

TTP and other Thrombotic Microangiopathies

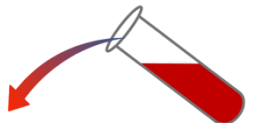


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Disclosures

- Research Support: BHF, Thrombosis UK, Anthos
- Advisory Boards (In past 5 years) Sanofi, Bayer, Anthos



Learning Objectives

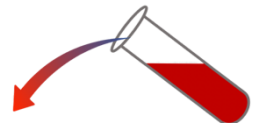
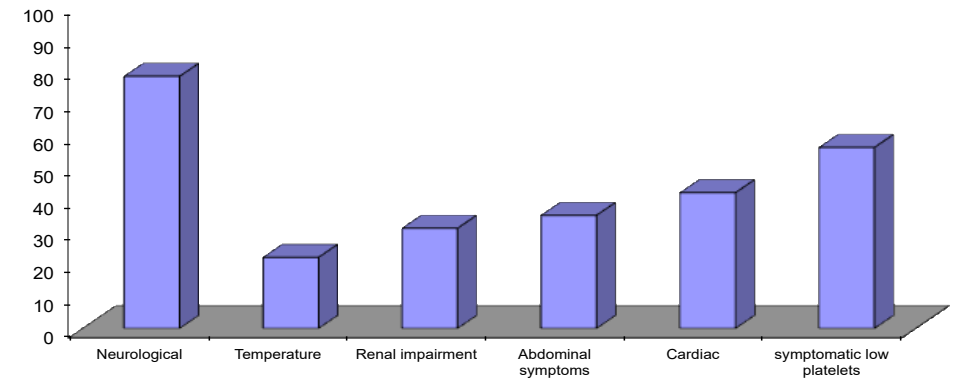
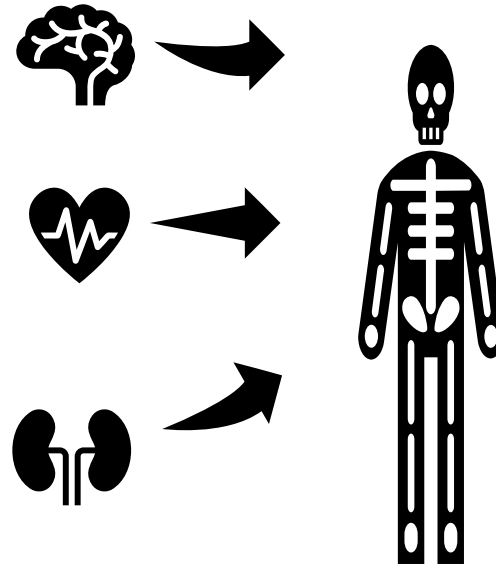
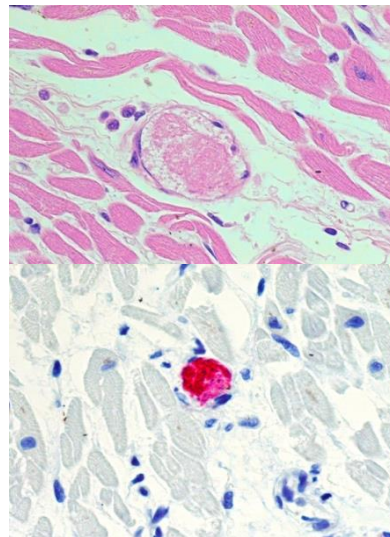
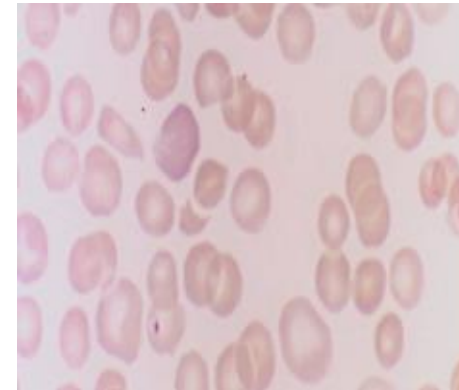
1. What is a TMA?
2. TTP
 - Pathophysiology
 - Diagnosis
 - Therapies
 - Long term effects and monitoring
- Congenital TTP
3. Complement mediated HUS
4. Other TMA



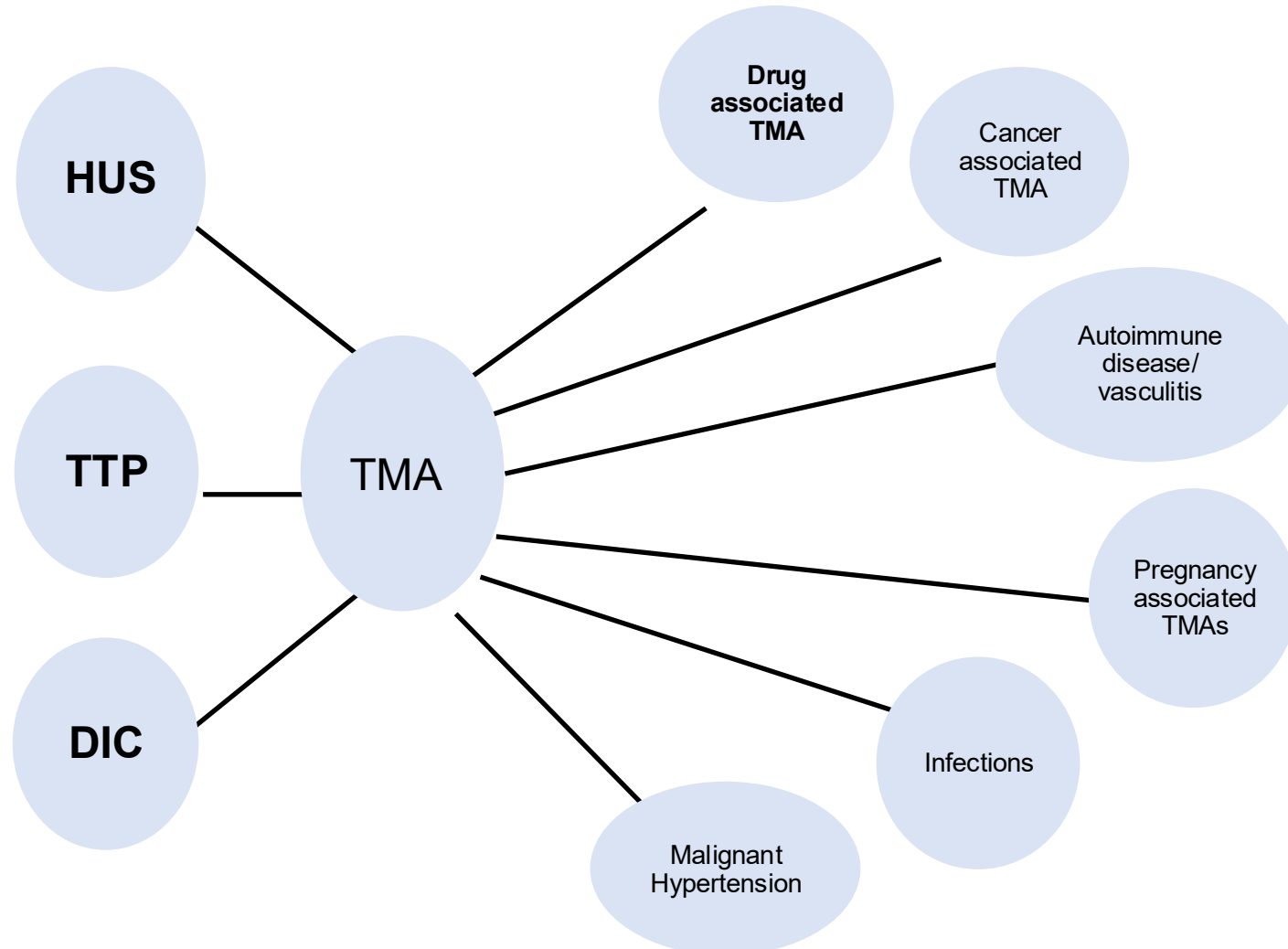
Current clinical diagnostic criteria of Thrombotic Microangiopathy

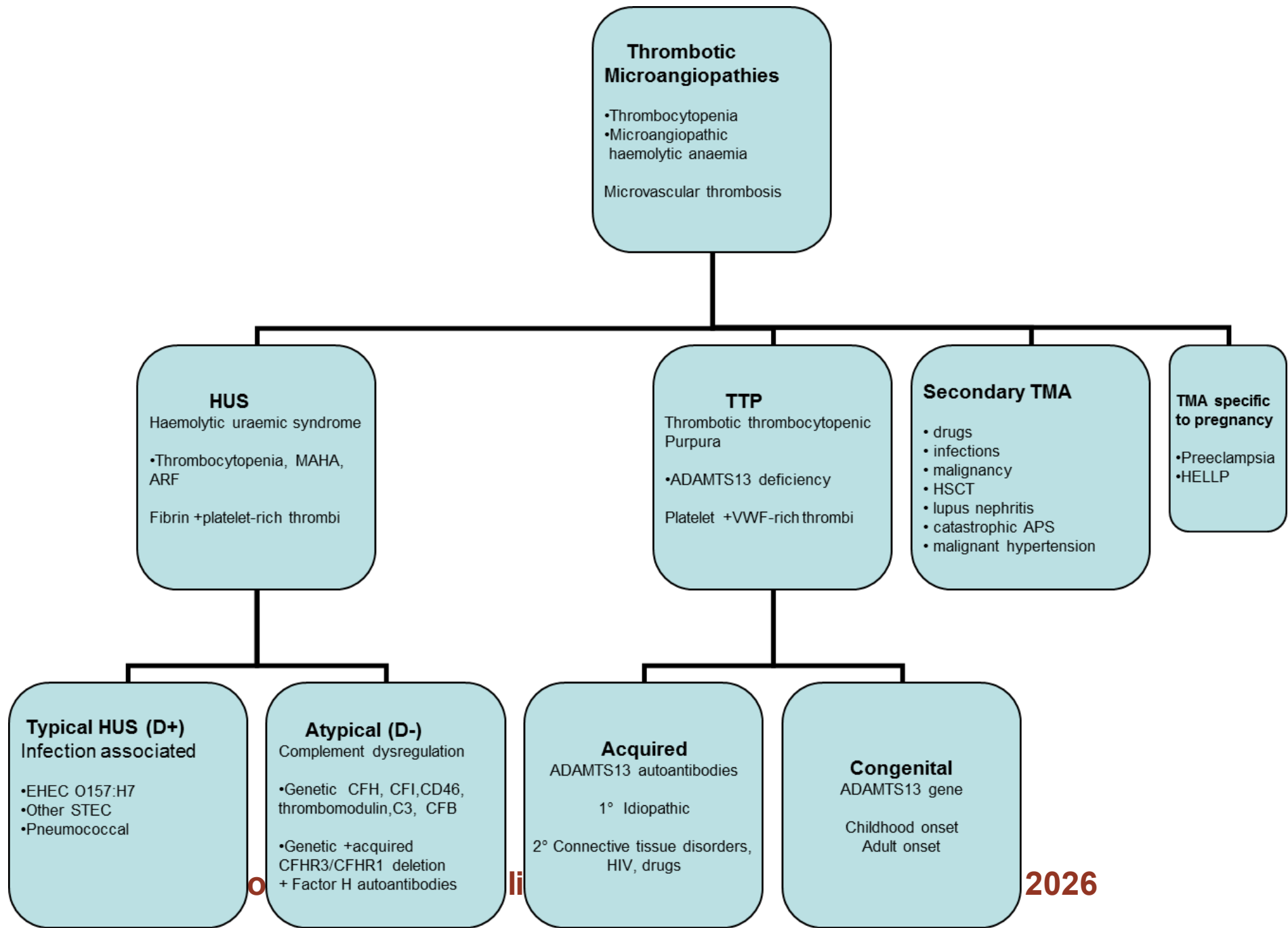
Thrombocytopenia

Microangiopathic haemolytic anaemia (MAHA)



Differential Diagnosis of Thrombotic Microangiopathy





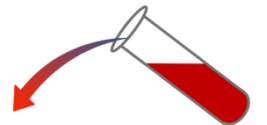
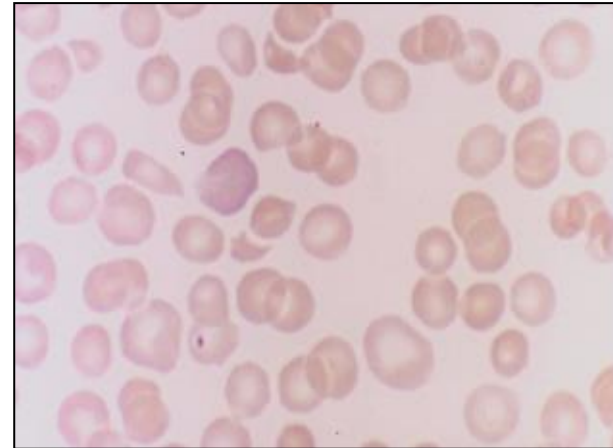
2026



Diagnosis of TTP – haematological emergency

- MAHA
- Thrombocytopenia
- Absence of underlying cause

Assume TTP
Commence PEX
urgently

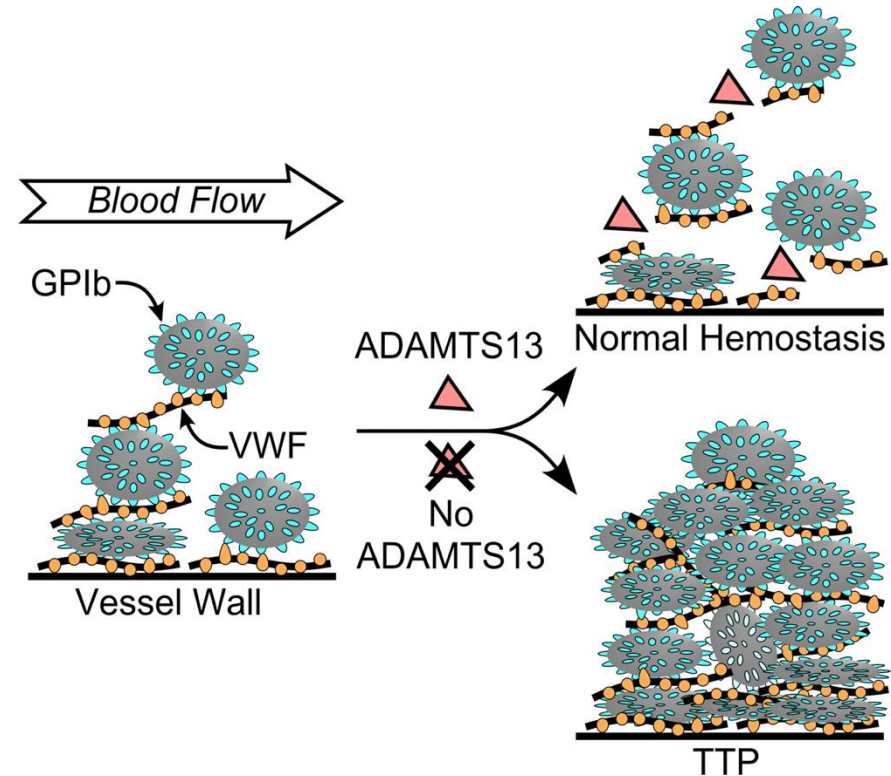


TTP and ADAMTS13 - background

A Disintegrin And Metalloproteinase with ThromboSpondin type-1 repeats 13



- ADAMTS13 is a Zn²⁺-dependent metalloprotease
- Secreted as active enzyme
- No natural inhibitor - long plasma ½-life
- Highly specific
 - Only cleaves VWF
 - Single site - A2 domain (Tyr1605-Met1606)
- Regulates VWF multimeric size/function in plasma



Laboratory tests

- FBC Anaemia & Thrombocytopenia ↑Reticulocytes
- Blood film MAHA - red cell fragmentation, polychromasia
- Normal coagulation
- -ve DAT
- ↑ bilirubin
- ↑ LDH
- Renal impairment
- Virology - HIV, Hepatitis A, B & C
- Pregnancy Test



ADAMTS13 assays

ADAMTS13 activity: in-house FRET assay



- Synthetic fluorogenic 73aa VWF peptide including scissile bond (FRET-VWF73).
- FRET design is a fluorescent molecule attached to a quenching group.
- If substrate is cleaved by ADAMTS13, then fluorescence is observed, but in the absence of ADAMTS13, cleavage does not occur and fluorescence is quenched

Kokame & Miyata, BJH, 2005

Anti-ADAMTS13 IgG: in-house ELISA



Diagnosis of TTP

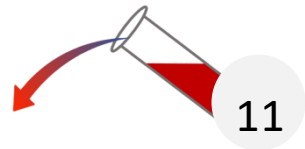
French Score		Point
Platelet count: X10 ⁹ /L	<30	1
Creatinine: mmol/L	<225	1

*The PLASMIC Score for TTP Prediction	
Component	Point
Platelet count <30 x 10 ⁹ per L	1
HemoLysis (indirect bilirubin >2 mg dL ⁻¹ , uncorrected reticulocyte > 2.5%, OR undetectable haptoglobin)	1
No Active cancer in previous year	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	1

Prediction of severe ADAMTS13 deficiency (Activity <10%)

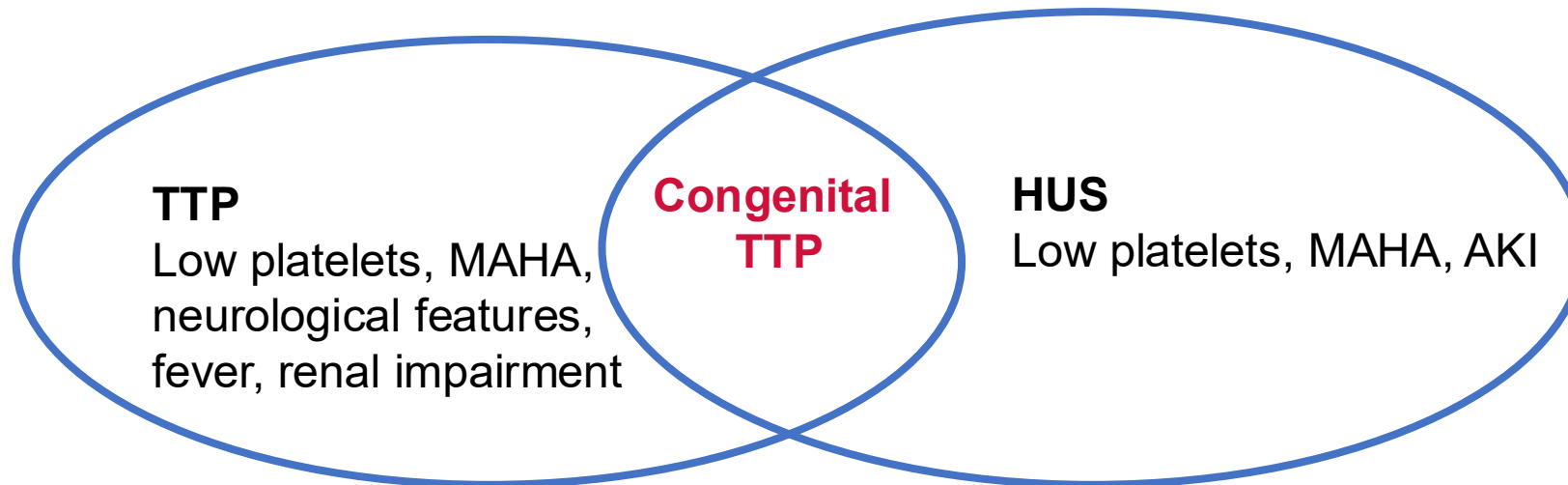
- 0 :2%
- 1: 70%
- 2: 94%

- High (**score 6 or 7**) vs low-intermediate risk (**score 0 to 5**)
- The model predicts severe ADAMTS-13 deficiency
- Positive predictive value of 72%
- Negative predictive value of 98%
- Sensitivity of 90%
- Specificity of 92%



Role of ADAMTS13 analysis in TTP/TMA diagnosis

ADAMTS13 analysis

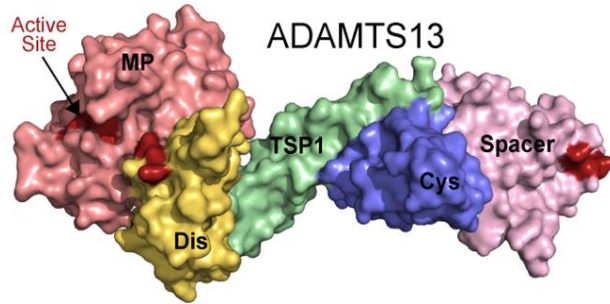


'Serum creatinine level $>150-200 \mu\text{mol/l}$ or a platelet count $>30,000/\text{mm}^3$ almost eliminates a diagnosis of severe ADAMTS13 deficiency'

Zuber J et al. Nat Rev Nephrol 2012;7

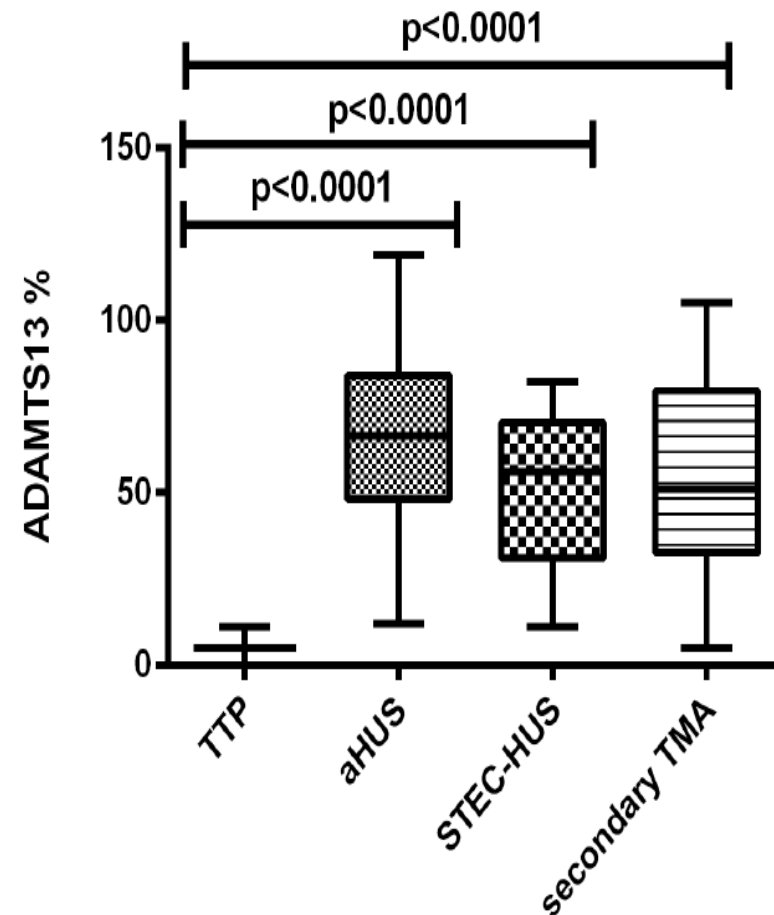


ADAMTS13 levels in TTP, HUS and TMAs

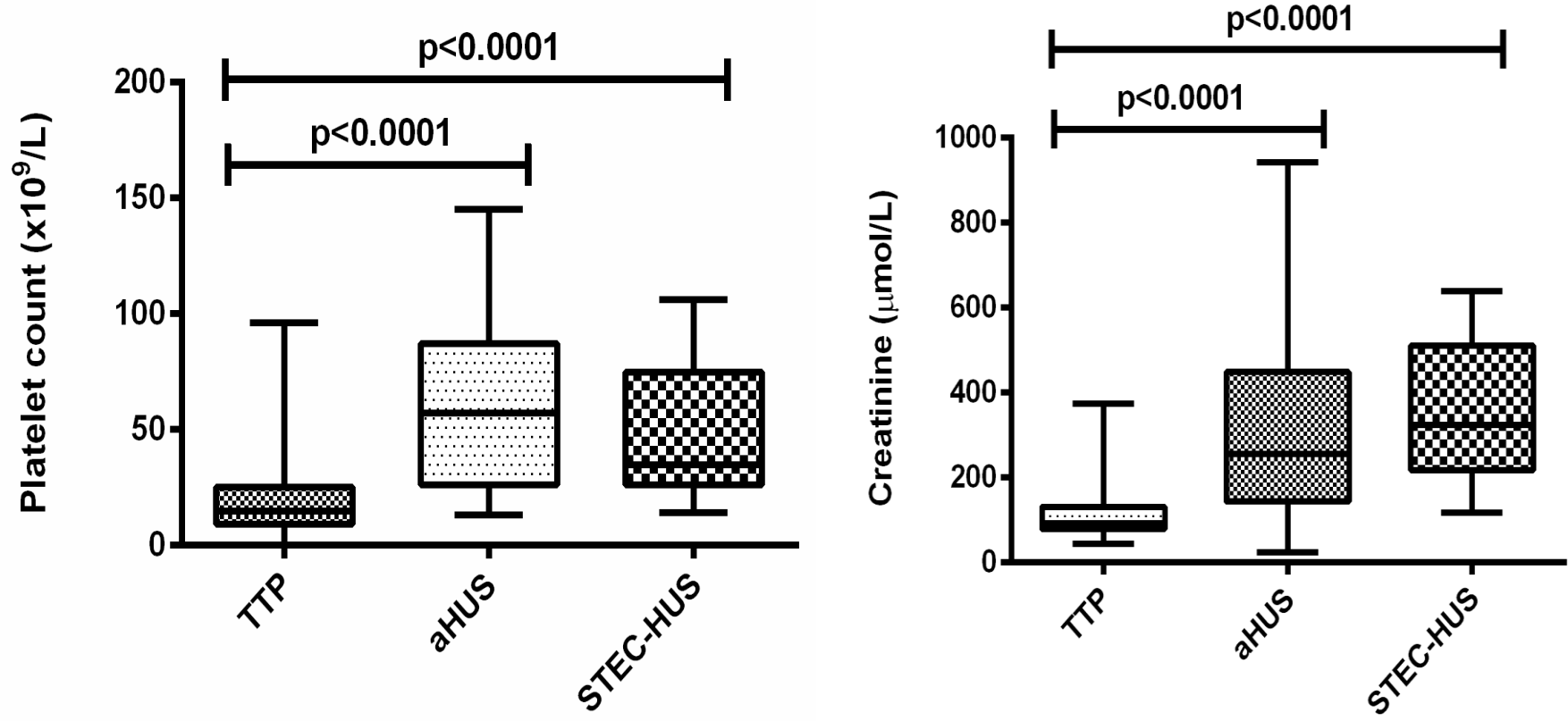


Patients with TTP had significantly lower median ADAMTS13 levels than aHUS, HUS or MAHA/TMA.

No significant difference in ADAMTS13 levels between patients in the aHUS, HUS or MAHA/TMA groups.

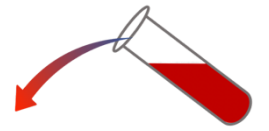


Platelets & Creatinine: from UK TTP Registry



35.3% aHUS group: platelet count <30 x 10⁹/L
 17.3% of TTP had a platelet count >30 x 10⁹/L

15.3% of TTP had a Creatinine >150 µmol/L



PLASMIC score to differentiate TTP from other causes of MAHA



Consecutive, unselected patients with new TTP diagnosis from UK TTP registry
'Non-TTP' (other TMAs) from UK TTP registry screening log
PLASMIC score applied retrospectively

Results 185 confirmed TTP 303 'Non-TTP' patients

Median PLASMIC score in TTP = 6 vs Non-TTP = 4

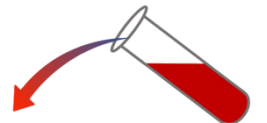
16% confirmed TTP cases had score < 5 → cannot reliably rule out TTP.

45% non-TTP cases had score ≥5 → potential unnecessary testing.

PLASMIC score sensitivity 84%, specificity 55%, PPV 53.5% and NPV 84.9% .

Conclusion Reliance on PLASMIC score < 5 alone to exclude TTP is not sufficient

Sharif *et al* ISTH 2024



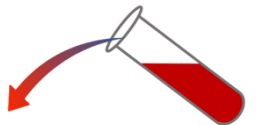
The future?

Can Machine Learning Supplant the
Plasmic Score in Improving the Early
Diagnosis of TTP?

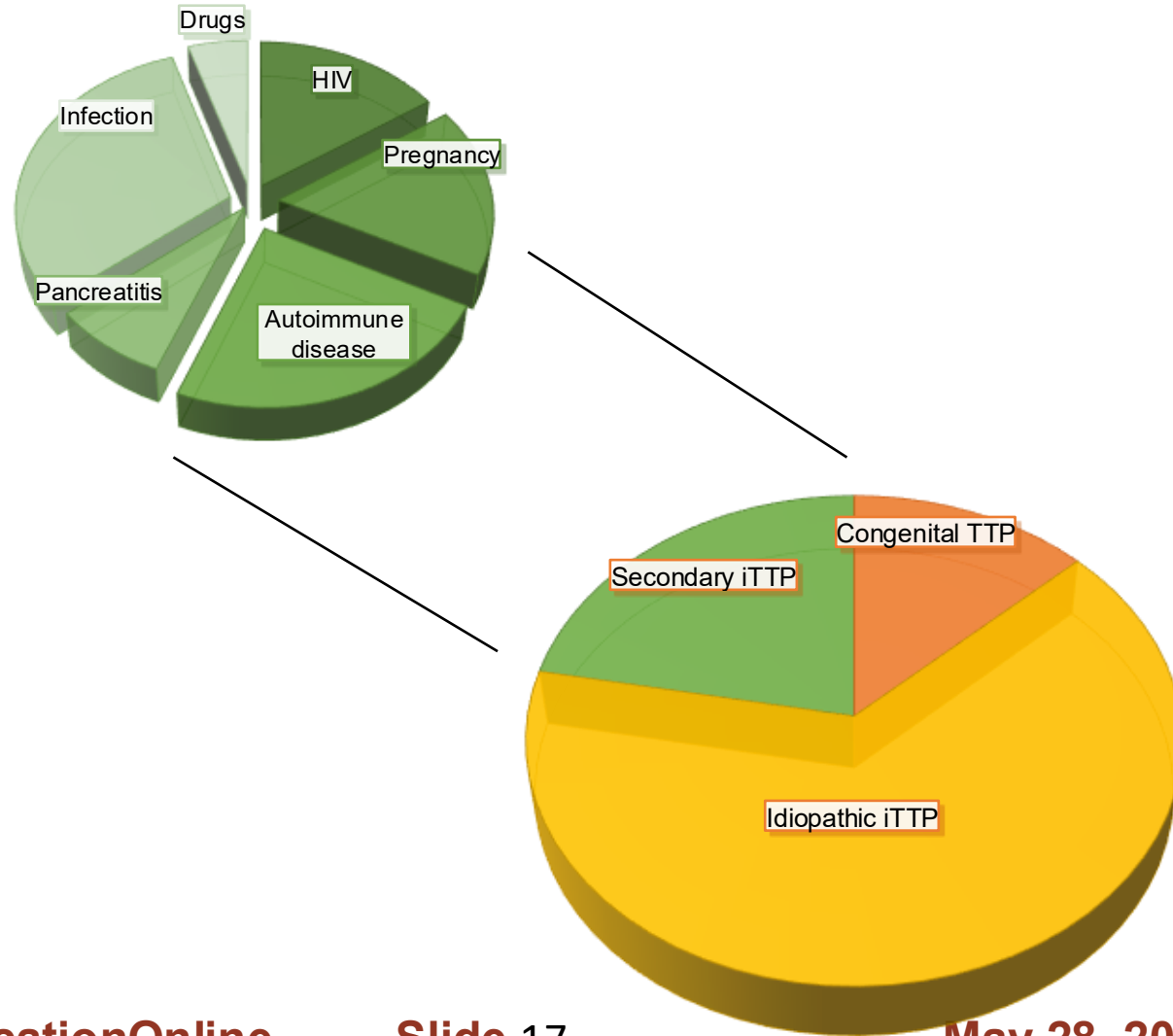
Abou-Ismaïl *et al* ASH 2024

Leveraging Generative AI in
Diagnosis of TMAs: Focus on TTP

Choi *et al* ASH 2024



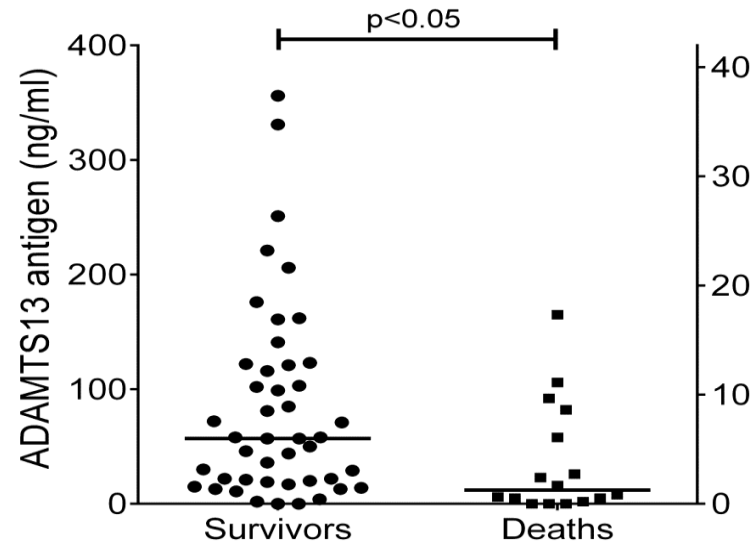
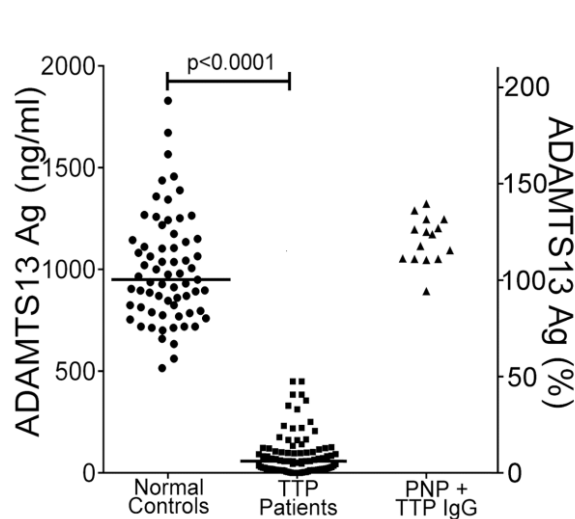
Subgroups of TTP



Anti-ADAMTS13 IgG are NOT all inhibitory

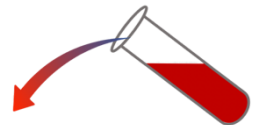
Group	N or C	Inhibitory potential	Number of patients
I	N	Inhibitory	10
II	N+C	Inhibitory	9
III	N+C	Mildly inhibitory	9
IV	N+C	Non-inhibitory	12
V	C	Non-inhibitory	3

- 15/43 patients had autoantibodies with no detectable inhibitory action
- 9/43 had only mildly inhibitory antibodies

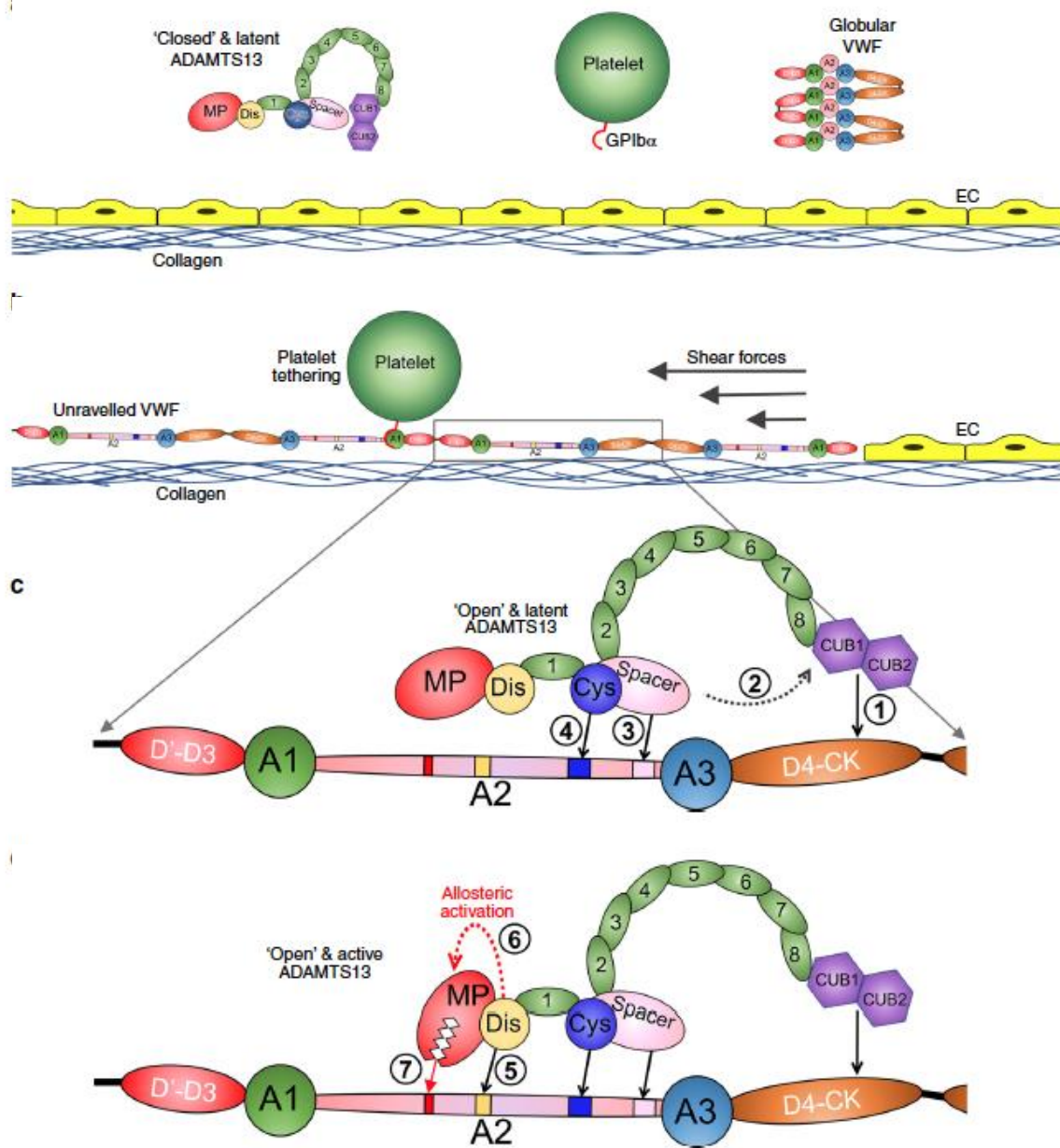


ADAMTS13 antigen < 13.5 ng/ml
 \uparrow likelihood of mortality
OR 5.7
 (95% CI 1.5-21.8; $p < 0.05$)

Thomas *et al* EBioMED 2015



Mode of action of ADAMTS13 – open and closed conformation

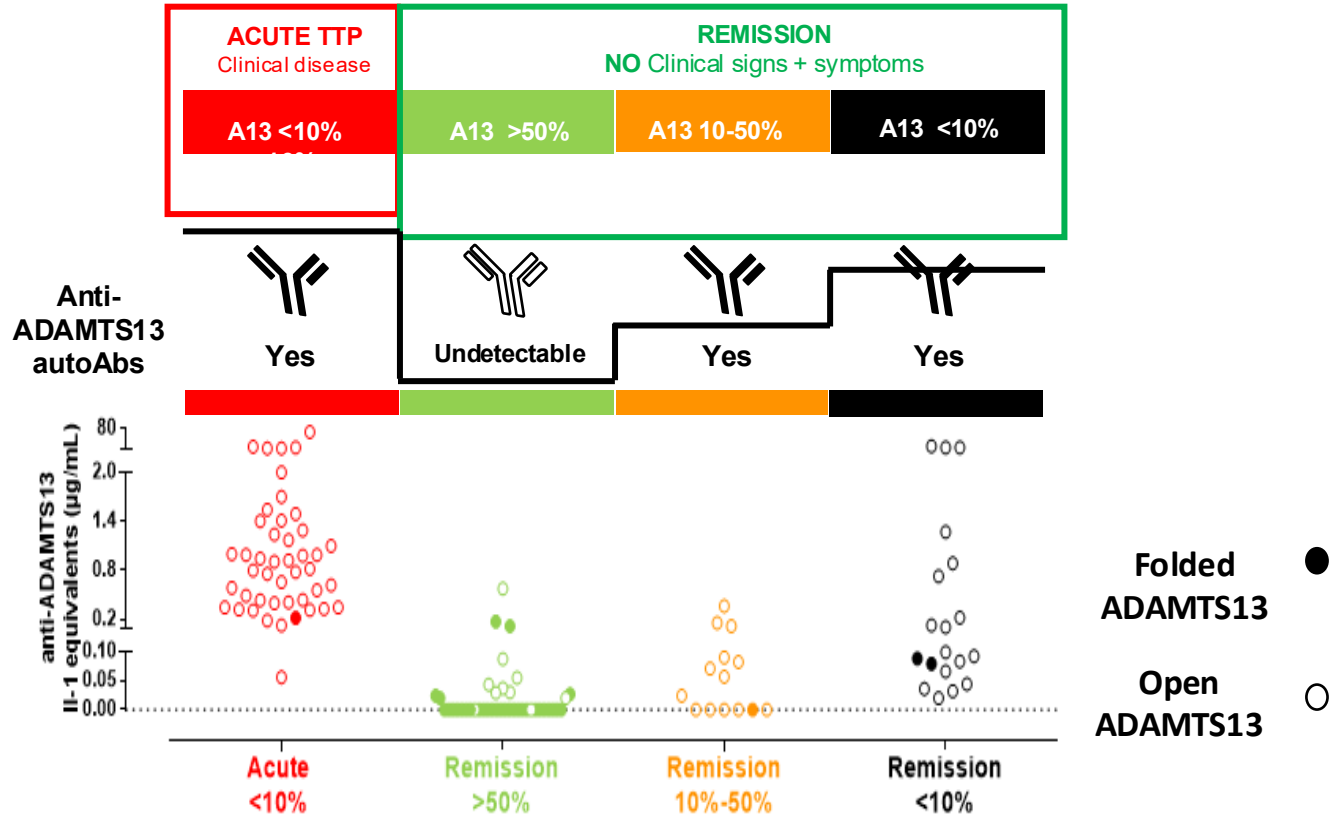


Petri et al Nat Comm 2019

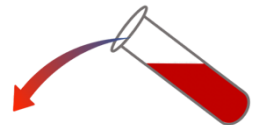
May 28, 2026



ADAMTS13 confirmation and TTP disease state



Roose *et al* JTH 2020



Prognostic Factors in acute iTTP

- ↑**Troponin** 68% at presentation 6 fold ↑ in mortality
- ↓**GCS** 28% at presentation 9 fold ↑ in mortality

➤ **Anti ADAMTS13 IgG levels**



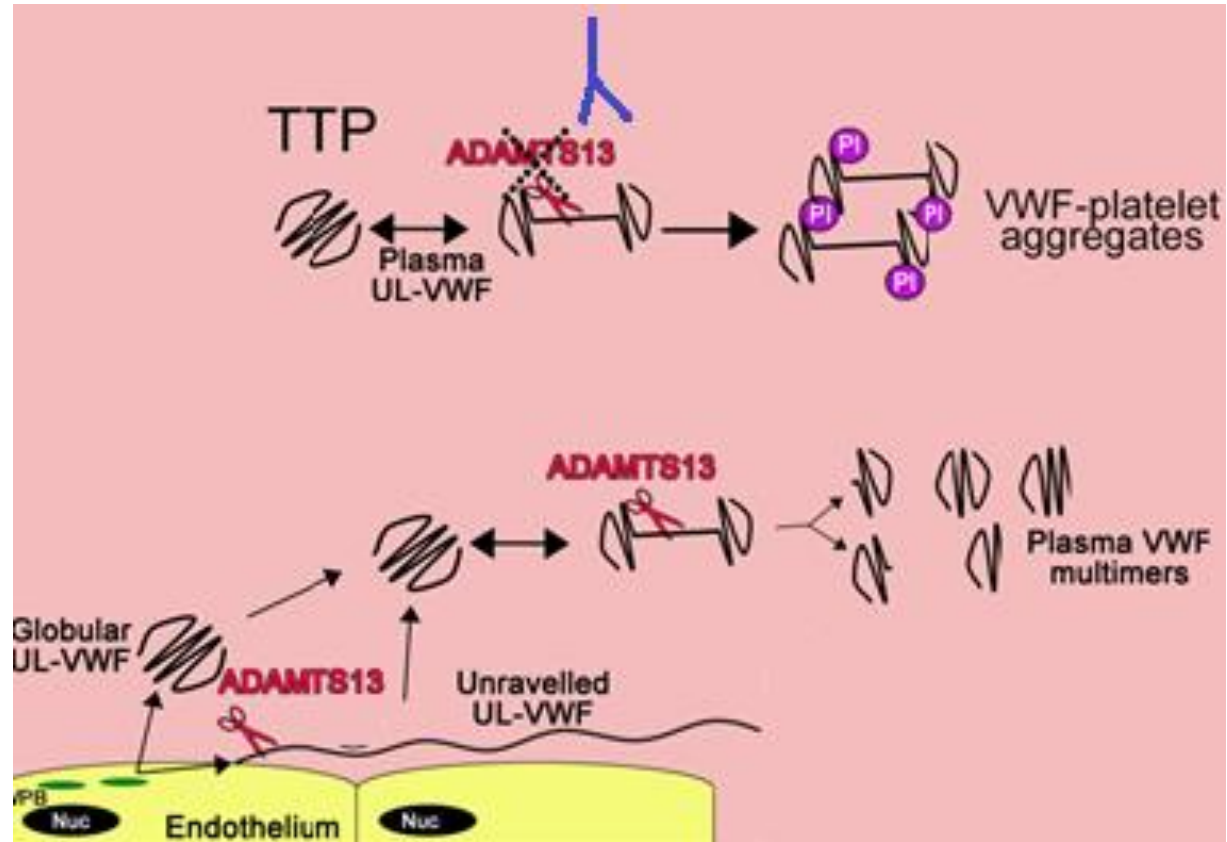
- Q4**
 - More likely to have ↑troponin (44% vs 87%, $p<0.0001$)
 - More likely to have ↓GCS (19% vs 41%, $p=0.035$)
 - More PEX to remission (10 vs. 20, $p=0.006$)
 - Increased mortality (5.0% vs 16.9%)

➤ **ADAMTS13 antigen levels**

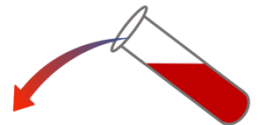
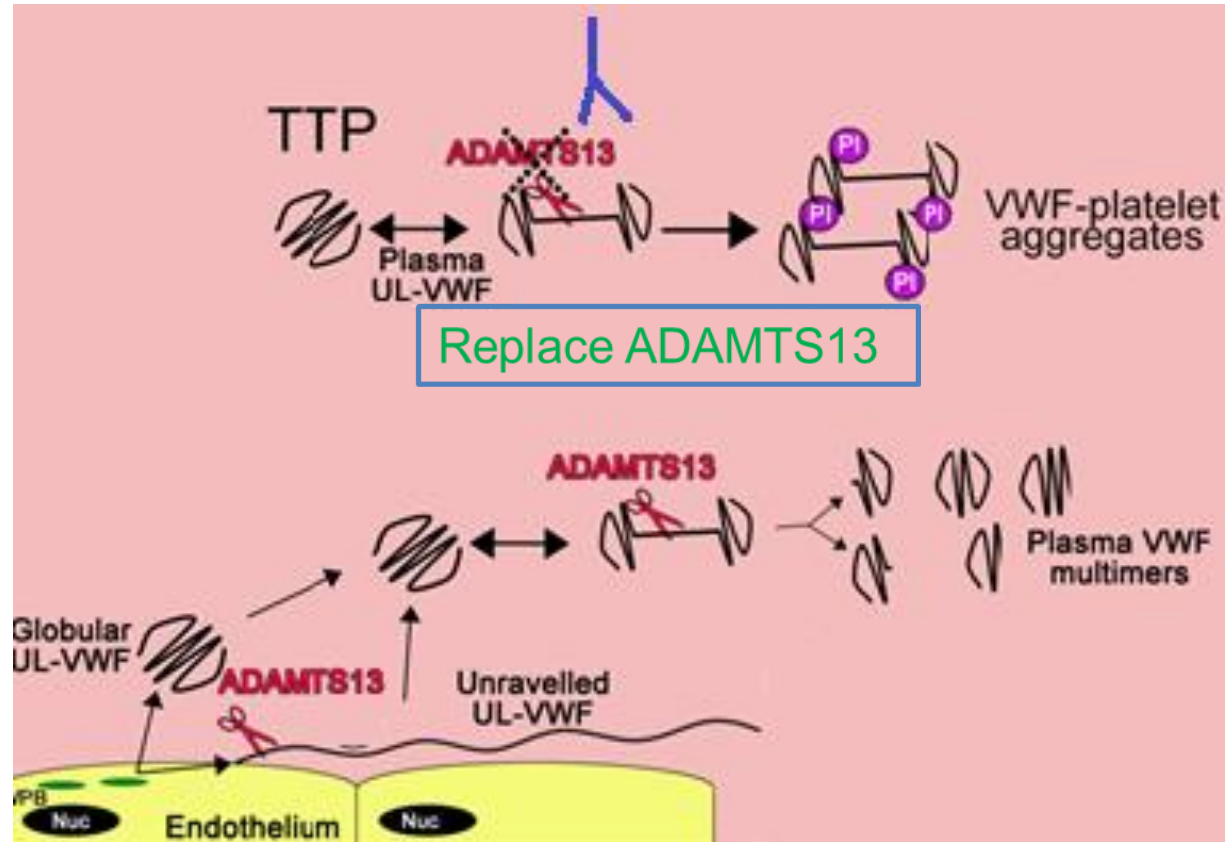
Highest mortality = ADAMTS 13 IgG >77% (Q4) and ADAMTS13 antigen <1.5% (Q1)
Mortality = 27.3%



How drugs work in TTP



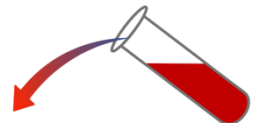
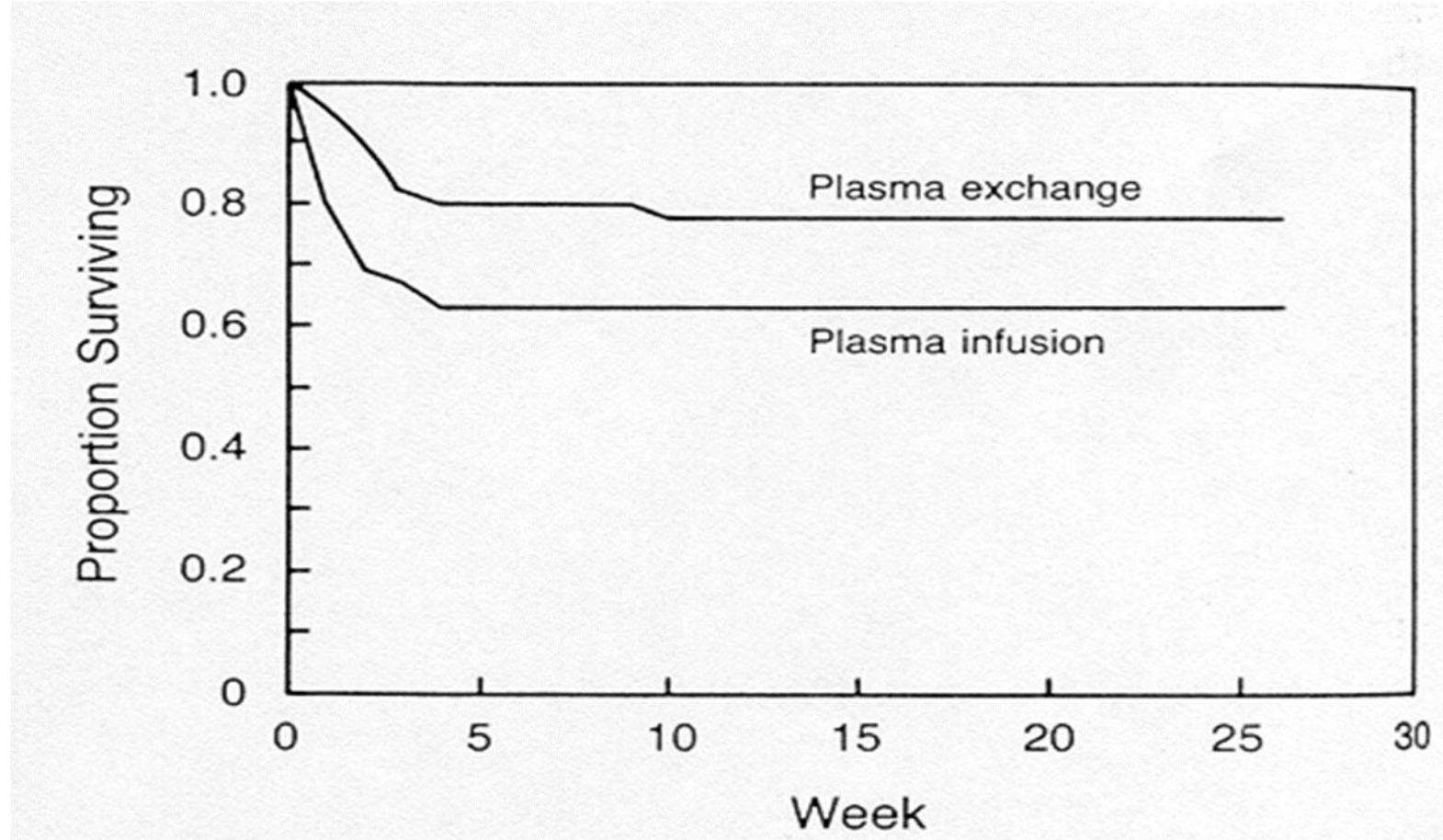
How drugs work in TTP

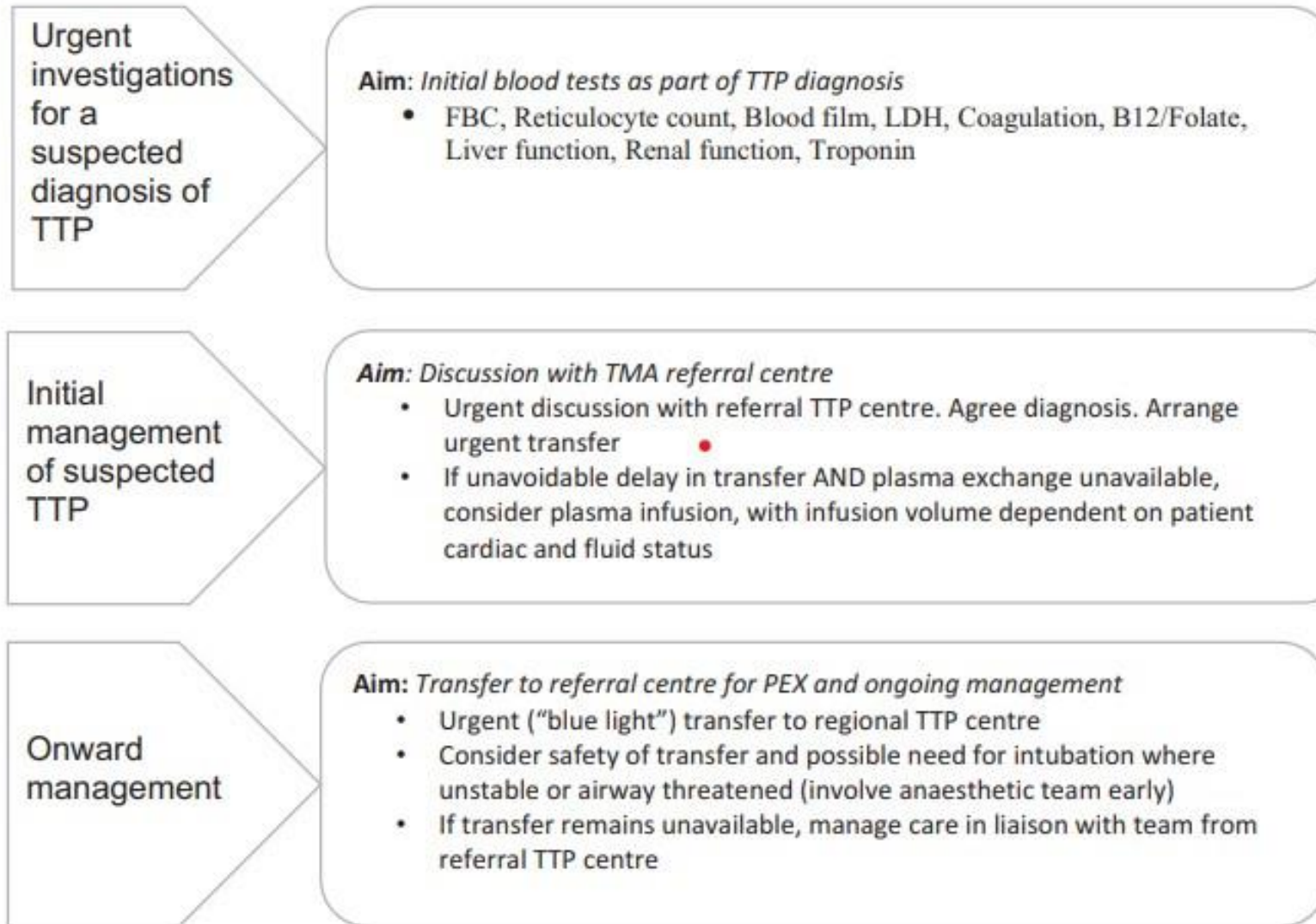


Treatment of TTP

Survival of patients with thrombotic thrombocytopenic purpura

Rock *et al*, NEJM 1991

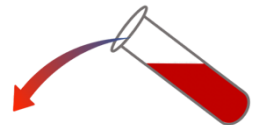
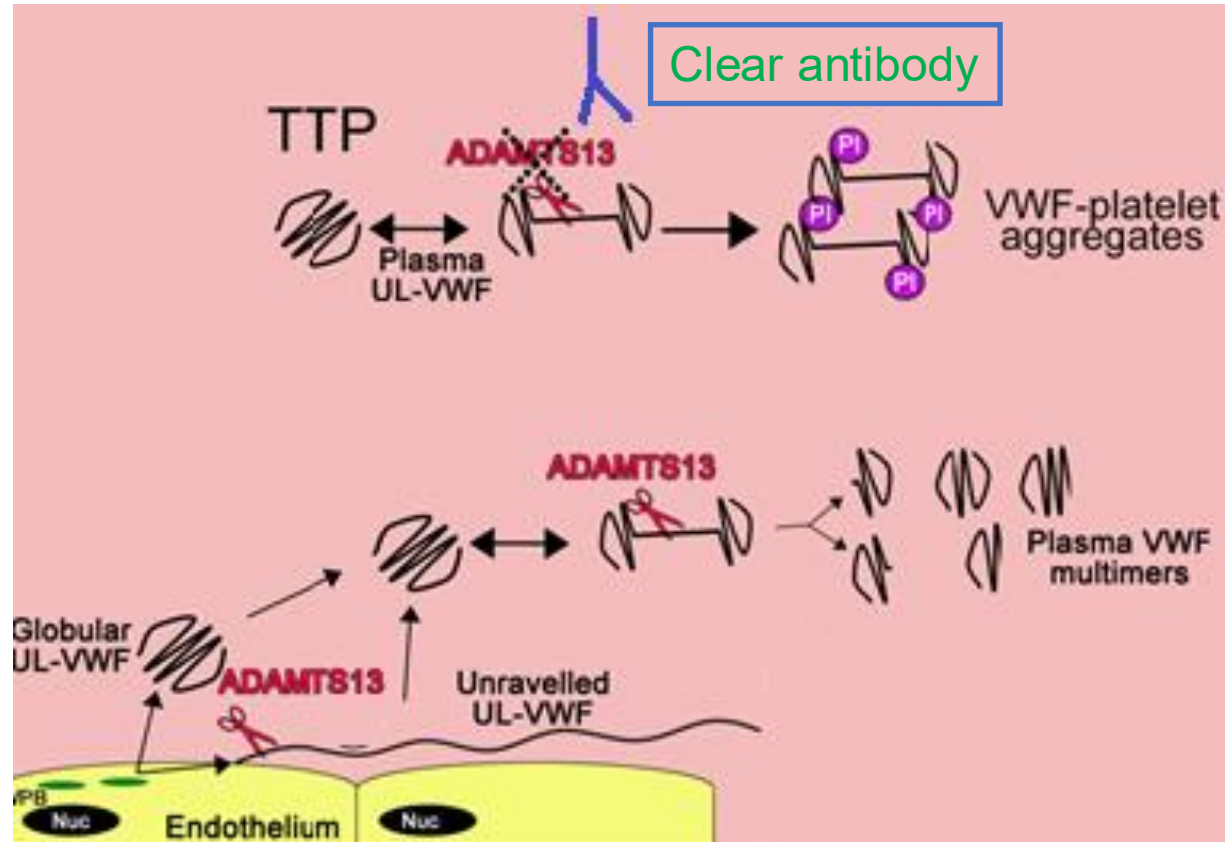




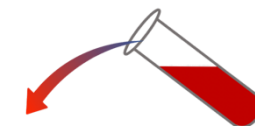
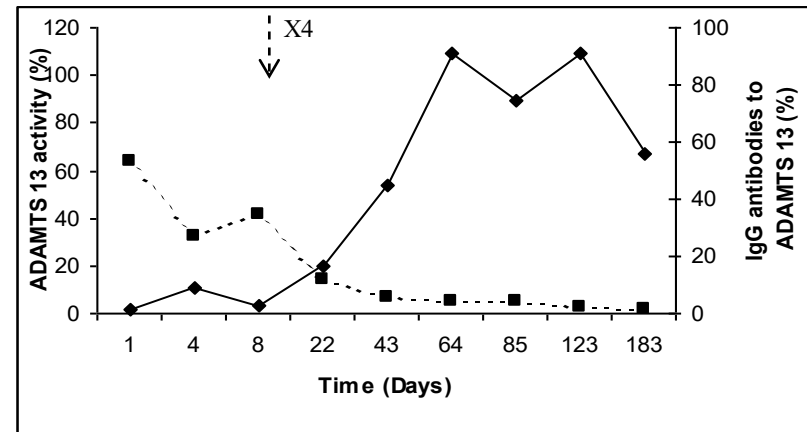
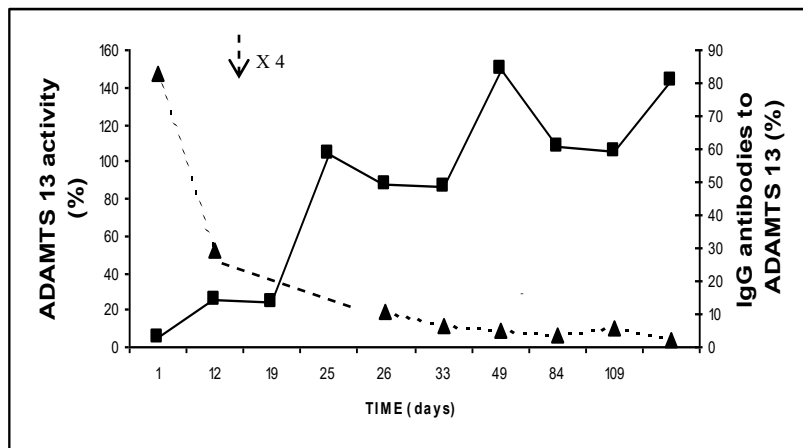
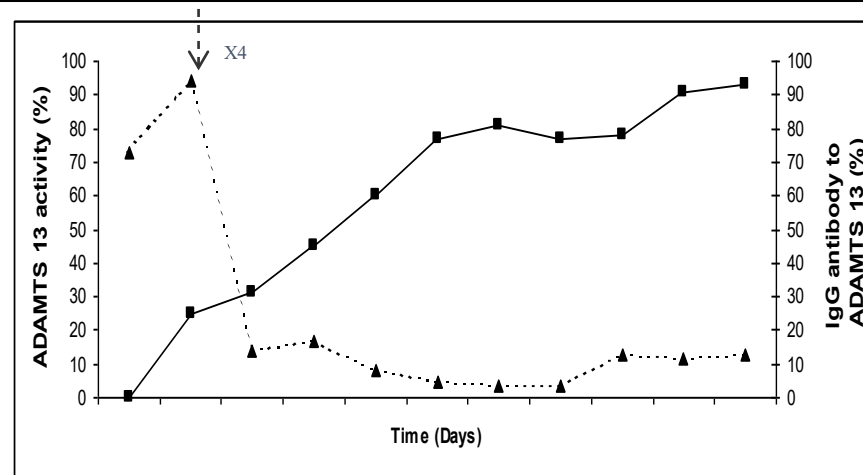
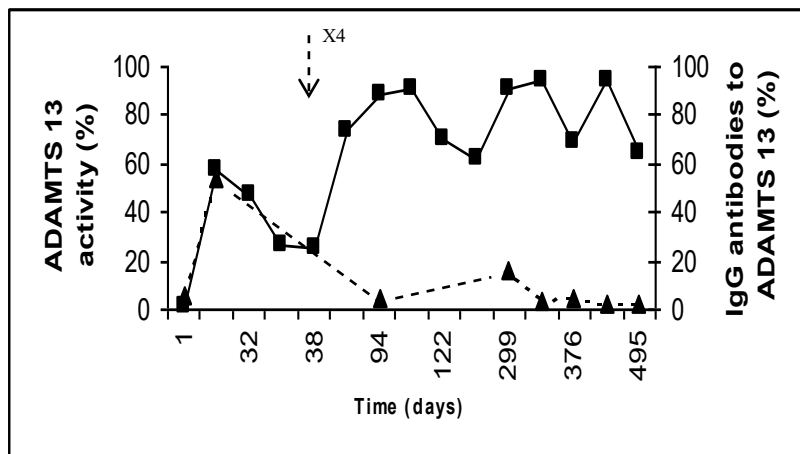
Scully *et al*, BJH 2024



How drugs work in TTP



ADAMTS13 activity & anti ADAMTS13 IgG antibodies and response to Rituximab in refractory TTP

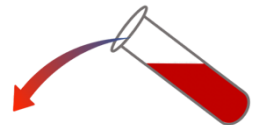
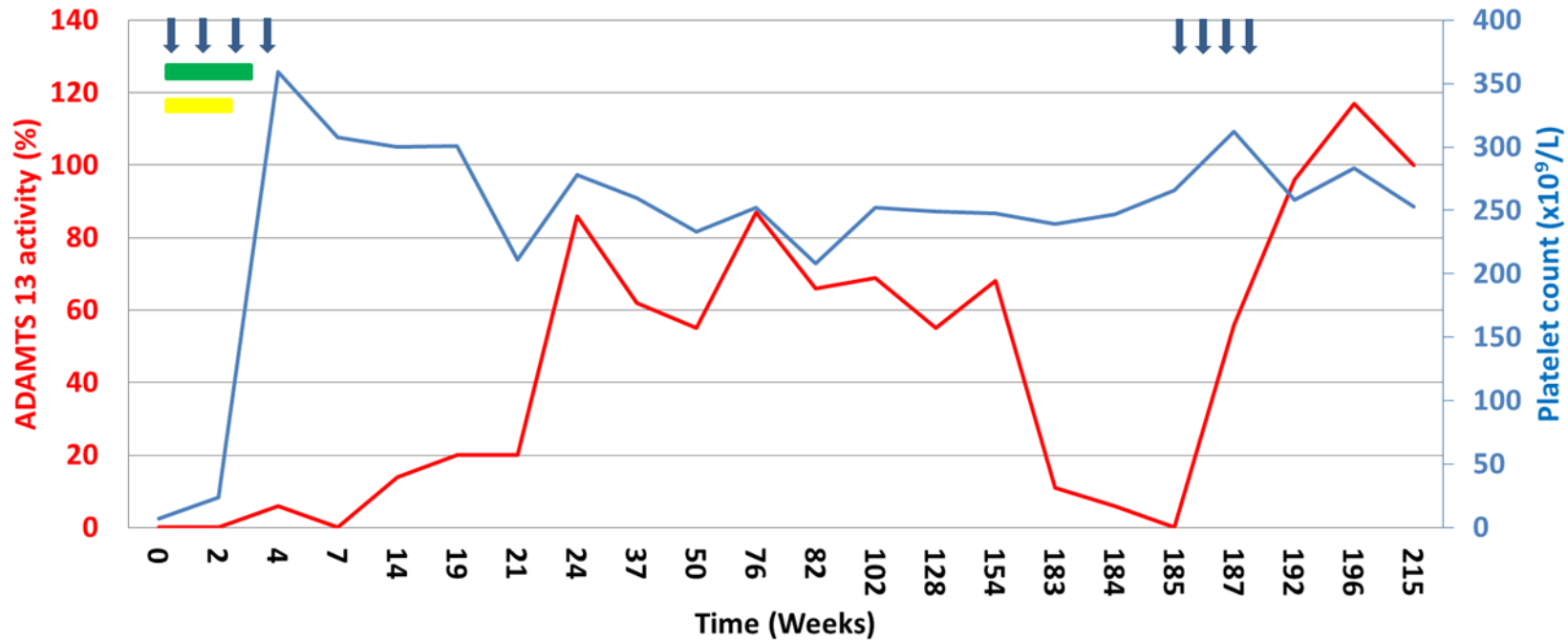


Upfront Rituximab - timing and outcome

	≤3 days from admission (n=52)	>3 days from admission (n=30)	
Median No. of PEX to CR (range)	16 (4-36)	24 (6-40)	p=0.03
Median Length of admission (range)	16 (4-86)	23 (7-52)	p=0.01
Median Time to CR from admission (range)	12 (4-52)	20 (4-42)	P<0.001
Median Time to CR from first infusion (range)	10 (2-50)	9 (0-30)	P=0.67

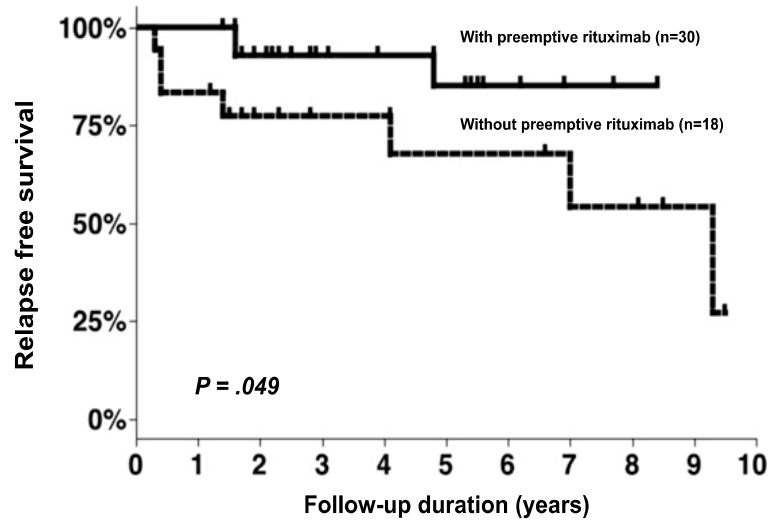


Elective Rituximab



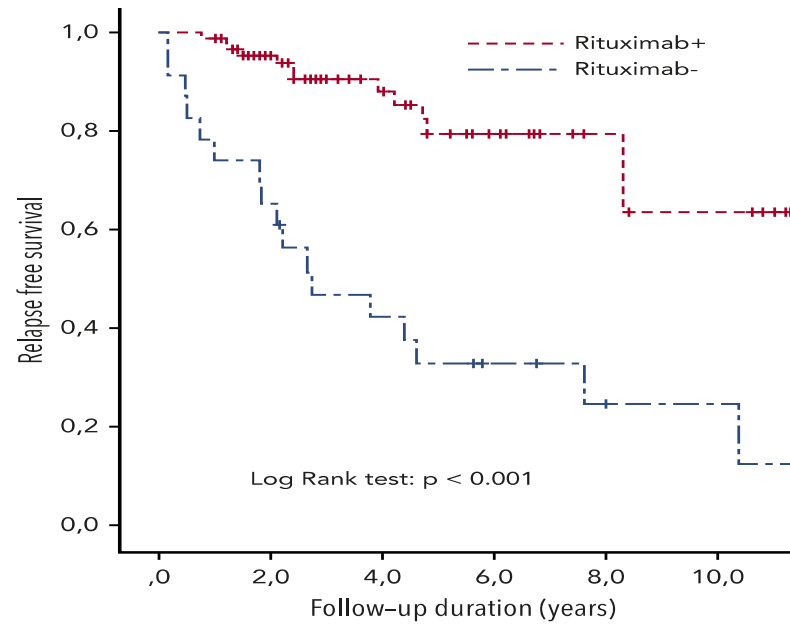
Elective Rituximab

Hie *et al*
Blood 2014

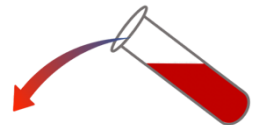


Numbers at risk

Rituximab	30	30	24	15	13	12	7	3	2	1
No rituximab	18	17	11	9	9	8	8	5	5	3

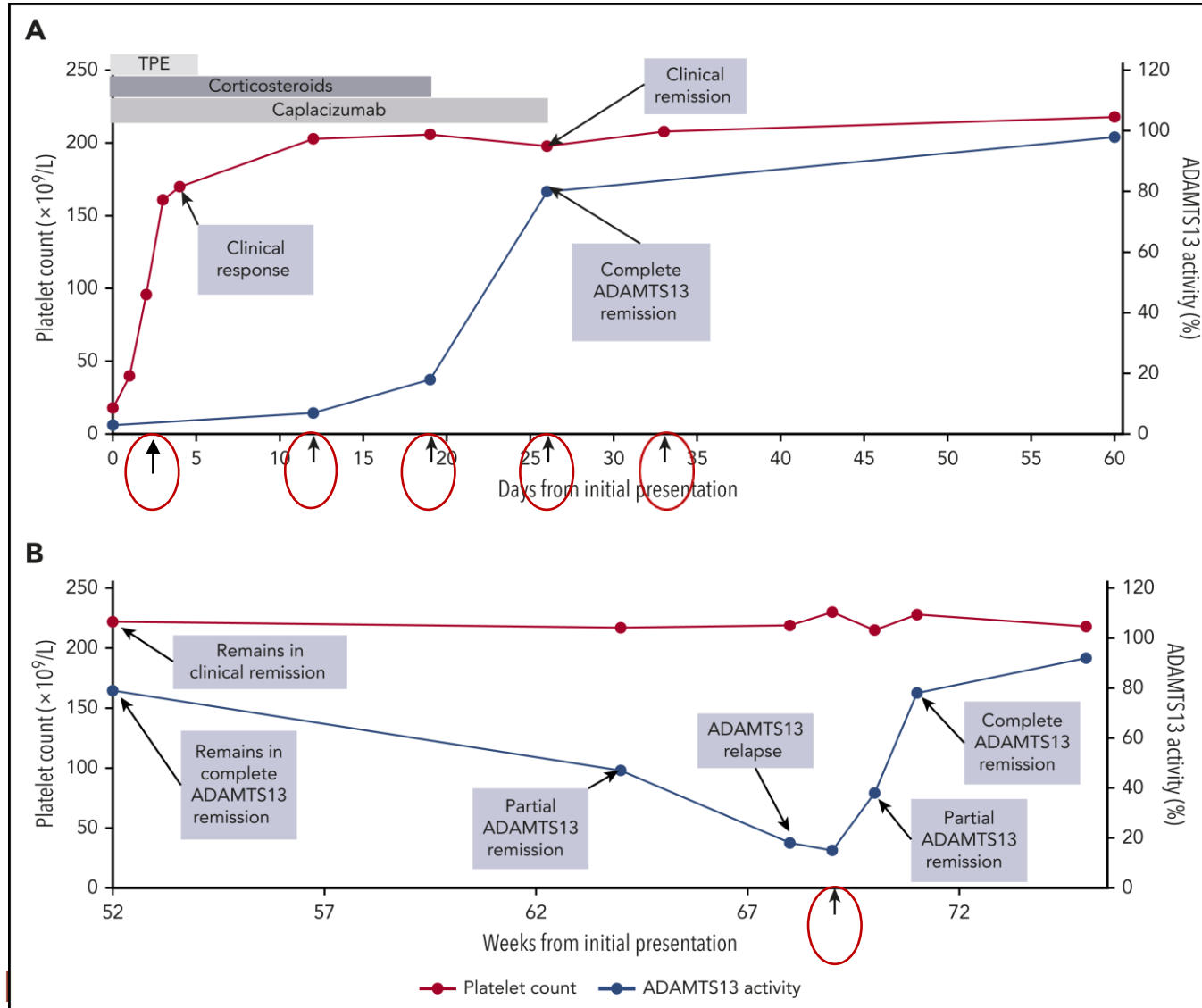


Jestin *et al*,
Blood 2018



Rituximab in iTTP

Early rituximab
in acute episode

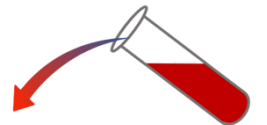


↑ Rituximab

Goal of iTTP therapy
= ongoing ADAMTS13 CR

Adapted from Cuker *et al* 2021

May 28, 2026



Elective rituximab
for ADAMTS13
relapse

Immune TTP – treatment

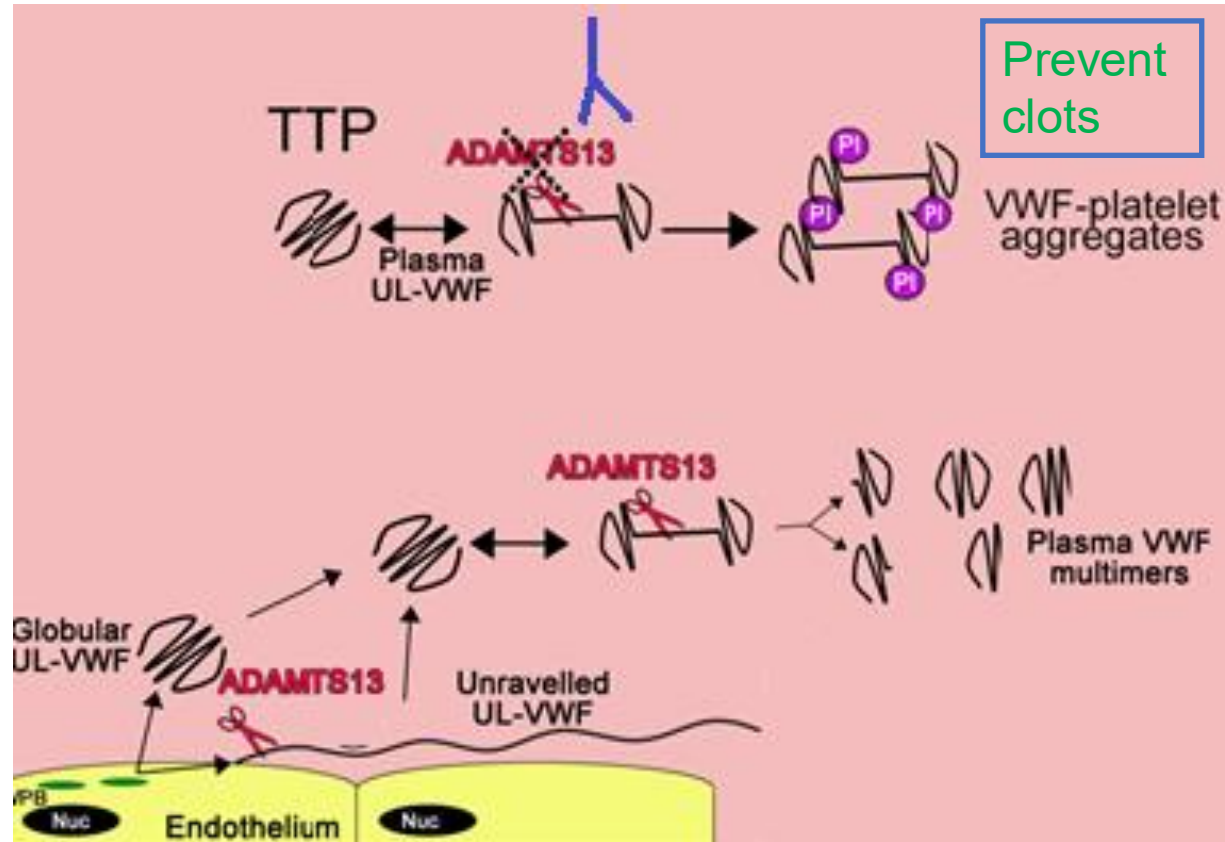
Current therapy	
Daily plasma exchange (PEX)	Immunosuppression (corticosteroids and/or rituximab)
<ul style="list-style-type: none">• removes ULvWF• removes autoantibodies• replenishes ADAMTS13	<p>inhibits autoantibody formation</p>

Issues:

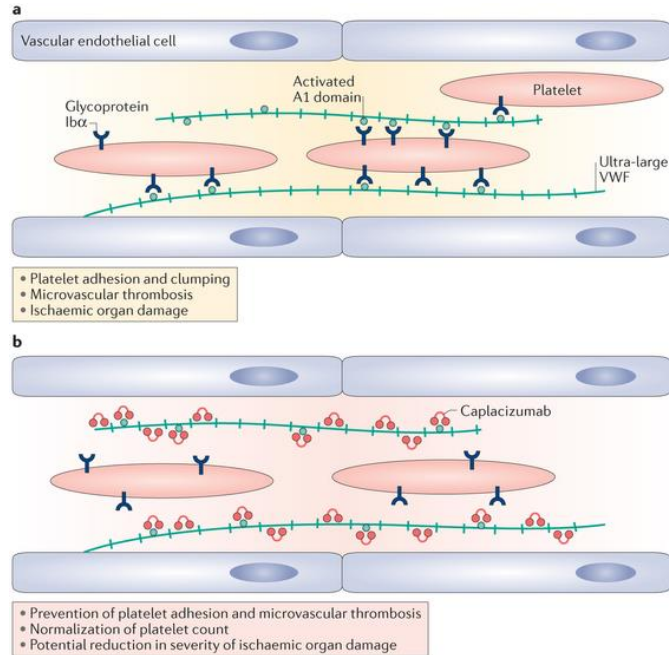
- Mortality of 10-20%
- Refractoriness to treatment (assoc with poor outcomes)
- Disease exacerbations



How drugs work in TTP



Caplacizumab – anti VWF nanobody



A single-domain antibody fragment - single monomeric variable antibody domain able to bind selectively to a specific antigen

Nature Reviews | Nephrology



The NEW ENGLAND
JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura

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

N Engl J Med 2016; 374:511-522 | February 11, 2016 | DOI: 10.1056/NEJMoa1505533

hematologyEducationOnline

ORIGINAL ARTICLE

Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura

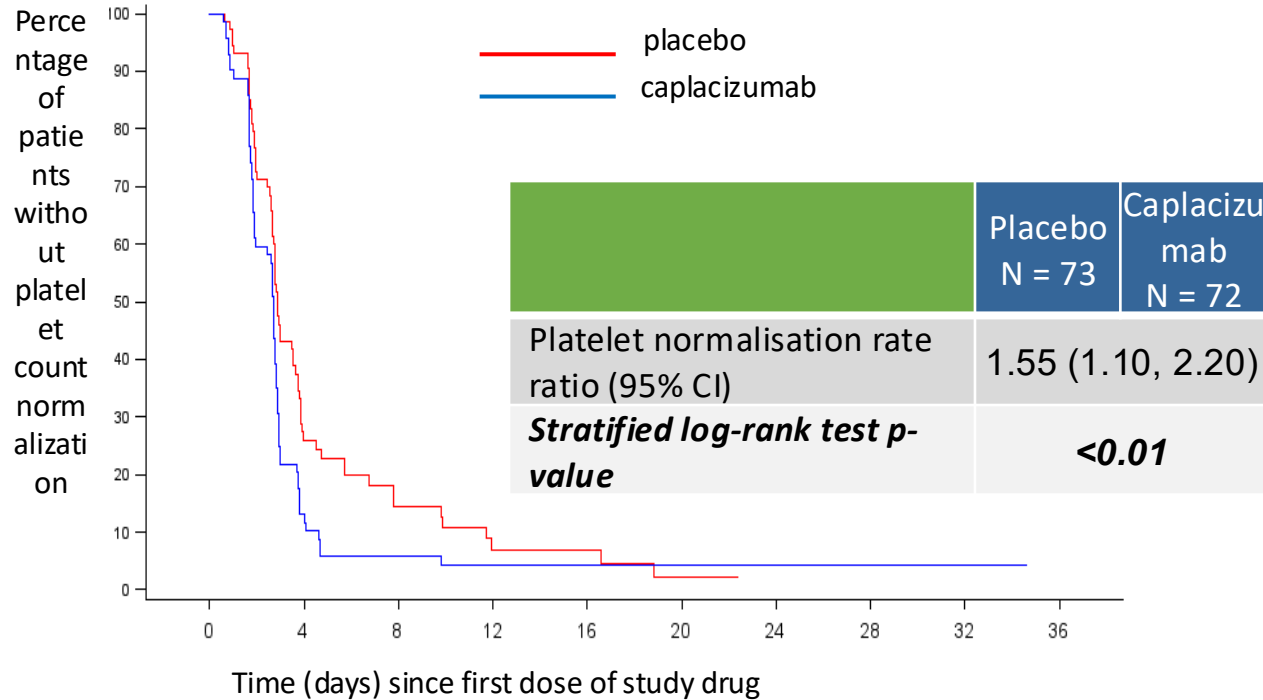
M. Scully, S.R. Cataland, F. Peyvandi, P. Coppo, P. Knöbl, J.A. Kremer Hovinga, A. Artoni, J. de la Rubia, K. Pavenski, F. Callewaert, B. Biswas, C. De Winter, and R.K. Zeldin, for the HERCULES Investigators*

slide 34

May 28, 2026



Hercules: Phase III Trial



Platelet count response was defined as initial platelet count $\geq 150 \times 10^9/L$ with subsequent stop of daily PE within 5 days

Scully *et al*, NEJM 2019

Number of subjects (%)	Placebo N=73	Caplacizumab N=72*
aTTP-related death ²	3 (4.1)	0
recurrence (exacerbation) of aTTP ³	28 (38.4)	3 (4.2)
Recurrence during follow-up period (relapses)	0	6 (9.1) ²



Capla '500' project

10 worldwide countries - 942 patients
Unprecedented, international academic effort on rare disease

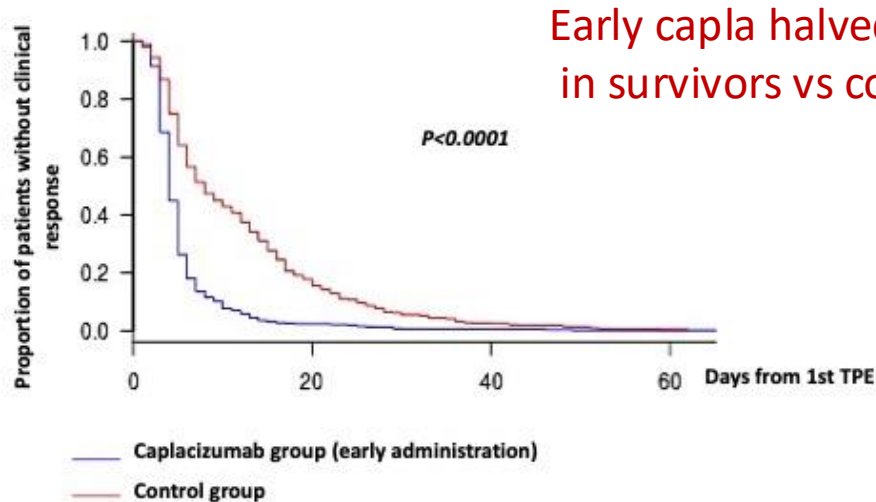
Table. Clinical presentation at diagnosis and main outcomes according to therapeutic groups.

	Caplacizumab group (N=942)	Historic control group (N=495)	p-value
Clinical presentation			
Age (years)	46 (33-58)	43 (33-56)	0.32
Females	67%	68%	0.82
Number of previous iTTP episodes			
None	82%	82.6%	0.80
1	13%	16.4%	
≥2	5%	1%	
Neurologic involvement			
Headache	37%	31.5%	0.60
Confusion	26.1%	19.6%	0.01
Seizure	8.4%	9.2%	0.67
Coma (Glasgow Coma Scale ≤8)	3.7%	2.8%	0.59
Focal deficiency	38.7%	23.4%	<0.0001
Troponin > upper normal value	71.2%	69.1%	0.50
Hemoglobin level (g/dL)	8.4 (7-10)	8.6 (7.3-10.4)	0.05
Platelet count (x10 ⁹ /L)	12 (8-21)	13 (9-25)	0.05
Serum creatinine (μmol/L)	92.8 (72-124)	88 (71-118)	0.12
Estimated glomerular filtration rate (ml/min/1.73m ²)	74 (52-97)	76 (56-100)	0.14
LDH level (x upper normal value)	3.9 (2.3-5.7)	3.74 (2.3-6)	0.61
French severity score*			
0	15.1%	20%	0.7
1	35.1%	35.2%	
2	34.8%	29.2%	
3	14.8%	14.5%	
4	0.20%	1.1%	
ADAMTS13 activity			
Detectable free anti-ADAMTS13 antibodies	<5% (<5%-<5%)	<5% (<5%-<5%)	0.45
	91.3%	85.1%	0.001
Outcome			
3-month survival	98.6%	93.3%	<0.0001
Clinical response	99.2%	94.7%	<0.0001
Exacerbation rate	4.8%	35%	<0.0001
Refractoriness	2.5%	12.7%	<0.0001
Number of TPE to achieve clinical response	5 (4-7)	8 (5-15)	<0.0001
Time to ADAMTS13 activity ≥20% (days)	29 (18-50)	33 (18-74)	0.001

Abbreviations: iTTP: immune-mediated thrombotic thrombocytopenic purpura; LDH: lactate dehydrogenase; ADAMTS13: a disintegrin and metalloproteinase with thrombospondin-1 motifs; member 13. *Based on age, cerebral involvement, and LDH level. Continuous variables are provided as median [IQR]; qualitative variables are provided as percentage of patients in the respective treatment group. P-value was considered significant when < 0.05.

Capla started <3d n=715
≥4 d n=218

Figure. Cumulative daily rate of event (clinical response)-free survival after first therapeutic plasma exchange within 3 months in patients of the caplacizumab group who received early caplacizumab administration (within 3 days following first therapeutic plasma exchange [TPE]) versus patients of the control group.



Failure to achieve clinical response 5x less likely with capla
↓ refractoriness + exacerbations
↓ PEX to clinical remission regardless of rituximab use.
46 pt exacerbations following capla interruption while A13 activity <10%
Time to ADAMTS13 ≥20% shorter in capla group - ritux more used.

Capla 500 project

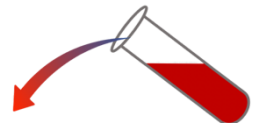
Unfavorable outcomes very low with early caplacizumab initiation

- death 1%
- refractoriness 1.1%
- exacerbations 5.3%

Capla-related AE in 220 pt (23%)

- major bleeding (N=19, 2.2%) including GI bleeding (N=8) ICH, severe CVC insertion bleeding, PV bleeding (N=2 each)
- clinically relevant non-major bleeding (N=34, 3.7%)
- non-clinically relevant non-major bleeding (N=114, 14%)
- injection site reaction (N=35, 4.5%)

Coppo *et al*, ASH 2023



Capla 500 project

Caplacizumab added to PEX and immunosuppression

↓ unfavorable outcomes during acute iTTP including mortality

↓ alleviates burden of care

at the potential expense of rare, major bleeding events

Coppo *et al*, ASH 2023



PEX-free management of iTTP: the Austrian-German experience

43 patients (33F) with 45 acute iTTP episodes 2018 -22. Median 38y (20-83)
TMA with organ dysfunction, severe ADAMTS13 deficiency and anti-A13 Ab

- Robust increase in platelet count in majority of patients
- Median time to initial platelet count normalisation 4 days (IQR 3-4 days, n = 23).
- 3 patients did not improve with platelet counts after the first capla dose and received additional PEX. Underlying conditions - CMV viremia, HIV, ITP.
- One patient with recurrent TTP was first treated with PI due to ?cTTP , later switched to capla once antibodies were detected.
- 4 patients had exacerbations managed with capla alone, after initial SOC treatment.

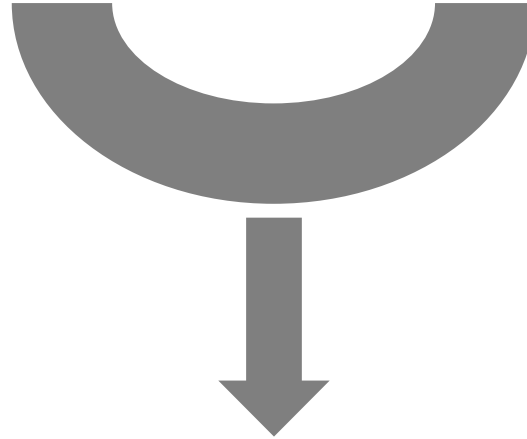
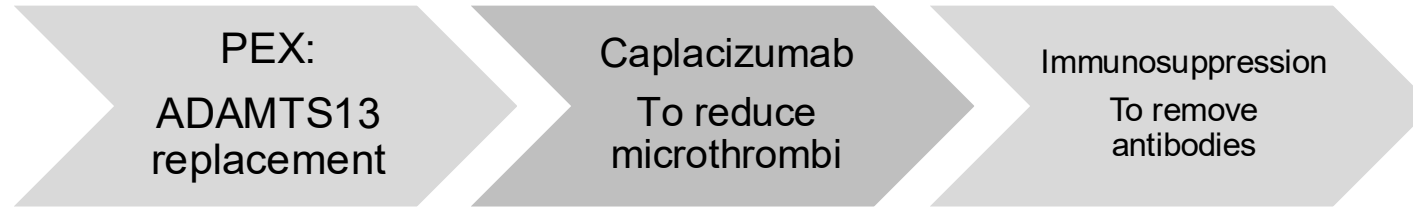
PEX is not mandatory for acute iTTP management

- clinical remission with capla + immunosuppression alone in majority of cohort.

Knoebl *et al*, ISTH 2023



The Current...



Normal platelet count
Normal ADAMTS13 activity
Reduced time to remission and mortality



Additional immunosuppression- Bortezomib

bjh research paper

Bortezomib in the treatment of refractory thrombotic thrombocytopenic purpura

Christopher J. Patriquin,¹ Mari R. Thomas,² Tina Dutt,³ Siobhan McGuckin,⁴ Piers A. Blombery,⁴ Tanya Cranfield,⁵ John P. Westwood⁴ and Marie Scully²

¹Division of Hematology & Thromboembolism, McMaster University, Hamilton, Ontario,

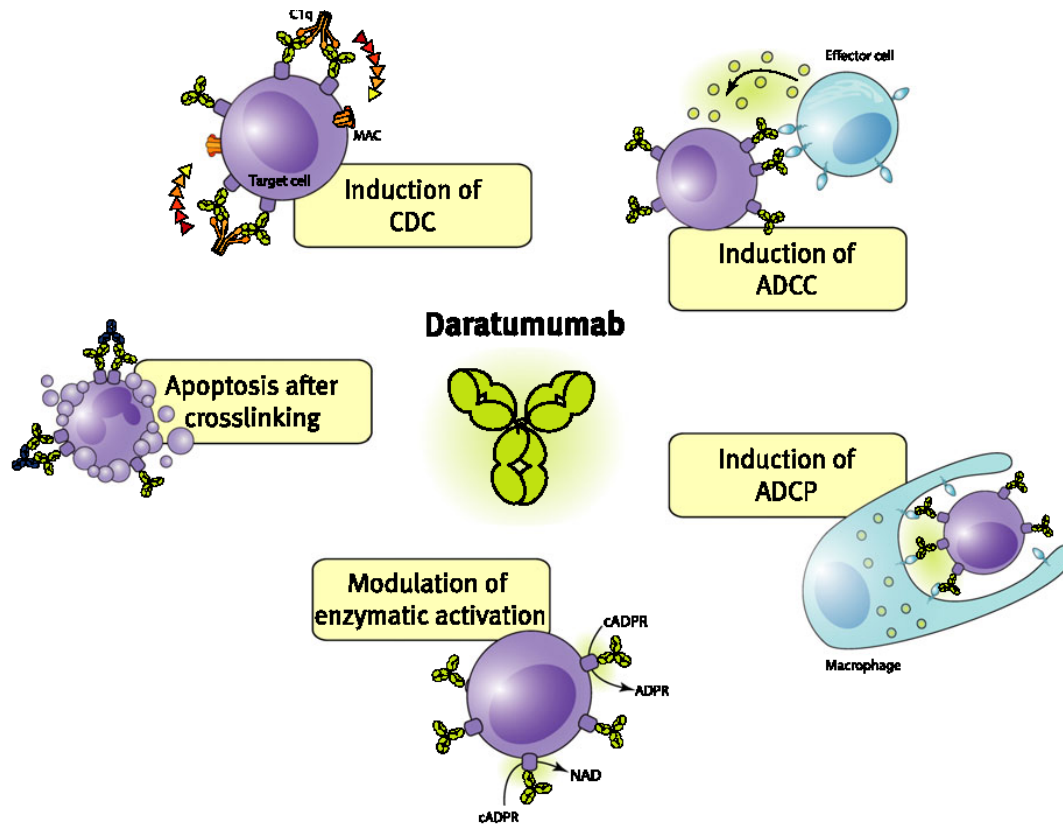
Summary

Acquired thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening condition caused by autoantibody-mediated inhibition of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type-1 motif, 13). Therapeutic plasma exchange (TPE) improves survival, but disease may be refractory despite therapy. Management and treatment

- Case reports/small series of bortezomib use as additional immunosuppression in refractory cases
- Rapid clearance of anti ADAMTS13 IgG
- Difficult to assess contribution of single agent in heavily treated patients



Additional immunosuppression- Bortezomib



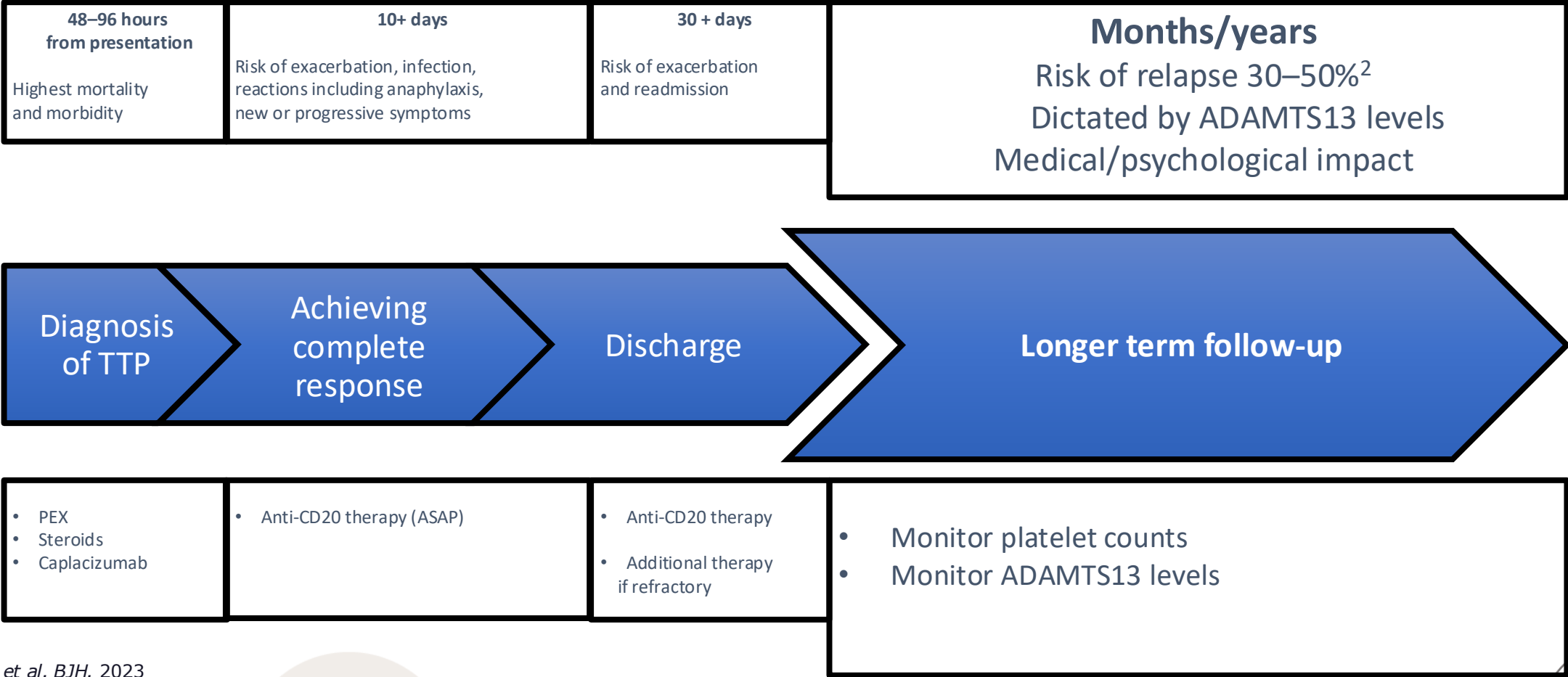
Swiss case series 2014 –24
Daratumumab for ADAMTS13 < 5%
whilst still in clinical remission.

- 87.5% ADAMTS13 response (7/8 treatment episodes)
- 6 x CR 1 x 'near CR'
- Median response time 2.5 w (2-4)
- Median response duration 19 months

Schimmer R *et al*, ASH 2024



TTP Pathway – Lifelong Care





Scully et al. BJH. 2023




Congenital TTP

Recurring, non-overt symptoms are seen in congenital TTP despite normal blood counts

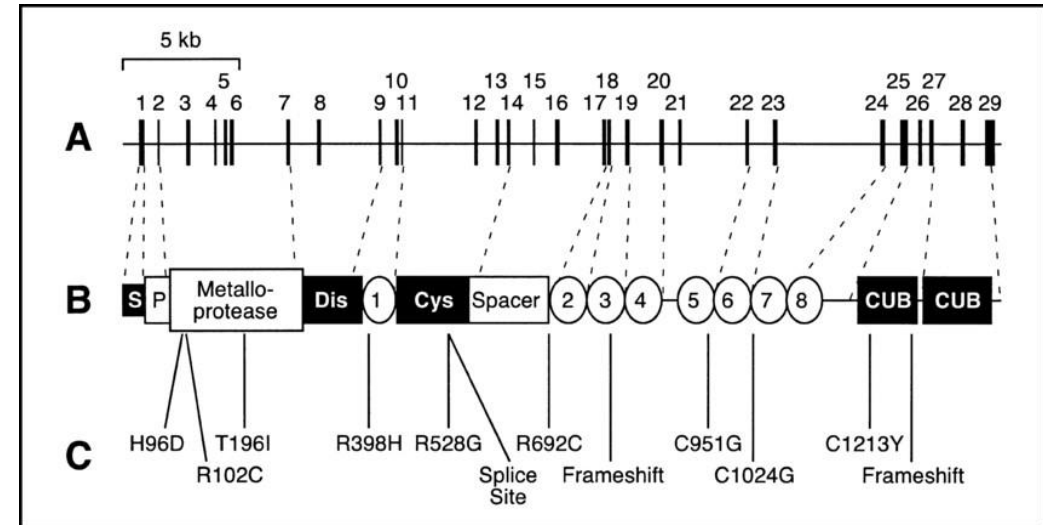


Regular prophylaxis improved symptoms



& decreased stroke incidence (2% vs 17%)

Alwan *et al* 2020



Natural history of congenital TTP: International Hereditary TTP Registry

Prospective follow up 82/182 pt (45%) had 265 acute TTP episodes
Overall event rate of 297/1000 person-years.

n=8 died during FU, 5/8 on regular PI.
n=3 acute TTP; age 33, 44, 52y
n=3 cardiac; age 39, 49, 56 y
n=2 unknown; age 75, 79 y

Significant clinical burden

Recurrent acute TTP episodes → neuro, CV, renal sequelae + early mortality
Delayed diagnosis & insufficient treatment likely contributed

Awareness, timely diagnosis and sufficient ADAMTS13 replacement therapy (for acute episodes and prophylactically) crucial for improving short- and long-term clinical outcomes

Schraner *et al* ASH 2023



Estimating the population-based prevalence of congenital TTP using large-scale sequencing data

Table 1. Estimated prevalence of cTTP using pathogenic reported variants only.

Population	Total Number Of Alleles	Total Number Of affected alleles	Colletive Frequency Of Variants	Prevalence in 10 ⁶ Individuals (recessively-inherited)	Prevalence in 100 Individuals (Carrier)
All	282912	1159	0.004	17	0.8
Africans and African Americans	24974	62	0.002	6	0.5
Latinos/Admixed Americans	35440	134	0.004	14	0.7
Ashkenazi Jewish	10370	8	0.001	0.6	0.2
East Asians	19954	42	0.002	4	0.4
Finnish	25124	129	0.005	26	1.0
Europeans (not Finnish)	129206	710	0.005	30	1.1
South Asians	30616	49	0.002	3	0.3
Other ethnicities	7228	25	0.003	12	0.7

True cTTP prevalence >10 x previously reported
 - suggests that many patients might be undiagnosed
 Mutational burden of ADAMTS13 higher
 - 167 novel variants (302 previously reported).

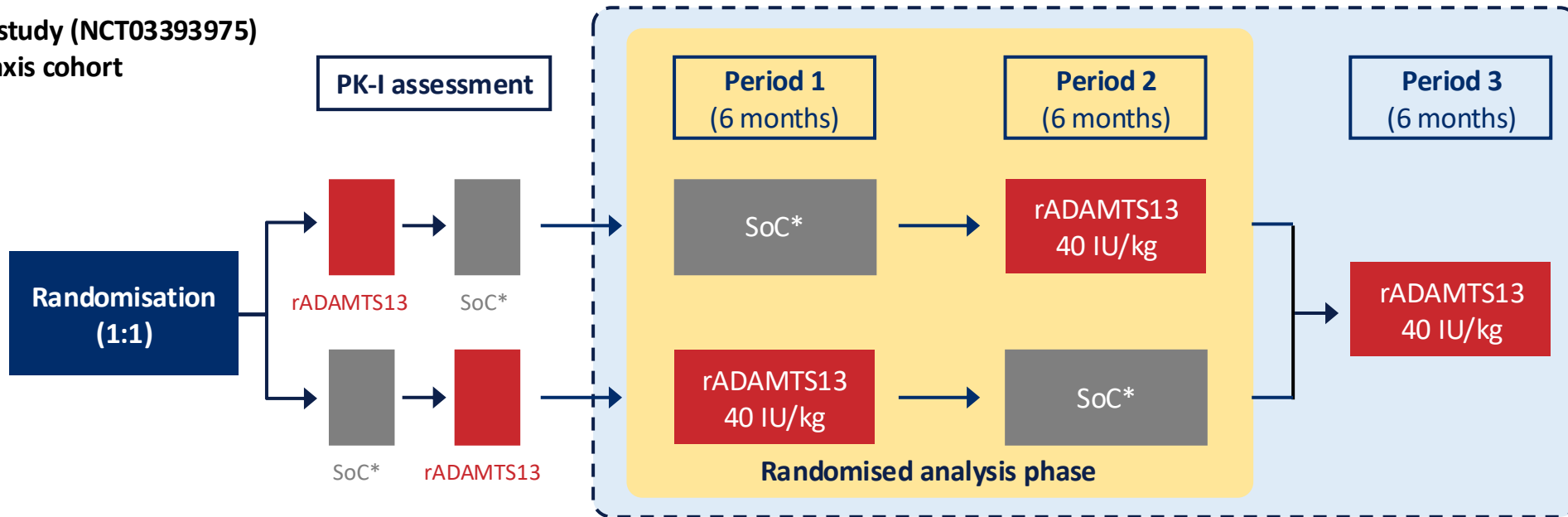
gnomAD + ClinVar +literature

Peyvandi *et al* ASH 2023



Phase 3 RCT open-label, multicenter, crossover rADAMTS13 in patients with congenital TTP

Phase 3 study (NCT03393975)
Prophylaxis cohort



Pre-planned interim analysis of prophylaxis treatment cohort
(after 30 adolescents/adults had completed study; data cutoff: August 12, 2022)

Scully *et al*, 2024 NEJM



Phase 3 RCT open-label, multicenter, crossover rADAMTS13 in patients with congenital TTP

Age 12-58 years 61% F

Primary outcome

No acute TTP events occurred during rADAMTS13 prophylaxis

Mean rADAMTS13 exposure: 13.2 months

One event occurred during SoC.

Secondary outcomes

TTP manifestations eg thrombocytopenia - lower with rADAMTS13

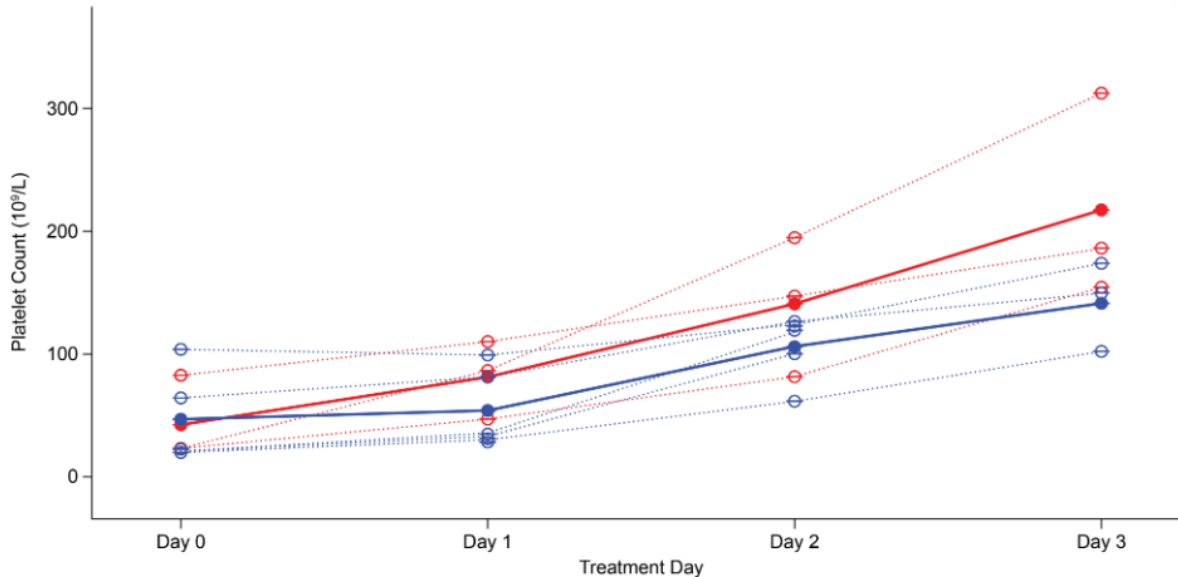
No rADAMTS13-related SAEs were reported.

No neutralising antibodies developed during rADAMTS13 prophylaxis



rADAMTS13 for treatment of acute TTP events in congenital TTP: Phase 3 Crossover RCT & 3b Continuation

Figure. Platelet counts during the first 3 days of treatment for an acute TTP event in patients with cTTP enrolled in either the phase 3 study or the phase 3b continuation study



8 suspected acute TTP events were treated in 7 patients
No acute events occurred while patients were receiving rADAMTS13 prophylaxis

Table. Summary of acute TTP events reported in patients with cTTP enrolled in either the phase 3 study or the phase 3b continuation study


	Treatment	Platelet count, 10 ⁹ /L		LDH, U/L	
		Event Start	Event End	Event Start	Event End
Phase 3 (NCT03393975)					
Patient 1	SoC (FFP)	104 (56.5% decrease from baseline [239])	279	454 (2.41× baseline)	194 (1.03× baseline)
Patient 2	rADAMTS13	84	270	236 (1.10×ULN)	205 (0.96×ULN)
Patient 3	rADAMTS13	24	155	598 (2.43×ULN)	278 (1.13×ULN)
Patient 4, event 1	SoC (FFP)	23	62	685 (2.78×ULN)	320 (1.30×ULN)
Patient 4, event 2	SoC (FFP)	23	101	652 (2.65×ULN)	323 (1.31×ULN)
Patient 5	SoC (S/D-treated plasma)	20	276	458 (2.04×ULN)	263 (1.17×ULN)
Patient 6	SoC (S/D-treated plasma)	65	150	211 (1.06×ULN)	187 (0.94×ULN)
Phase 3b (NCT04683003)					
Patient 7	rADAMTS13	20	546	1027.4	282.4

cTTP, congenital thrombotic thrombocytopenic purpura; FFP, fresh frozen plasma; LDH, lactate dehydrogenase; rADAMTS13, recombinant ADAMTS13; S/D, solvent/detergent; SoC, standard of care; TTP, thrombotic thrombocytopenic purpura; ULN, upper limit of normal.

- All 3 acute TTP events treated with rADAMTS13 resolved promptly with the treatment protocol
- No serious TEAEs related to rADAMTS13 and no neutralising antibodies against ADAMTS13

Takeda's ADZYNMA (ADAMTS13, recombinant-krhn) Approved by U.S. FDA as the First and Only Recombinant ADAMTS13 Enzyme Replacement Therapy for the Treatment of Congenital Thrombotic Thrombocytopenic Purpura (cTTP)



 November 9, 2023

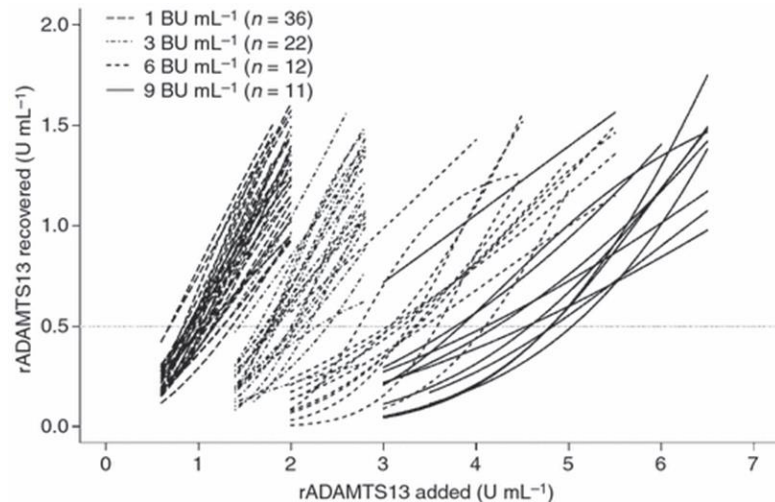
 Share

FDA approved for the prophylactic and on-demand treatment of adult and pediatric patients with cTTP
EMA approved



Phase 2 studies rADAMTS13 for iTTP

- Phase 2a RCT of supplementing PEX with rADAMTS13
- Planned phase 2b RCT without PEX



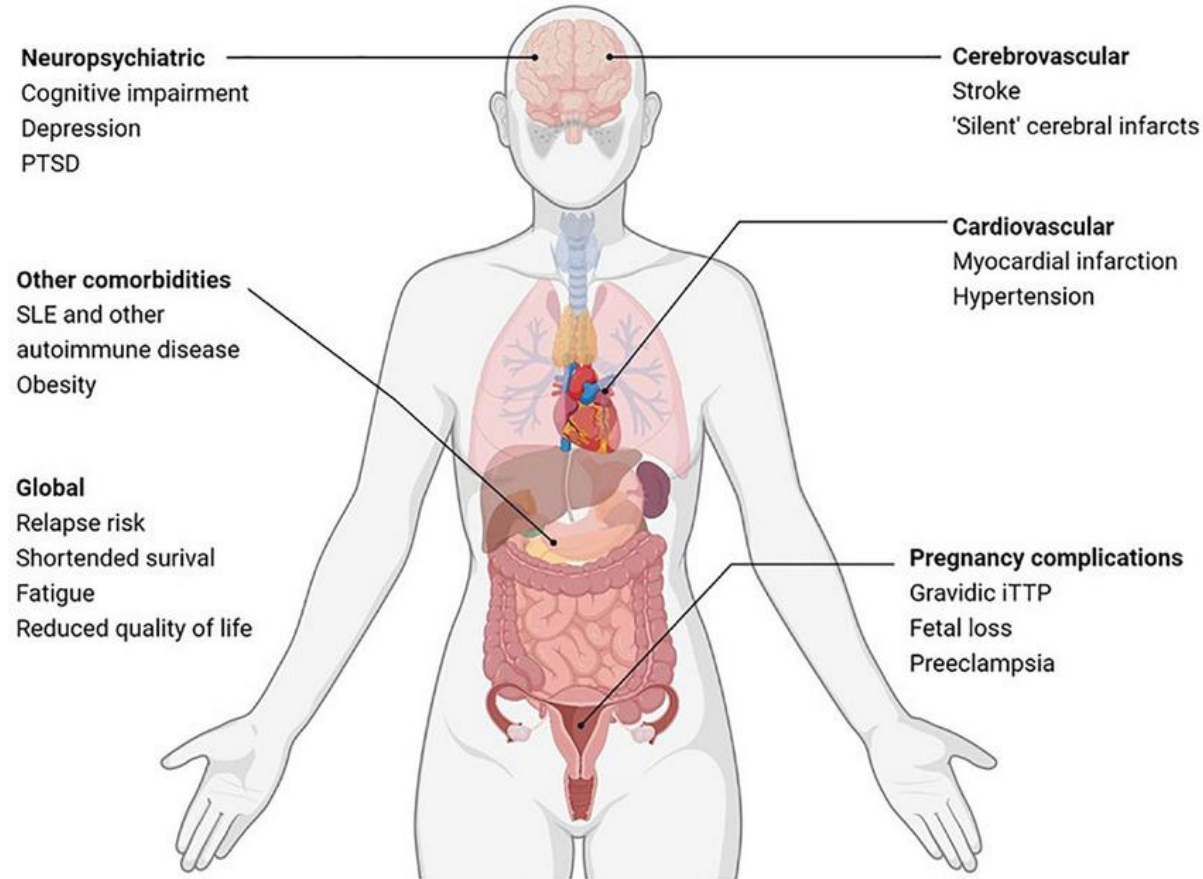
Plasma samples from 36 different TTP patients with neutralizing anti-ADAMTS13 antibodies adjusted to 1, 3, 6 and 9 BU / mL.

Effective concentration to restore 0.5 U/mL ADAMTS13 activity (EC50) shown by horizontal line.

Plaimauer *et al*, JTH 2011



TTP - Long term effects and monitoring



Selvakumar *et al* 2023



What is the impact of acute TTP ?

J Clin Psychiatry. **1984** Nov;45(11):477-9.

The cost of surviving thrombotic thrombocytopenic purpura: case report.

Greenberg DB, Carey RW.

The **neuropsychiatric sequelae of thrombotic thrombocytopenic purpura (TTP) have not been discussed previously since most patients did not survive. The affective disorder, personality change, and cognitive deficits which resulted from TTPThe neurologic and psychiatric residua did not indicate a chronic form of the disease.**

Am J Hematol. **2011** Jan;86(1):87-9

Evidence of persistent neurologic injury following thrombotic thrombocytopenic purpura Cataland et al

.....evaluation of neurologic injury that included a magnetic resonance imaging (MRI), a neurocognitive testing, and health-related quality of life. Twenty-seven patients with a history of idiopathic TTP functioning normally in their activities of daily living. **39% of the MRI studies were abnormal; 63% patients demonstrated neurocognitive impairment, particularly in visual learning and memory.** Health-related quality of life scores were also significantly lower than age- and gender-matched US norms for both the composite mental component score and physical component score.

.....the prevalence of neurologic findings in TTP patients in remission is quite high and is largely undetected by routine clinical evaluations.



TTP survivors exhibit impaired stress perfusion on cardiac MRI

Characteristics	TTP Survivors (n = 10)	Control (n = 13)	p-value
Age (years, IQR)	44.5 (40.8 – 49.5)	53 (37 – 61.5)	.232
Sex (%)	Male 20% Female 80%	Male 31% Female 69%	.66
Race (%)	White 70% Black 30%	White 92% Black 8%	.281
BMI (mg/m ² , IQR)	34.5 (29.3 – 41.6)	26.5 (21.5 – 31.4)	.012
Hypertension	70%	46%	.402
Systolic BP (mmHg, IQR)	144 (136 – 157)	132 (129 – 152)	.313
Diastolic BP (mmHg, IQR)	94 (90 – 97)	82 (72 – 87)	.003
Diabetes	20%	0%	.178
Known Cardiac Disease	10%	85%	<.001

Asymptomatic structural changes +
 ↓ perfusion common in TTP survivors
 ?clinical significance
 Subclinical myocardial damage
 ↑CV morbidity & mortality

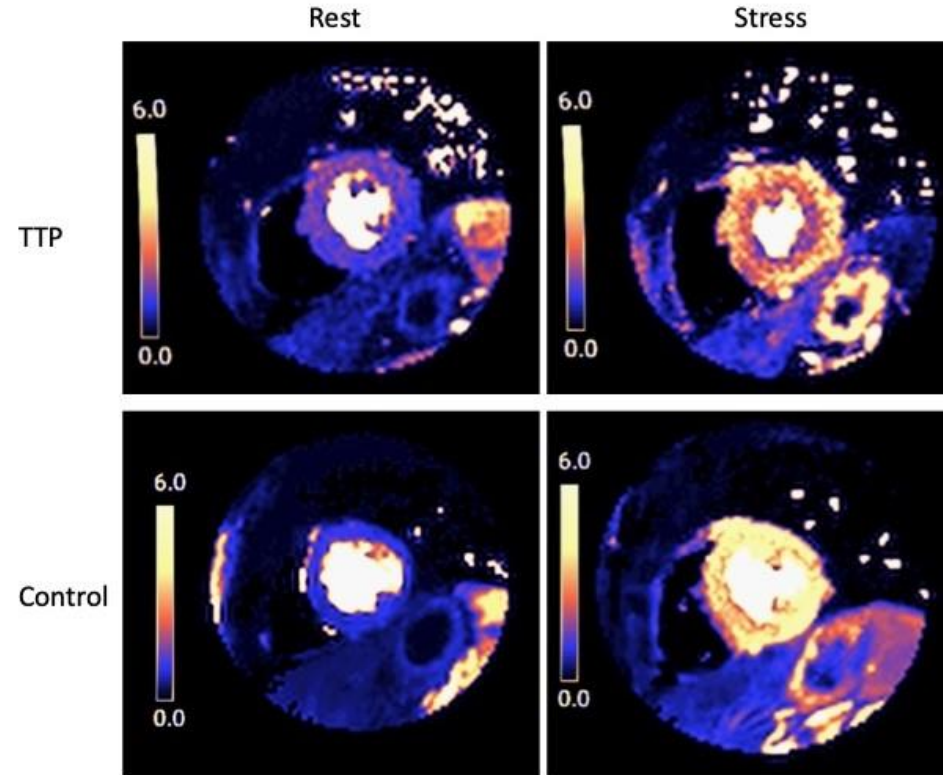


Figure 1. Quantitative perfusion maps of a TTP (top row) and a control subject (bottom row). Rest images are on the left and stress images are on the right.

The color maps shows perfusion in ml/min/g with brighter colors indicating higher perfusion. Stress imaging of the iTTP patient shows decreased flow in the subendocardium.

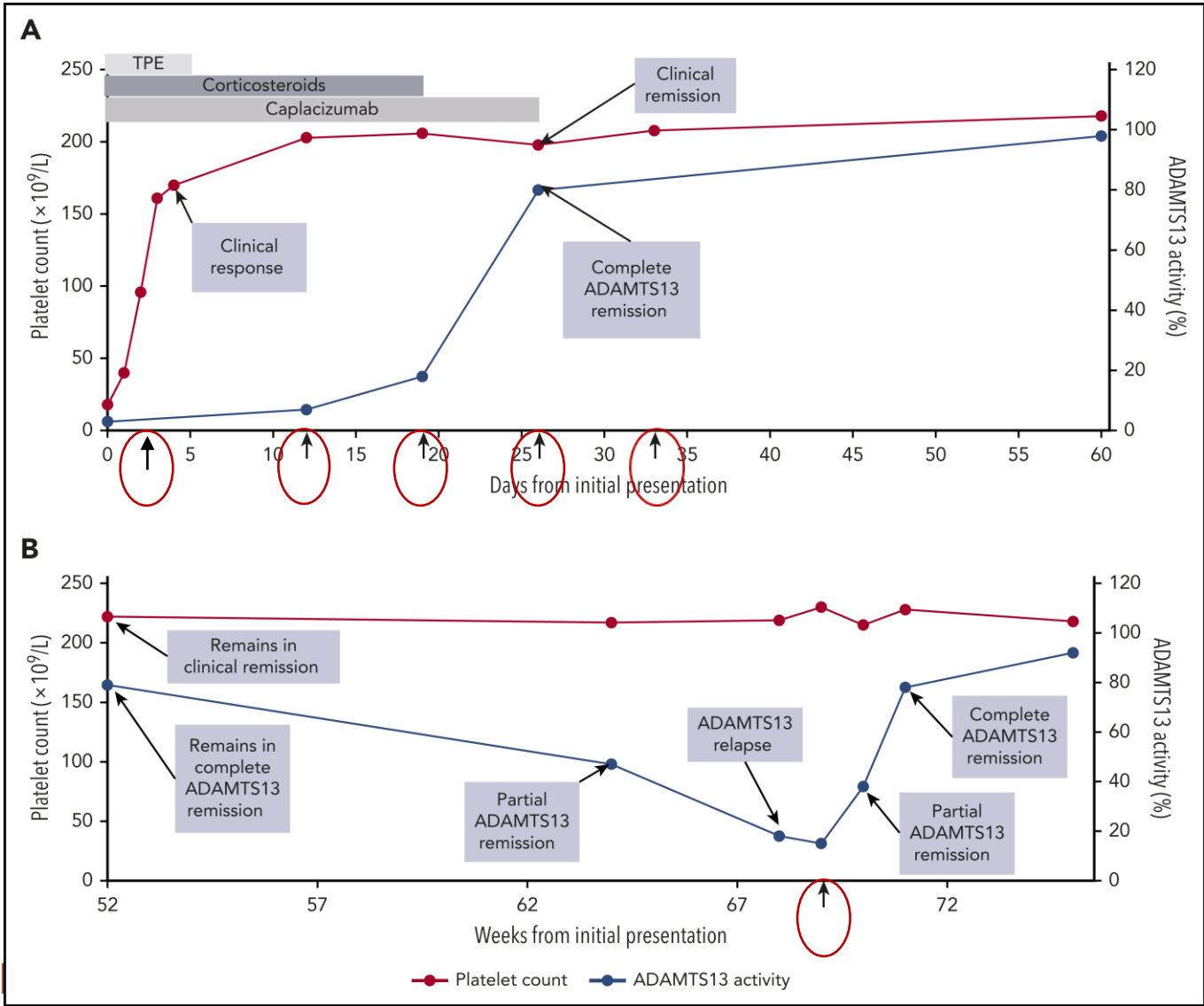
Sukumar *et al*, ASH 2023



Rituximab in iTTP

Early rituximab
in acute episode

Elective rituximab
for ADAMTS13
relapse



↑ Rituximab

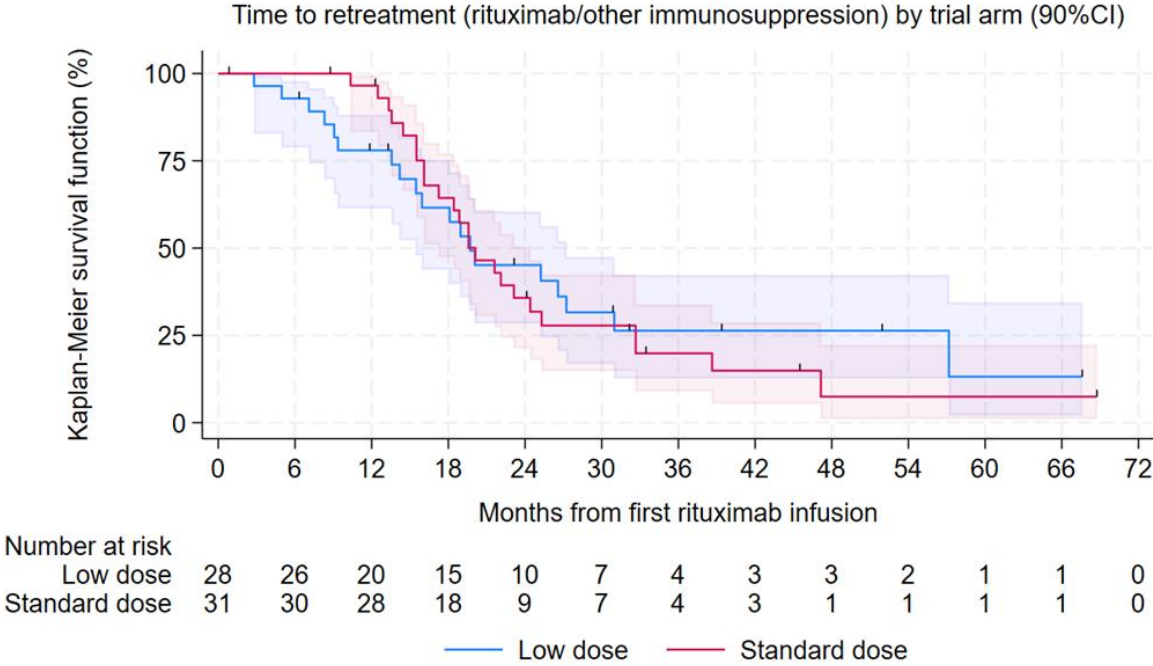
**Goal of iTTP therapy
= ongoing ADAMTS13 CR**

Adapted from Cuker *et al* 2021

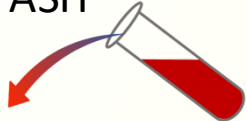
May 28, 2026



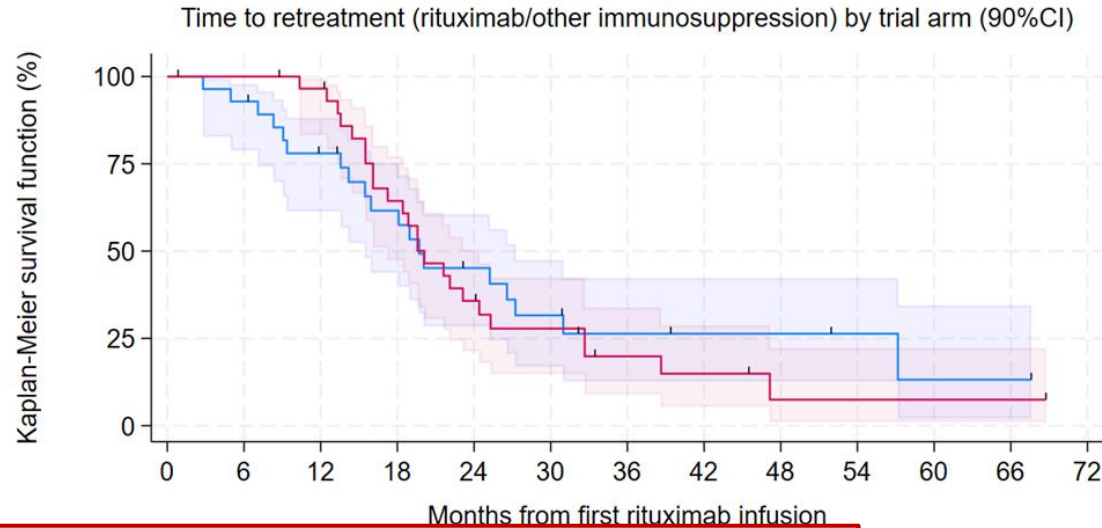
Elective rituximab in iTTP - dosing



- First RCT in prevention of acute episodes in iTTP
- No difference in median time to retreatment after low dose rituximab (200mg x4) vs. standard dose (19.7 vs 20.1 months)
- Treatment effect was not constant over time, with more retreatments observed in first 12 months in low dose RTX arm.



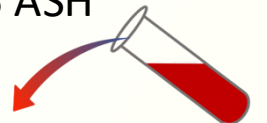
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- Treatment effect was not constant over time, with more retreatments observed in first 12 months in low dose RTX arm.

Clinical relapse rate <5% with monitoring & pre-emptive therapy
 Long follow up
 Can retreat repeatedly without losing efficacy
 Well tolerated
 No XS infections

1 1 0
 1 1 0



So what ADAMTS13 level should we be aiming for?

Journal of Thrombosis and Haemostasis, 14: 2114-2120

DOI: 10.1111/jth.13479

ORIGINAL ARTICLE

Low ADAMTS-13 activity and the risk of coronary heart disease – a prospective cohort study: the Rotterdam Study

From www.bloodjournal.org by guest on May 15, 2019. For personal use only.

Regular Article

THROMBOSIS AND HEMOSTASIS

Low ADAMTS13 activity is associated with an increased risk of ischemic stroke

Arterioscler Thromb Vasc Biol. 2016 Dec;36(12):2446-2451. Epub 2016 Oct 13.

Von Willebrand Factor, ADAMTS13, and the Risk of Mortality: The Rotterdam Study.



CM-HUS



Haemolytic Uraemic Syndrome (HUS)

HUS and TTP are Thrombotic Microangiopathies with similar features

Microangiopathic haemolytic anaemia

Thrombocytopenia

Organ dysfunction

- acute renal failure in HUS
- CNS, cardiac complications in TTP

due to thrombi forming in arterioles and capillaries

but *different* pathogenesis

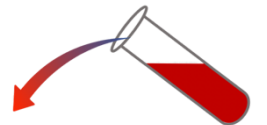


D+ HUS

- Commonest form
- Accounts for 90-95% cases in children
- Abrupt onset following diarrhoea (e.g. E.coli) in preceding weeks
- Supportive treatment alone
- Good prognosis
- 5% die or ESRF
- Recurrence rare post transplant

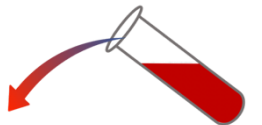
CM-HUS

- Rare
- 5-10% cases in children
- Majority of adult cases
- Diarrhoeal prodrome less frequent
- Poorer prognosis
- Mortality, ESRF in 25%
- Long-term 50% evolve to ESRF
- High disease recurrence post transplant

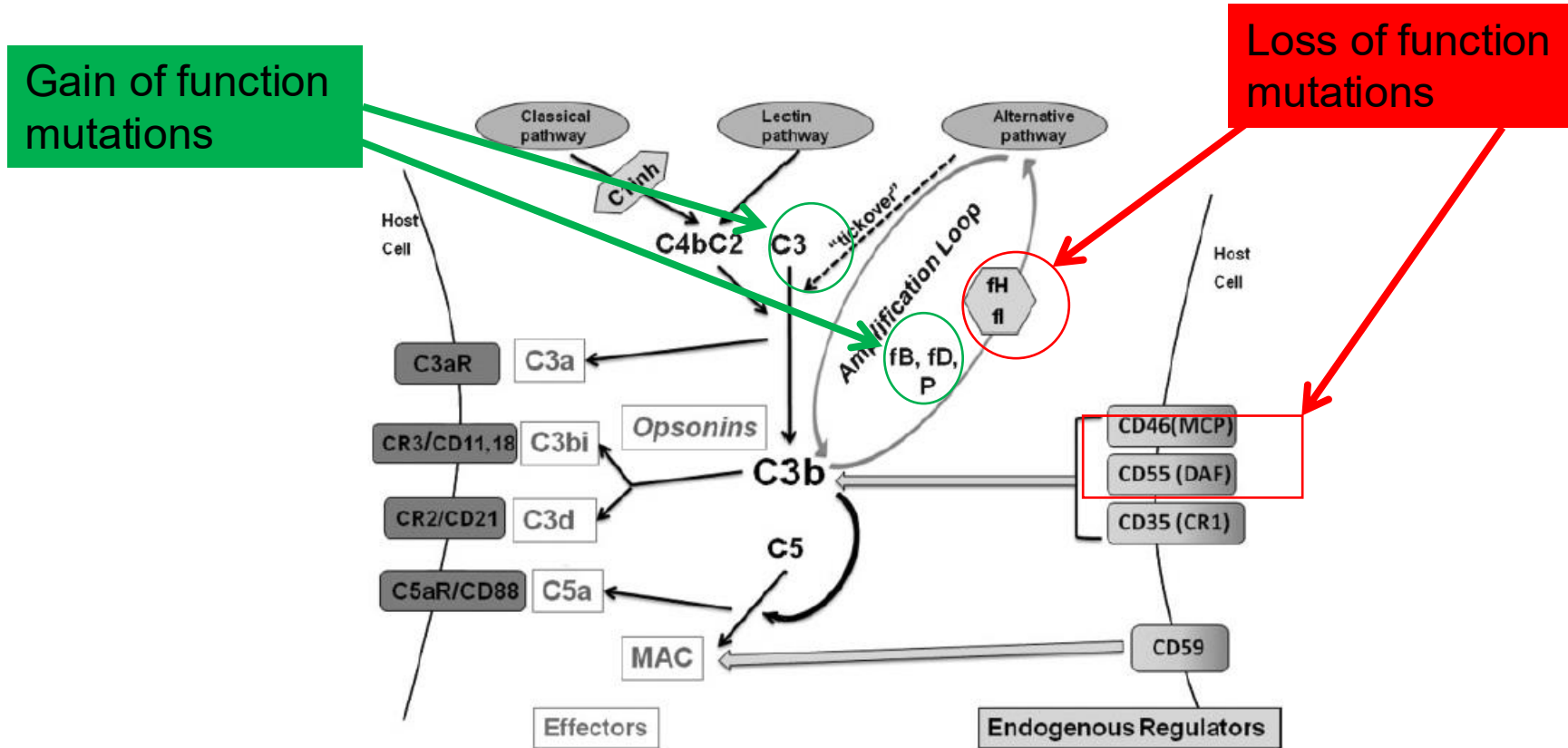


Aetiology of CM-HUS (aHUS)

- Can be familial and sporadic
- Mutations or polymorphisms (or both) in genes for **Complement proteins**
- ? Triggered by infection, pregnancy
- Likely multifactorial



CM-HUS & Complement



CM-HUS prognosis correlated with genetic defect

Table 3 Main clinical characteristics of patients with atypical hemolytic uremic syndrome according to complement abnormality

Gene or subgroup	Frequency in aHUS	Minimal age at onset		Risk of death or ESRD at 1 st episode or within < 1 y	Risk of relapses	Risk of recurrence after renal transplantation	Plasma therapy indicated
		Children	Adults				
<i>CFH</i>	20-30%	Birth	any age	50-70%	50%	75-90%	Yes
<i>CFI</i>	4 -10%	Birth	any age	50%	10-30%	45-80%	Yes
<i>MCP</i>	5 -15%	> 1 y	any age	0-6%	70-90%	< 20%	Questionable
<i>C3</i>	2 -10%	7 m	any age	60%	50%	40-70%	Yes
<i>CFB</i>	1-4%	1 m	any age	50%	3/3 not in ESRD	100%	Yes
<i>THBD</i>	3 -5%	6 m	rare	50%	30%	1 patient	Yes
Anti-CFH Ab	6%	Mostly 7-11 y		30-40%	40-60%	Yes if high Ab titer	Yes (+ IS)

CFH: factor H; CFI: factor I; MCP: membrane cofactor protein; CFB: factor B; THBD: thrombomodulin; Ab, antibodies; ESRD: end stage renal disease; IS: immunosuppressive treatment.

- CFH mutations have worst outcome
- Within 1 year, up to 70% with CFH mutations die or have ESRF
- High rate of recurrence in patients post transplant with mutations in CFH and CFI as these are synthesised in liver

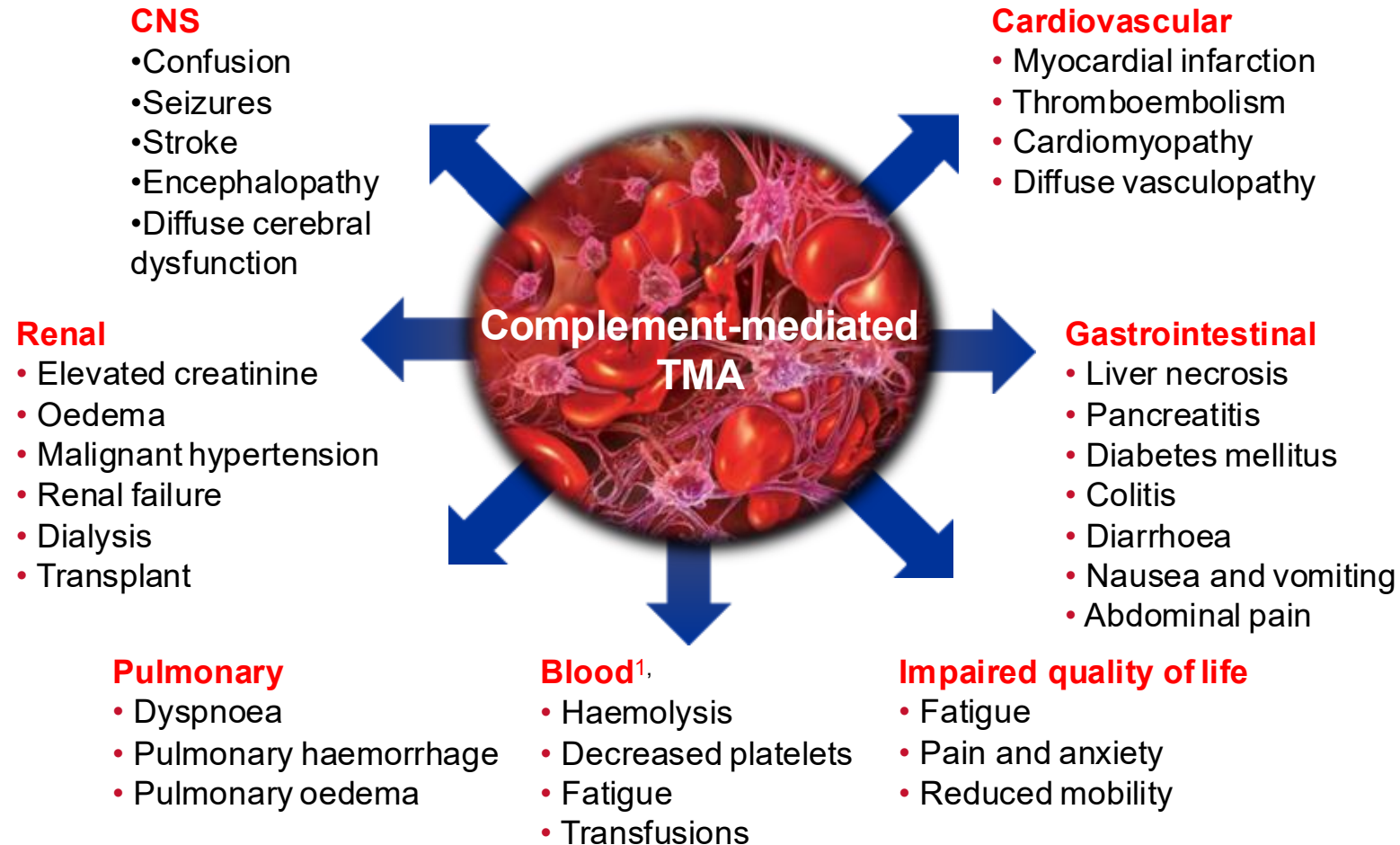


Clinical presentation alone does not fully differentiate CM-HUS from TTP

CM-HUS	TTP
Well-recognised CM-HUS signs: <ul style="list-style-type: none">• Decreased platelet count• Microangiopathic haemolysis• Renal insufficiency	Well-recognised TTP signs: <ul style="list-style-type: none">• Decreased platelet count• Microangiopathic haemolysis• Neurological dysfunction
Under-recognised CM-HUS signs: <ul style="list-style-type: none">• Neurological dysfunction (up to 48%)• Cardiac symptoms (up to 43%)	Under-recognised TTP signs: <ul style="list-style-type: none">• Renal pathology (96%)• Renal insufficiency (47%)



CM-HUS is a multisystem disorder



Complement analysis does not support diagnosis of CM-HUS

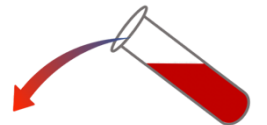
- Levels of complement proteins and inhibitors are sometimes measured to look for evidence of complement activation or dysfunction

eg low C3 indicates C3 consumption by activation

eg low FH could indicate a FH mutation

In CM-HUS these tests do not reliably support the diagnosis

- Most CM-HUS patients (including patients with identifiable mutations) have normal C3 and C4 levels
- Factor H levels – normal in up to 87% of CM-HUS patients with identified CFH mutation



Diagnosis of CM-HUS does not require identification of a genetic mutation

- Genetic mutation cannot be identified in 30–50% of patients with CM-HUS
- Absence of identifiable genetic mutations does not exclude CM-HUS
- Genetic analysis generally takes weeks to months
- Prognosis comparable (patients with identifiable mutations vs no identifiable mutation)

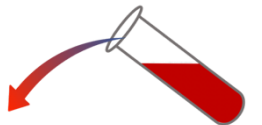
Identification of genetic mutation is not required for initial CM-HUS management decisions



CM-HUS treatment

Plasma exchange/infusion forms mainstay of initial treatment:

- Removes factor H autoantibodies and hyper functional complement components
- Replaces non-functioning complement regulators



CM-HUS treatment

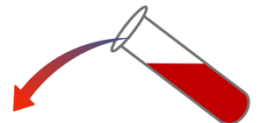


Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

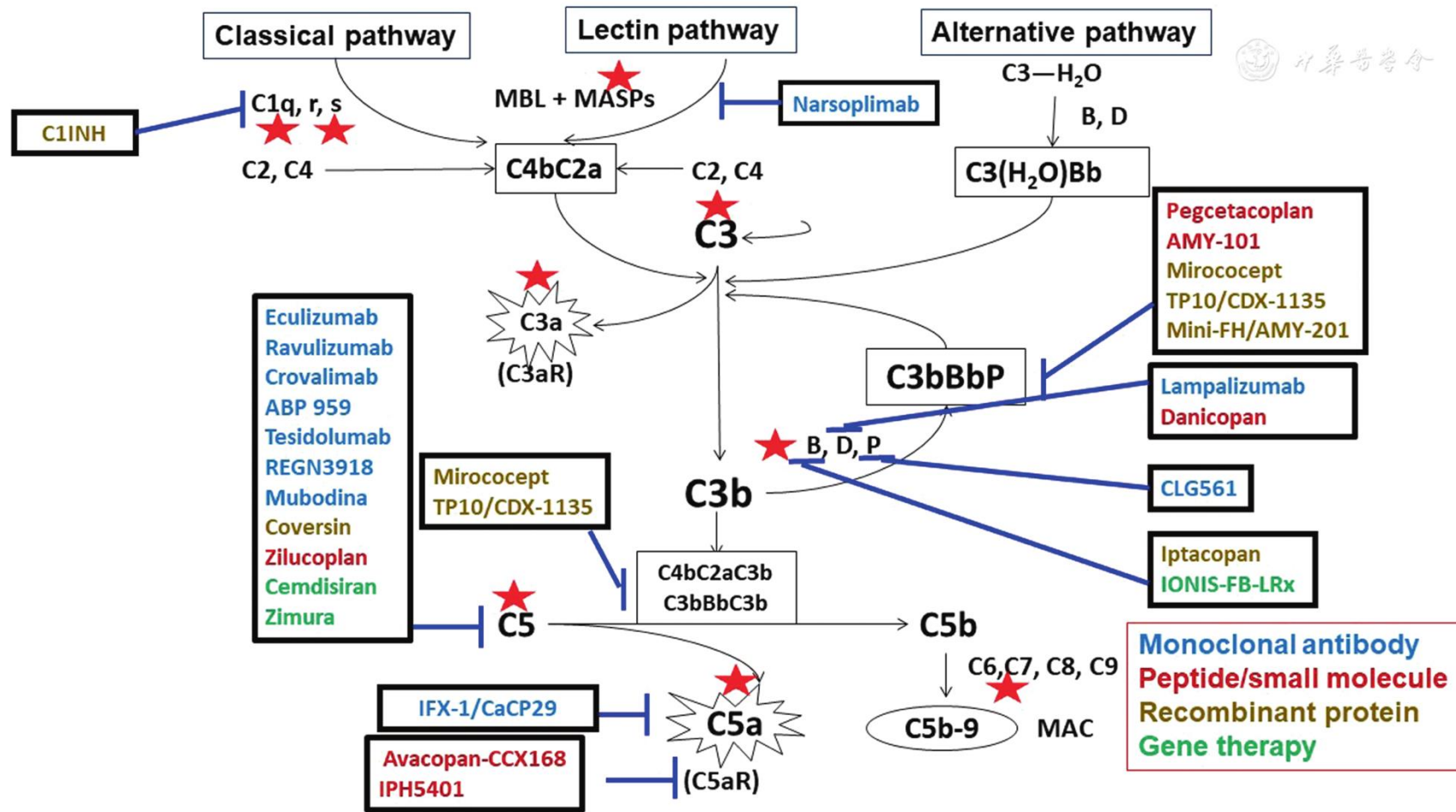
C.M. Legendre, C. Licht, P. Muus, L.A. Greenbaum, S. Babu, C. Bedrosian, C. Bingham, D.J. Cohen, Y. Delmas, K. Douglas, F. Eitner, T. Feldkamp, D. Fouque, R.R. Furman, O. Gaber, M. Herthelius, M. Hourmant, D. Karpman, Y. Lebranchu, C. Mariat, J. Menne, B. Moulin, J. Nürnberger, M. Ogawa, G. Remuzzi, T. Richard, R. Sberro-Soussan, B. Severino, N.S. Sheerin, A. Trivelli, L.B. Zimmerhackl,* T. Goodship, and C. Loirat

Legendre et al, NEJM 2012

Vaccinate against meningococcus
Prophylactic antibiotics



Complement inhibitors

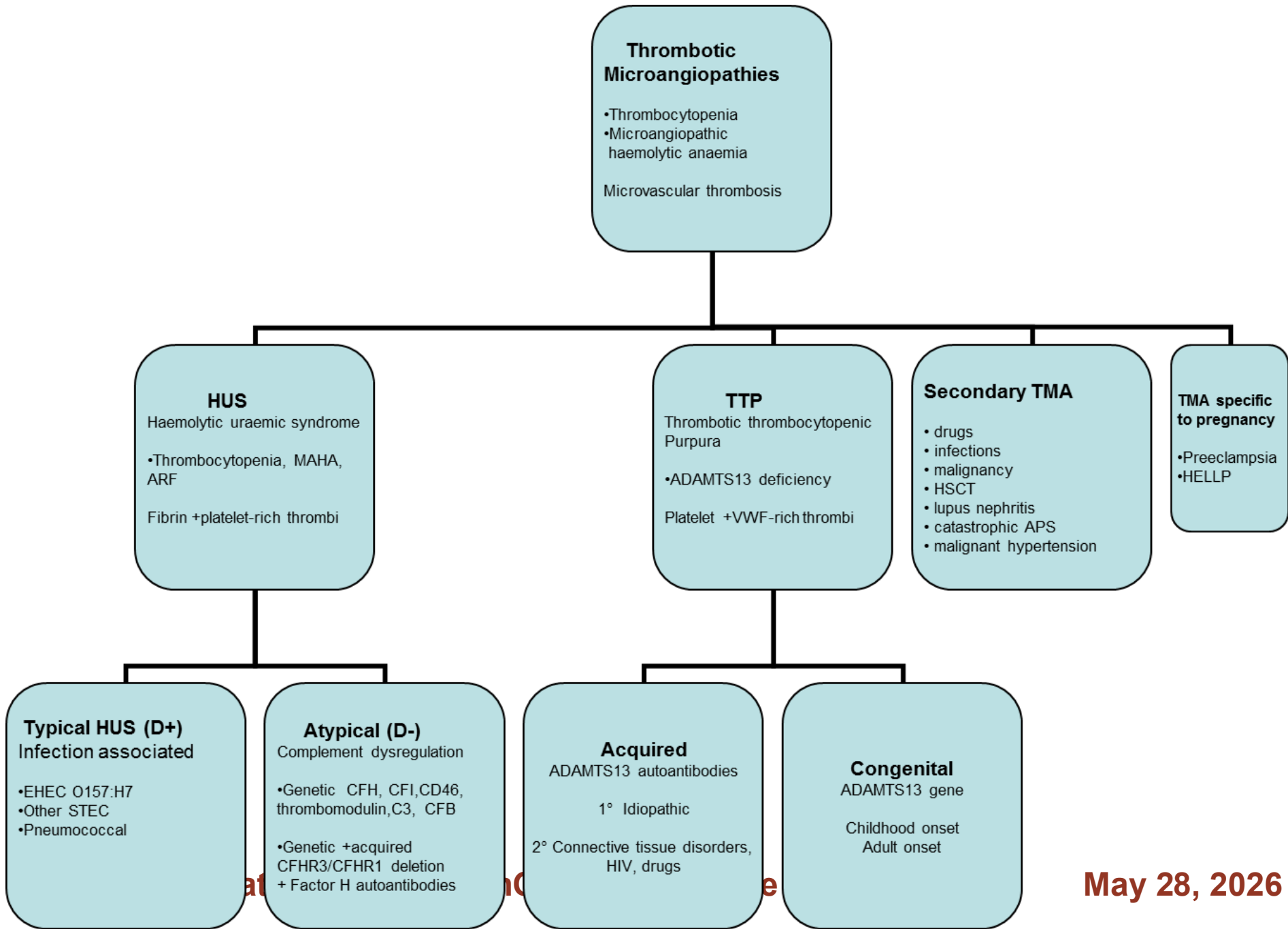


Jia et al, 2022



Secondary TMAs





May 28, 2026



Transplant-associated TMA

- MAHAT, renal dysfunction, ↑BP, neurological features eg seizures
- High mortality, no definitive diagnostic criteria

No beneficial role for PEX

- ↓immunosuppression
- Treat coexisting infections
- Meticulous BP control
- General supportive therapy
- ??use of eculizumab



Drug-Induced TMA

Primarily renal impairment + MAHAT

- Drug-dependent antibody - sudden onset of symptoms that recur with repeated administration of drug e.g oxaliplatin
- Dose-dependent toxicity - slowly progressive kidney injury with MAHAT e.g. gemcitabine, mitomycin C

Stop drug
Generally no role for PEX
?complement inhibition eg gemcitabine

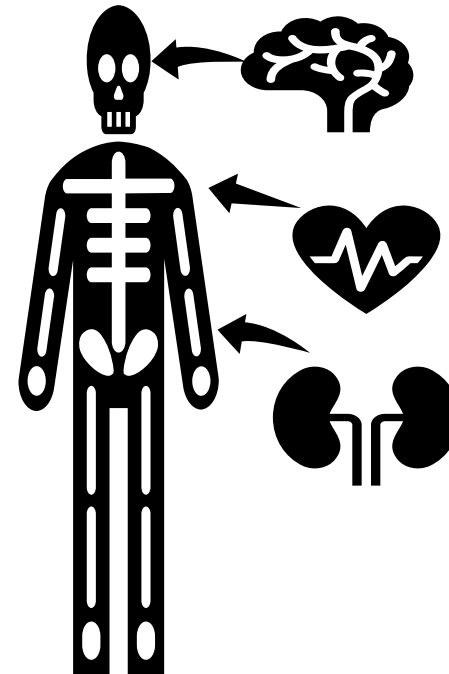
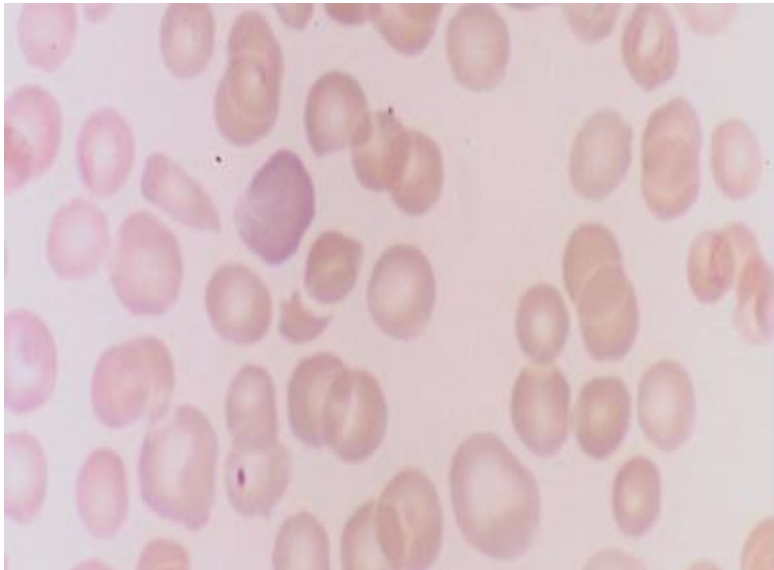


Diagnosis of TMA in pregnancy

Platelet count $<100 \times 10^9/L$

Hb $<100 \text{ g/L}$

LDH $>1.5 \text{ ULN}$



DDx pregnancy TMAs

	MAHA	Thrombocytopenia	Coagulopathy	HBP	Abdominal symptoms	Renal Impairment	Neurological symptoms
PET	+	+	±	+++	±	±	++
HELLP	+	+	±	+	+++	+	±
TTP	++	+++	-	±	+	++	+++
HUS	+	++	±	++	+	+++	±
AFLP	±	+	++	+	++	+	±
SLE	+	+	±	+	±	++	+
APS	+	++	±	++	-	++	++

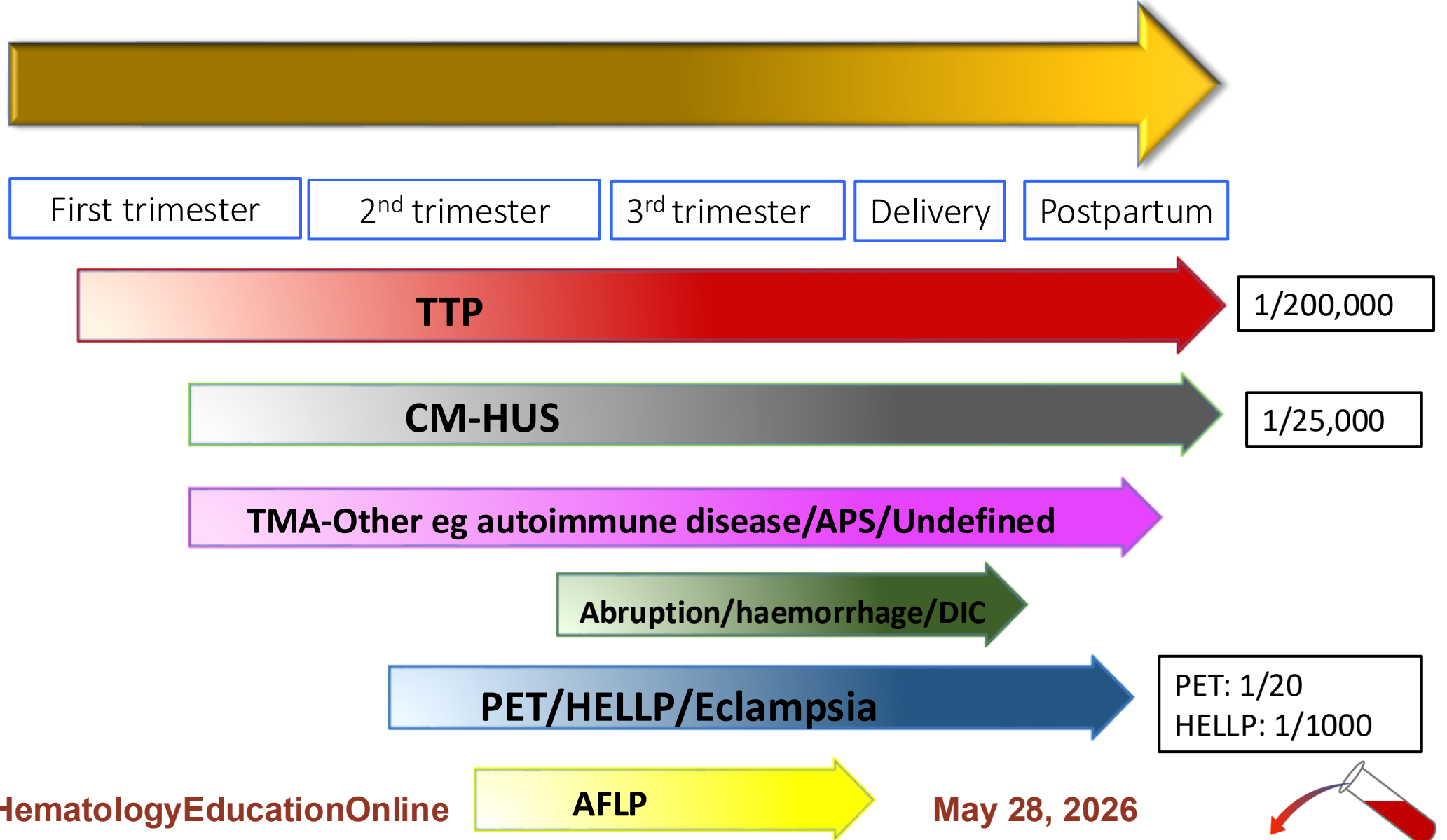
PET: pre-eclampsia, HELLP: hemolysis, elevated liver enzymes and low platelets, TTP: thrombotic thrombocytopenia HUS: hemolytic uraemic syndrome AFLP: acute fatty liver of pregnancy SLE: systemic lupus erythematosus APS:

±: possibly occurs.

+++ : definitive feature. HBP: high blood pressure.



Pregnancy-associated TMAs



Regulated complement

Dysregulated complement

Fetal Development

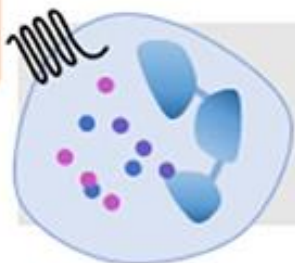
Pre-implantation

Implantation

Placental development

Cervical remodeling
Myometrial contractility

Parturition



neutrophil

Mechanism

↓ complement regulators
↑ complement activators

↓ complement regulators
↑ complement activators

macrophage

C5aR
C5aR
C5a

MMPs

myometrium

Implantation failure

Miscarriage

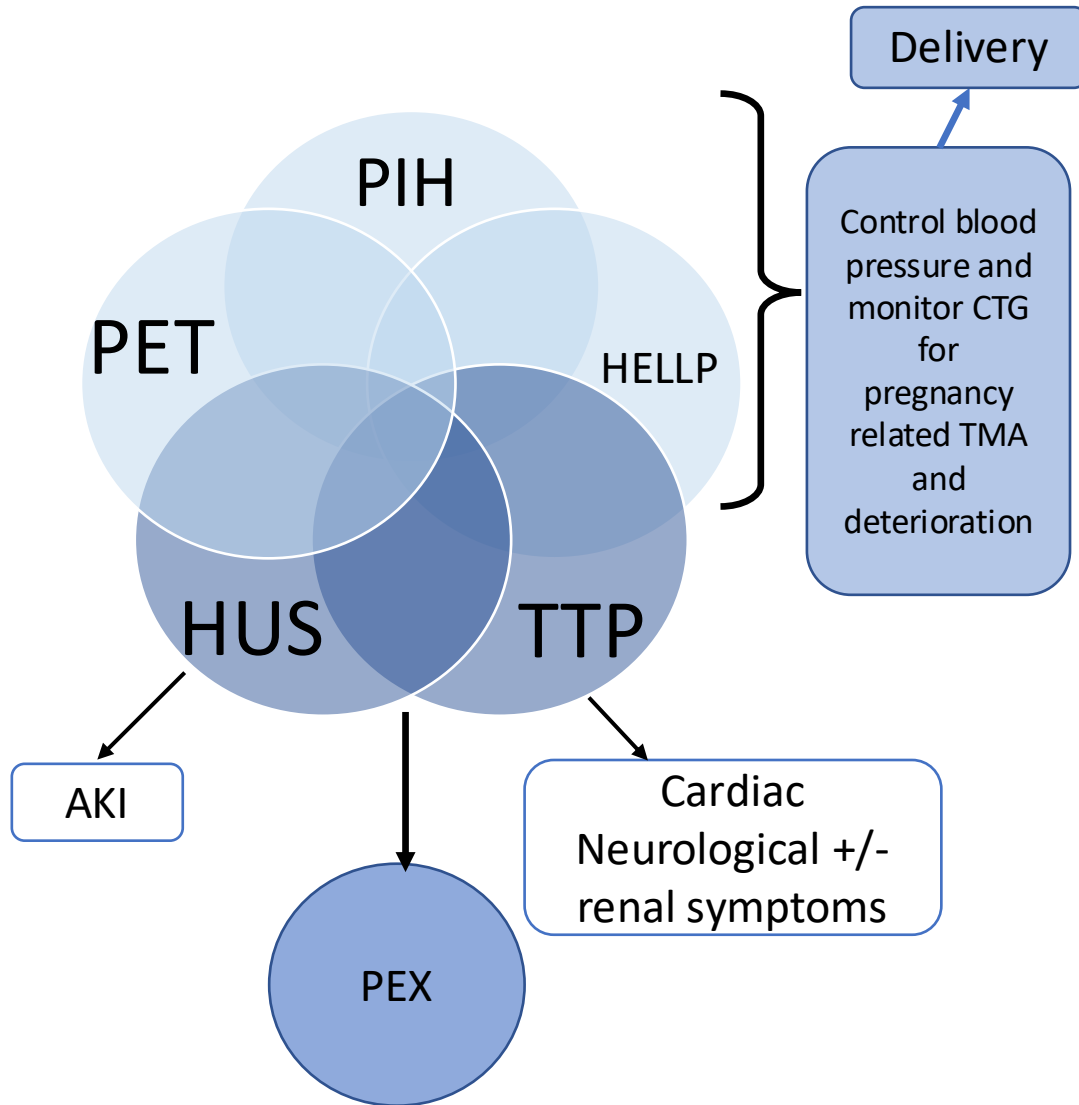
Placenta malperfusion and damage

Preeclampsia

Preterm birth



Management of pregnancy-related and pregnancy-associated TMAs



TTP & HUS:

- May have features of PET/HELLP/PIH

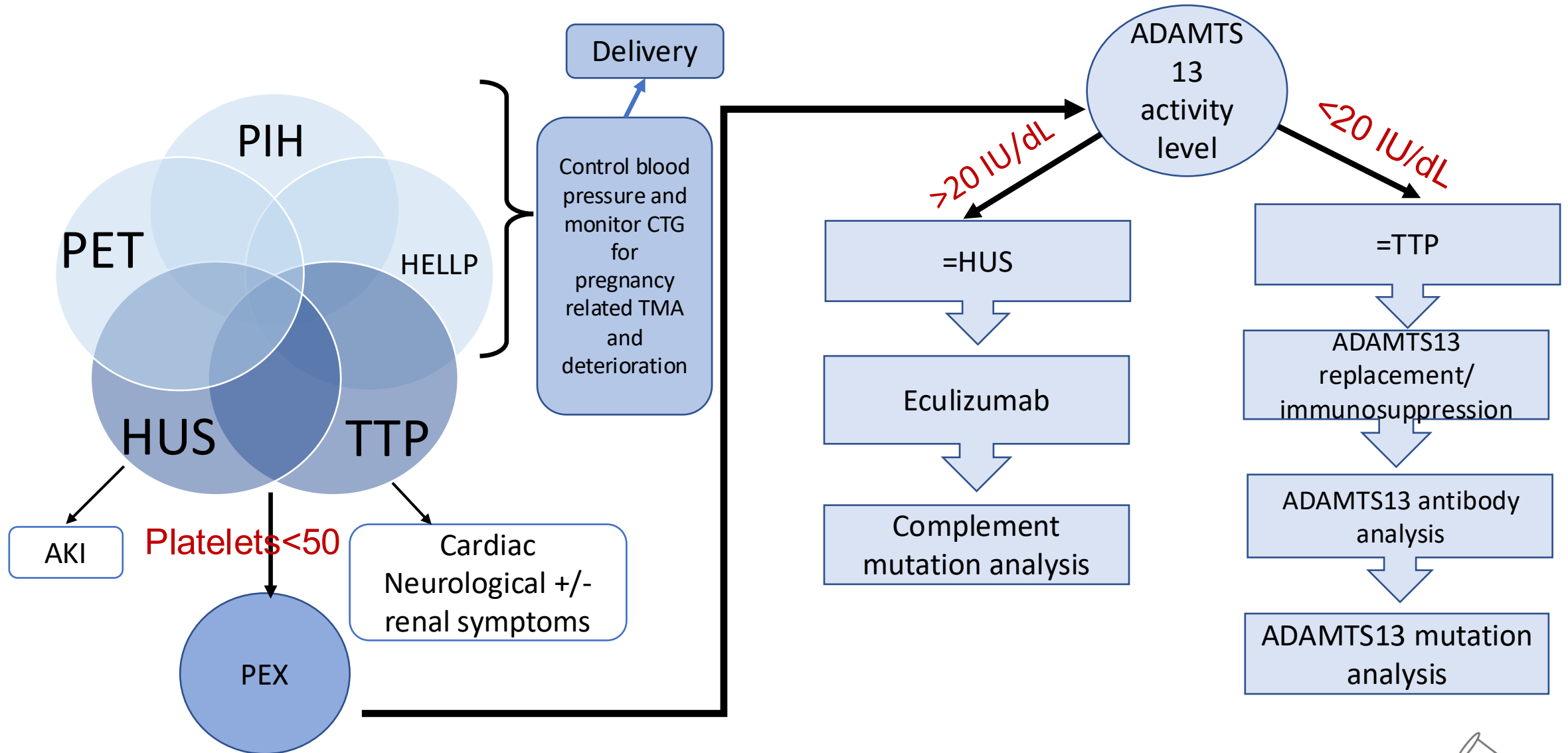
TTP & HUS:

- Medical emergencies
- Thrombocytopenia-may not be severe
- TMA remains active after delivery

PET/HELLP:

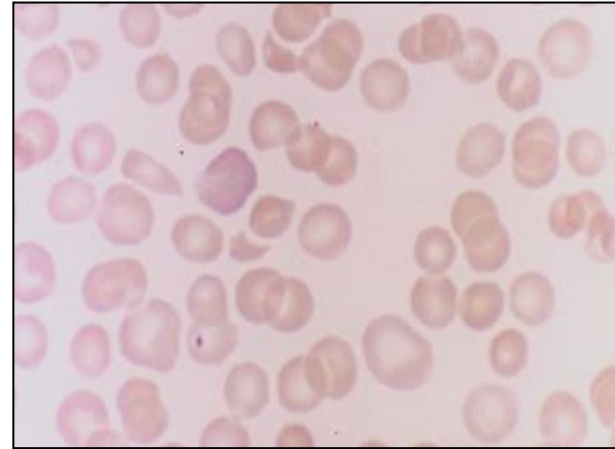
- Resolution with delivery
- BUT: Needs monitoring 48-72 hours post delivery

Management of pregnancy-related and pregnancy-associated TMAs



Differential diagnosis of TMAs: summary

- MAHA
- Thrombocytopenia
- Absence of underlying cause



Assume TTP
Commence PEX
urgently

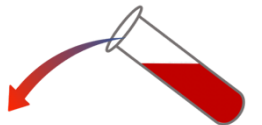
Haematological emergency



Differential diagnosis of TMAs: summary

Early differential diagnosis critical to improve patient outcomes

- ADAMTS13 <10% = TTP
- Clinical presentation alone does not fully differentiate CM-HUS from TTP or STEC-HUS
- CM-HUS ADAMTS13 activity >10%
STEC test negative



TTP conclusion

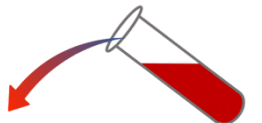
TTP = acute life threatening illness with severe ADAMTS13 activity

Treatment:

- ADAMTS13 replacement
- Immunosuppression
- Caplacizumab

Chronic condition:

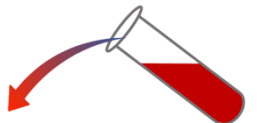
- Long term follow up to prevent relapse
- Longer term impact of acute disease/chronically reduced ADAMTS13 levels



MCQ 1

How is a TMA defined clinically?

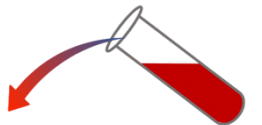
- a. Hemolytic anemia and thrombocytopenia
- b. Microangiopathic hemolytic anemia and thrombocytopenia
- c. Microangiopathic hemolytic anemia and thrombosis
- d. Synchronous venous and arterial thrombosis



MCQ 1

How is a TMA defined clinically?

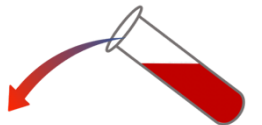
- a. Hemolytic anemia and thrombocytopenia
- b. **Microangiopathic hemolytic anemia and thrombocytopenia**
- c. Microangiopathic hemolytic anemia and thrombosis
- d. Synchronous venous and arterial thrombosis



MCQ 2

The diagnosis of TTP requires severely reduced levels of which protein?

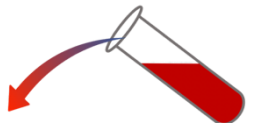
- a. VWF
- b. ADAMTS13
- c. Thrombospondin
- d. Complement C3



MCQ 2

The diagnosis of TTP requires severely reduced levels of which protein?

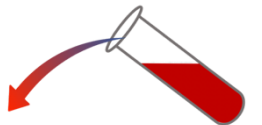
- a. VWF
- b. **ADAMTS13**
- c. Thrombospondin
- d. Complement C3



MCQ 3

What is the mechanism of action of caplacizumab?

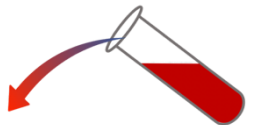
- a. Anti ADAMTS13 nanobody
- b. Anti VWF nanobody
- c. BAFF inhibitor
- d. Anti platelet nanobody



MCQ 3

What is the mechanism of action of caplacizumab?

- a. Anti ADAMTS13 nanobody
- b. **Anti VWF nanobody**
- c. BAFF inhibitor
- d. Anti platelet nanobody



MCQ 4

What is the mechanism of action of eculizumab?

- a. Anti VWF nanobody
- b. Complement C3 inhibitor
- c. Complement C5 inhibitor
- d. Complement Factor B inhibitor



MCQ 4

What is the mechanism of action of eculizumab?

- a. Anti VWF nanobody
- b. Complement C3 inhibitor
- c. **Complement C5 inhibitor**
- d. Complement Factor B inhibitor





- Prof Marie Scully
- UCLH TTP team
- Collaborators & Investigators of the UK TTP registry
- National and International Collaborators



