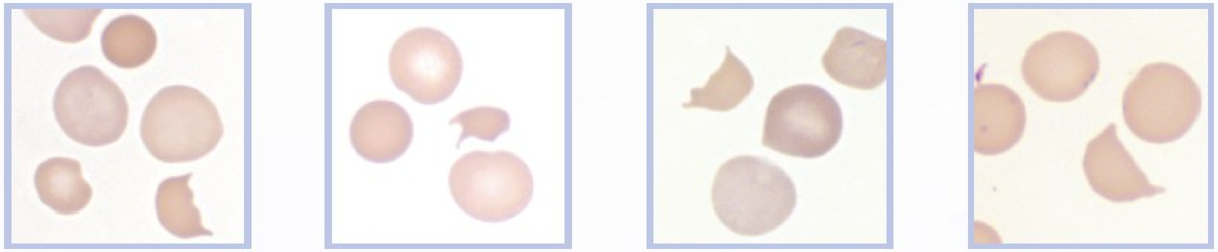
Thrombotische Mikroangiopathie



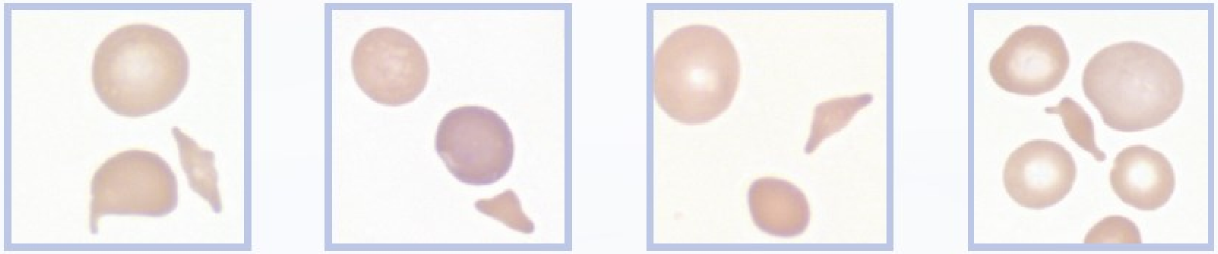


Fragmentozyten

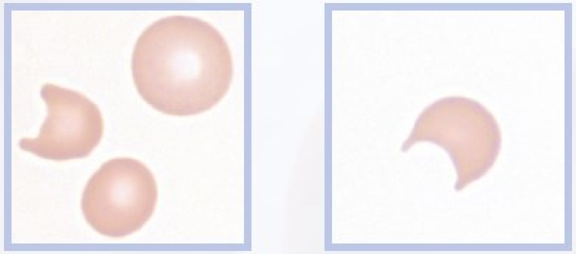
Fragmentozyten als klassische Helmform bei TTP



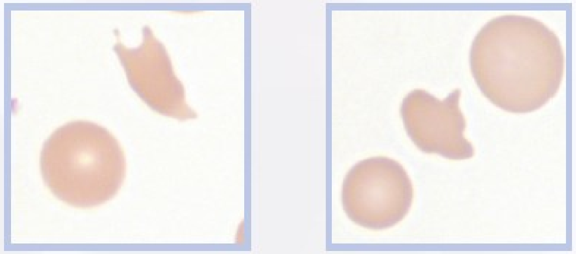
Fragmentierte Erythrozyten (Schistozyten) bei TTP



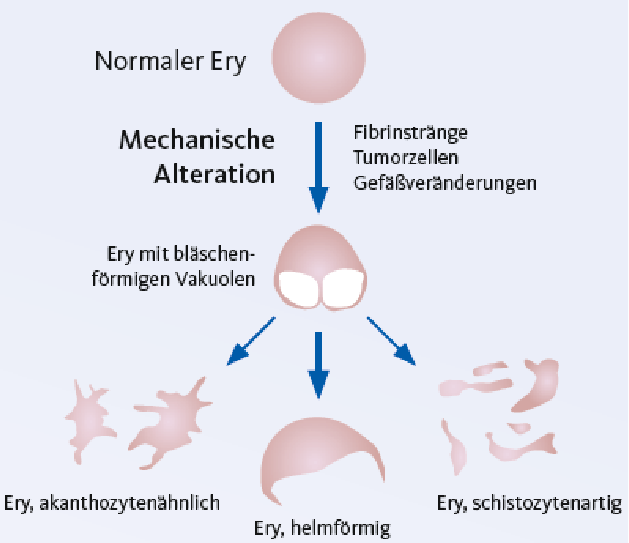
Fragmentozyten bei HUS



Akanthozyten-ähnliche Formen bei HUS



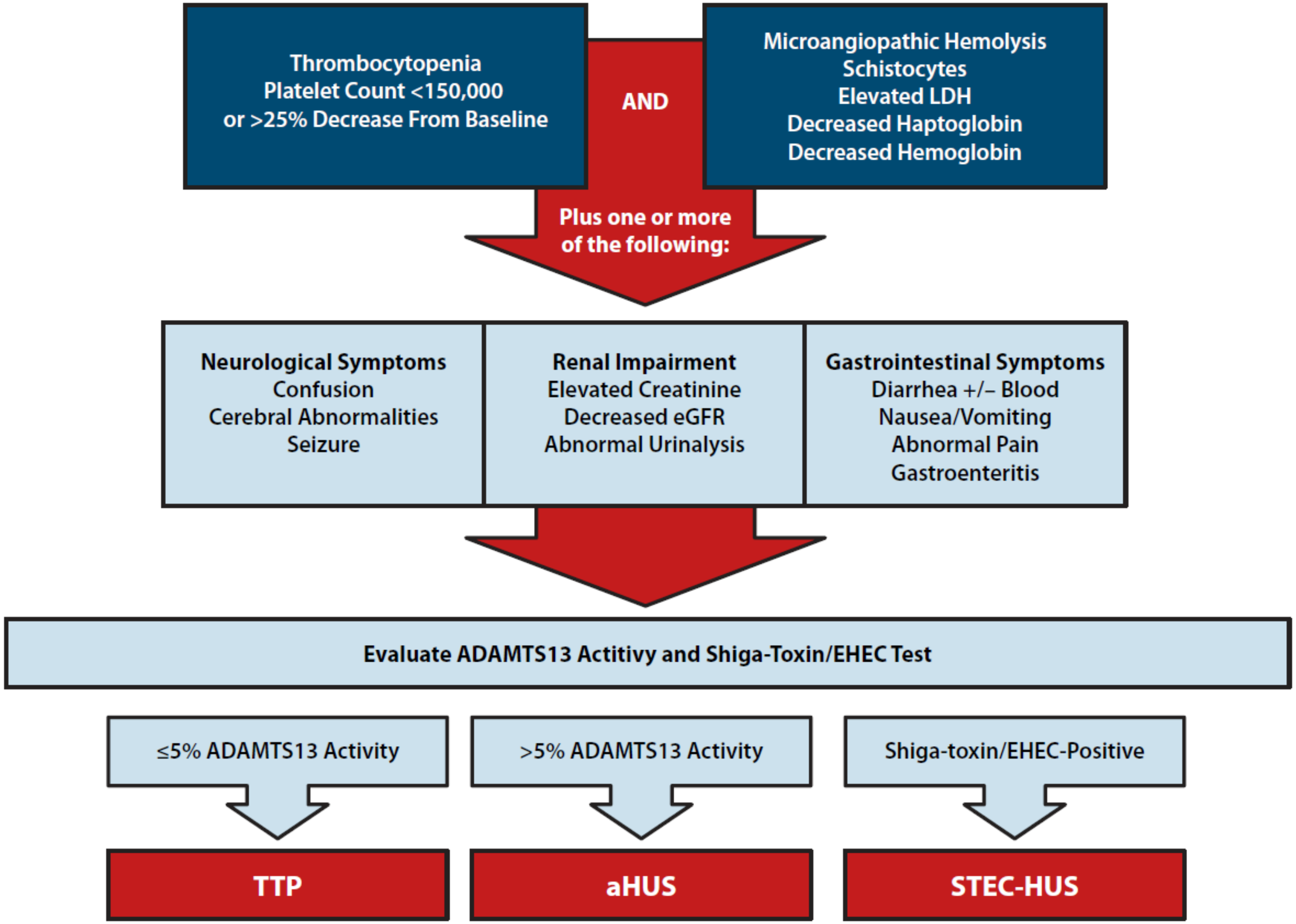
Erythrozytenfragmentation


Normaler Ery
Mechanische Alteration
Fibrinstränge
Tumorzellen
Gefäßveränderungen
Ery mit bläschenförmigen Vakuolen
Ery, akanthozytenähnlich
Ery, helmförmig
Ery, schistozytenartig

https://www.sysmex.de/fileadmin/media/f101/Xtra/Themenblaetter/Xtra_01_2017_Card_Fragmentozyten.pdf

Differentialdiagnose der TMA

Differential Diagnosis for Thrombotic Microangiopathies (TMAs)



Thrombocytopenia
Platelet Count <150,000
or >25% Decrease From Baseline

AND

Microangiopathic Hemolysis
Schistocytes
Elevated LDH
Decreased Haptoglobin
Decreased Hemoglobin

Plus one or more
of the following:

Neurological Symptoms
Confusion
Cerebral Abnormalities
Seizure

Renal Impairment
Elevated Creatinine
Decreased eGFR
Abnormal Urinalysis

Gastrointestinal Symptoms
Diarrhea +/– Blood
Nausea/Vomiting
Abnormal Pain
Gastroenteritis

Evaluate ADAMTS13 Actitivy and Shiga-Toxin/EHEC Test

≤5% ADAMTS13 Activity → **TTP**

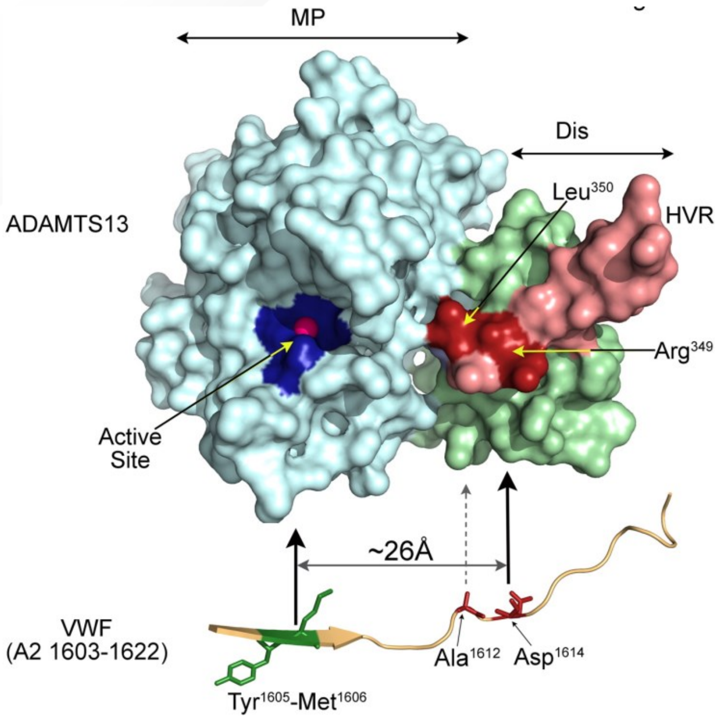
>5% ADAMTS13 Activity → **aHUS**

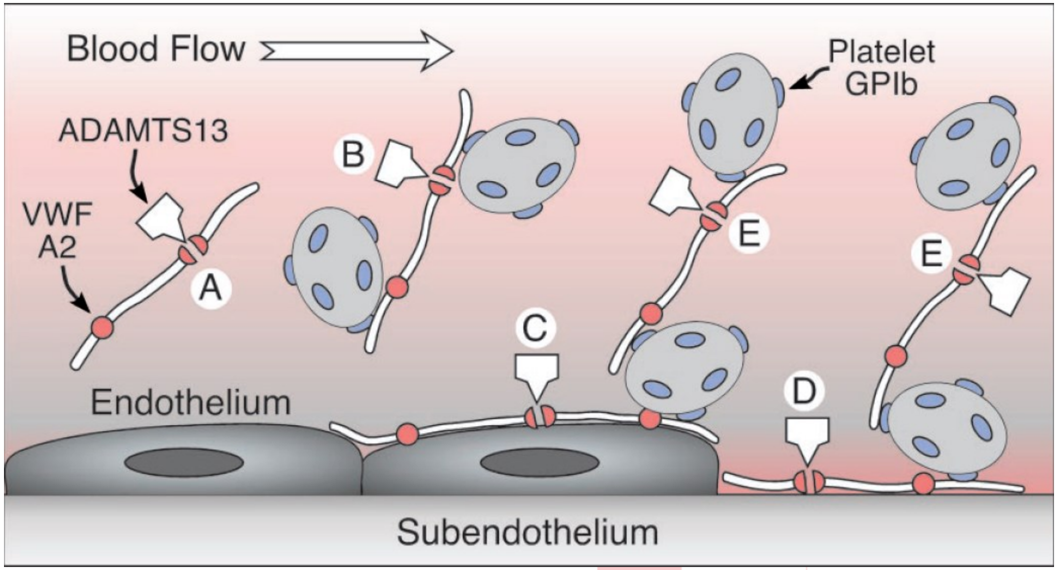
Shiga-toxin/EHEC-Positive → **STEC-HUS**

J. Laurence: Clinical Advances in Hematology & Oncology Vol 10, Issue 10, Suppl 17 Oct 2012

ADAMTS13

A Disintegrin **A**nd **M**etalloprotease with a **T**hrombo**S**pondin type 1 motif, member **13**


MP
Dis
Leu^{350}
HVR
ADAMTS13
Arg^{349}
Active Site
~26Å
VWF (A2 1603-1622)
Ala^{1612}
Asp^{1614}
Tyr^{1605}-Met^{1606}


Blood Flow
Platelet GPIb
ADAMTS13
VWF A2
A
B
C
D
E
E
Endothelium
Subendothelium

Sadler. PNAS Sept 3, 2002, vol. 99, no. 18

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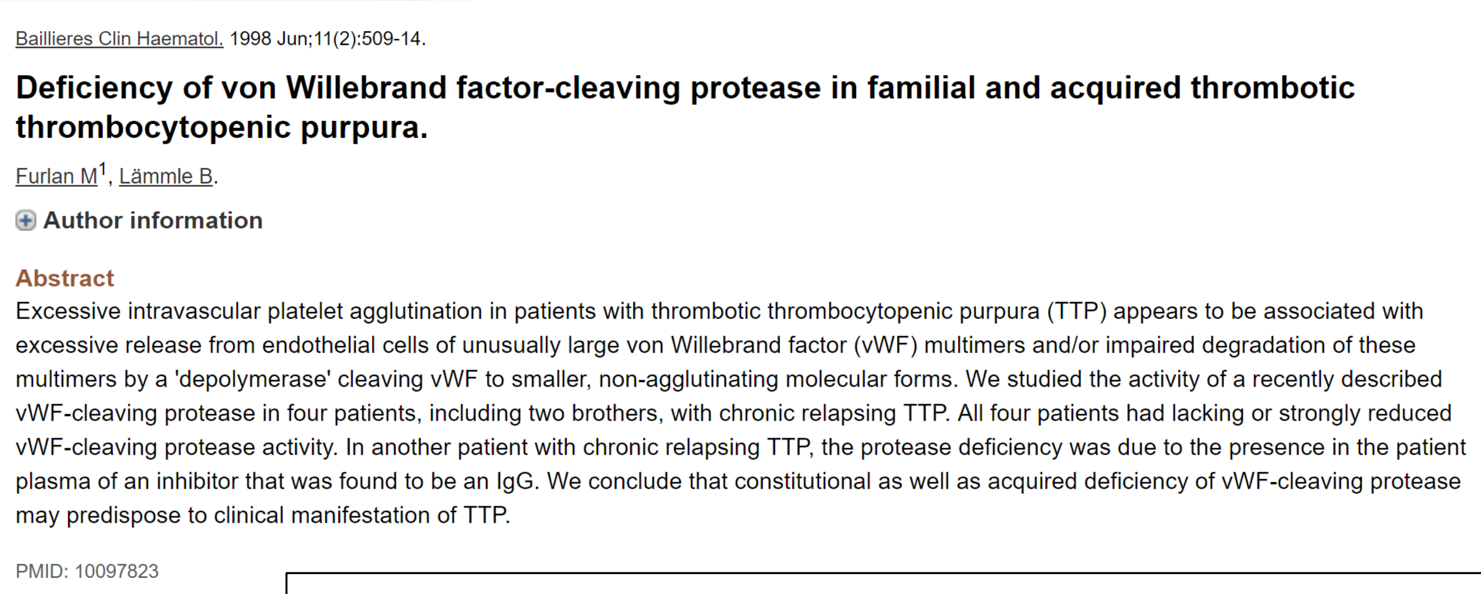
INSELSPITAL

UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL

Klinikum St.GEORG

Die Entdeckung der ADAMTS13: 1998 in Bern



Baillieres Clin Haematol. 1998 Jun;11(2):509-14.

Deficiency of von Willebrand factor-cleaving protease in familial and acquired thrombotic thrombocytopenic purpura.

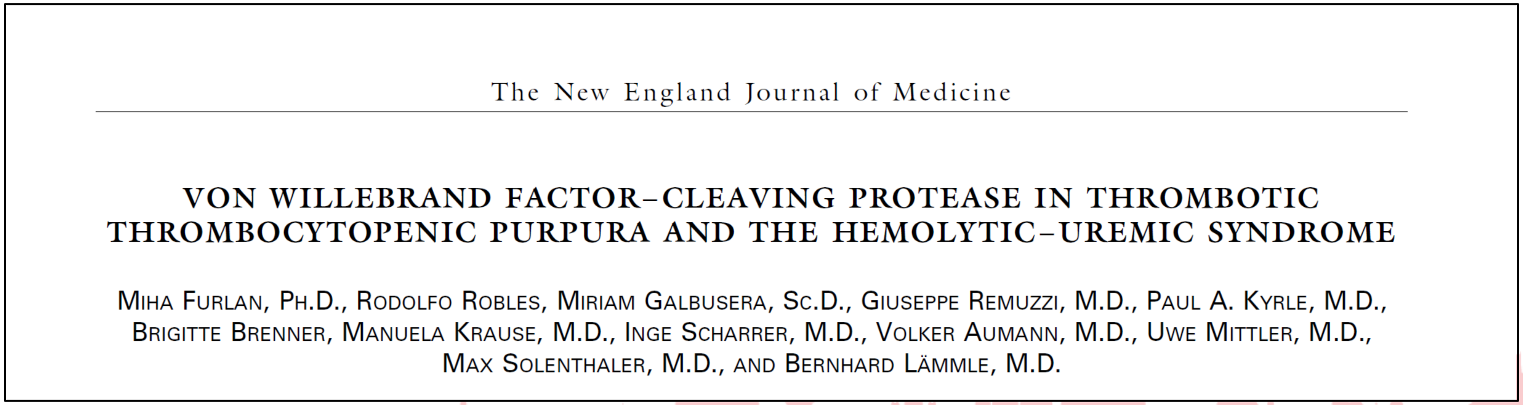
Furlan M[1], Lämmle B.

⊕ **Author information**

Abstract

Excessive intravascular platelet agglutination in patients with thrombotic thrombocytopenic purpura (TTP) appears to be associated with excessive release from endothelial cells of unusually large von Willebrand factor (vWF) multimers and/or impaired degradation of these multimers by a 'depolymerase' cleaving vWF to smaller, non-agglutinating molecular forms. We studied the activity of a recently described vWF-cleaving protease in four patients, including two brothers, with chronic relapsing TTP. All four patients had lacking or strongly reduced vWF-cleaving protease activity. In another patient with chronic relapsing TTP, the protease deficiency was due to the presence in the patient plasma of an inhibitor that was found to be an IgG. We conclude that constitutional as well as acquired deficiency of vWF-cleaving protease may predispose to clinical manifestation of TTP.

PMID: 10097823



The New England Journal of Medicine

VON WILLEBRAND FACTOR–CLEAVING PROTEASE IN THROMBOTIC THROMBOCYTOPENIC PURPURA AND THE HEMOLYTIC–UREMIC SYNDROME

Miha Furlan, Ph.D., Rodolfo Robles, Miriam Galbusera, Sc.D., Giuseppe Remuzzi, M.D., Paul A. Kyrle, M.D., Brigitte Brenner, Manuela Krause, M.D., Inge Scharrer, M.D., Volker Aumann, M.D., Uwe Mittler, M.D., Max Solenthaler, M.D., and Bernhard Lämmle, M.D.

N Engl J Med 1998;339:1578-84

Prof. Dr. Bernhard Lämmle

Emeritus Professor und Direktor Universitätsklinik für Hämatologie, Bern
Senior Professor am CTH der Universitätsmedizin Mainz

CTH
Centrum für Thrombose und Hämostase
Mainz

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BERN UNIVERSITY HOSPITAL

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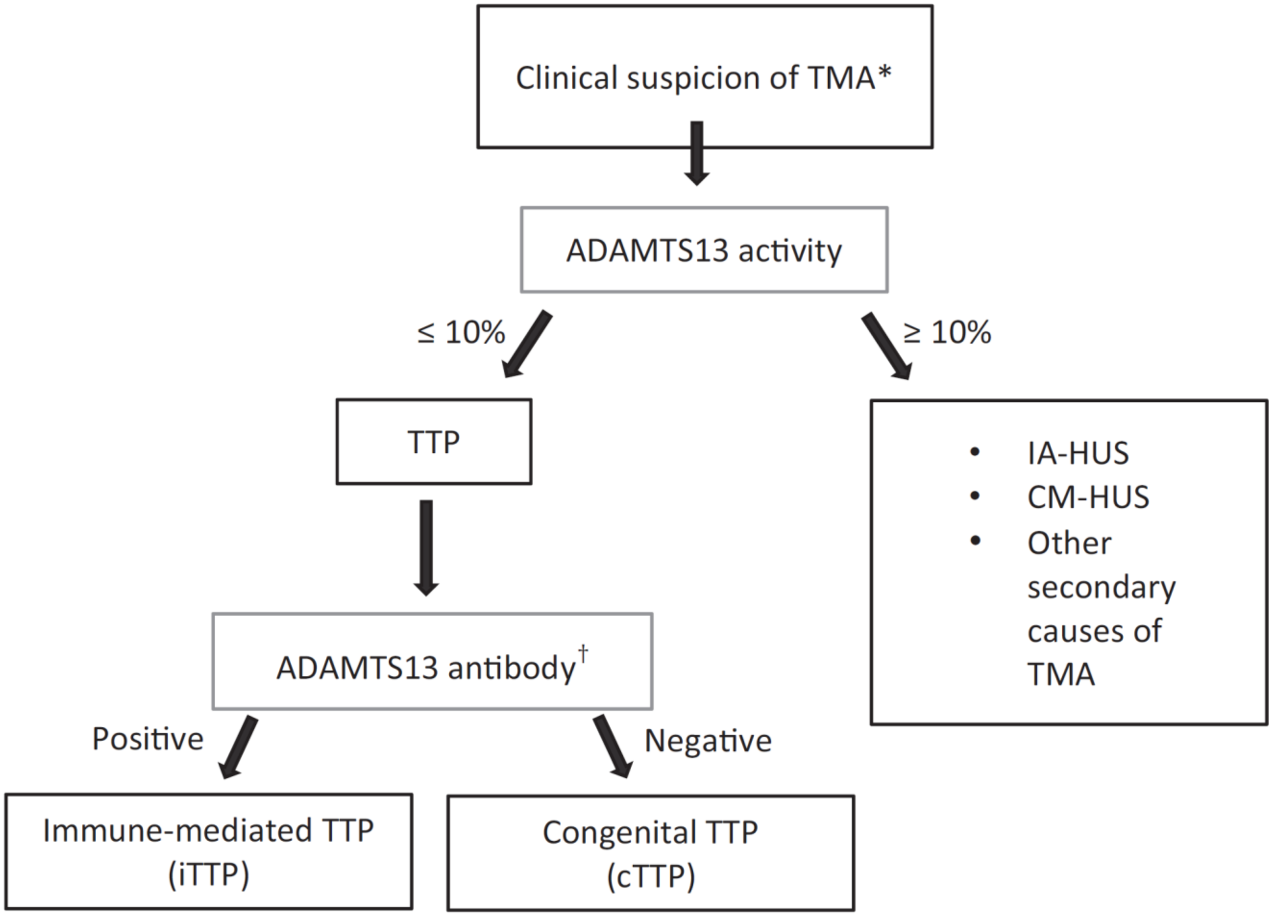
TTP: Prä-Test-Risikoabschätzung und Diagnose

- Plasmic (oder auch French-) Score
- ADAMTS13 Schnelltest
- ADAMTS13 Aktivität im (spezialisierten) Labor (+ Inhibitor/Antikörper)

Algorithmus TMA-Abklärung



Clinical suspicion of TMA*

ADAMTS13 activity

≤ 10%

TTP

ADAMTS13 antibody†

Positive

Immune-mediated TTP (iTTP)

Negative

Congenital TTP (cTTP)

≥ 10%

- IA-HUS
- CM-HUS
- Other secondary causes of TMA

Mackie et al., Int J Lab Hematol. 2020;00:1–12

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Unterscheidung TTP und aHUS

Hohe Thrombozytenzahlen (>30,000 mm^3) und S-Kreatininwerte (>150–200 µmol/l) schließen die Diagnose einer schweren ADAMTS13-Defizienz (TTP) nahezu aus

	TTP	**aHUS**	
Patientencharakteristika*	**ADAMTS13 defizient n=160** **(Standardabweichung)**	**ADAMTS13 messbar n=54** **(Standardabweichung)**	***p*-Wert**
Thrombozytenzahl, × 10^9/l	17,4 (14,2)	66,6 (49,3)	<0,0001
Kreatininlevel, µmol/l	114 (68,4)	454 (326)	<0,0001

* Erwachsene Patienten

Coppo P et al. PLoS ONE 5(4): e10208. doi:10.1371

Zuber J et al. Nat Rev Nephrol 2012 Nov;8:643–657.

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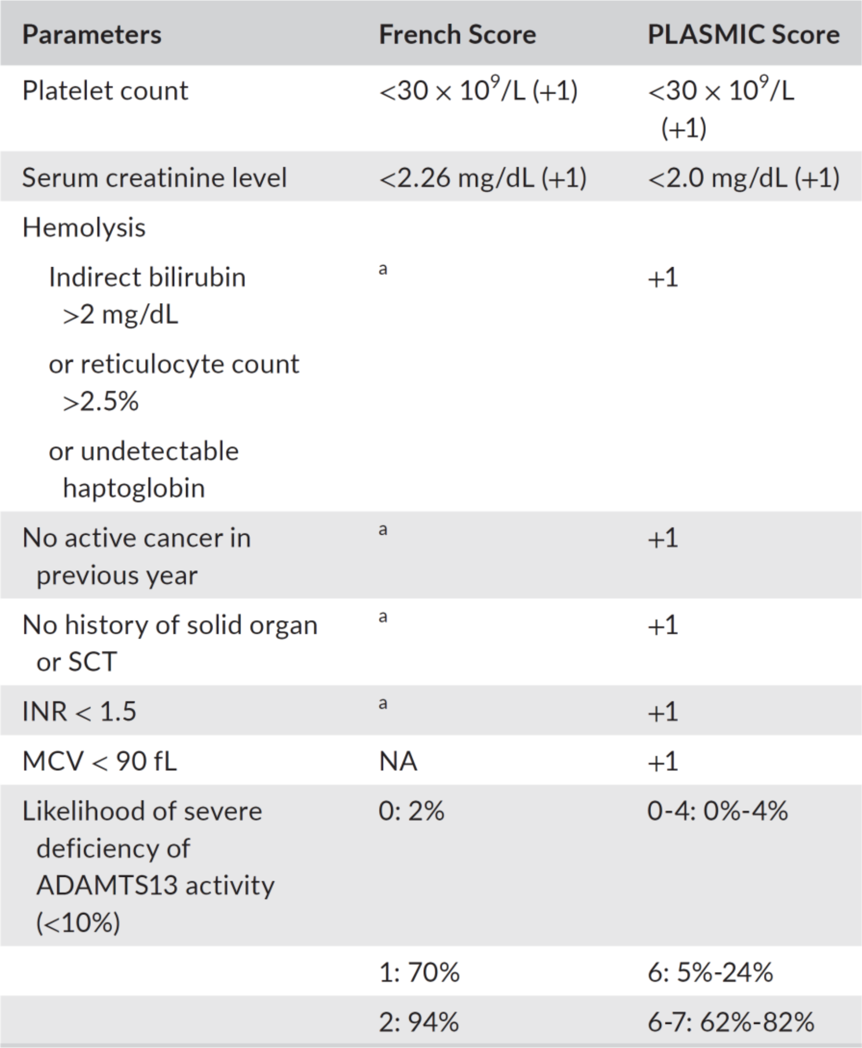
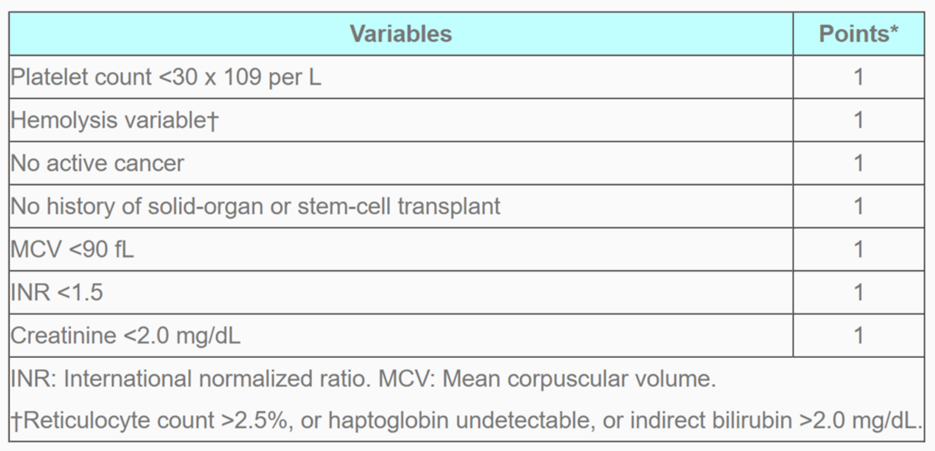
TTP Plasmic score



Parameters	French Score	PLASMIC Score
Platelet count	<30 × 10^9/L (+1)	<30 × 10^9/L (+1)
Serum creatinine level	<2.26 mg/dL (+1)	<2.0 mg/dL (+1)
Hemolysis Indirect bilirubin >2 mg/dL or reticulocyte count >2.5% or undetectable haptoglobin	[a]	+1
No active cancer in previous year	[a]	+1
No history of solid organ or SCT	[a]	+1
INR < 1.5	[a]	+1
MCV < 90 fL	NA	+1
Likelihood of severe deficiency of ADAMTS13 activity (<10%)	0: 2%	0-4: 0%-4%
	1: 70%	6: 5%-24%
	2: 94%	6-7: 62%-82%



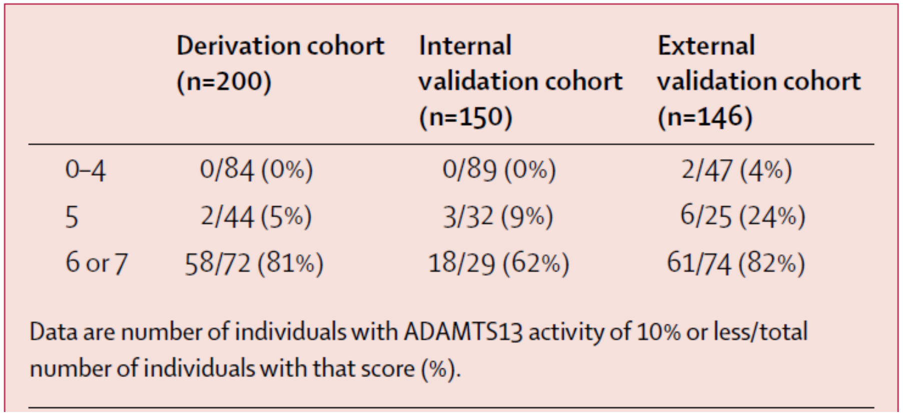
Variables	Points*
Platelet count <30 x 109 per L	1
Hemolysis variable†	1
No active cancer	1
No history of solid-organ or stem-cell transplant	1
MCV <90 fL	1
INR <1.5	1
Creatinine <2.0 mg/dL	1

INR: International normalized ratio. MCV: Mean corpuscular volume.

†Reticulocyte count >2.5%, or haptoglobin undetectable, or indirect bilirubin >2.0 mg/dL.

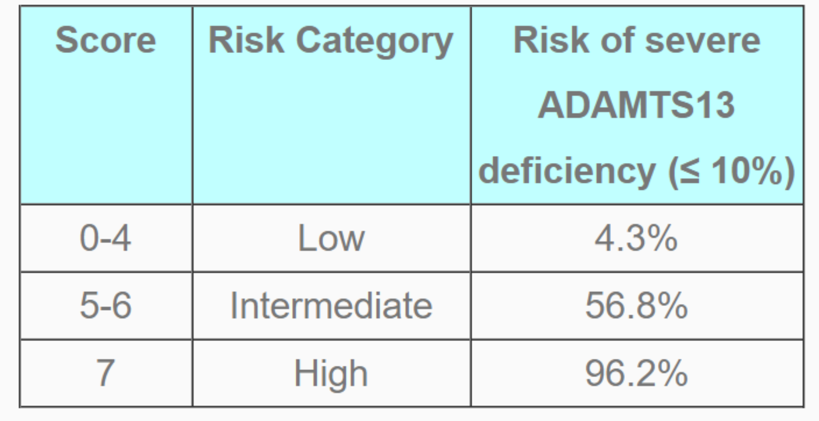
Long Zheng et al., J Thromb Haemost. 2020;18:2486–2495

TTP Plasmic score Validierungen



	Derivation cohort (n=200)	Internal validation cohort (n=150)	External validation cohort (n=146)
0–4	0/84 (0%)	0/89 (0%)	2/47 (4%)
5	2/44 (5%)	3/32 (9%)	6/25 (24%)
6 or 7	58/72 (81%)	18/29 (62%)	61/74 (82%)

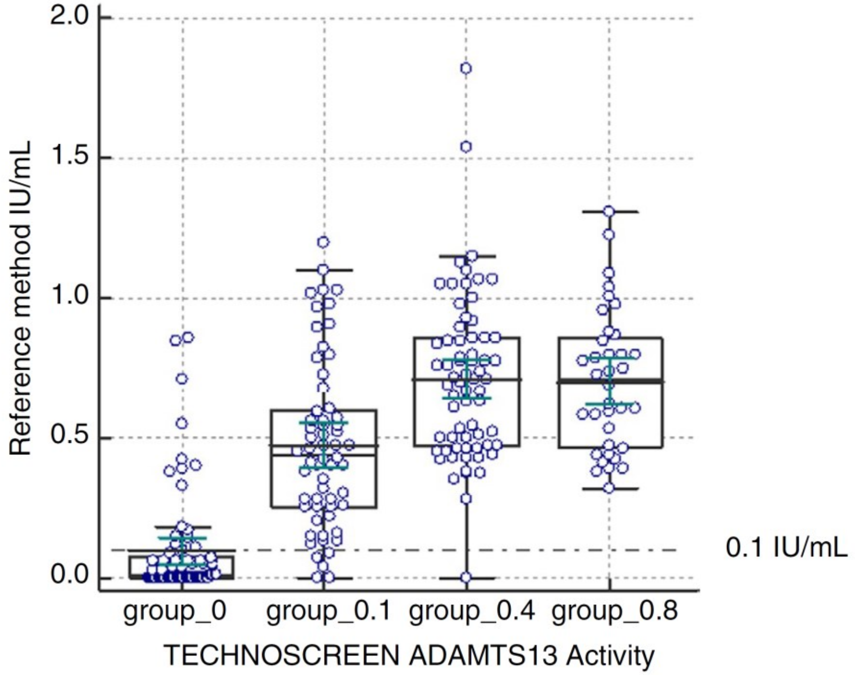
Data are number of individuals with ADAMTS13 activity of 10% or less/total number of individuals with that score (%).



Score	Risk Category	Risk of severe ADAMTS13 deficiency (≤ 10%)
0-4	Low	4.3%
5-6	Intermediate	56.8%
7	High	96.2%

Jamme et al., Lancet Haematol. 2017;4(4):e148
Bendapudi et al., Lancet Haematol. 2017;4(4):e157

Schnelltest versus ELISA



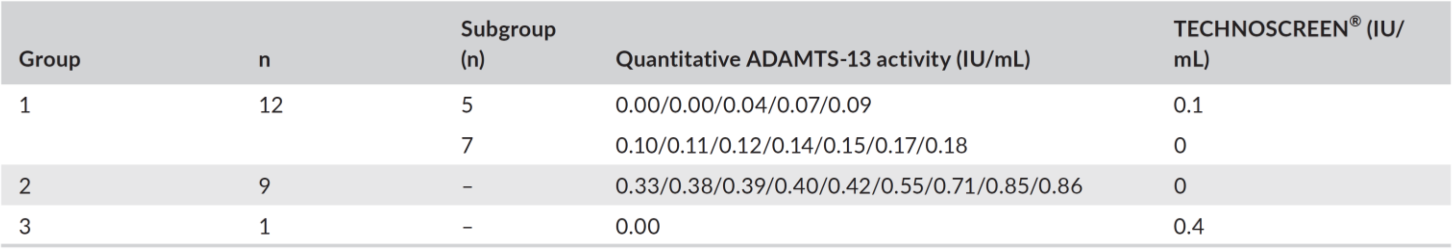
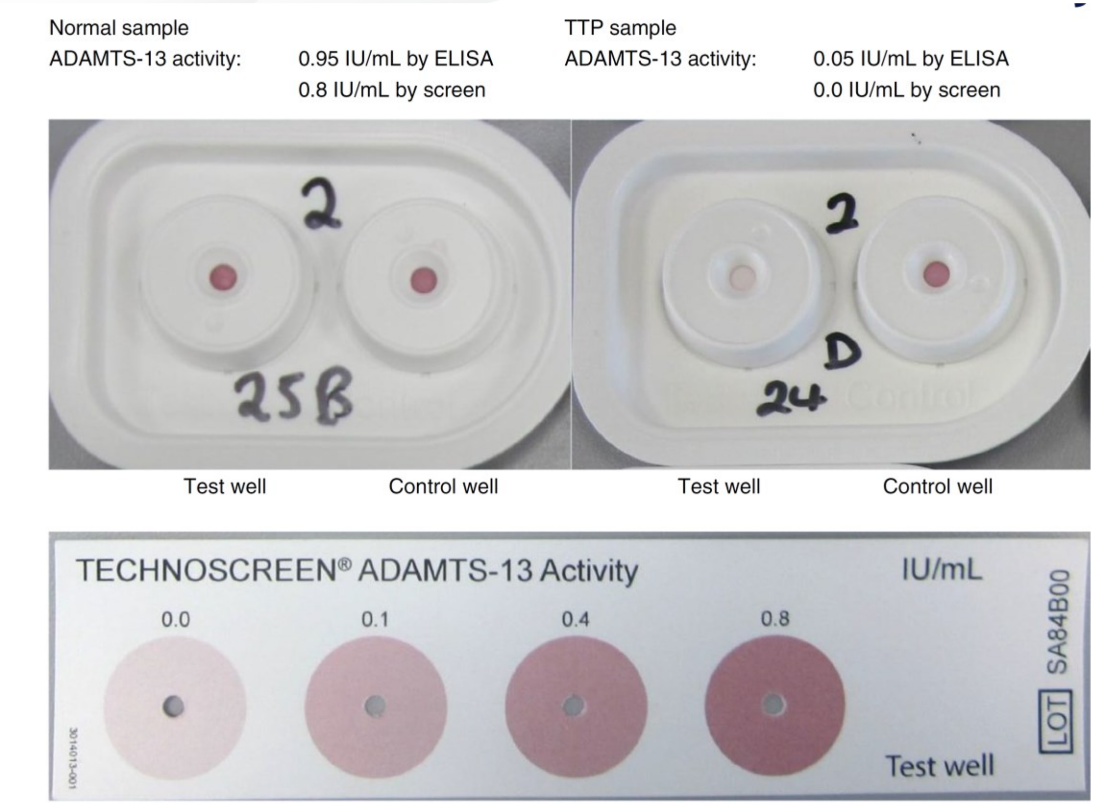


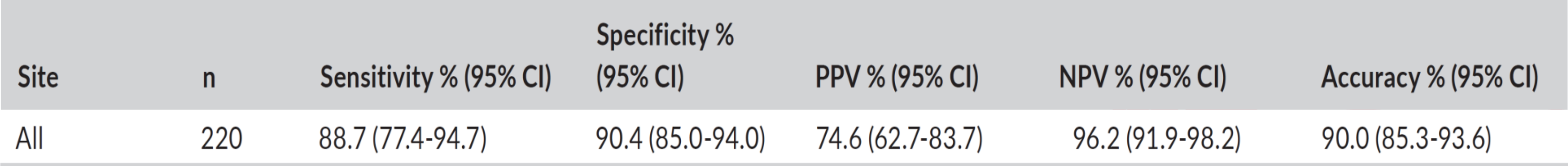
TABLE 4 Misclassified results at ADAMTS-13 activity cutoff of 0.1 IU/mL

Group	n	Subgroup (n)	Quantitative ADAMTS-13 activity (IU/mL)	TECHNOSCREEN® (IU/mL)
1	12	5	0.00/0.00/0.04/0.07/0.09	0.1
		7	0.10/0.11/0.12/0.14/0.15/0.17/0.18	0
2	9	–	0.33/0.38/0.39/0.40/0.42/0.55/0.71/0.85/0.86	0
3	1	–	0.00	0.4

Moore et al., J Thromb Haemost. 2020;18:1686–1694

ADAMTS13 Schnelltest


Normal sample
ADAMTS-13 activity: 0.95 IU/mL by ELISA
0.8 IU/mL by screen
TTP sample
ADAMTS-13 activity: 0.05 IU/mL by ELISA
0.0 IU/mL by screen
2
25B
2
D
24
Test well
Control well
Test well
Control well
TECHNOSCREEN® ADAMTS-13 Activity
IU/mL
0.0
0.1
0.4
0.8
Test well
LOT SA84B00



Site	n	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Accuracy % (95% CI)
All	220	88.7 (77.4-94.7)	90.4 (85.0-94.0)	74.6 (62.7-83.7)	96.2 (91.9-98.2)	90.0 (85.3-93.6)

Moore et al., J Thromb Haemost. 2020;18:1686–1694

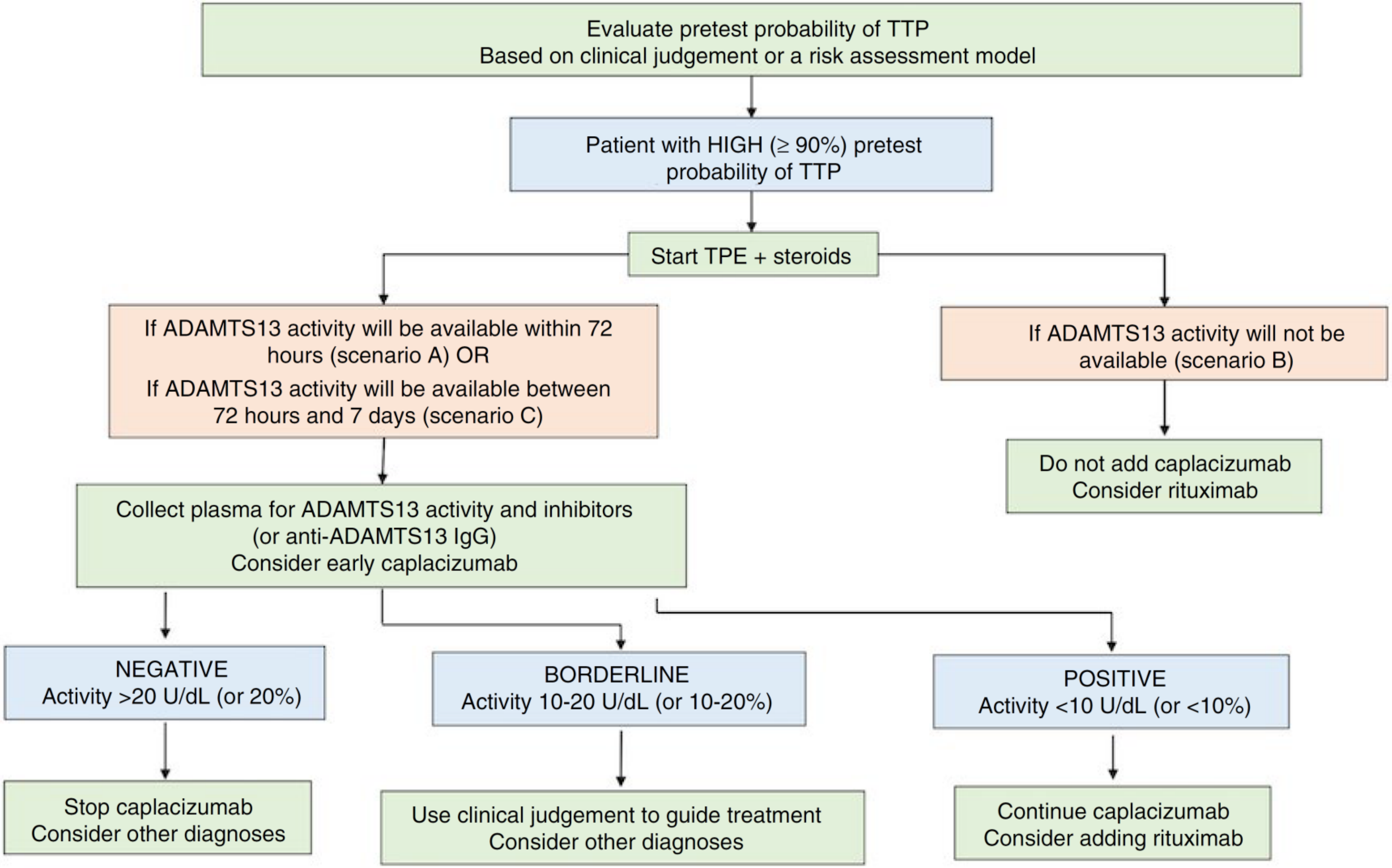
ISTH Leitlinie verwendet 3 Szenarien:

1) Szenario A: ADAMTS13 Aktivität *jederzeit* verfügbar

2) Szenario B: ADAMTS13 Aktivität *nicht* verfügbar

3) Szenario C: ADAMTS13 Aktivität *verzögert* verfügbar

Diagnostische Strategie für Patienten mit **sehr hoher (≥90%) Prä-Test-Wahrscheinlichkeit** für eine TTP



Evaluate pretest probability of TTP
Based on clinical judgement or a risk assessment model

Patient with HIGH (≥ 90%) pretest probability of TTP

Start TPE + steroids

If ADAMTS13 activity will be available within 72 hours (scenario A) OR
If ADAMTS13 activity will be available between 72 hours and 7 days (scenario C)

Collect plasma for ADAMTS13 activity and inhibitors (or anti-ADAMTS13 IgG)
Consider early caplacizumab

NEGATIVE
Activity >20 U/dL (or 20%)

Stop caplacizumab
Consider other diagnoses

BORDERLINE
Activity 10-20 U/dL (or 10-20%)

Use clinical judgement to guide treatment
Consider other diagnoses

POSITIVE
Activity <10 U/dL (or <10%)

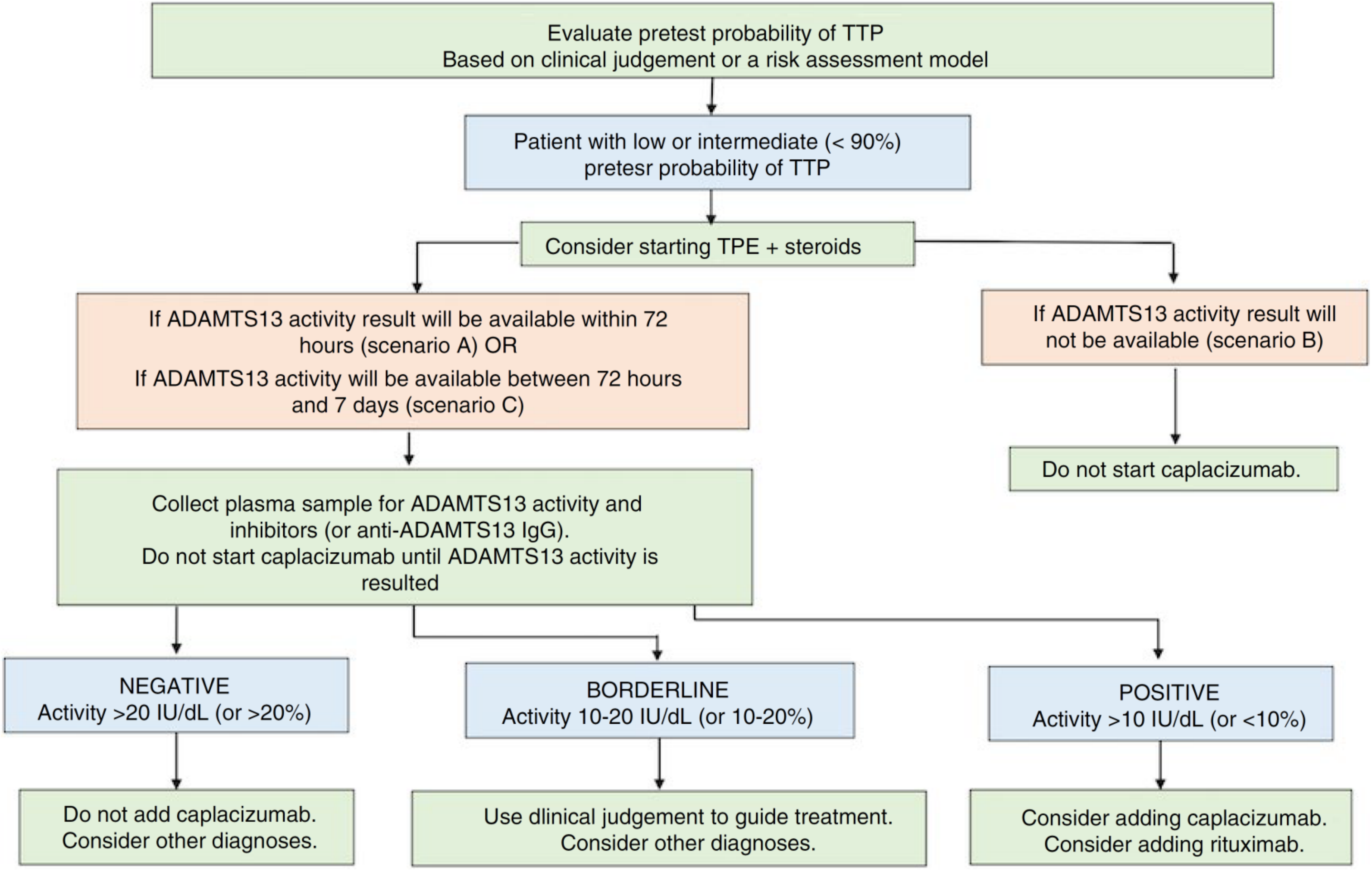
Continue caplacizumab
Consider adding rituximab

If ADAMTS13 activity will not be available (scenario B)

Do not add caplacizumab
Consider rituximab

Long Zheng et al., J Thromb Haemost. 2020;18:2486–2495

Diagnostische Strategie für Patienten mit **intermediater oder kleiner Prä-Test-Wahrscheinlichkeit** für eine TTP



Evaluate pretest probability of TTP
Based on clinical judgement or a risk assessment model

Patient with low or intermediate (< 90%)
pretesr probability of TTP

Consider starting TPE + steroids

If ADAMTS13 activity result will be available within 72 hours (scenario A) OR
If ADAMTS13 activity will be available between 72 hours and 7 days (scenario C)

Collect plasma sample for ADAMTS13 activity and inhibitors (or anti-ADAMTS13 IgG).
Do not start caplacizumab until ADAMTS13 activity is resulted

NEGATIVE
Activity >20 IU/dL (or >20%)

Do not add caplacizumab.
Consider other diagnoses.

BORDERLINE
Activity 10-20 IU/dL (or 10-20%)

Use dlinical judgement to guide treatment.
Consider other diagnoses.

POSITIVE
Activity >10 IU/dL (or <10%)

Consider adding caplacizumab.
Consider adding rituximab.

If ADAMTS13 activity result will not be available (scenario B)

Do not start caplacizumab.

Long Zheng et al., J Thromb Haemost. 2020;18:2486–2495

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Was hat “Der” denn nun über Diagnostik erzählt ?

- Biomarker für Diagnose und Verlauf vorhanden (ADAMTS13-Aktivität)

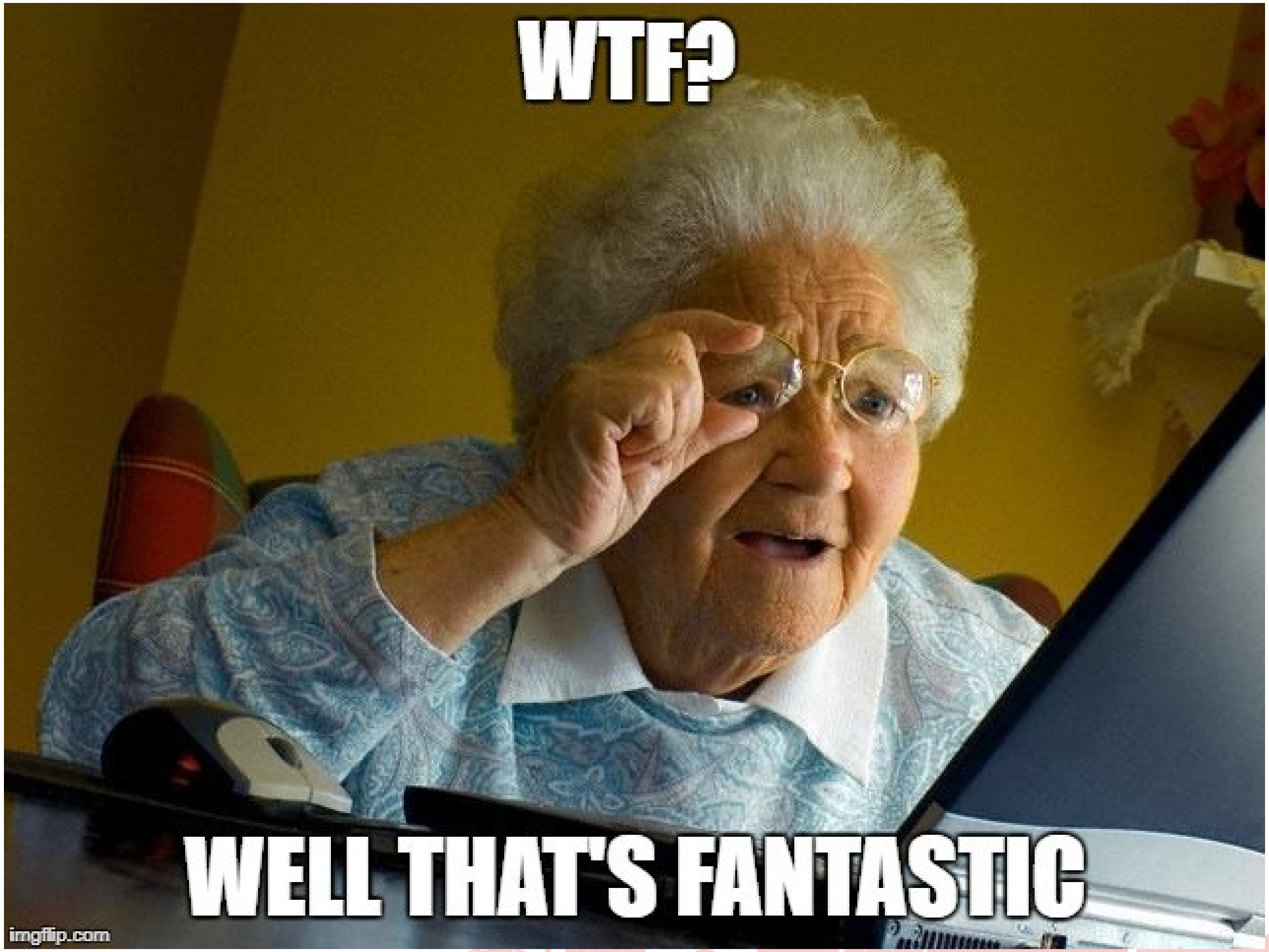
- Schnellteste sind verfügbar, Limitationen

- Zeit bis zur Verfügbarkeit der ADAMTS13 Aktivität hat Einfluss auf Therapieentscheidungen

- Rascher unkomplizierter Kontakt zu einem TTP-Zentrum oder TTP-“Experten” für ambulante Kollegen fulminant wichtig!

- TTP ist eine lebensbedrohliche Erkrankung. Im Zweifelsfall behandeln.

➡ Prof. Lämmle ist next – WTF ?


WTF?
WELL THAT'S FANTASTIC
imgflip.com

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Besten Dank!

Kontakt: ralph.wendt@sanktgeorg.de