Laboratory diagnosis of thrombotic microangiopathies

Measurement of ADAMTS-13

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Thrombotic microangiopathies (TMA)

1. Thrombocytopenia
2. Hemolytic anemia (non-immunological)
3. Microvascular ischemia (parenchymal organs)

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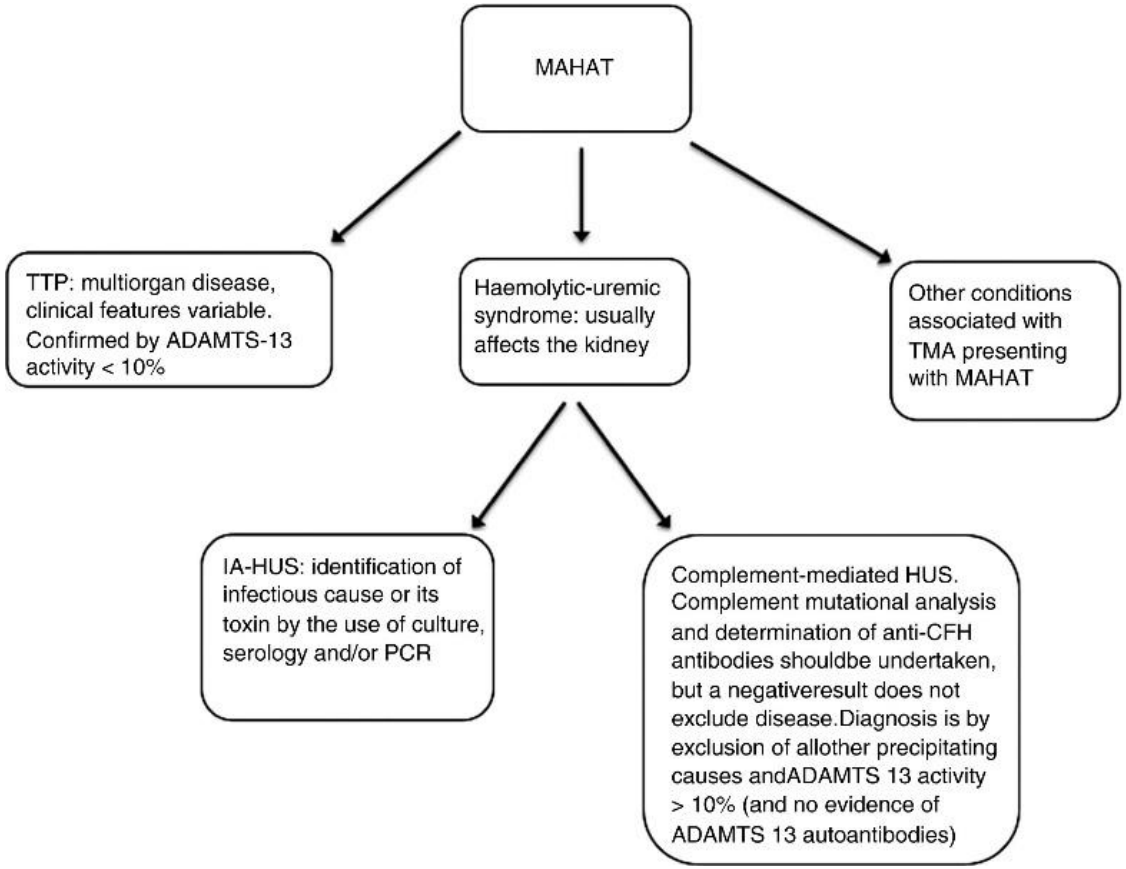
ORIGINAL ARTICLE

Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies



Scully M et al, *J Thromb Haemost* 2016;15: 312-22

Thrombotic Microangiopathies (TTP, HUS, HELLP)

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KEYWORDS

• Thrombocytopenia • Microangiopathies • Hemolytic anemia • TTP • HUS • ITP • HELLP • DIC

KEY POINTS

- Thrombotic microangiopathies, including thrombotic thrombocytopenic purpura (TTP), HUS and HELLP and its cousins—ITP, HIT, and DIC—are serious conditions that the emergency physician must recognize early to initiate life-saving treatments.
- The diagnosis of TTP only requires evidence of a microangiopathic hemolytic anemia with thrombocytopenia and no other explanation.
- A high clinical suspicion for thrombotic microangiopathies should be maintained in any patient presenting with thrombocytopenia or a precipitous drop in their platelet count within the normal range.

Kappler S et al, *Hematol Oncol Clin N Am* 2017*:* 1081–103

Table 1
Causes of pregnancy-associated TMA

Pregnancy-associated TMA	TMA presenting in pregnancy
Hypertension of pregnancy	Lupus nephritis/SLE
Preeclampsia	Vasculitis
	APLS
HELLP syndrome	Sepsis
AFLP	Severe hemorrhage
Placental abruption	TTP
Undefined TMA	CM HUS

Review of TMAs inherent to pregnancy vs those precipitated by pregnancy and result in anemia and thrombocytopenia.
AFLP, acute fatty liver of pregnancy; APLS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

Neave L & Scully M, *Transfus Med Rev* 2018;32: 230-6

HemolysisElevatedLiverenzymesLowPlatelets

THROMBOTIC THROMBOCYTOPENIC PURURA TTP
Moschcowitz syndrome
Hemolytic uremic syndrome (HUS)

Antiphospholipid syndrome (APS)

Disseminated intravascular coagulation DIC

- Coagulation activation - microthrombosis
- Platelets, fibrinogen, coagulation factor consumptions

Heparin induced thrombocytopenia (HIT)

- No anemia

Idiopathic thrombocytopenic purpura ITP

- No microthrombosis

FALLBESKRIVNING

Tilltagande anemi och trombocytopeni hos gravida kan vara trombotisk trombocytopen purpura

Utveckling av hemolytisk anemi och trombocytopeni hos en gravid kvinna bör föra tanken till diagnosen trombotisk trombocytopen purpura (TTP). Denna diagnos är mycket ovanlig och förekommer vid cirka 1/100 000–1/200 000 graviditeter [1-2]. På Karolinska universitetssjukhuset i Solna har fem fall av TTP under graviditet diagnostiserats under de senaste åren. HELLP-syndromet (hemolysis, elevated liver enzymes, low platelet count), med oklar etiologi, kan vara förvillande likt TTP i sin symtombild. Vid båda tillstånden är det dock oerhört viktigt att snabbt inleda korrekt behandling [1-3]. I Fakta 1 visas några differentialdiagnoser till TTP.

Vid TTP bildas mikrotromber som innehåller stora mängder av von Willebrands faktor (vWF) och trombocyter. von Willebrands faktor utsöndras från endotelceller i form av stora multimerer. Patofysiologin vid TTP utgår från en brist på enzymet ADAMTS13, som normalt klyver von Willebrands faktor. Eftersom detta är ett adhesivt protein, som binder trombocyter, leder denna enzymbrist till en ackumulering av trombocyter, och sekundärt bildas mikrotromboser (Figur 1). Kraftigt sänkt koncentration av aktivt ADAMTS13-protein vid TTP kan antingen bero på genetiska defekter (10 procent av fallen) eller på autoantikroppar riktade mot ADAMTS13 (90 procent av fallen) [4]. Oftast debuterar den ärftliga formen av TTP i samband med graviditet. Andra utlösande faktorer för kliniska symtom kan vara infektion, trauma eller operation.

HUVUDBUDSKAP

- Hemolytisk anemi och trombocytopeni kan vara tecken på trombotisk trombocytopen purpura (TTP).
- Obehandlad TTP har hög mortalitet.
- Hos gravida är leverpåverkan vanlig vid TTP.
- Med plasmaferes och immunsupprimerande behandling reduceras mortaliteten för den gravida kvinnan och fostret.

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Vid TTP förekommer alltid trombocytopeni och hemolytisk anemi [1-3]. Ofta finns också neurologiska symtom och mer sällan njurpåverkan och feber. Alla dess symtom utgör den klassiska »pentaden» vid TTP (Fakta 2). Gravida kvinnor med TTP har dock en annorlunda symtomatologi där leverpåverkan är mer framträdande [5]. Hjärtpåverkan på grund av trombocytrika koagler i koronarartärer och/eller myokardium kan vid TTP leda till allvarliga komplikationer såsom arytmier, hjärtinfarkt, hjärtsvikt och kardiogen chock – tillstånd förknippade med hög mortalitet [6]. Vid låga trombocytnivåer förekommer petekier, blåmärken och blödningar.

TTP hos icke-gravida har tidigare beskrivits i Läkartidningen 2008 [7-8], och därför fokuserar denna artikel endast på diagnostik och symtomatologi hos gravida kvinnor med detta tillstånd.

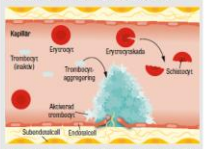
GRAVID KVINNA MED TTP – FALLBESKRIVNING

En tidigare helt frisk 22-årig kvinna i graviditetsvecka 31 sökte hjälp på mödravårdscentralen på grund av trötthet, orkeslöshet, diarré och blåmärken. Kvinnan remitterades akut vidare till sjukhus eftersom det var svårt att höra fosterljud. Vid ankomsten konstaterades tyvärr intrauterin fosterdöd. Blodprov visade grav anemi och trombocytopeni (Hb 34 g/l, TPK 25 × 10⁹/l; normal LPK samt förhöjda värden av LD (40 µkat/l) och transaminaser (ASAT och ALAT båda cirka 5 µkat/l). Blodtrycket var ökat (150/105 mm Hg).

Den initiala bedömningen var att detta rörde sig om ett HELLP-syndrom, och man beslöt att inducera en vaginal förlossning. Patienten fick behandling med kortison samt tranexamsyra och transfunderades med erytrocyt- och trombocytkoncentrat. Efter förlossningen, som komplicerades av bland annat placentaretention, var Hb 80 g/l och TPK 110 × 10⁹/l. Blödningsmängden under förlossningen var cirka 500 ml.

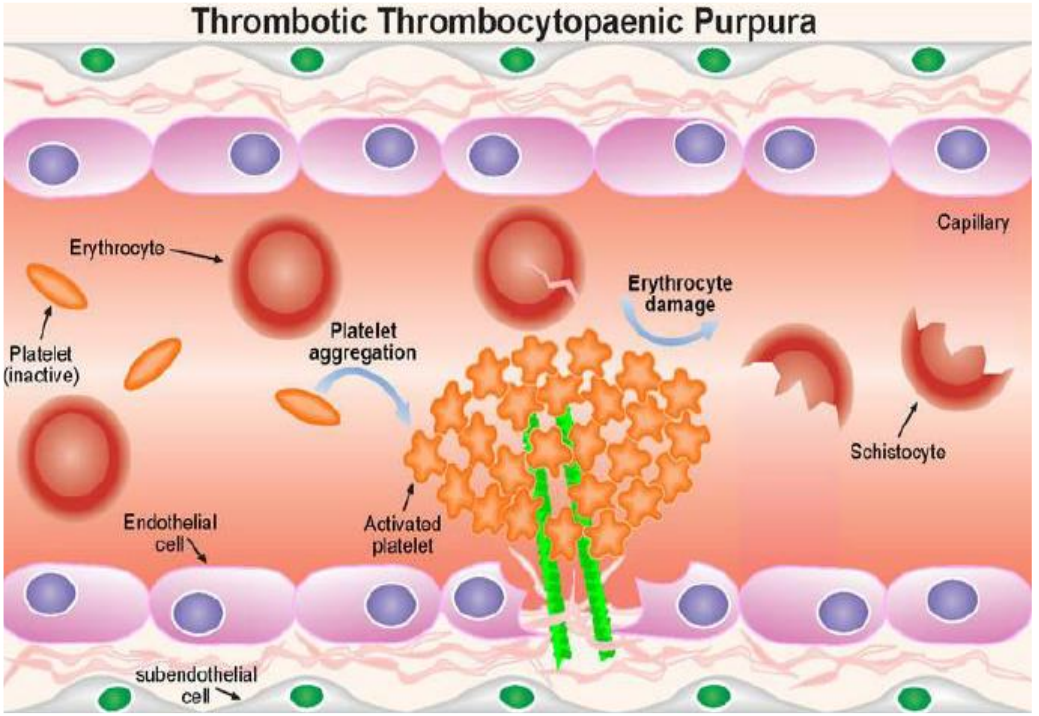
Tre dagar senare var levervärdena förbättrade, men TPK sjönk återigen till 25 × 10⁹/l, Hb till 61 g/l och LD

FIGUR 1. Trombotisk trombocytopen purpura

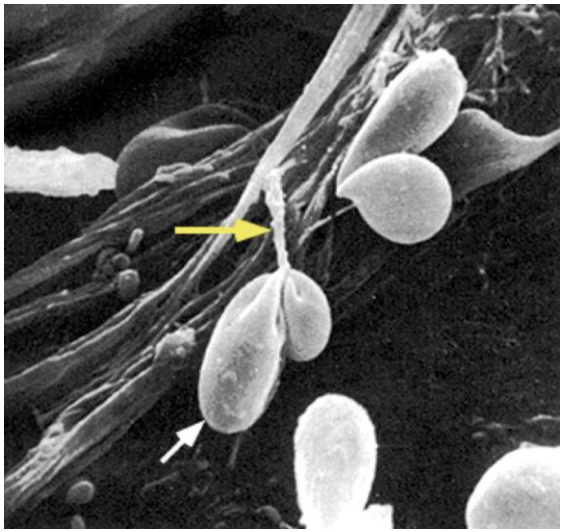


▸ Vid brist på enzymet ADAMTS13, kommer von Willebrandfaktorn inte att klyvas i mindre fragment. Trombocyterna kommer att bindas till det långa, adhesiva von Willebrand-proteinet och bilda mikrotromboser i kärlet. Trombocytbildningen leder till att trombocytnivåerna minskar i blodet. Erytrocyterna fragmenteras av mikrotromboserna i kärlet och hemolys uppstår. Efter förlaga med tillstånd från Immunopaedia (www.immunopaedia.org.za).

2 Läkartidningen #X 2018



Due to ADAMTS13 deficiency the VWF is not cleaved. The platelets are bound to the long, adhesive VWF and form microthrombosis and platelet levels decreased in the blood. The RBC are fragmented by the microthrombosis inducing hemolysis.



Agren A et al, *Läkartidningen* 2018 Mar 16;115

TTP is linked to a classic pentad

1. Thrombocytopenia (100 %)
2. Microangiopathic hemolytic anemia (100 %)
3. Neurological symptoms (about 60 % half with mild symptoms)
4. Kidney impact (30 %)
5. Fever (20 %)

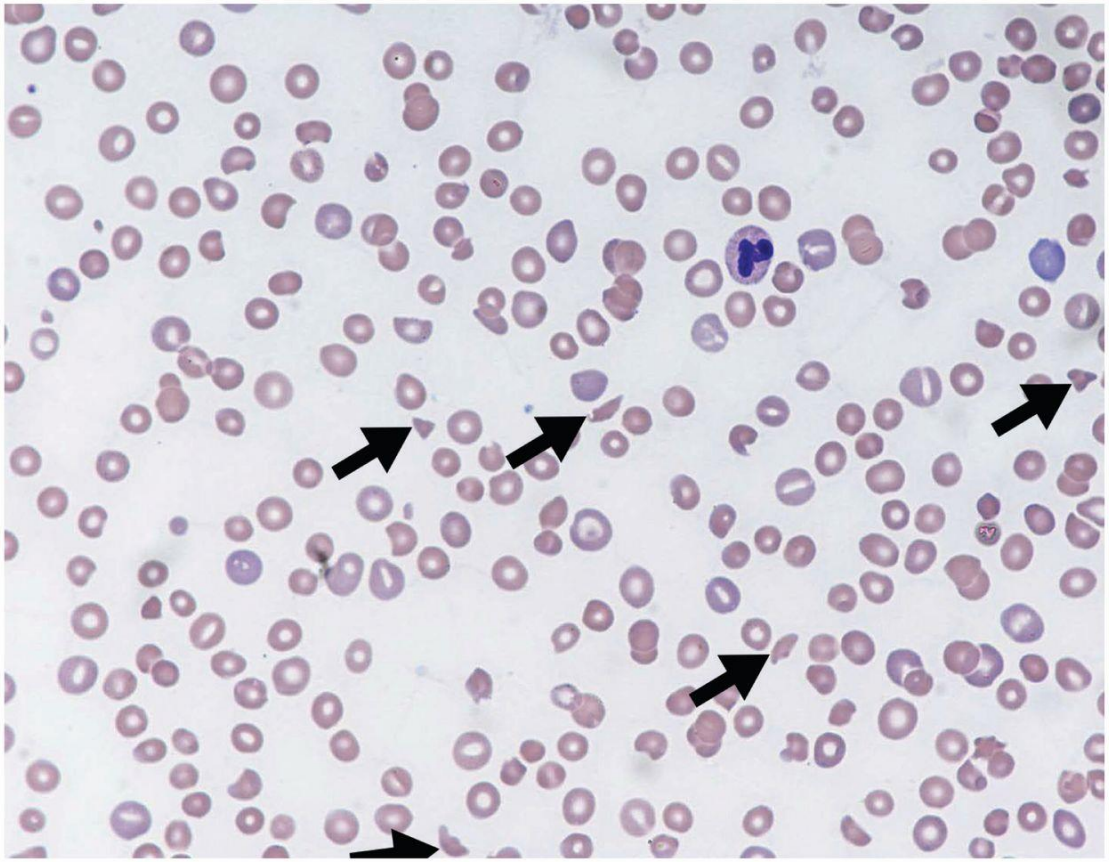
NOTE! In pregnancy, the liver may commonly be affected

TTP is difficult to distinguish from it much more common preeclampsia / HELLP Syndrome…

Agren A et al, *Läkartidningen* 2018 Mar 16;115

Case 1

Previously healthy 22-year-old woman, pregnancy week 31 presented with fatigue, diarrhea and bruising, and intrauterine fetal death was diagnosed in the hospital.



BP 150/105 m … 10^9/L), normal WBC, LD 40 (r… f. < 0.7 µkat/L).

First diagnosis … rythrocyte and platelet concen… acental retention.

3 days later live… , Hb 61 g/L and LD 32 µkat/L, h… while reticulocytes in… mmunoglobulins.

A few days late… cted thrombotic thrombocytope… near.

Low ADAMTS-…

Daily plasmaph… charged from the hospital a week later.

Agren A et al, *Läkartidningen* 2018 Mar 16;115

Three months later, pregnant again

To prophylactically increase ADAMTS13 with the goal of achieving at least 15% of normal value, treatment with plasma 400 ml once a week.

Despite the treatment, symptoms of bruising during pregnancy week 36. Hb 109 g/L, platelets 32 x 10^9/L, LD 7 µkat/L, AST and ALT 3 µkat / L. Plasmapheresis started and she became symptom free.

Induced delivery was complications-free in week 36 + 6. The child was closely monitored with normal level of Hb, platelets, bilirubin, and ADAMTS-13 activity.

Both mother and child were well and discharge from the hospital a few days later.

Agren A et al, *Läkartidningen* 2018 Mar 16;115

Laboratory findings in TTP

1. Low Hb and signs of hemolysis, i.e. high LD, high bilirubin, high number of reticulocytes and low haptoglobin

2. Schistocytes on blood smear

3. No RBC antibodies, negative direct antiglobulin test

4. Pronounced thrombocytopenia

5. Low ADAMTS-13 level (<5 %) (antibodies)

6. PT (INR), APTT, fibrinogen, D-dimer and antithrombin usually normal or mildly affected

IMPORTANT! In pregnancy the liver may also be affected

Agren A et al, *Läkartidningen* 2018 Mar 16;115

TABELL 1. Jämförelse mellan typiska kliniska symtom och laboratorieanalyser vid preeklampsi/HELLP och TTP.

Diagnos	Trombo-cytopeni	Blod-tryck	Neurologiska symtom	Lever-påverkan	Njur-påverkan	Tidpunkt under graviditet/post partum	Förlopp efter partus	ADAMTS13
• Preeklampsi/ HELLP	Måttlig	Förhöjt	Huvudvärk och synpåverkan. Mer sällan kramper och stroke	Kraftig	Varierande svårighetsgrad	Efter graviditetsvecka 20 till och med 3 dagar post partum	Vanligen förbättrad inom 3–5 dygn	Normal till lätt sänkt
• TTP	Svår	Normalt	30 procent lindriga symtom såsom huvudvärk och förvirring. 30 procent svåra symtom såsom medvetandepåverkan, fokal neurologi, kramper och stroke	Lindrig/ måttlig	Lindrig	Hela graviditeten och flera veckor post partum	Vanligen ingen förbättring	Mindre än 5 procent

TTP: Trombotisk trombocytopen purpura; HELLP: Hemolysis, elevated liver enzymes, low platelet count. Tabell modifierad från [1].

Diagnosis	Thrombocytopenia	Blood pressure	Neurological symptoms	Liver symptoms	Renal symptoms	Occurrence	Course after delivery	ADAMTS-13
Preeclampsia /HELLP	Moderate	High	Headache and visual problems rare stroke and seizures	Severe	Different severity	From pregnancy week 20 to 3 days after delivery	Improvement 3-5 days after delivery	Normal or mildly decrease
TTP	Severe	Normal	30% mild symptoms 30% impaired consciousness	Mild/ moderate	Mild	Entire pregnancy and few weeks after delivery	No improvement	<5%

Agren A et al, *Läkartidningen* 2018 Mar 16;115

Pathology Consultation on the Diagnosis and Treatment of Thrombotic Microangiopathies (TMAs)

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From the Department of Pathology, University of Alabama at Birmingham.

Key Words: Thrombotic microangiopathy (TMA); Thrombotic thrombocytopenic purpura (TTP); Hemolytic uremic syndrome (HUS); Microangiopathic hemolytic anemia (MAHA)

Am J Clin Pathol February 2016;145:158-165

DOI: 10.1093/AJCP/AQV086

Williams LA et al, *Am J Clin Pathol* 2016; 145: 158-65

Case 2

A 21-year-old white woman, no medical history transferred from another hospital due to worsening of anemia (Hb 77 g/L) and thrombocytopenia (platelets 45 x 10^9/L). After normal pregnancy, an elective caesarean section the previous day for delivery of first child. Morning after surgeryshe got severe abdominal and lower back pain.

Vital signs were within normal limits, Hb 74 (113-152 g/L); MCV 93 (80-96 fL); reticulocytes, 2.8 [0.7%-2.4%]), platelets 41 [150-400 x10^9/L]), and 3-4 schistocytes per x 100 power field. Hemolysis indirect bilirubin of 4.7 (0.2-0.7mg/dL), haptoglobin 4 (33-200 mg/dL), and LDH of 1 832 (<200 IU/L), creatinine of 4.1 (0.6-1.2mg/dL). Liver enzymes normal no proteinuria. Negative direct antiglobulin test (DAT), and screening coagulation tests (ie, PT, PTT and fibrinogen) were within normal limits.

Plasma exchange (PE) for the presumptive diagnosis of postpartum TTP started immediately following the collection of blood samples for ADAMTS13 to confirm the diagnosis of TTP.

After two daily TPE, the ADAMTS13 61%. PLASMIC score 4, placing her in the low-risk category for having TTP. Platelet increased 68 x 10^9/L, LDH decreased 870 IU/L, creatinine decreased 3.2 mg/dL.

Williams LA et al, *Am J Clin Pathol* 2016; 145: 158-65

Table 1

The PLASMIC Scoring System to Predict the Likelihood of ADAMTS13 Less Than 10%[a]

Criteria
1. Platelet count $<30 \times 10^9$/L
2. MCV <90 fL
3. Creatinine <2.0 mg/dL
4. INR <1.5
5. Evidence of hemolysis based on any of the following:
Reticulocyte count >2.5%
Indirect bilirubin >2.0 mg/dL
Undetectable haptoglobin
6. No active cancer
7. No history of bone marrow or solid organ transplantation

ADAMTS13, a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13; INR, international normalized ratio; MCV, mean corpuscular volume; PLASMIC, platelets, lysis, active cancer, stem cell or solid organ transplant, MCV, INR, and creatinine.
[a]If the total criteria are 0-4, the risk is low; 5-6, intermediate; 7, high.

Williams LA et al, *Am J Clin Pathol* 2016; 145: 158-65

The most likely diagnosis was aHUS. PE was discontinued eculizumab started. Two months later, genetic testing revealed a mutation in complement factor H. Over an 8-month period, she received 26 additional doses of eculizumab, and her primary care physicians reported an excellent clinical response, with near normalization of her creatinine.

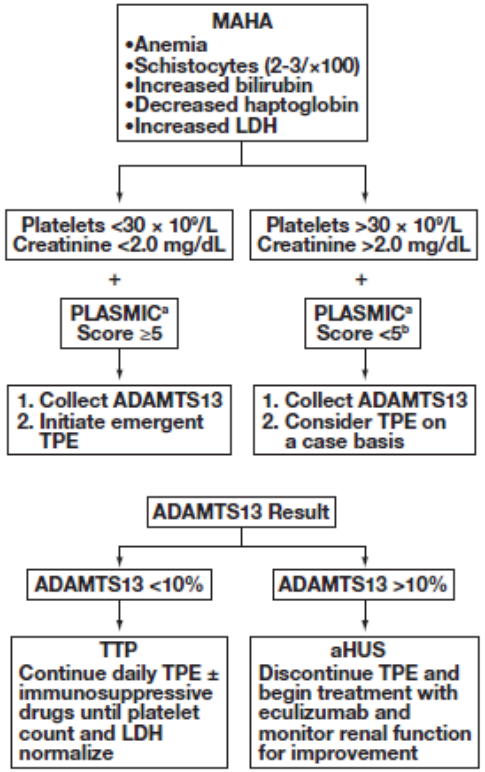
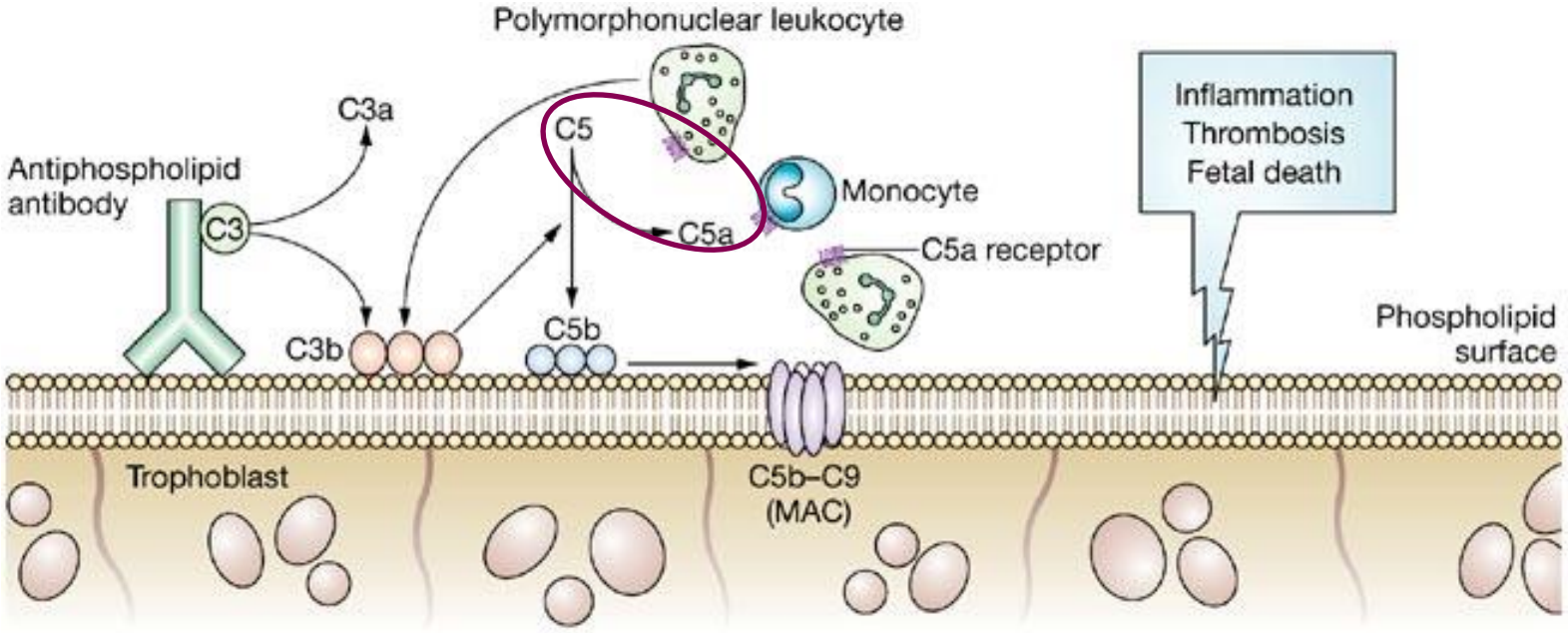


Figure 1 Algorithmic approach to the diagnosis of TTP and aHUS. ADAMTS13, a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13; aHUS, atypical hemolytic uremic syndrome; LDH, lactate dehydrogenase; MAHA, microangiopathic hemolytic anemia; PLASMIC, platelets, lysis, active cancer, stem cell or solid organ transplant, mean corpuscular volume, international normalized ratio (INR), and creatinine; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura. [a]All components of the PLASMIC score must be evaluated for an accurate score. [b]Preexisting liver or renal disease may falsely lower the PLASMIC score due to baseline elevations in the INR and creatinine.

Williams LA et al, *Am J Clin Pathol* 2016; 145: 158-65

APS pathogenesis - still a matter of debate

different mechanisms involved in the vascular and the obstetrical manifestations of APS



Case 3

42-year-old women, no children, works in sales, non-smoker diagnosed with SLE in the `80s (photosensitivity, malar rash, arthritis, hair loss, ANA positivity)

1992 diagnosed with APS after eclampsia and miscarriage in the late pregnancy, associated with cardiac arrest (most probably catastrophic APS)

2005 epileptic seizures, treated with carbamazepine in 3 years

Single kidney, impairment of renal function

SLE symptoms under control during treatment with low dose Prednisolon

Anticoagulant treatment: Warfarin, INR 2-3

2011 pulmonary infiltrates – SLE (inflammation) related. Started azathioprine

January 2012 new epileptic seizures levetiracitam started

Hospitalized due to cough, fever, fatigue, weight loss ongoing treatment: Prednisolon 10mg; azathioprine 150mg and Warfarin INR 2-3

Laboratory: RBC 3.2 (ref. 3.9-5.2 x 10^{12}/L), WBC 2.8 (ref. 3.5-8.8 x 10^{9}/L), Platelets 96 (ref. > 165 x 10^{9}/L), CRP 103 (ref. < 3mg/L), SR 85 (ref. < 20mm), creatinine 150 (ref. < 90 mmol(L), complement activation, ANA Ø, proteinuria

HRCT thorax: pulmonary infiltrates in the upper part of the right lung – difficult to exclude bleeding or malignancy

Pancytopenia and renal involvement due to SLE activity
Prednisolon 60mg + Cellcept 500mgx2

Laboratory: CRP 1, SR 50, creatinine 152

Warfarin → LMWH 5 days before the transthoracic lung biopsy on April 17th

On April 16th admitted to hospital due to weakness, increased heart rate

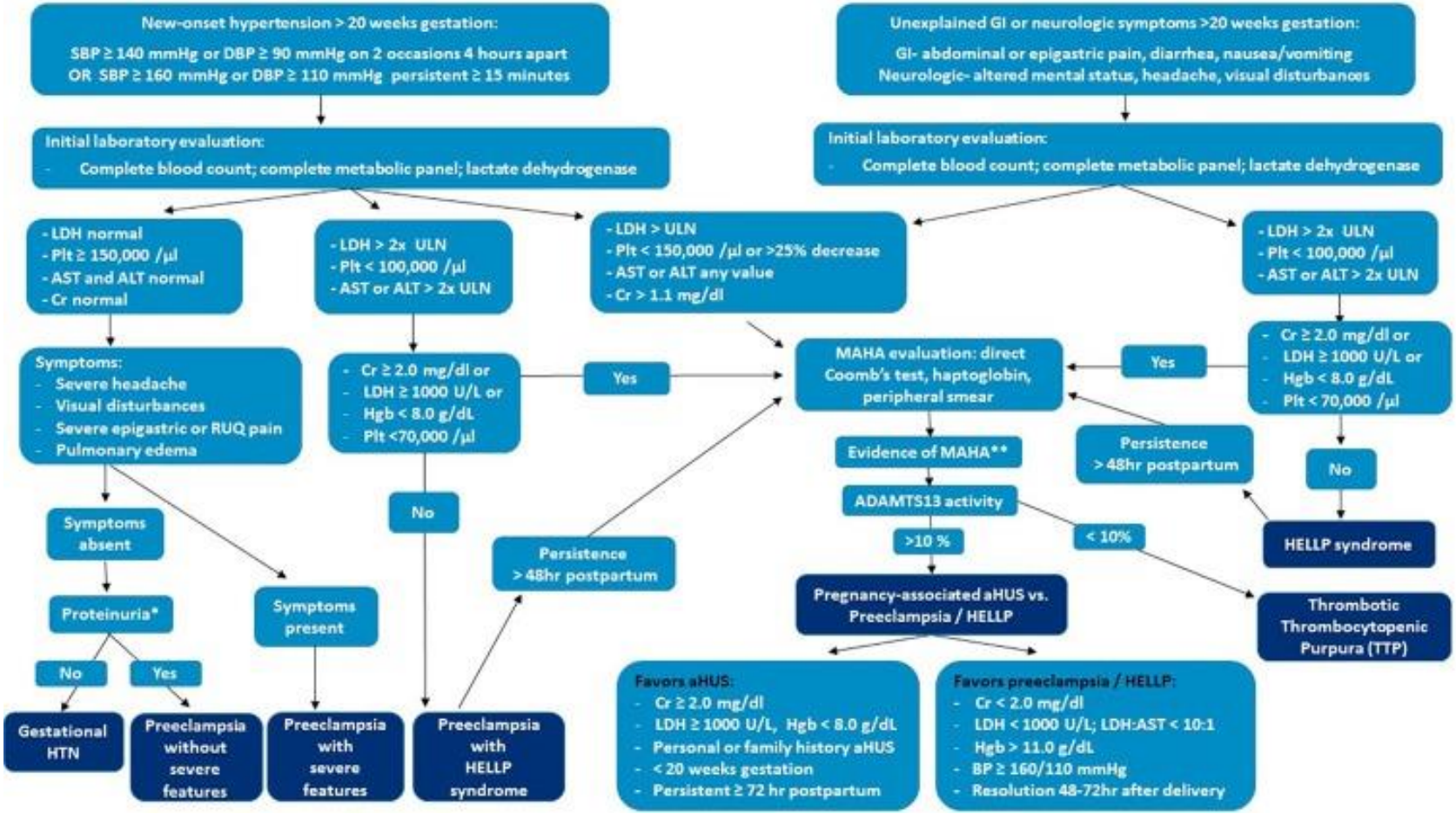
Laboratory SR 97, Platelets 37 - 24, RBC 2.0, Hb 85(ref. > 117 g/L) , reticulocytes 202 (ref. < 115 10^9/L), WBC 4.0 creatinine 224

LAC positive, Cardiolipin-Ab (IgG) >120 (<10E/mL) β2-GPI-Ab (IgG)>100 (<5E/mL)

Diff. Diagnosis:

- **Hemolytic anemia due to APS/SLE activity?**
- **HEPARIN INDUCED THROMBOCYTOPENIA (HIT)?**

  - 4 T' score **(4)**
  - ID-PaGIA **+**
  - IgG specific ELISA **+**
  - Heparin induced platelets aggregation **+**



Gupta M et al, *Pregnancy Hyper*tens 2018; 12: 29-34

Syndrome	Laboratory
Hypertension / Preeclampsia / Eclampsia HELLP	Platelet count RBC, Hb, schistocytes, DAT Ø LDH, haptoglobin, AST, ALT Creatinine
TTP (a)HUS	ADAMTS-13
SLE/APL	ANA, LA, cardiolipin Ab
DIC	Fibrinogen, D-dimer, PT, coagulation factors

	PE	HELLP	TTP	(a)HUS	SLE/APS	DIC
BP	↑↑	↑	→	→	→	↓
Platelet count	↓	↓	↓↓	↓↓	↓	↓↓
RBC	↓	↓	↓	↓	↓	↓
Schistocytes	↑	↑	↑↑	↑↑	→	↑
LD	↑	↑	↑↑	↑↑	→	↑
ASAT/ALAT	→	↑	→	→	→	→
Creatinine	→	→	↑	↑	↑	→
ADAMTS-13	→	→	↓↓	↓	→	→
bacteria	Ø	Ø	Ø	(+)	Ø	+
ANA/LA/ACA	Ø	Ø	Ø	Ø	+	Ø
PT (INR)	→	→↑	→↑	→↑	→	↑↑
D-dimer	→	→	↑	↑	→	↑↑

- **TMA is clinico-pathological syndrome**
- **PE/HELLP vs TTP/HUS vs SLE/APS vs DIC**
- **Simple laboratory tests useful**
- **Specific ADAMTS-13**

TTP/HUS Laboratory investigation of ADAMTS-13

Monoclonal antibody to VWF 73 peptide

- FRET (fluorescence resonance energy) assay
- Requires specific fluoremeter

- ELISA assay
- Manual
- 4-5 hours
- Simple plate reader

Technoclone ADAMTS-13 ELISA

"Prov som skickas till laboratoriet kan vid akuta fall analyseras närmast följande vardag. Det ska framgå på remissen att det är akut och ALLTID stödjas av resultat på LD och Shistocyter. Övriga prover analyseras en gång per vecka."

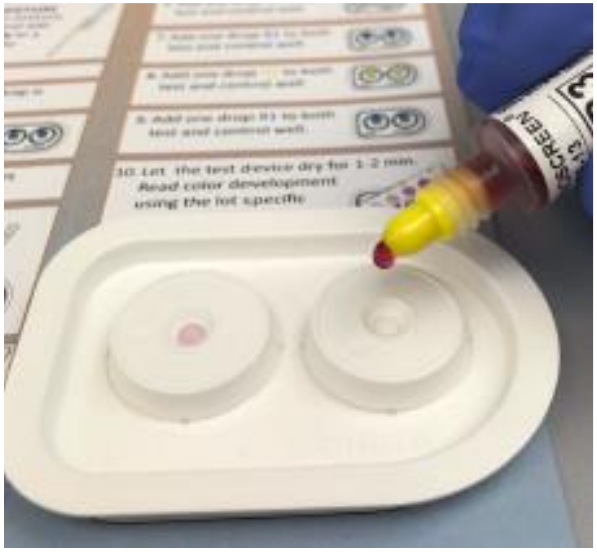
"Samples that are sent to the laboratory can be analyzed in emergency cases next weekday. It should be stated on the referral that it is urgent and ALWAYS supported by results on LD and Schistocytes. Other samples are analyzed once a week. "

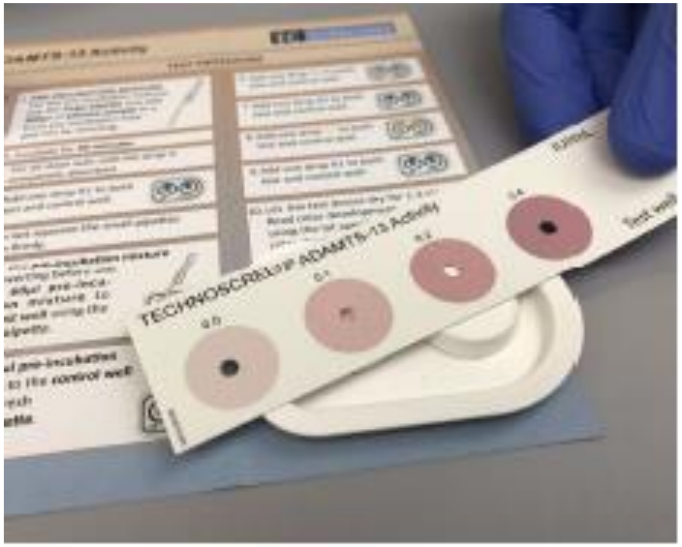
Practically 3-4 times / week

Analysis take > 4 hours

Unsustainable

TECHNOSCREEN ADAMTS-13





43 samples previosly tested with TECHNOZYM ADAMTS-13 ACTIVITY

ELISA %	SCREEN %	RESULT		ELISA %	SCREEN %	RESULT		ELISA %	SCREEN %	>UTFALL
13,7	10	FALSE PATHOLOGICAL		6,9	10	PATHOLOGICAL		29,1	10	FALSE PATHOLOGICAL
0	0	PATHOLOGICAL		10,3	10	PATHOLOGICAL		19,4	10	FALSE PATHOLOGICAL
3,9	0	PATHOLOGICAL		9,8	10	PATHOLOGICAL		74,2	40	NORMAL
4,1	10	PATHOLOGICAL		0	0	PATHOLOGICAL		80,4	80	NORMAL
8,6	10	PATHOLOGICAL		8,4	10	PATHOLOGICAL		76,5	80	NORMAL
1,6	10	PATHOLOGICAL		11,9	10	FALSE PATHOLOGICAL		75,4	40	NORMAL
0,15	0	PATHOLOGICAL		17,7	10	FALSE PATHOLOGICAL		96,5		LIP/IKT
4,5	10	PATHOLOGICAL		24,2	40	GREYZONE		50,1	80	NORMAL
0	0	PATHOLOGICAL		10	10	PATHOLOGICAL		45,8		LIP
1,5	10	PATHOLOGICAL		7,9	10	PATHOLOGICAL		50,4	80	NORMAL
2	10	PATHOLOGICAL		7,9	10	PATHOLOGICAL		53	10	FALSE PATHOLOGICAL
0,6	10	PATHOLOGICAL		34	40	GREYZONE		58	40	NORMAL
9,4	10	PATHOLOGICAL		13,3	40	GREYZONE		59,4	10	FALSE PATHOLOGICAL
5,2	10	PATHOLOGICAL		30,3	80	NORMAL		57,6	80	NORMAL
9,6	10	PATHOLOGICAL		10,2	0	PATHOLOGICAL				

RED: PATHOLOGICAL ≤ 10%, GREEN : NORMAL ≥ 40%, GREYZONE:>15%-40%

TECHNOSCREEN ADAMTS-13

True pathologic 23

False pathologic 7

True normal 12

False normal 0

SENSITIVITY 100%

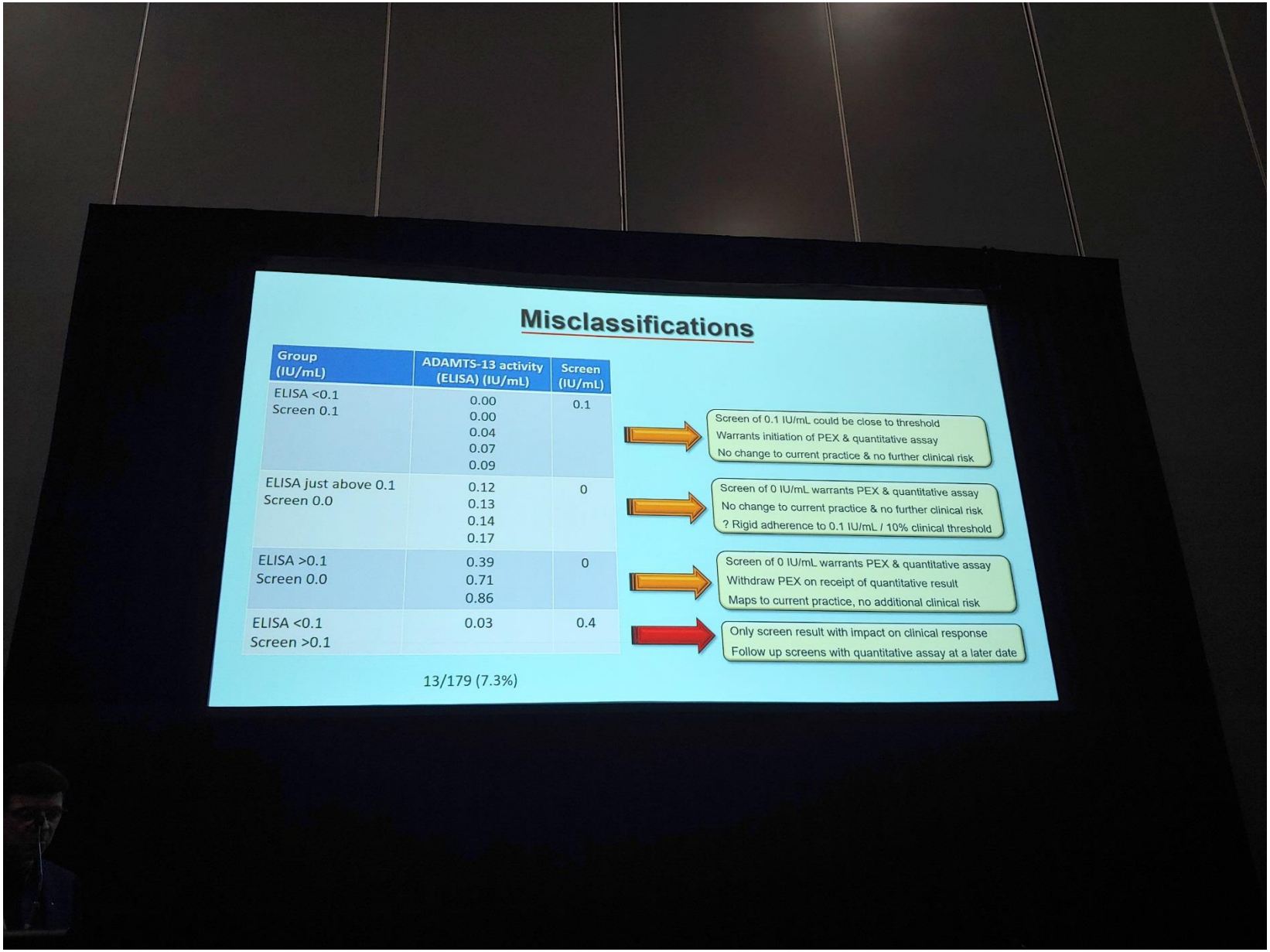
SPECIFICITY 61%(73%)

	Lot 1 (n = 86)	Lot 2 (n = 93)
Sensitivity %	100	96.3
Specificity %	66.7	75
PPV %	87.1	89.7
NPV %	100	90

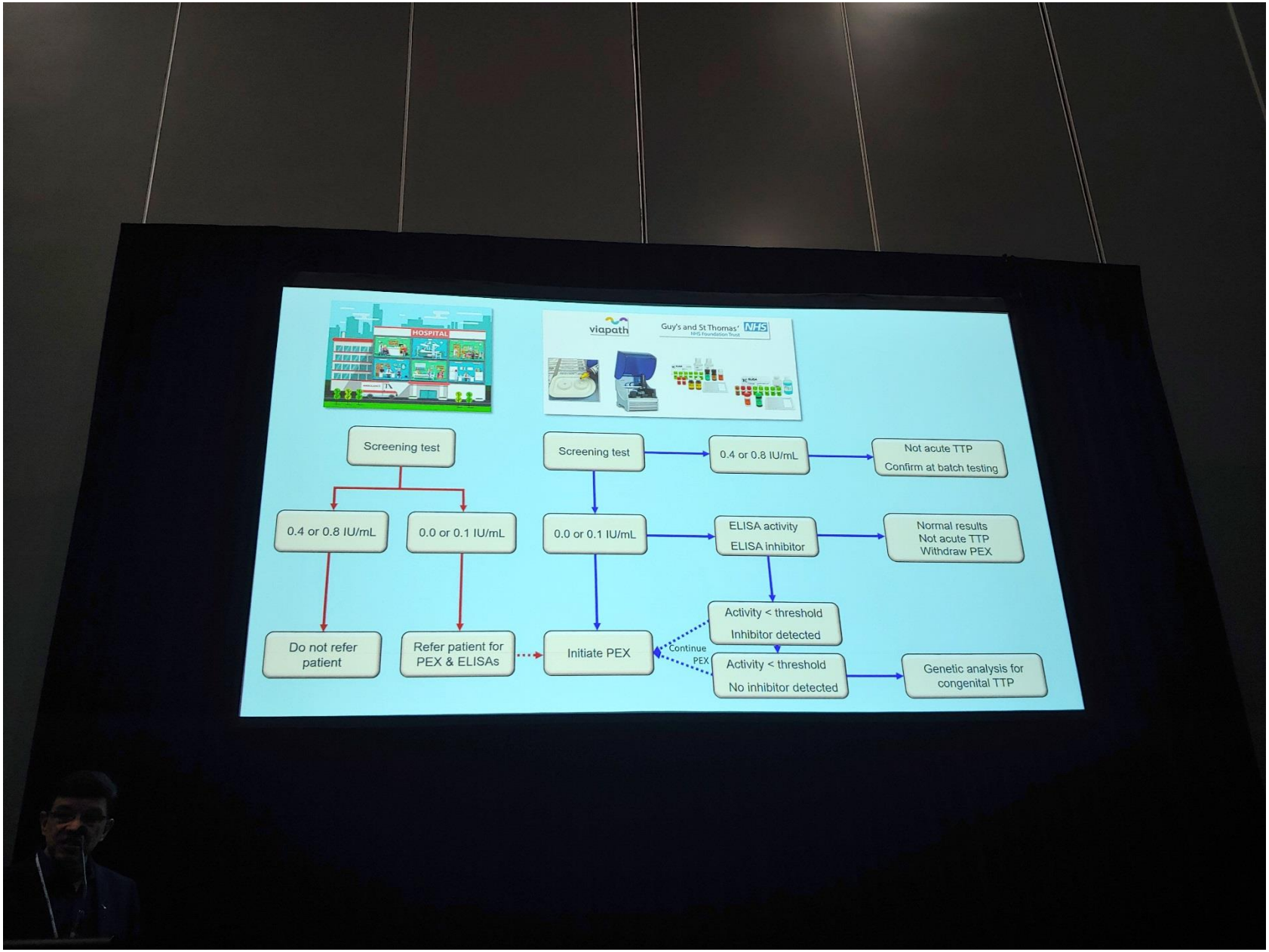
Griffiths et al, *ISTH* 2019

	Site 1 (n = 86)	Site 2 (n = 93)	Combined (n = 179)
Sensitivity %	94.7	96.5	95.6
Specificity %	81.8	86.1	84.0
PPV %	97.3	91.7	94.5
NPV %	69.2	93.9	81.6

Moore, *ISTH* 2019



Moore, *ISTH* 2019



Moore, *ISTH* 2019

PROPOSAL

Panel B: Laboratory data at presentation				
	All events	First events	Relapses	Difference of medians (95% CI)[a]
Platelet count, 10^9/L (median, IQR)	18 (10–32)	13 (8–22)	27 (12–47)	–11 (–14 to –7)
Haemoglobin, g/dL (median, IQR)	9.8 (7.8–11.8)	8.0 (6.9–9.4)	11.6 (10.2–12.8)	–3.4 (–3.7 to –3.0)
WBC, 10^9/L (median, IQR)	8.4 (6.6–11.1)	8.9 (6.7–12.4)	8.1 (6.5–10.3)	0.7 (0.1–1.4)
Schistocytes, % of positive samples	97	99	96	3 (–1 to 9)[b]
LDH, IU/L (median, IQR)	1,177 (628–1,777)	1,462 (939–2,147)	756 (506–1,369)	607 (445–765)
Total bilirubin, mg/dL (median, IQR)	2.1 (1.3–3.1)	2.2 (1.6–3.4)	1.8 (1.1–2.8)	0.5 (0.3–0.8)
Direct bilirubin, mg/dL (median, IQR)	0.5 (0.3–0.7)	0.5 (0.4–0.7)	0.4 (0.2–0.5)	0.15 (0.09–0.20)

- ≤ 0.1 likely to be deficient (< 10 – 12 %) - confirmation and quantification
- ≥ 0.4 No deficiency other diseases, aHUS cannot rule out (PLASMIC score?)
- Confirmation and quantification antibodies once a week Wednesday?
- Acustar?

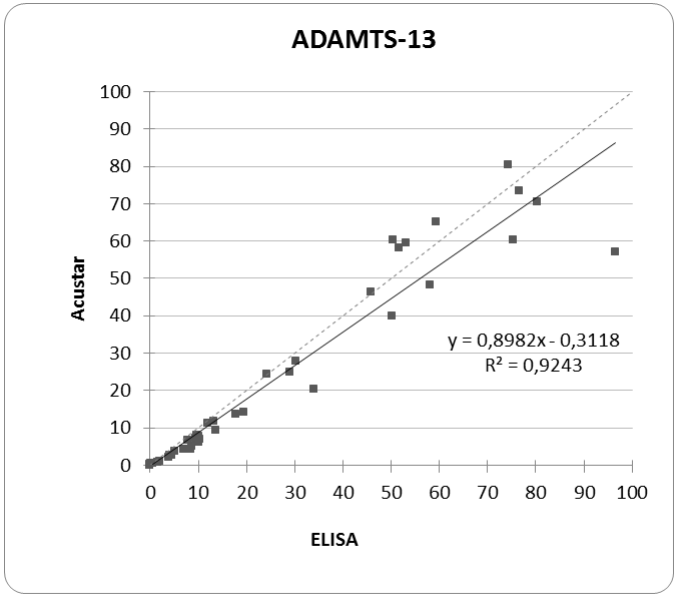
Mancini I et al, *Thromb Haemost* 2019; 119: 695-704

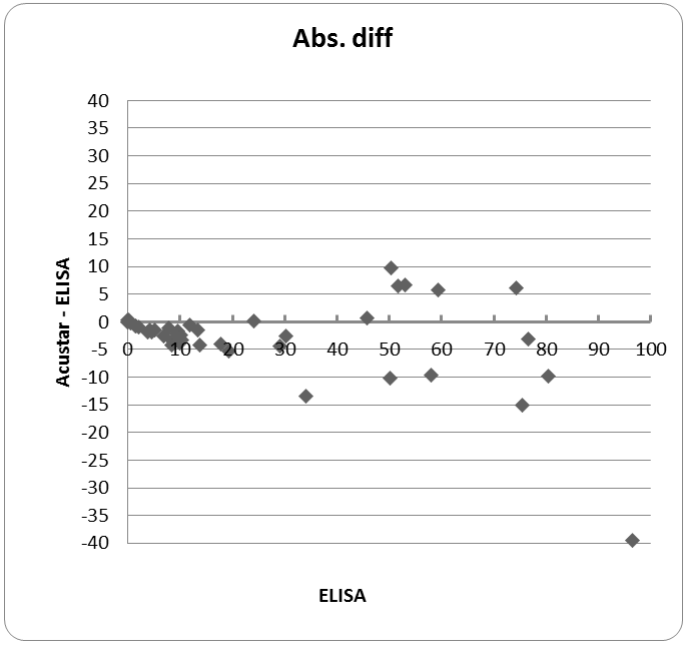
ACCUSTAR HEMOSIL ADAMTS-13

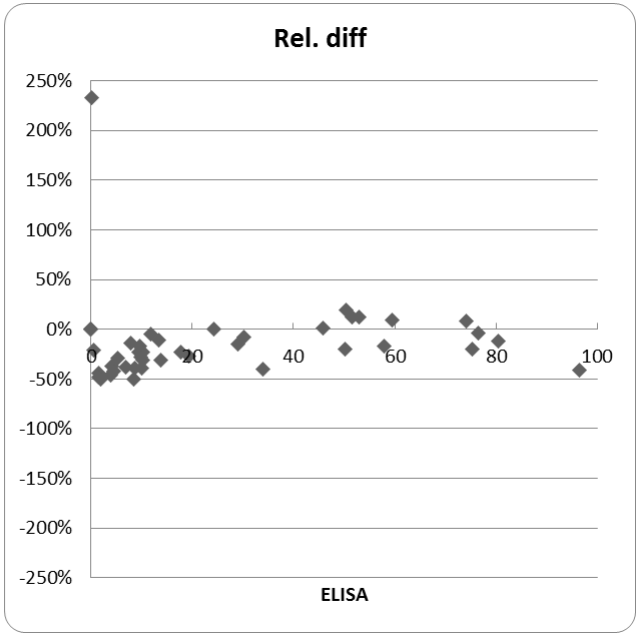
43 samples previosly tested with TECHNOZYM ADAMTS-13 ACTIVITY

ELISA %	ACCUSTAR %	RESULT		ELISA %	ACCUSTAR%	RESULT		ELISA %	ACCUSTAR %	>UTFALL
13,7	9,5	FALSE PATHOLOGICAL		6,9	4,3	PATHOLOGICAL		29,1	24,8	GREYZONE
0	<0,2	PATHOLOGICAL		10,3	7,1	PATHOLOGICAL		19,4	14,2	GREYZONE
3,9	2,1	PATHOLOGICAL		9,8	7,1	PATHOLOGICAL		74,2	80,3	NORMAL
4,1	2,6	PATHOLOGICAL		0	<0,2	PATHOLOGICAL		80,4	70,6	NORMAL
8,6	5,2	PATHOLOGICAL		8,4	4,2	PATHOLOGICAL		76,5	73,4	NORMAL
1,6	0,9	PATHOLOGICAL		11,9	11,3	GREYZONE		75,4	60,3	NORMAL
0,15	0,5	PATHOLOGICAL		17,7	13,6	GREYZONE		96,5	57	LIP/IKT NORMAL
4,5	2,6	PATHOLOGICAL		24,2	24,3	GREYZONE		50,1	39,9	NORMAL
0	0,4	PATHOLOGICAL		10	10	PATHOLOGICAL		45,8	46,5	LIP NORMAL
1,5	0,8	PATHOLOGICAL		7,9	10	PATHOLOGICAL		50,4	60,2	NORMAL
2	1	PATHOLOGICAL		7,9	10	PATHOLOGICAL		53	59,6	NORMAL
0,6	0,5	PATHOLOGICAL		34	40	GREYZONE		58	48,3	NORMAL
9,4	7,2	PATHOLOGICAL		13,3	40	GREYZONE		59,4	65,2	NORMAL
5,2	3,7	PATHOLOGICAL		30,3	27,8	GREYZONE				
9,6	8	PATHOLOGICAL		10,2	7,9	PATHOLOGICAL				

RED: PATHOLOGICAL ≤ 10%, GREEN : NORMAL ≥ 40%, GREYZONE:>15%-40%


ADAMTS-13
Acustar
ELISA
y = 0,8982x - 0,3118
R² = 0,9243


Abs. diff
Acustar - ELISA
ELISA


Rel. diff
ELISA

True pathologic 23

False pathologic 1

True normal 19

False normal 0

SENSITIVITY 100%

SPECIFICITY 95%

Bias -14%

Kappa = 0.97	FRETS		Total
Hemosil	< 10%	≥ 10%	
< 10 %	44	0	44
≥ 10%	2	130	132
Total	46	130	176

Kappa = 0.97	TECHNOZYM		Total
Hemosil	< 10%	≥ 10%	
< 10 %	44	0	44
≥ 10%	1	131	132
Total	45	131	176

Valsecchi et al, *ISTH* 2019

PROPOSAL

- THROMBOCYTOPENIA

- Schistocytes and LD obligatory no test without
- If high Hemosil ADAMTS-13 special coagulation Mo-Fr: 9-15 (routine coagulation all days 08-19)
- If ≤ 10% clear deficiency - confirmation not necessary antibodies (ELISA?)
- 10-40% grey zone
- > 40% no deficiency other diseases
- > 10% aHUS cannot rule out (PLASMIC score?)

PLASMIC score

Table 1
The PLASMIC Scoring System to Predict the Likelihood of ADAMTS13 Less Than 10%[a]

Criteria
1. Platelet count $<30 \times 10^9$/L
2. MCV <90 fL
3. Creatinine <2.0 mg/dL
4. INR <1.5
5. Evidence of hemolysis based on any of the following:
Reticulocyte count >2.5%
Indirect bilirubin >2.0 mg/dL
Undetectable haptoglobin
6. No active cancer
7. No history of bone marrow or solid organ transplantation

ADAMTS13, a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13; INR, international normalized ratio; MCV, mean corpuscular volume; PLASMIC, platelets, lysis, active cancer, stem cell or solid organ transplant, MCV, INR, and creatinine.
[a]If the total criteria are 0-4, the risk is low; 5-6, intermediate; 7, high.

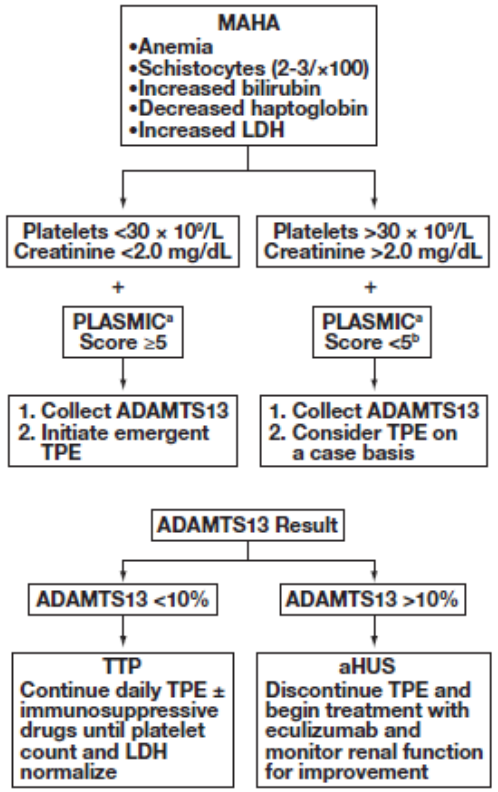


Figure 1 Algorithmic approach to the diagnosis of TTP and aHUS. ADAMTS13, a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13; aHUS, atypical hemolytic uremic syndrome; LDH, lactate dehydrogenase; MAHA, microangiopathic hemolytic anemia; PLASMIC, platelets, lysis, active cancer, stem cell or solid organ transplant, mean corpuscular volume, international normalized ratio (INR), and creatinine; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura. [a]All components of the PLASMIC score must be evaluated for an accurate score. [b]Preexisting liver or renal disease may falsely lower the PLASMIC score due to baseline elevations in the INR and creatinine.

Williams LA et al, *Am J Clin Pathol* 2016; 145: 158-65

Utvidgad komplementanalys

Skriv ut sidan

Följande analyser kan utföras.

	Sort	Normalfynd	Mätområde	Metod	Provtyp	Minsta mängd
C1 INH funktion	%	70-130	0-200	enzymreaktion	plasma	150 µL
C1r	%	71-133	5-400	Raket	serum	150 µL
C1s	%	72-146	5-500	Raket	serum	150 µL
C3NeF 1	%	<10	5-100	C3-klyvning	serum	300 µL
C3NeF 2	%	<10	5-100	Hämolys	serum	300 µL
C4-typning	Utlåtande			Immunfixation	serum	150 µL
C4BP	%	58-102	5-400	Raket	serum	150 µL
C5	%	73-170	2-400	Raket	serum	150 µL
C6	%	63-154	6-400	Raket	serum	150 µL
C7	%	64-154	6-400	Raket	serum	150 µL
C8	%	45-203	6-400	Raket	serum	150 µL
C9		+	+/-	Immundiffusion	serum	150 µL
Faktor B	%	59-154	2-400	Raket	serum	150 µL
Faktor D	%	65-171	6-800	HIG	serum	150 µL
Faktor I	%	60-152	5-400	Raket	serum	150 µL
Faktor H	%	69-154	2-400	Raket	serum	150 µL
Faktor H-funktion	%	<5	0-100	Hämolys	serum, till labbet inom 4 timmar, annars skickas fryst	200 µL
Typning av MBL-variant gener	Utlåtande			PCR	Helblod i EDTA	5 mL (1 rör)
C2-brist mutation	Utlåtande			PCR	Helblod i EDTA	5 mL (1 rör)
Antikropparmot faktor H (IgG)	Enh/ml	<99	0->20 000	ELISA	serum	150 µl
Antikroppar mot C1-inhibitor(IgG)	Enh/ml			ELISA	serum	150 µl
Antikroppar mot C1-inhibitor(IgA)	Enh/ml			ELISA	serum	150 µl
Antikroppar mot C1-inhibitor(IgM)	Enh/ml			ELISA	serum	150 µl

Faktaägare: Lillemor Skattum
Uppdaterad: 2016-03-31

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