TTP and other Thrombotic Microangiopathies

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Disclosures

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

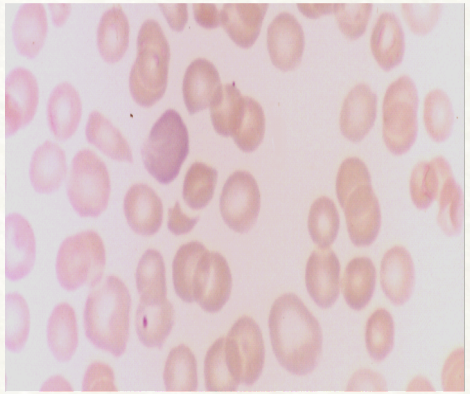
Topics To Cover

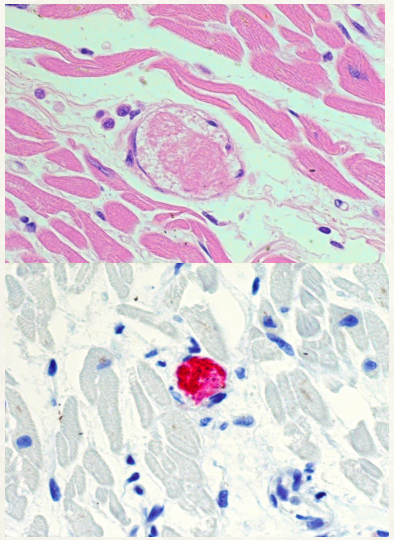
1. TMA overview
2. TTP
3. HUS
4. Other TMA

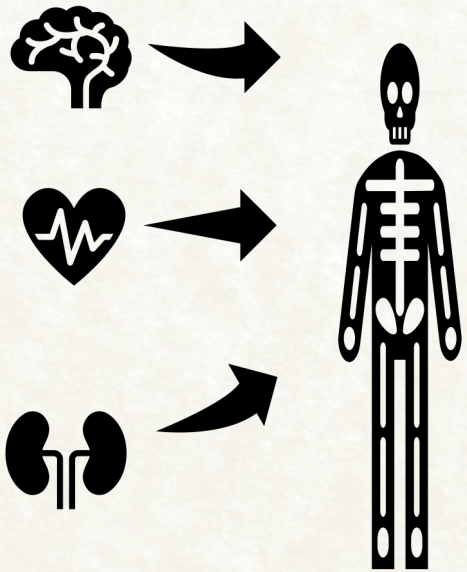
Current clinical diagnostic criteria of Thrombotic Microangiopathy

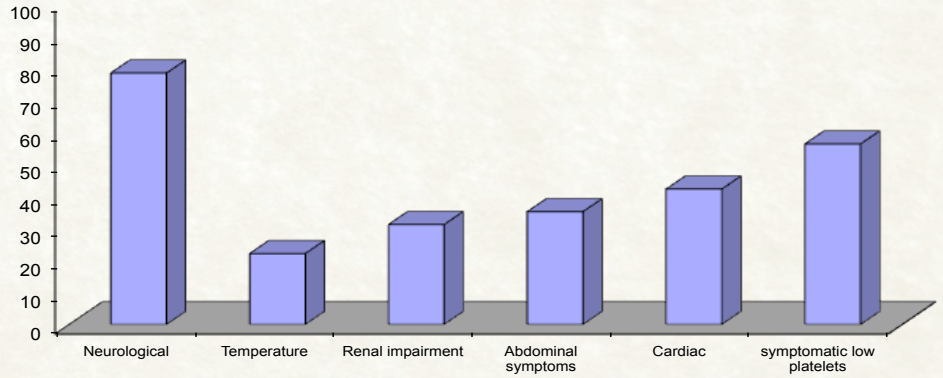
Thrombocytopenia

Microangiopathic haemolytic anaemia (MAHA)

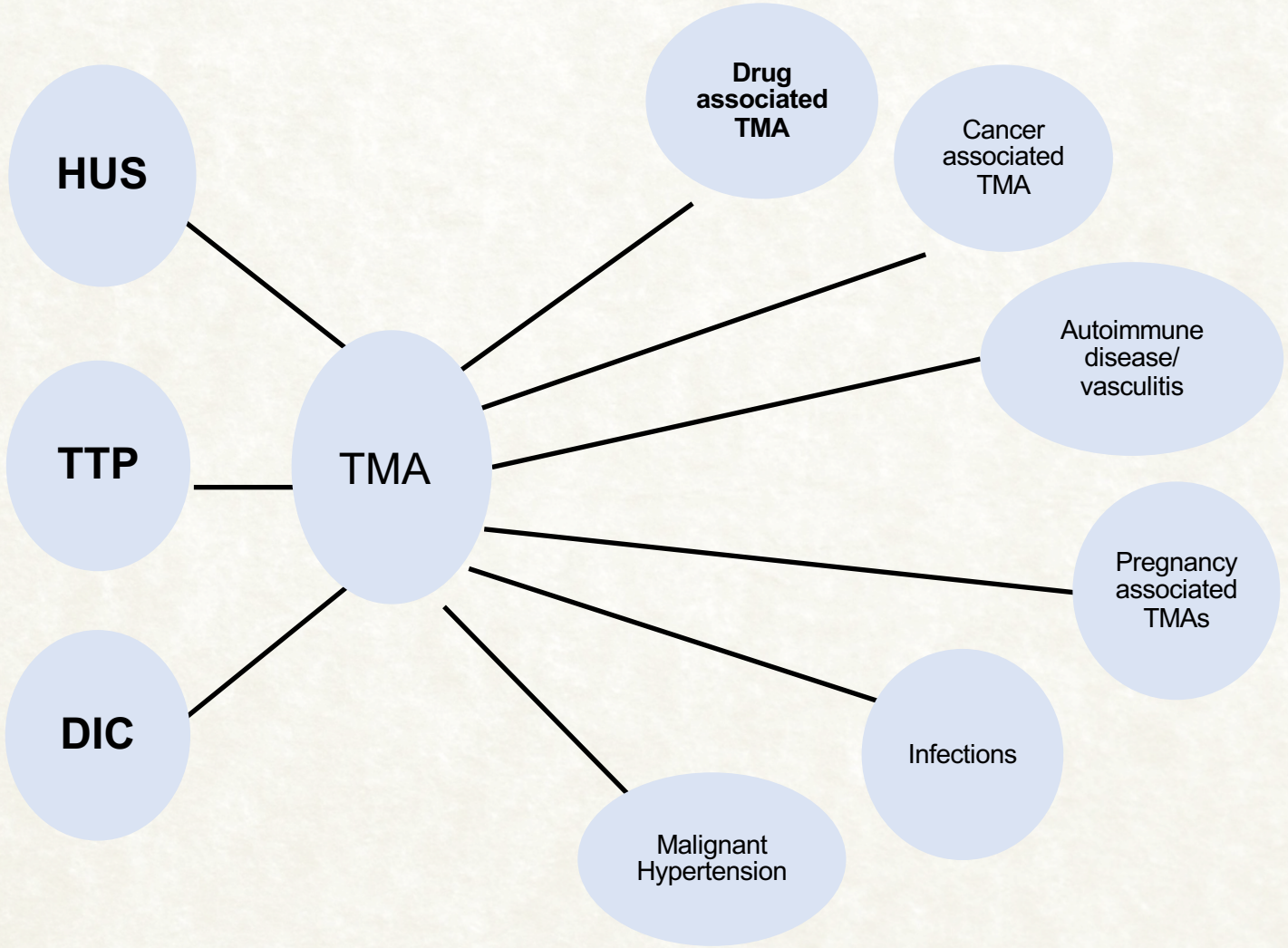


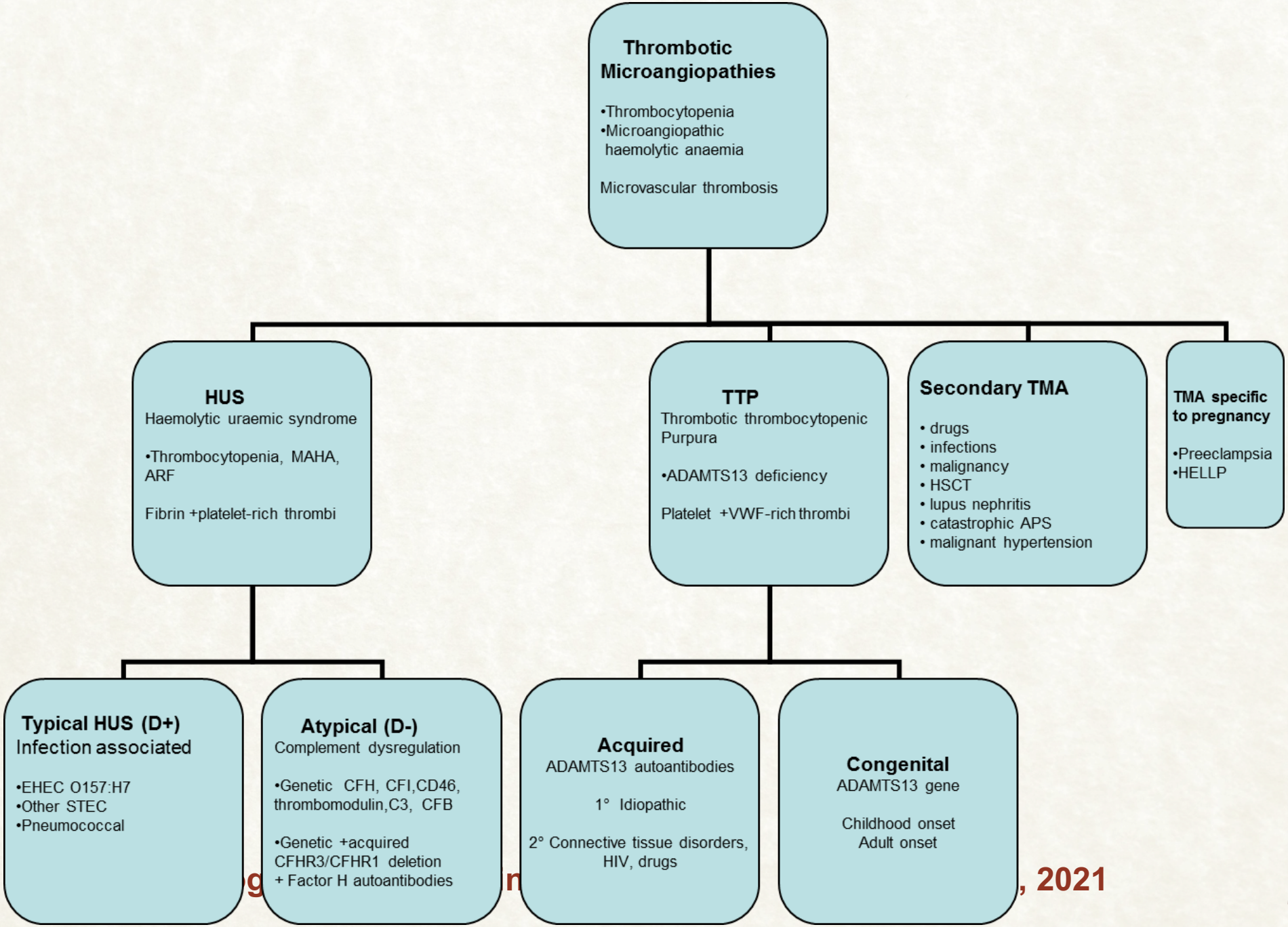






Differential Diagnosis of Thrombotic Microangiopathy

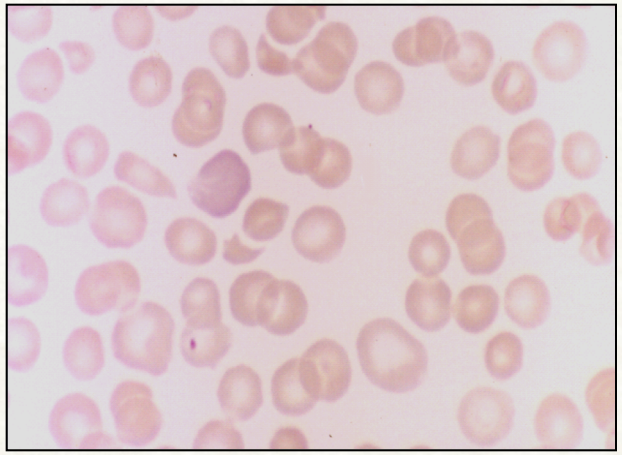



Thrombotic Microangiopathies
•Thrombocytopenia
•Microangiopathic haemolytic anaemia
Microvascular thrombosis
HUS
Haemolytic uraemic syndrome
•Thrombocytopenia, MAHA, ARF
Fibrin +platelet-rich thrombi
TTP
Thrombotic thrombocytopenic Purpura
•ADAMTS13 deficiency
Platelet +VWF-rich thrombi
Secondary TMA
• drugs
• infections
• malignancy
• HSCT
• lupus nephritis
• catastrophic APS
• malignant hypertension
TMA specific to pregnancy
•Preeclampsia
•HELLP
Typical HUS (D+)
Infection associated
•EHEC O157:H7
•Other STEC
•Pneumococcal
Atypical (D-)
Complement dysregulation
•Genetic CFH, CFI,CD46, thrombomodulin,C3, CFB
•Genetic +acquired CFHR3/CFHR1 deletion + Factor H autoantibodies
Acquired
ADAMTS13 autoantibodies
1° Idiopathic
2° Connective tissue disorders, HIV, drugs
Congenital
ADAMTS13 gene
Childhood onset
Adult onset

g n , 2021

Diagnosis of TTP – haematological emergency

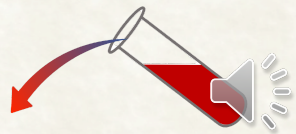
- MAHA
- Thrombocytopenia
- Absence of underlying cause



Assume TTP
Commence PEX urgently

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 FRETS assay

- Synthetic fluorogenic 73aa VWF peptide including scissile bond (FRETS-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

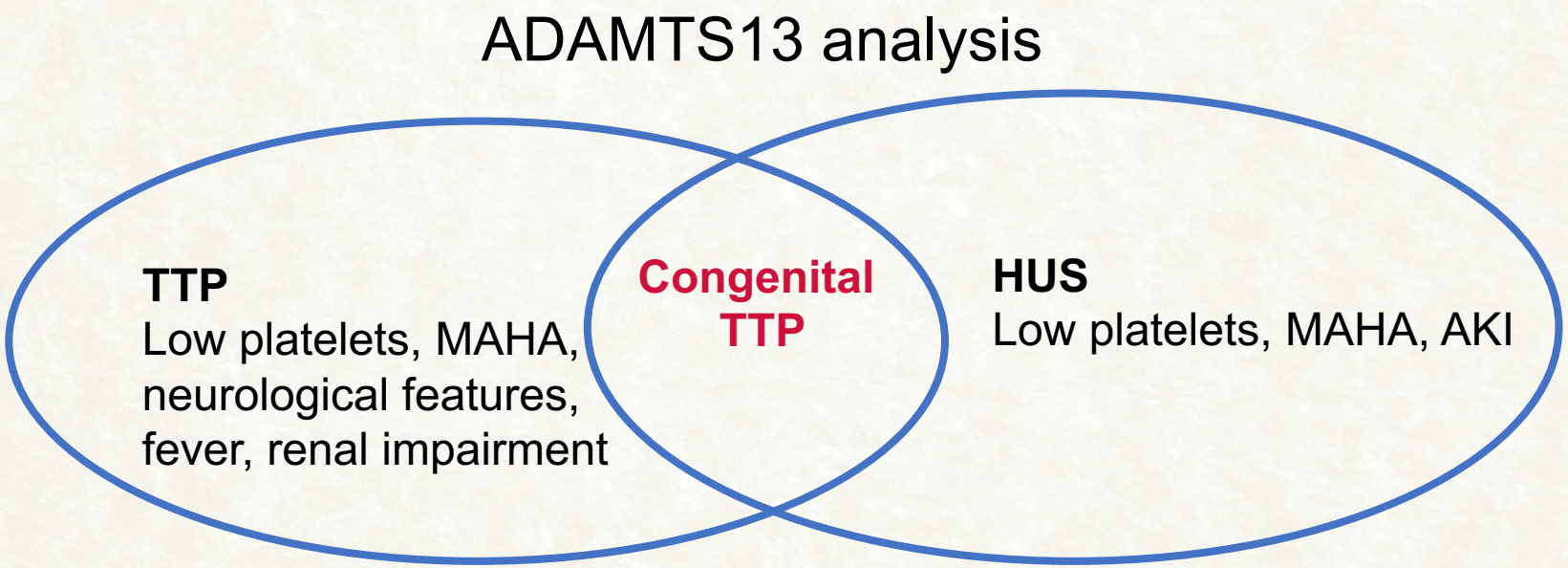
Prediction of severe ADAMTS13 deficiency (Activity <10%)

- 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%

➢ a. Bendapudi PK, et al. *Lancet Hematol.* 2017;4:e157-e164; b. Hassan S, et al. *Br J Haematol.* 2015;171:830-835.

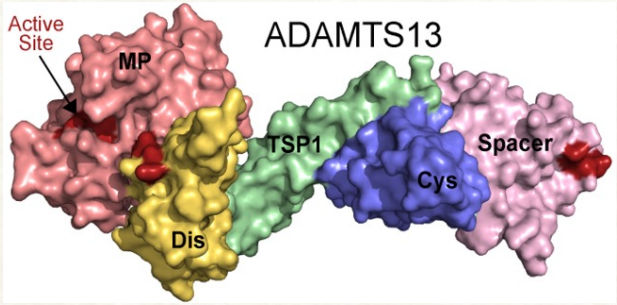
Role of ADAMTS13 analysis in TTP/TMA diagnosis



'Serum creatinine level >150–200 μmol/l or a platelet count >30,000/mm^3 almost eliminates a diagnosis of severe ADAMTS13 deficiency'

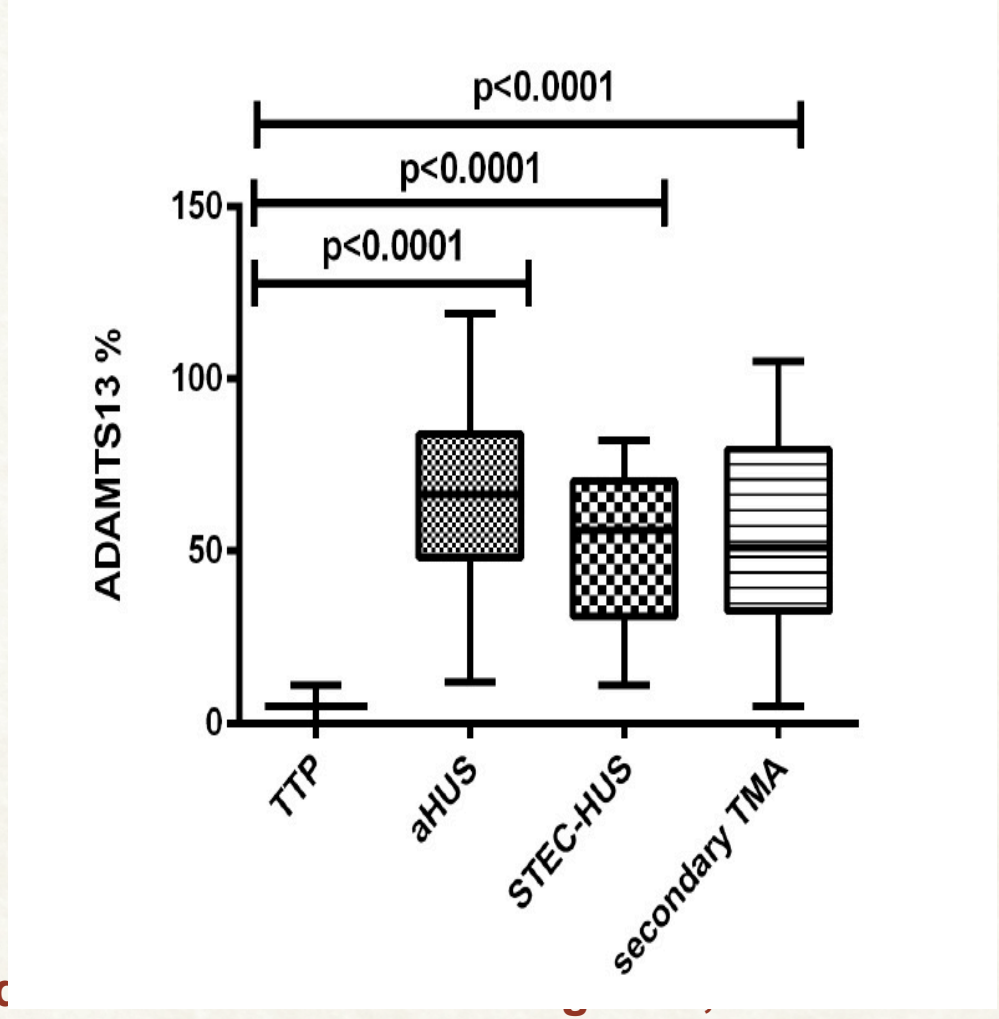
Zuber J et al. Nat Rev Nephrol 2012;8:643–57

ADAMTS13 levels in TTP, HUS and TMAs



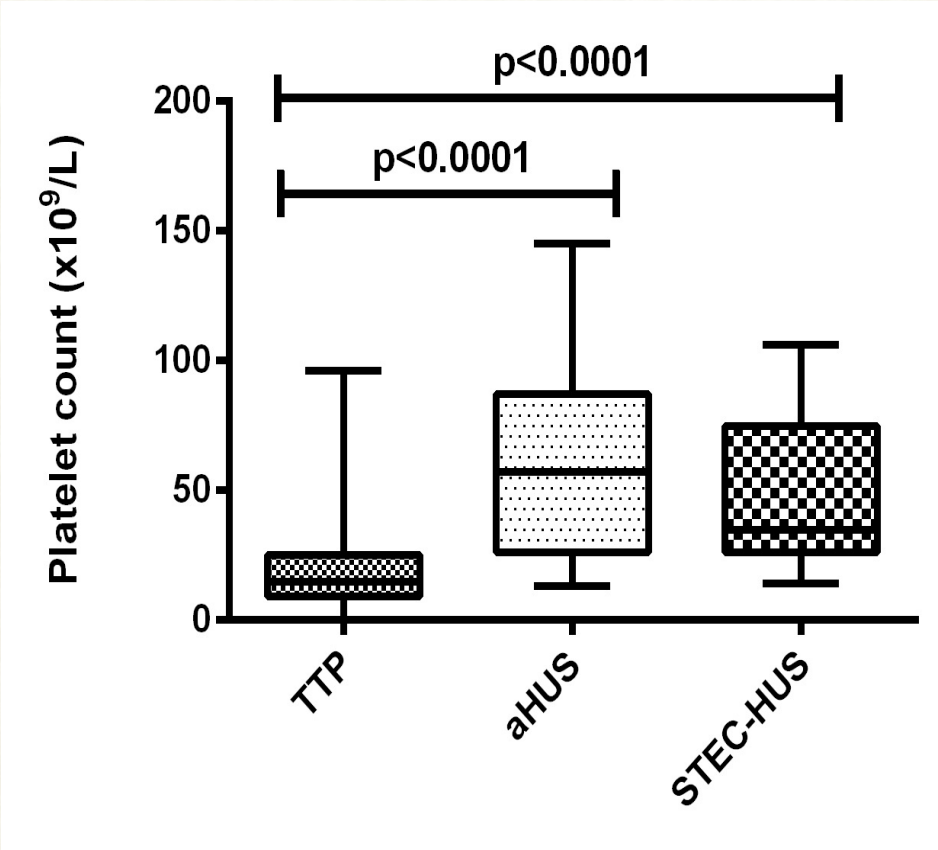
Patients with TTP had significantly lower median ADAMTS13 levels than aHUS, HUS or MAHA/TMA.

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

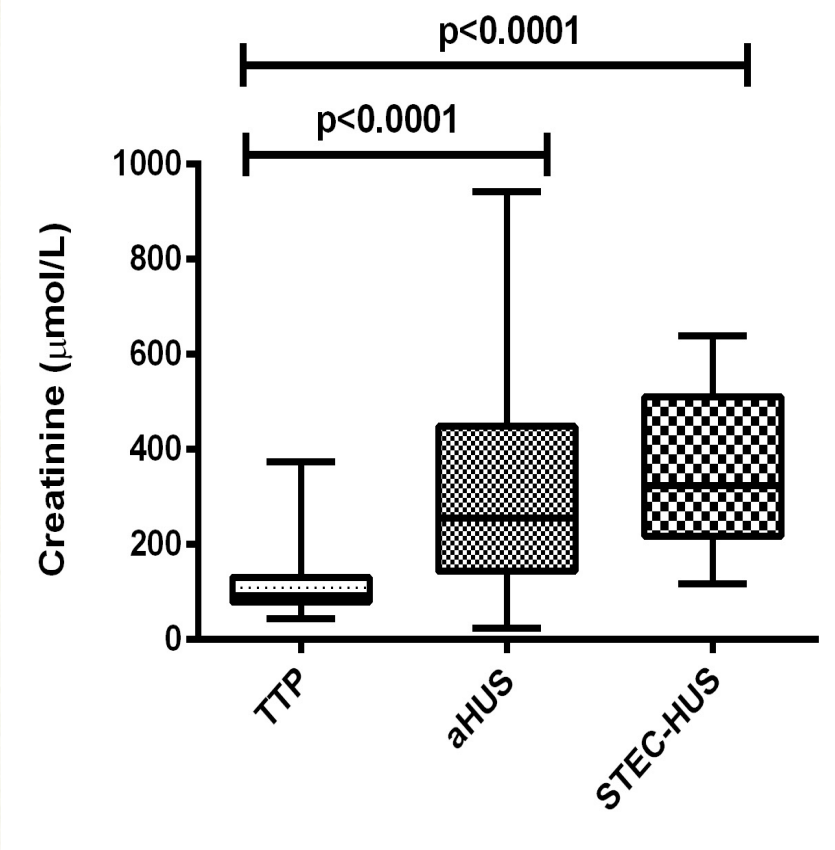


Hassan et al Br J Haematol. 2015;171(5):830-5

Platelets & Creatinine: from UK TTP Registry



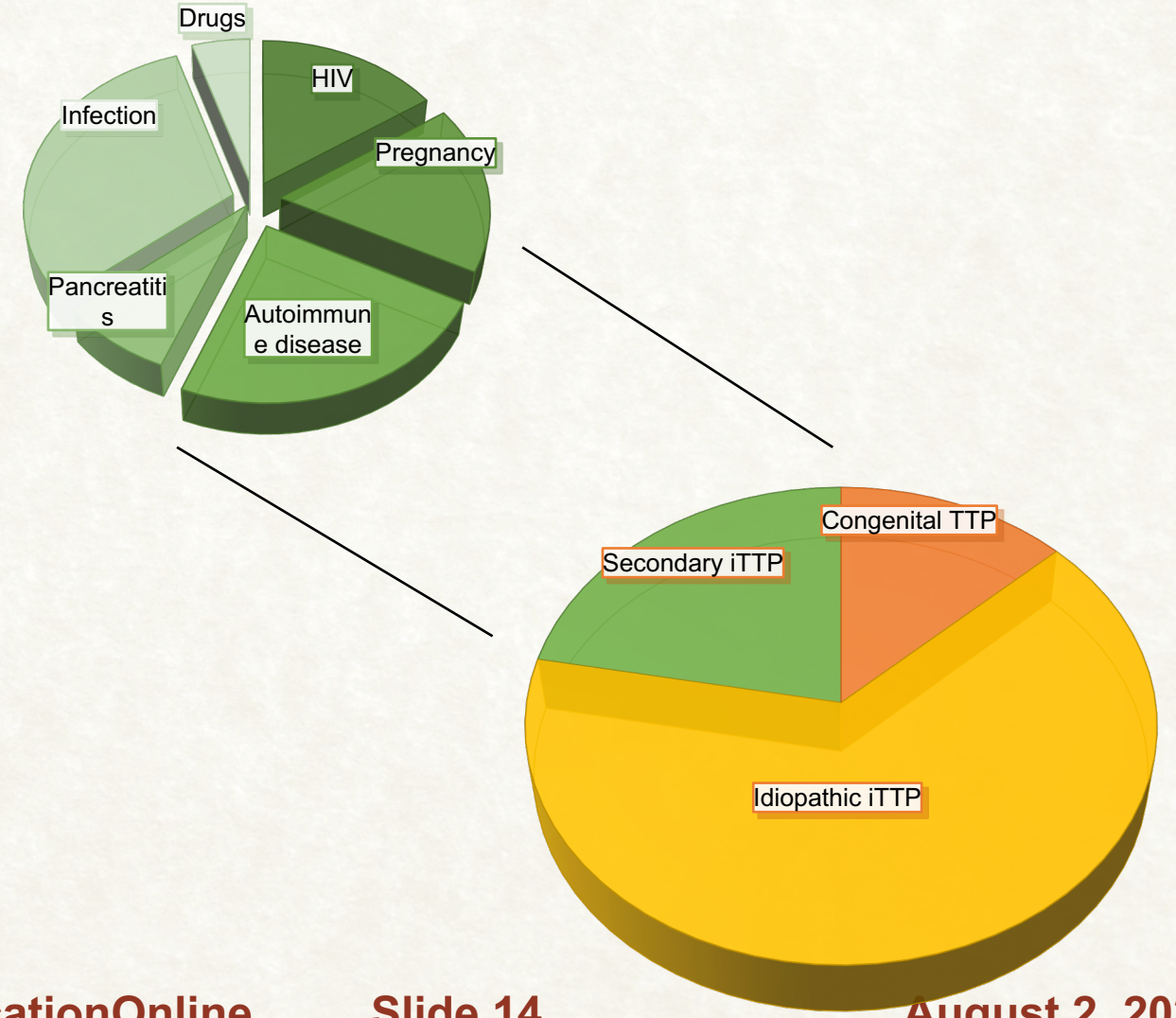
35.3% aHUS group: platelet count <30 x 10^9/L
17.3% of TTP had a platelet count >30 x 10^9/L



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

Hassan et al Br J Haematol. 2015;171(5):830-5

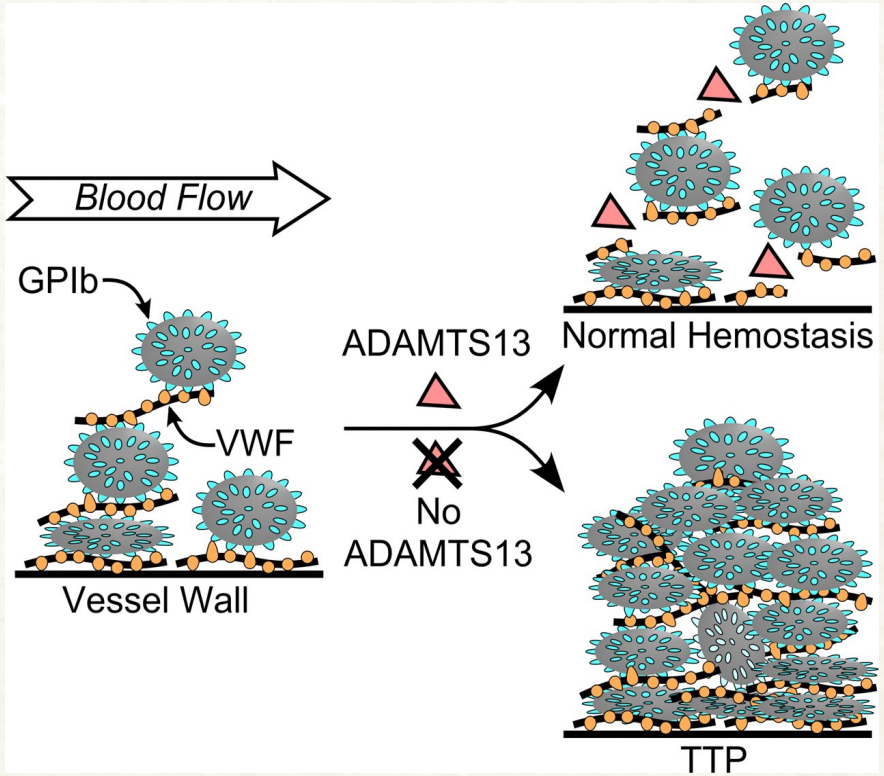
Subgroups of TTP



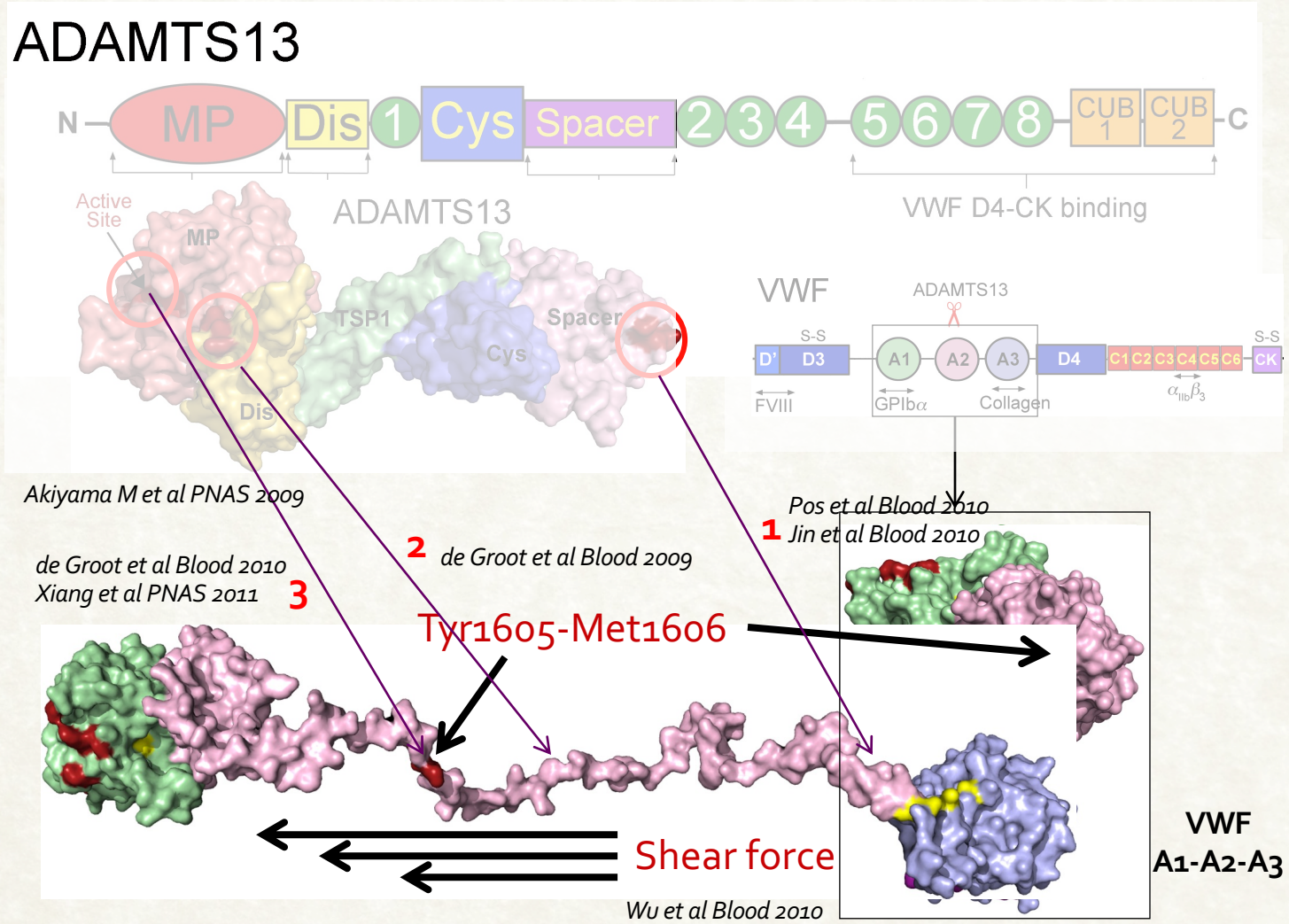
TTP - ADAMTS13 deficiency

A Disintegrin And Metalloproteinase with ThromboSpondin type-1 repeats 13

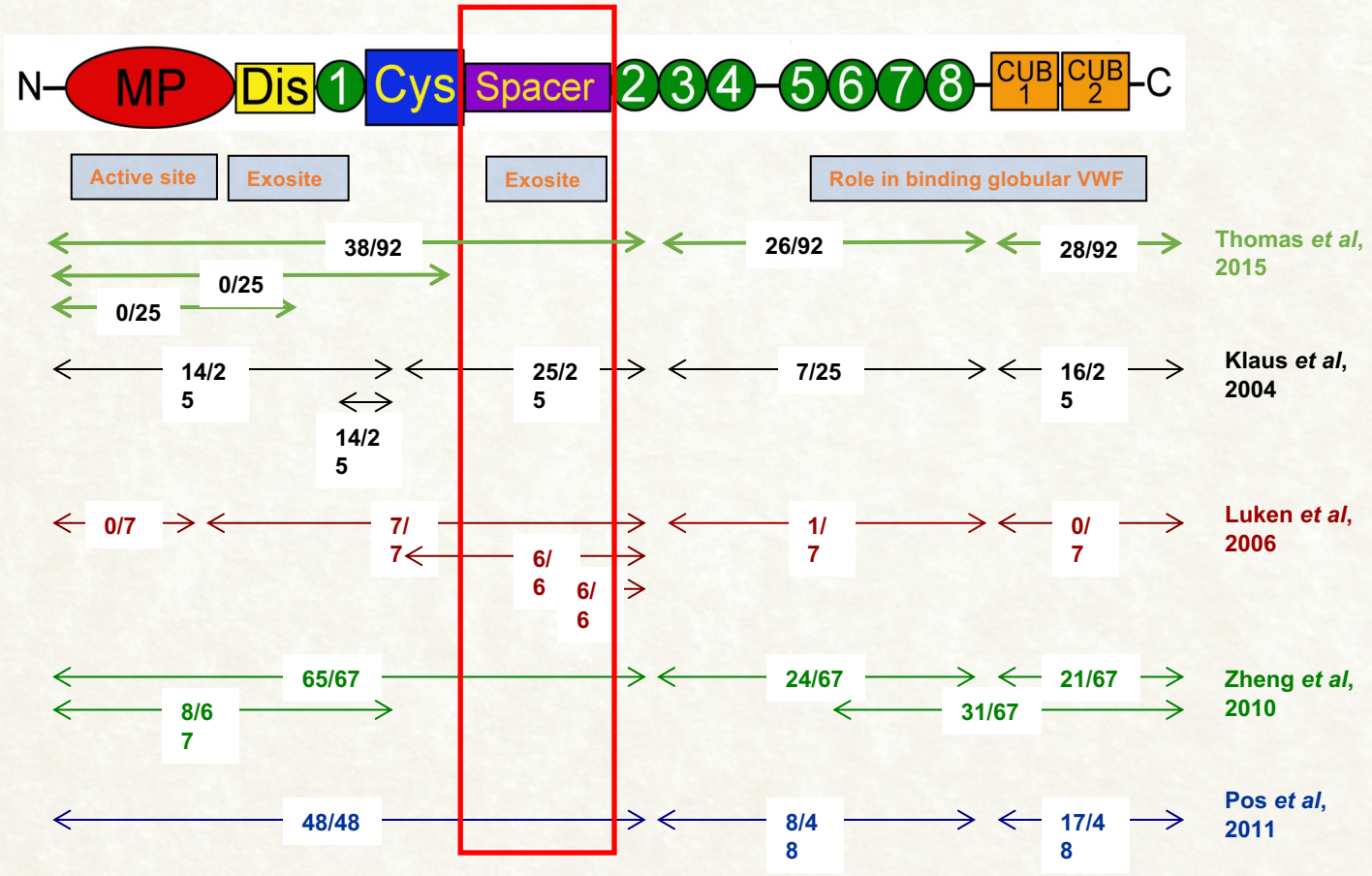
- ADAMTS13 is a Zn^{2+}-dependent metalloprotease (~190kDa)
- Secreted as active enzyme (5 – 10 nM)
- No natural inhibitor - long plasma ½-life (~2-3 days)
- Highly specific
  - Only cleaves VWF
  - Single site - A2 domain (Tyr1605-Met1606)
- Regulates VWF multimeric size/function in plasma



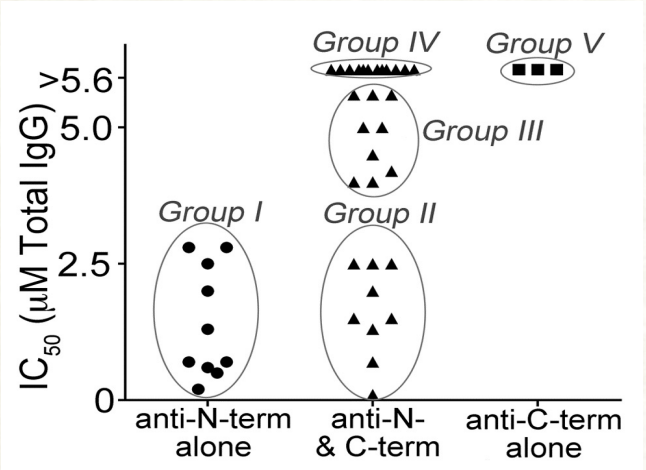
Sadler, Blood 2008


ADAMTS13
N
MP
Dis
1
Cys
Spacer
2
3
4
5
6
7
8
CUB 1
CUB 2
C
ADAMTS13
VWF D4-CK binding
Active Site
MP
TSP1
Spacer
Cys
Dis
VWF
ADAMTS13
S-S
D'
D3
A1
A2
A3
D4
C1 C2 C3 C4 C5 C6
CK
S-S
FVIII
GPIbα
Collagen
$\alpha_{IIb}\beta_3$
Akiyama M et al PNAS 2009
Pos et al Blood 2010
1 Jin et al Blood 2010
2 de Groot et al Blood 2009
de Groot et al Blood 2010
Xiang et al PNAS 2011
3
Tyr1605-Met1606
Shear force
Wu et al Blood 2010
VWF
A1-A2-A3

Domain specificity of anti-ADAMTS13 IgG

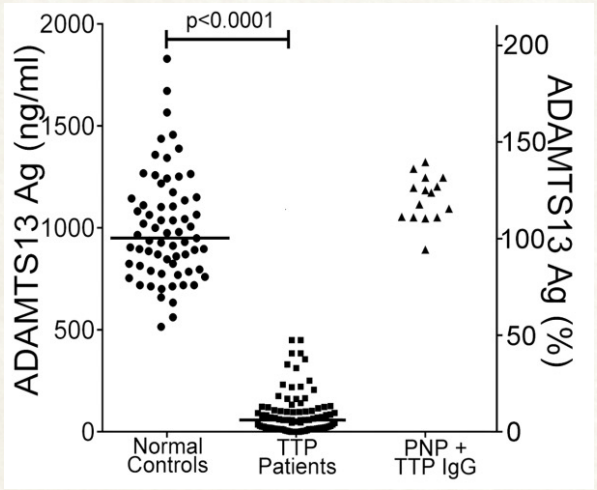


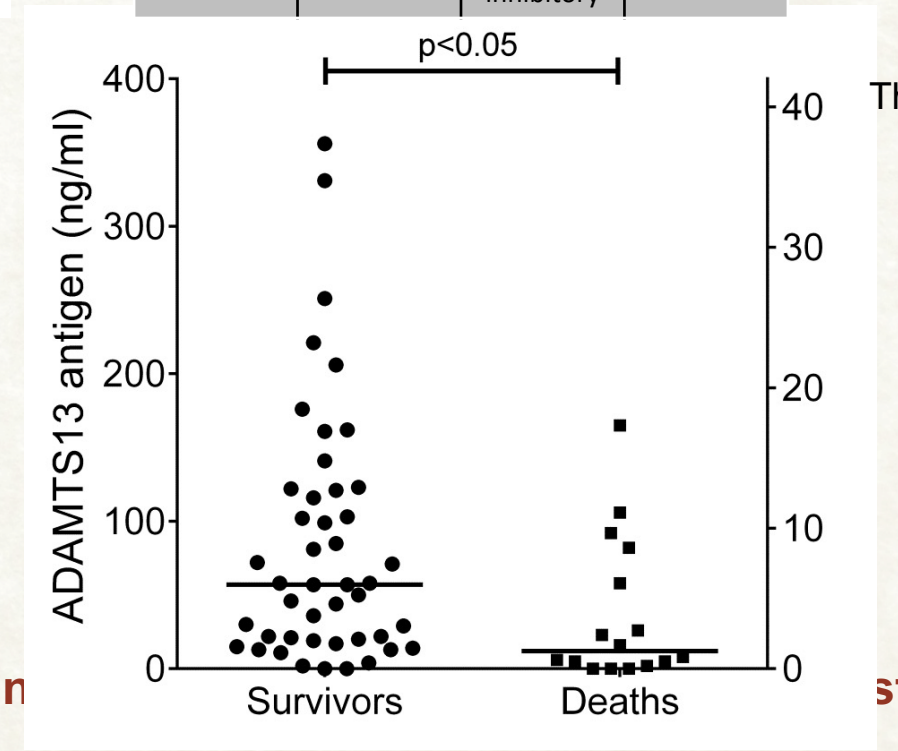
ADAMTS 13 IgG Abs are NOT all inhibitory



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





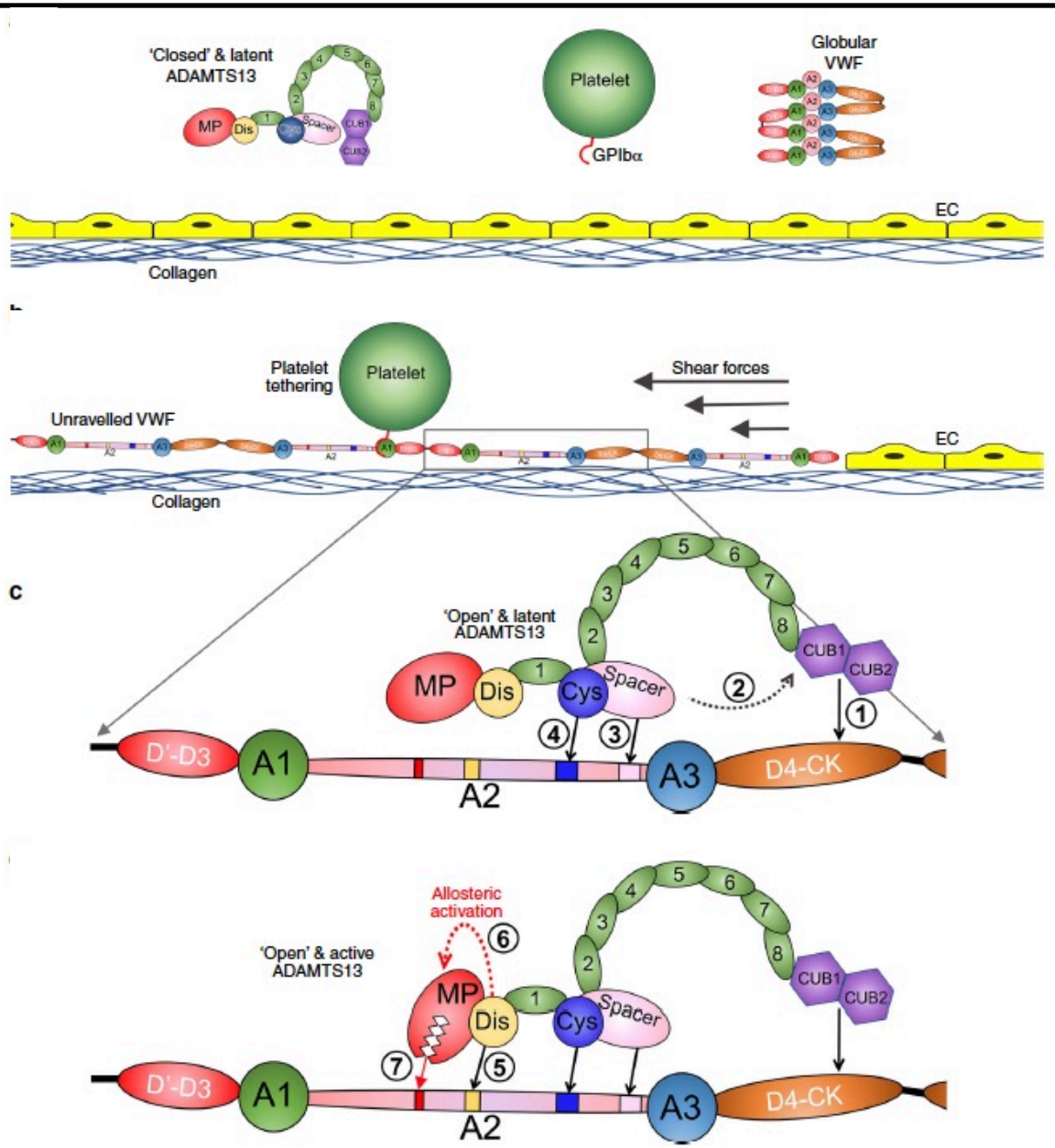
Thomas et al EBioMED 2015

ADAMTS13 antigen <13.5ng/ml associated with increased likelihood of mortality

OR 5.7

(95% CI 1.5-21.8; p<0.05)

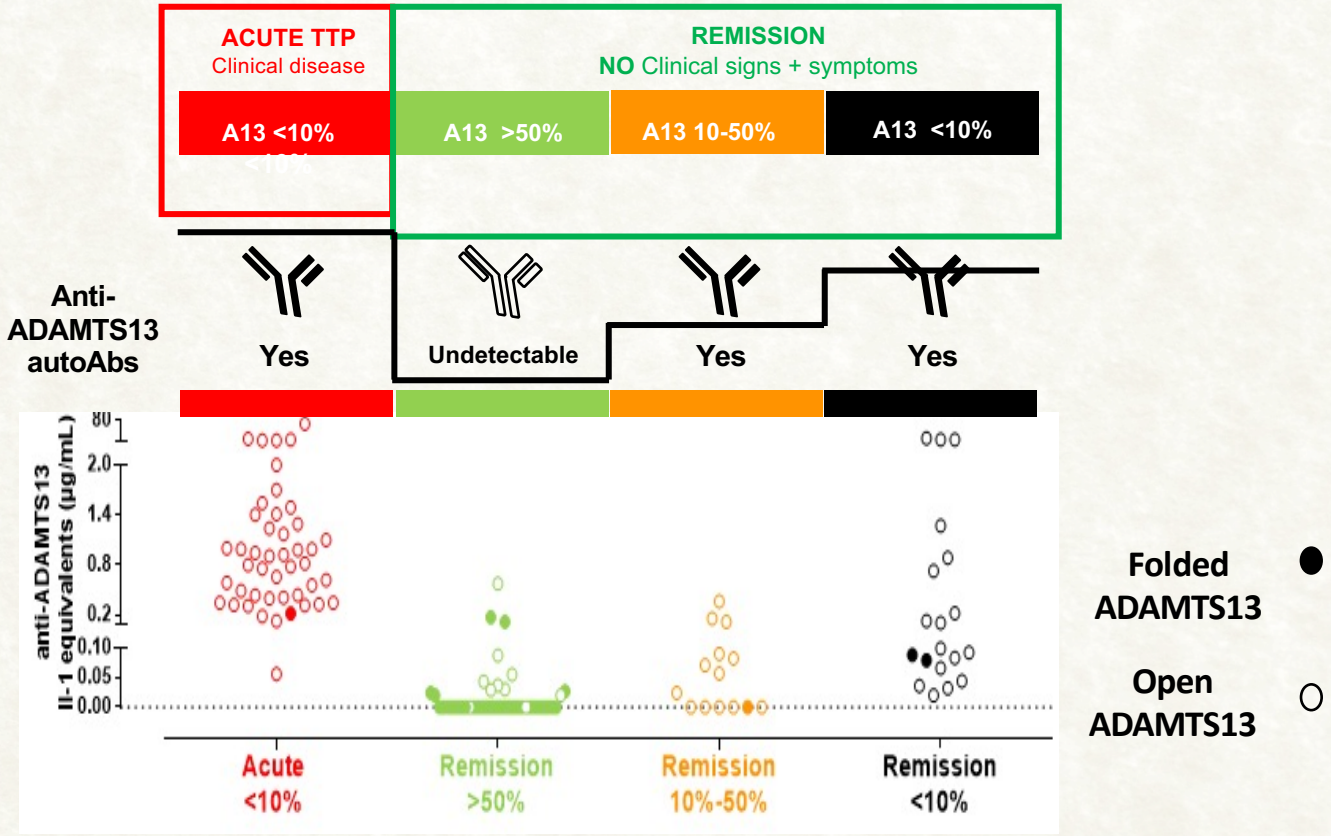
Mode of Action of ADAMTS 13



August 2, 2021

Petri et al Nat Comm 2019

ADAMTS13 antibody and TTP disease state



Roose et al JTH 2020

Prognostic Factors in acute TTP

- **Troponin**
  68% patients ↑troponin at presentation
  ↑troponin at presentation = **6 fold increase in mortality** (12.1% vs. 2.0%, p=0.04)

- **GCS**
  28% patients ↓ GCS at presentation
  ↓GCS (<15/15) at presentation = **9 fold increase in mortality** (20% vs. 2.2%, p<0.0001)

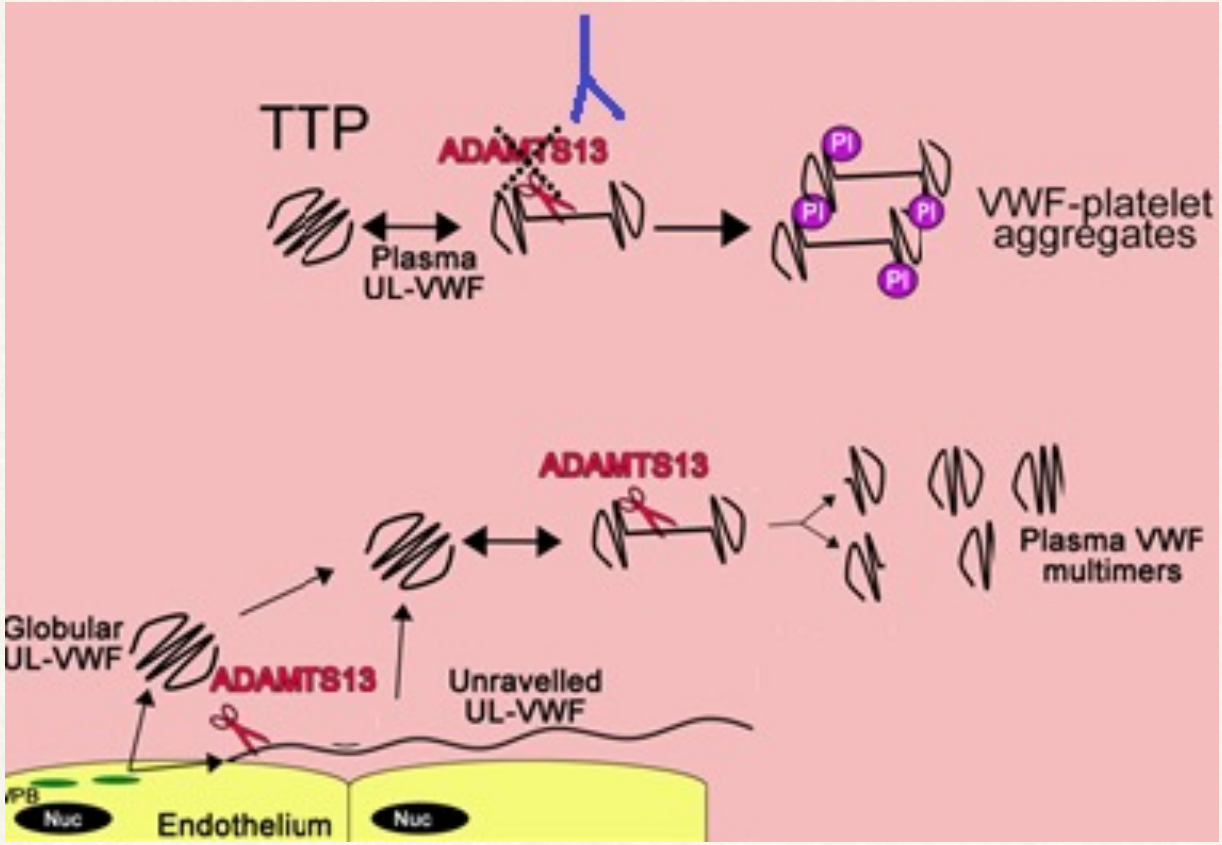
- **Anti ADAMTS13 IgG levels** Q1 (<20%) → Q2 → Q3 → Q4 (>77%)

Q4
- More likely to have raised troponin (44% vs 87%, p<0.0001)
- More likely to have decreased GCS (19% vs 41%, p=0.035)
- More plasma exchange needed to remission (10 sessions vs. 20 sessions, p=0.006)
- Increased mortality (5.0% vs 16.9%, p=0.02)

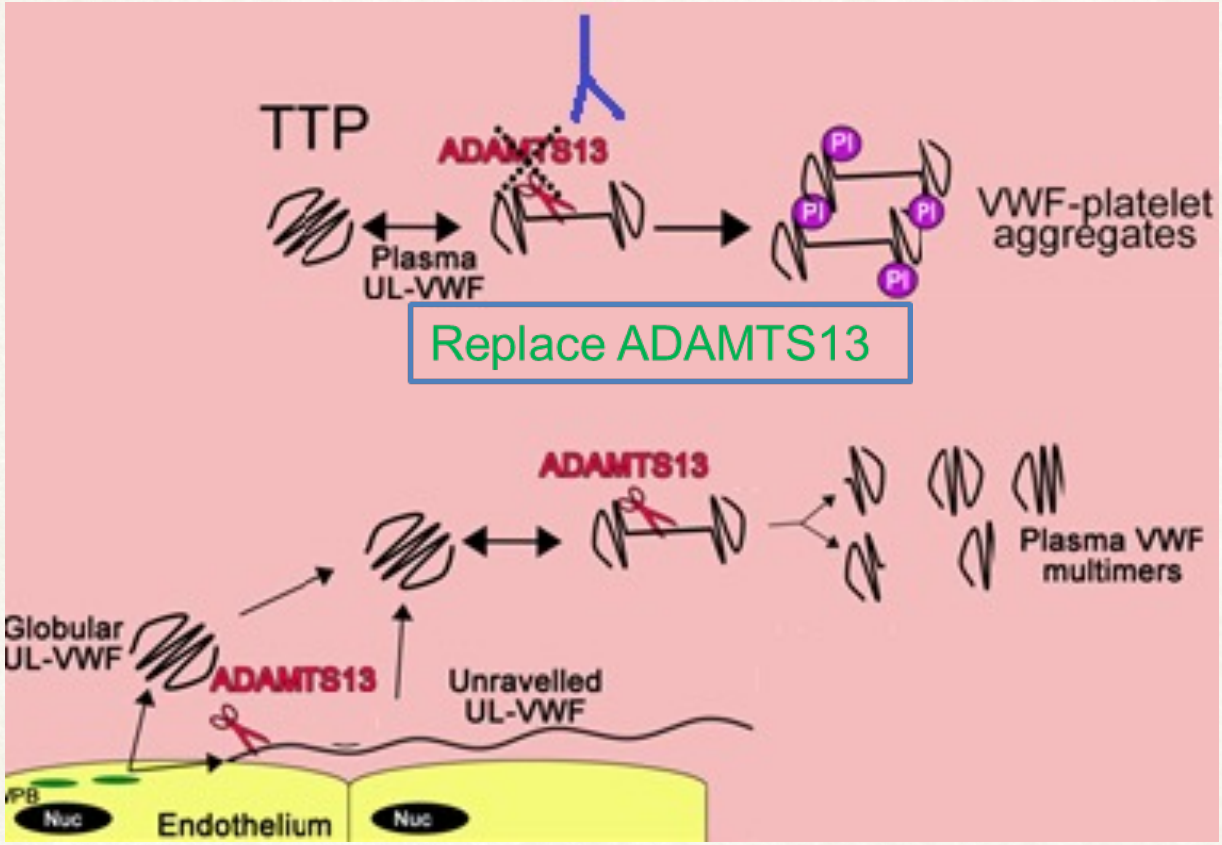
- **ADAMTS13 antigen levels**
  Highest mortality = ADAMTS 13 IgG >77% (Q4) and ADAMTS 13 antigen <1.5% (Q1) = **Mortality = 27.3%**

Alwan *et al*, Blood 2017

How drugs work in TTP

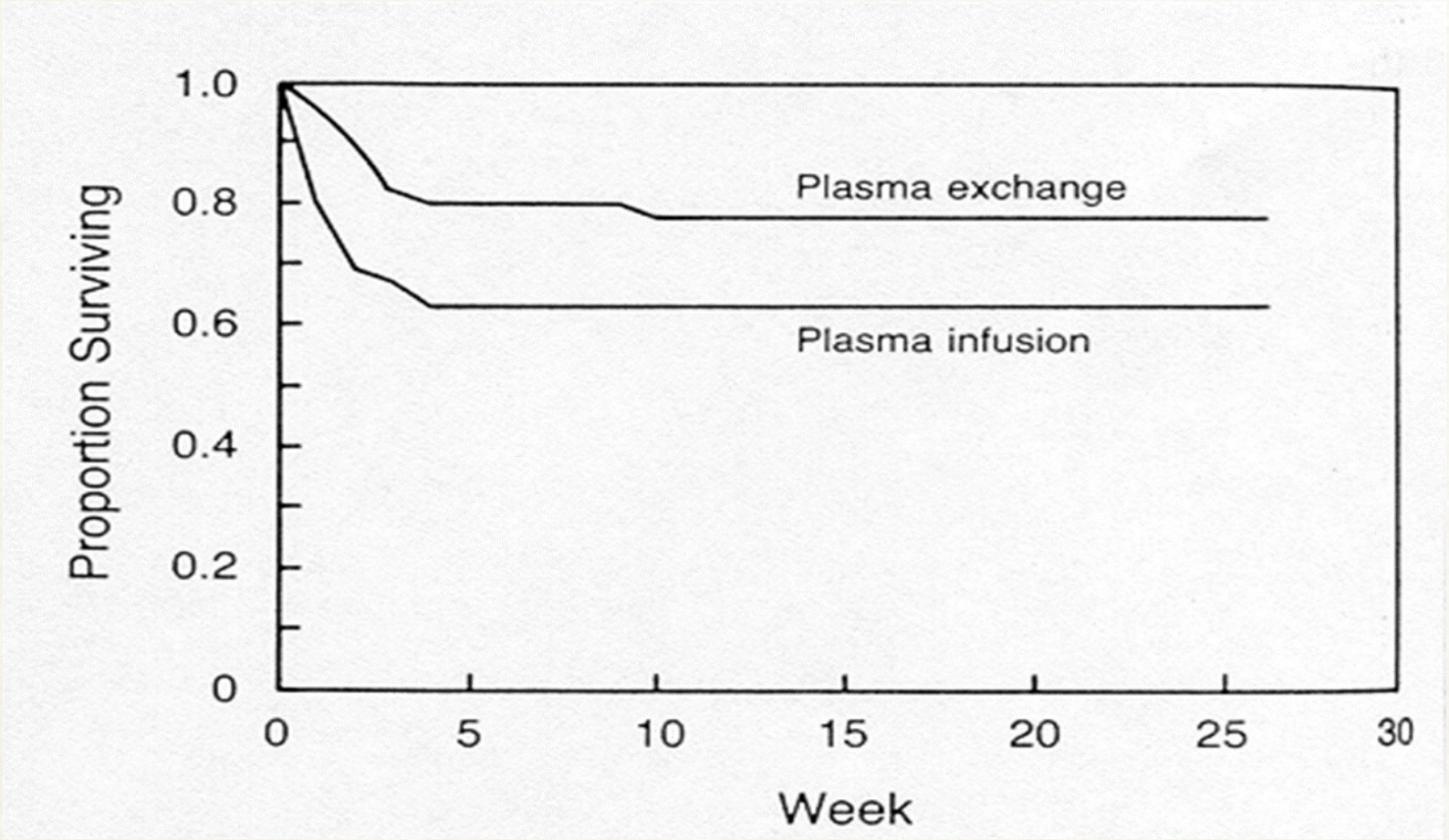


How drugs work in TTP



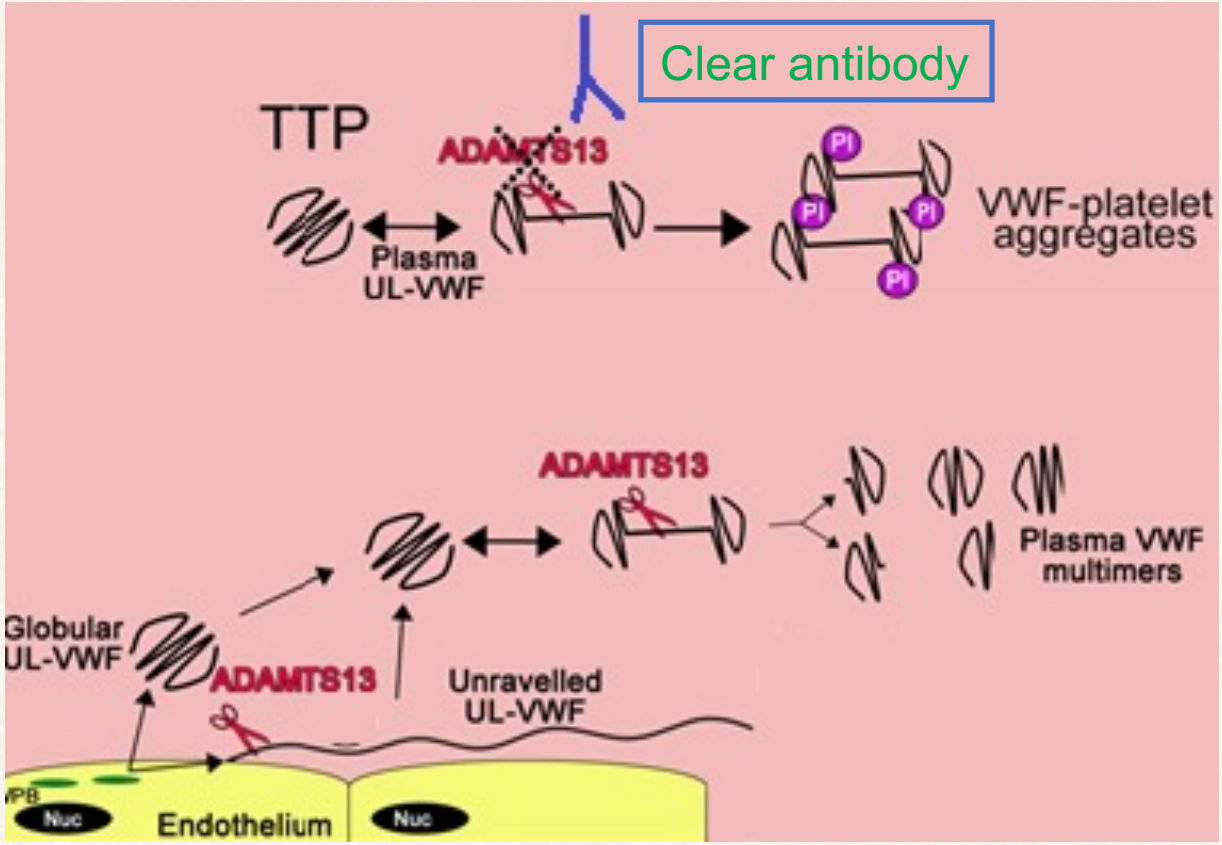
Treatment of TTP

Survival of patients with thrombotic thrombocytopenic purpura

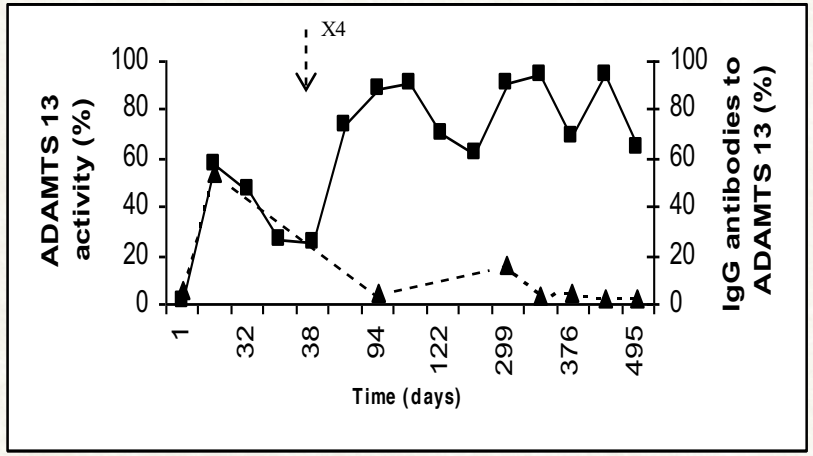


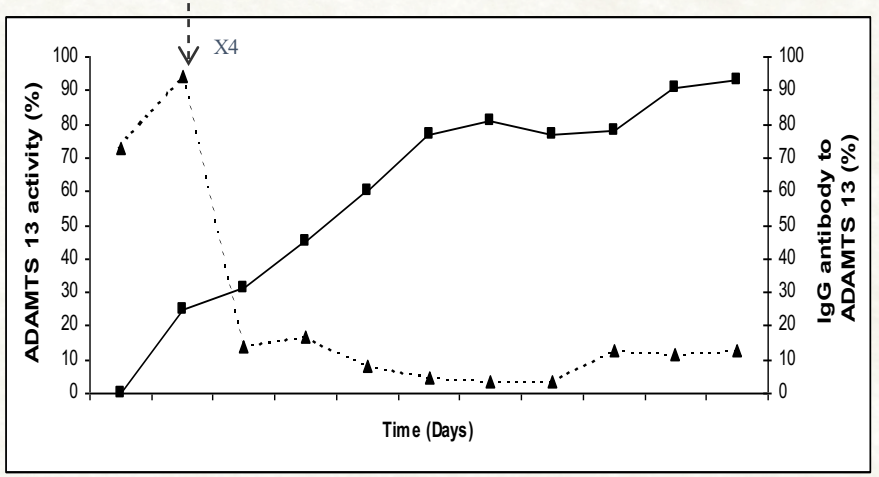
Rock et al, NEJM 1991

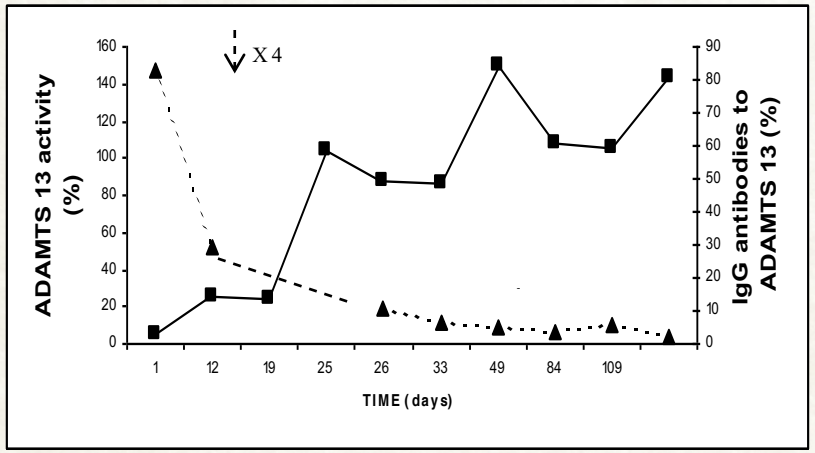
How drugs work in TTP

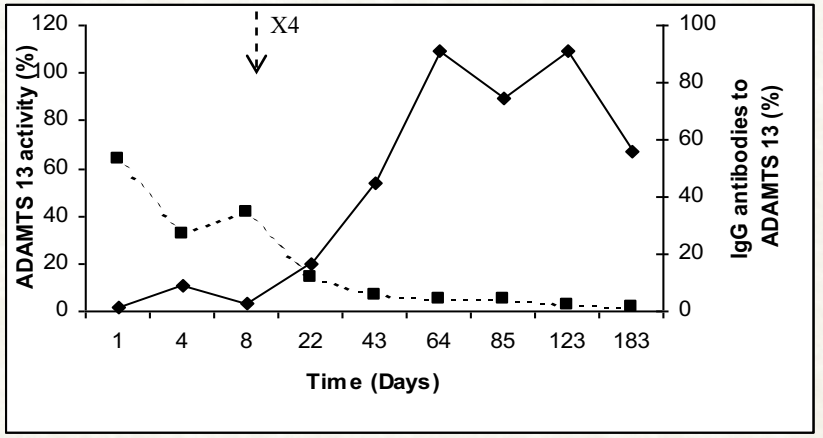


Longitudinal series of ADAMTS 13 activity and IgG antibodies to ADAMTS 13 and response to Rituximab in 4 cases with acute refractory TTP









Scully et al BJH 2007

Rituximab naïve group: timing of first infusion and outcome

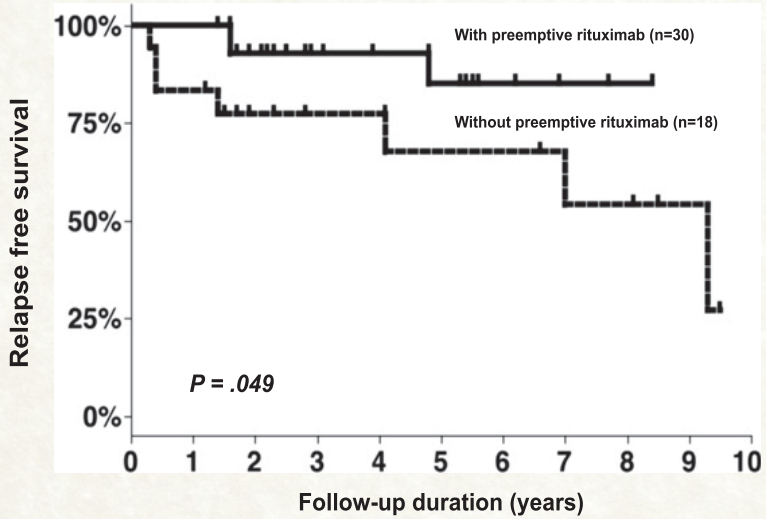
	≤3 days from admission (n=52)	>3 days from admission (n=30)	
Median No. of PEX to CR (range)	16 (4-36)	24 (6-40)	p=0.03
Median Length of admission (range)	16 (4-86)	23 (7-52)	p=0.01
Median Time to CR from admission (range)	12 (4-52)	20 (4-42)	P<0.001
Median Time to CR from first infusion (range)	10 (2-50)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

H

Westwood et al JTH 2013

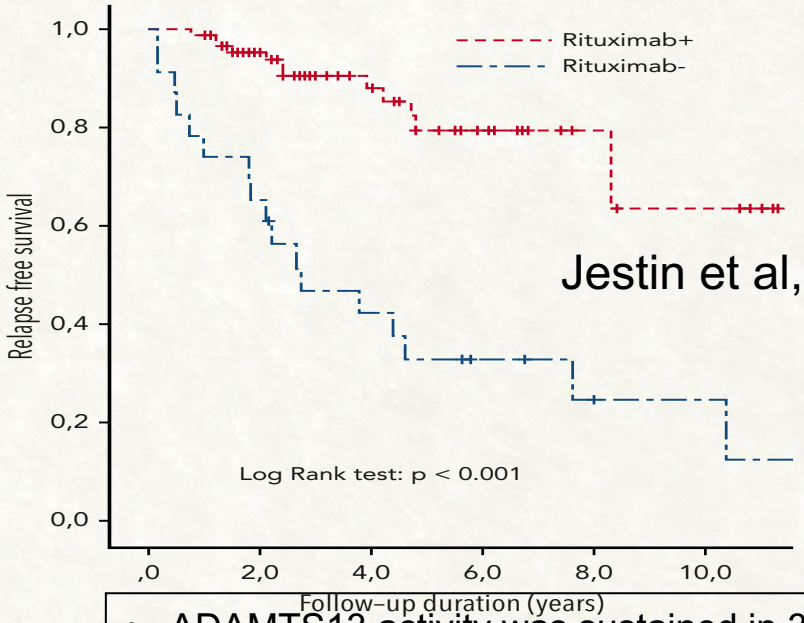
Elective Rituximab

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

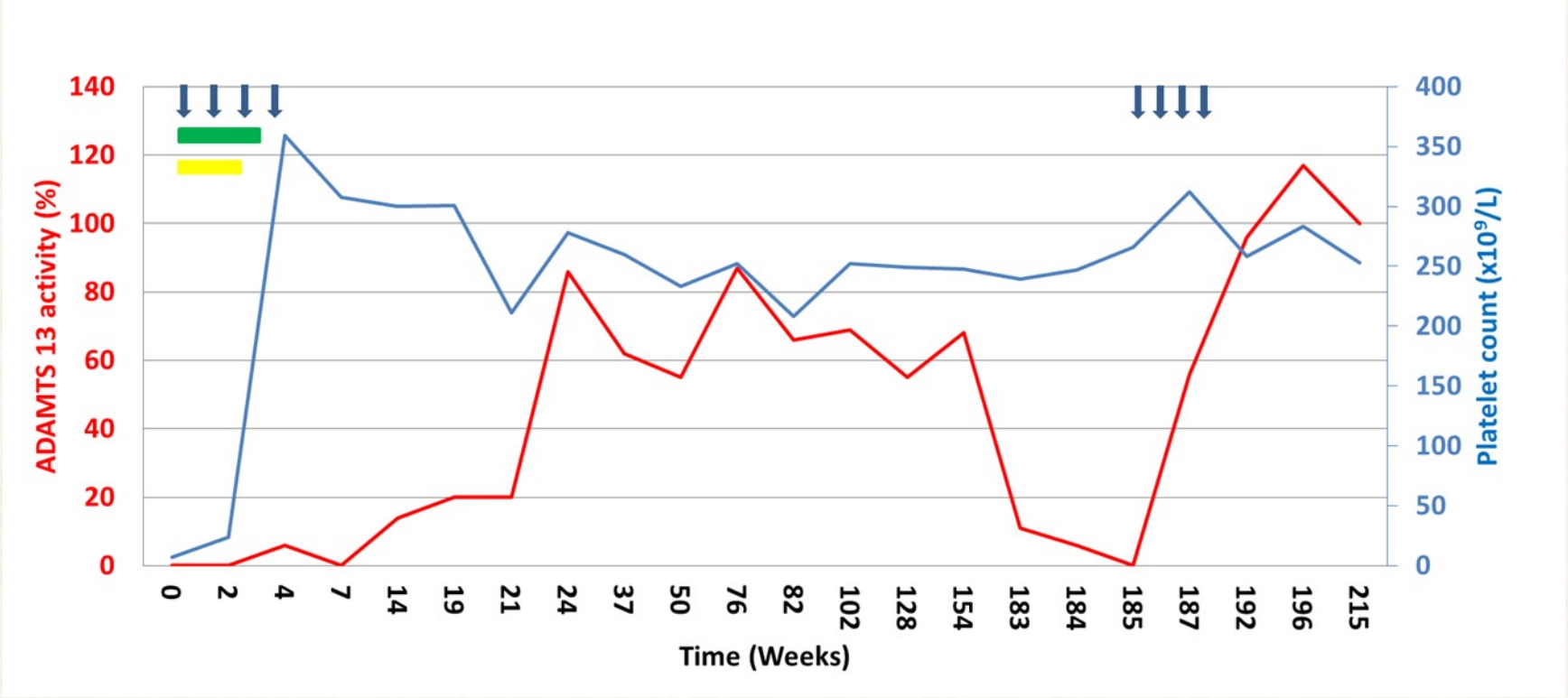
- Median relapse free survival: 9.3 years without rituximab, not reached with rituximab
- 2 patients died in relapsed group-non in elective rituximab group



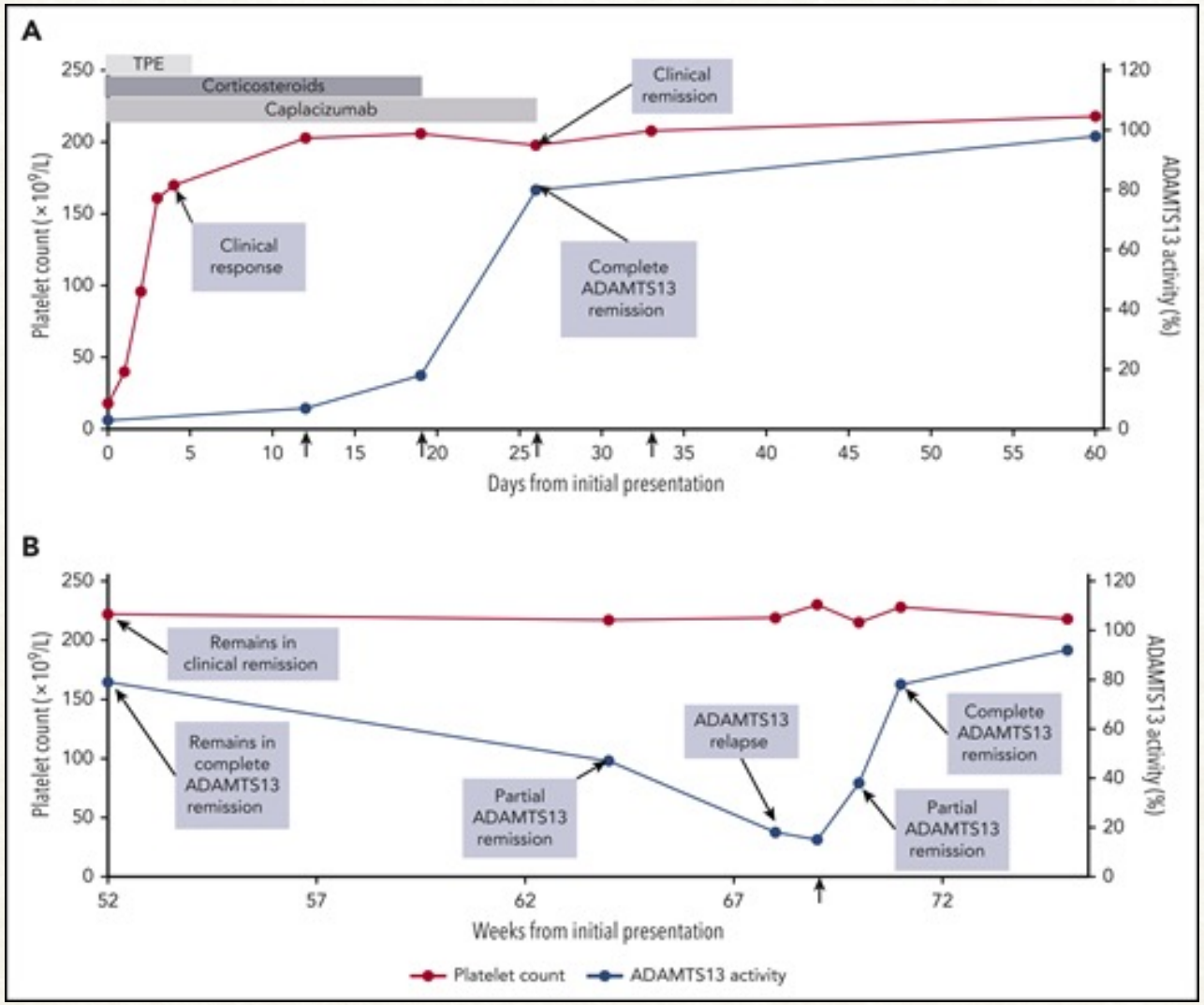
Jestin et al, Blood 2018

- ADAMTS13 activity was sustained in 34 patients (37%) during a follow-up of 31.5 months (IQR, 18-65)
- Severe ADAMTS13 deficiency recurred in 45 patients (49%)
- ADAMTS13 activity usually improved with additional courses of preemptive rituximab
- In historical iTTP with undetectable ADAMTS13 activity, 74% clinically relapsed after a 7-year follow-up

Elective Rituximab



Goal of iTTP therapy is ongoing ADAMTS13 CR



Cuker et al, Blood 2021

CR=complete remission

Immune TTP – treatment

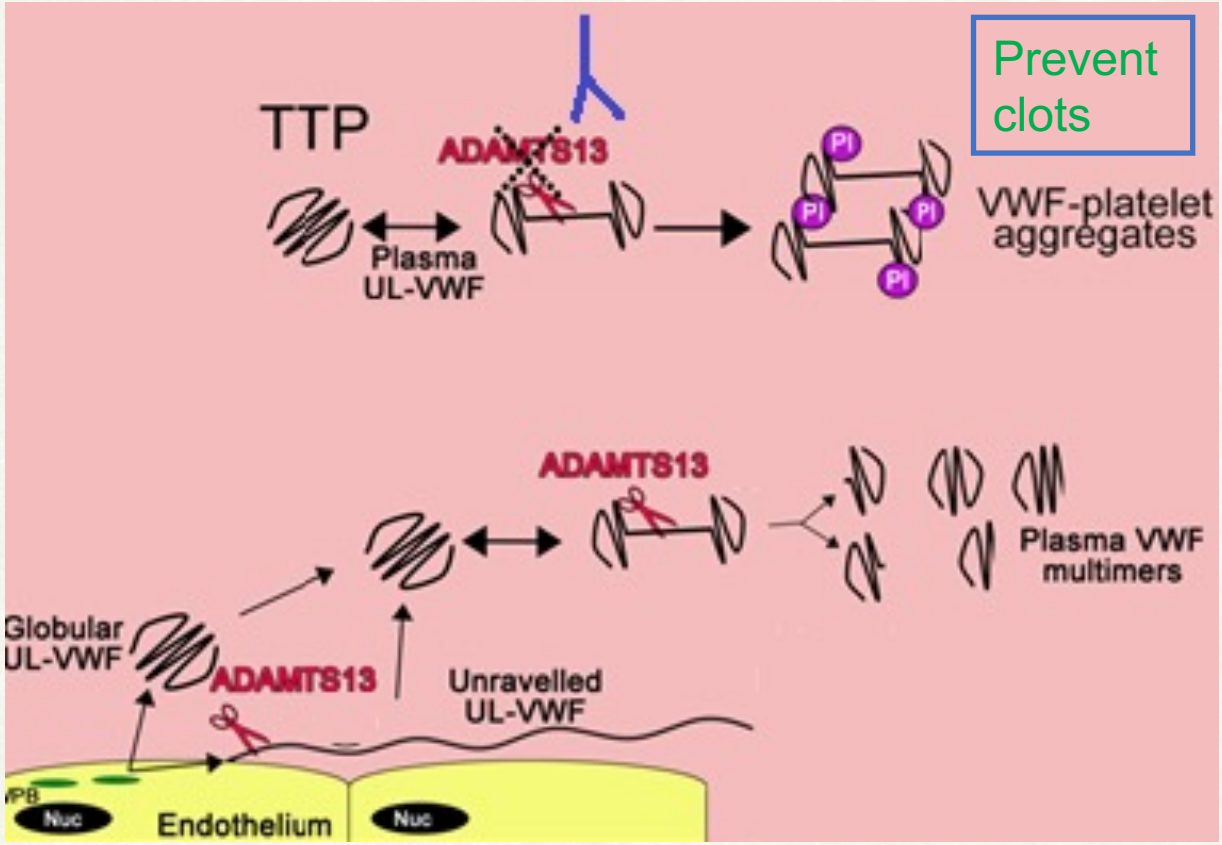
Current therapy

Daily plasma exchange (PEX)	Immunosuppression (corticosteroids and/or rituximab)
• removes ULvWF • removes autoantibodies • replenishes ADAMTS13	inhibits autoantibody formation

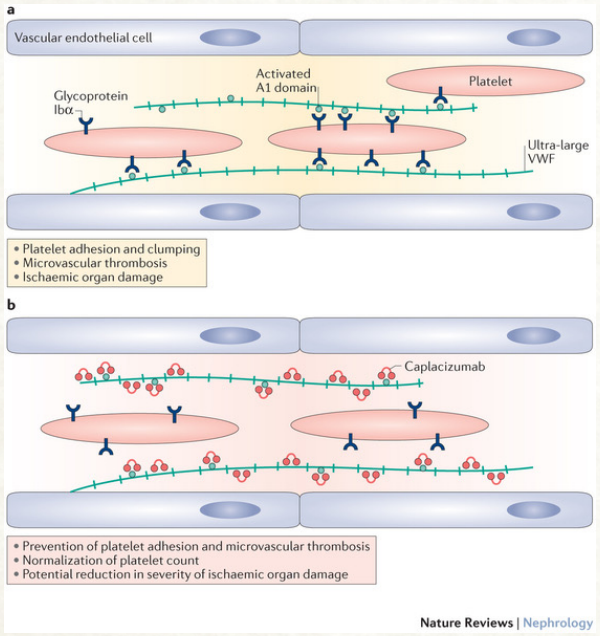
Issues:

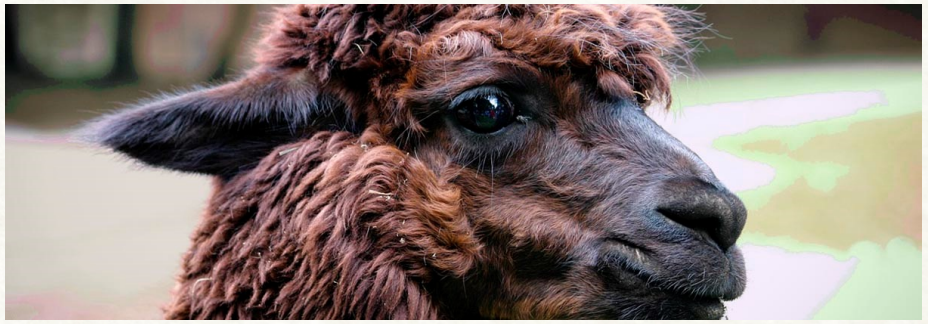
- Mortality of 10-20%
- Refractoriness to treatment (associated with poor outcomes)
- Disease exacerbations

How drugs work in TTP



Caplacizmab – anti VWF nanobody





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

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 Ulrichts, 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

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. Metjian, J. de la Rubia, K. Pavenski, F. Callewaert, D. Biswas, H. De Winter, and R.K. Zeldin, for the HERCULES Investigators*

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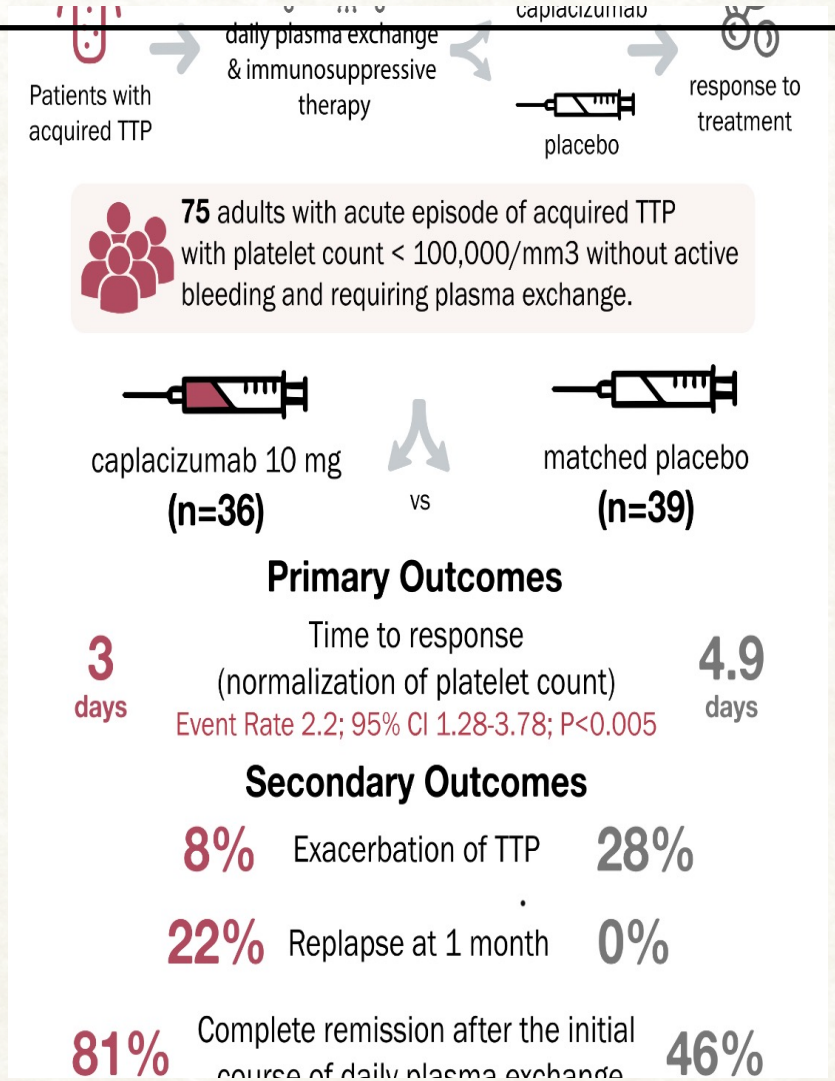
August 2, 2021

Phase II- TITAN study



Phase III- HERCULES study

Multicenter, randomized, double-blind, placebo controlled trial

Objective: To assess role of Caplacizumab, an anti–von Willebrand factor immunoglobulin in patients with acquired TTP.

145 adults with acute episode of acquired TTP based on clinical presentation and hx of one previous plasma-exhange transfusion were randomized:

caplacizumab 10 mg **(n=72)** vs matched placebo **(n=73)**

Primary Outcomes

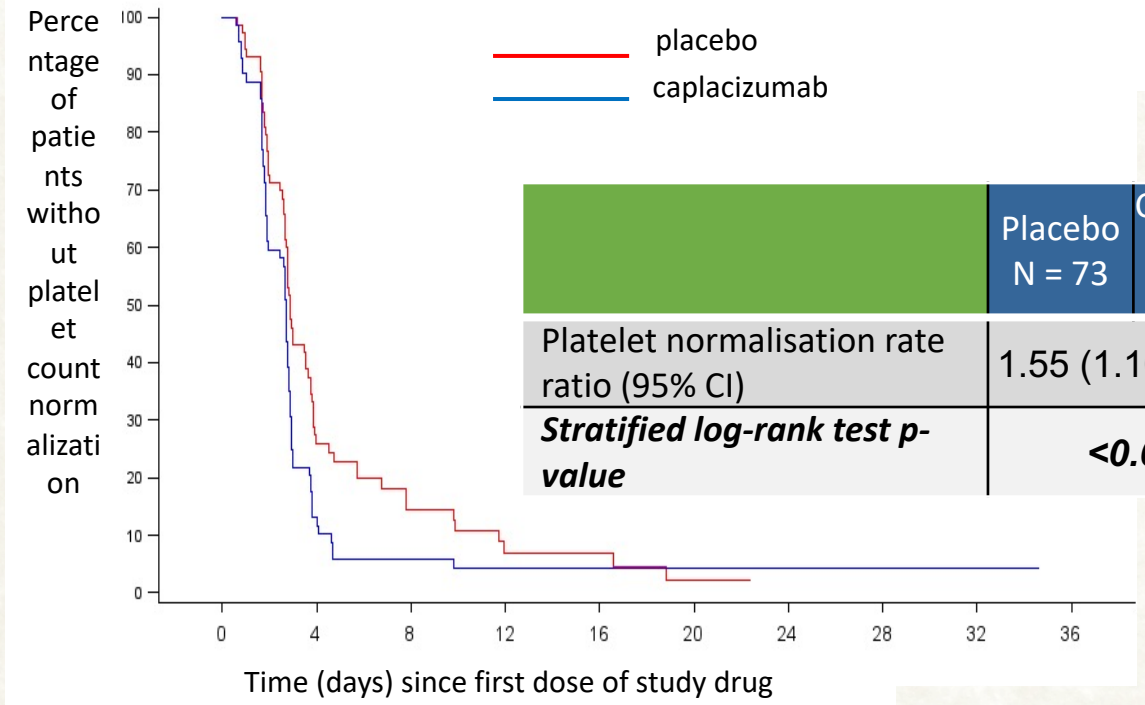
2.69 days	Time to response (normalization of platelet count) P=0.01	**2.88 days**

caplacizumab was 1.55 times likely to cause normalization of platelet count as compared with placebo

Secondary Outcomes

12%	TTP-related death, recurrence of TTP, or a thromboembolic event P<0.001	**49%**
12%	recurrence of TTP P<0.001	**38%**
65%	bleeding events	**48%**

Hercules: Phase III Trial



	Placebo N = 73	Caplacizumab N = 72
Platelet normalisation rate ratio (95% CI)	1.55 (1.10, 2.20)	
Stratified log-rank test p-value	***<0.01***	

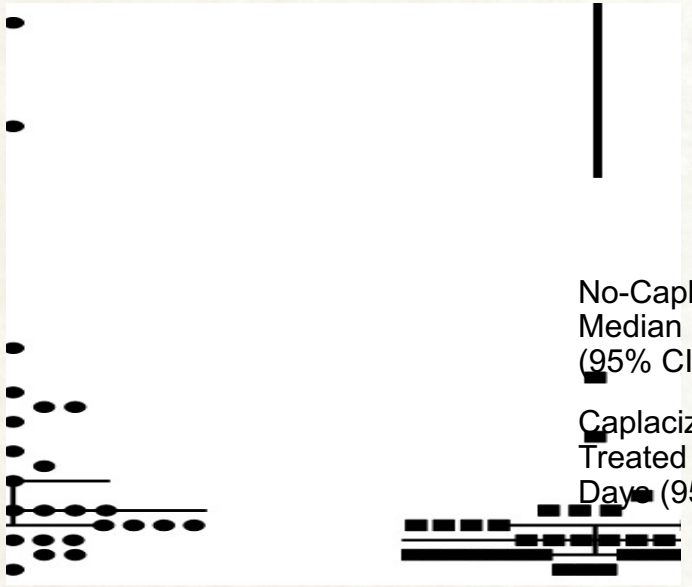
Platelet count response was defined as initial platelet count ≥ 150×10^9/L with subsequent stop of daily PE within 5 days

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]

Scully *et al, NEJM 2019*

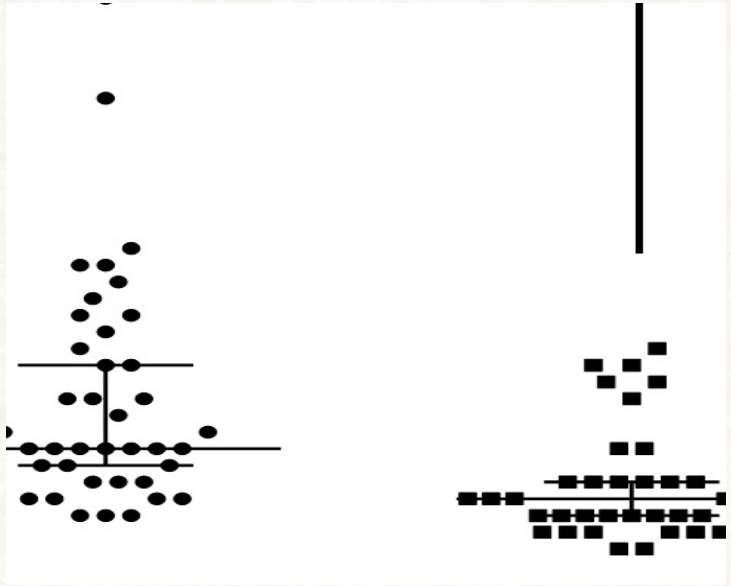
UCLH Capla experience

- Patients treated with Caplacizumab included:
  - Patients treated on the Hercules trial (n=10)
  - Patients treated with Caplacizumab compassionately (n=26)
- Patients not treated with Caplacizumab from Jan 2014 onwards were analysed as a comparator group (n=39)



No-Caplacizumab - Median n=6 days (95% CI 5-8)

Caplacizumab Treated – Median=4 Days (95% CI 3-5)



No-Caplacizumab – Median PEX =9 (95% CI 8-14)

Caplacizumab Treated – Median PEX =6 (95% CI 5-7)

Statistically significant shorted duration in time to platelet normalisation and no of PEX in Caplacizumab treated patients

The Current…

PEX:
ADAMTS13 replacement

Caplacizumab

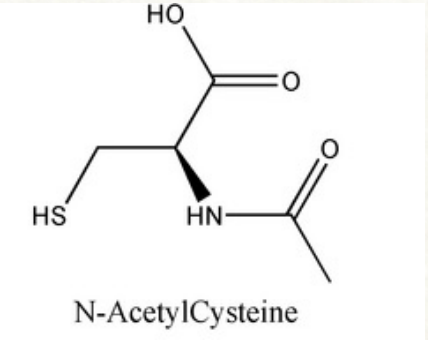
Immunosuppression
To remove causative antibodies

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

Current / future therapies

	Replace ADAMTS13	Immunosuppression (clear antibody)	Stop microvascular thrombi (clots)
Acute episode - Acquired TTP	Recombinant ADAMTS13 - Phase 2	Bortezomib	Anti VWF nanobody N acetylcysteine
Prevent relapse - Acquired TTP		Elective rituximab – low dose vs standard dose	
Congenital TTP	Recombinant ADAMTS13 - Phase 3		

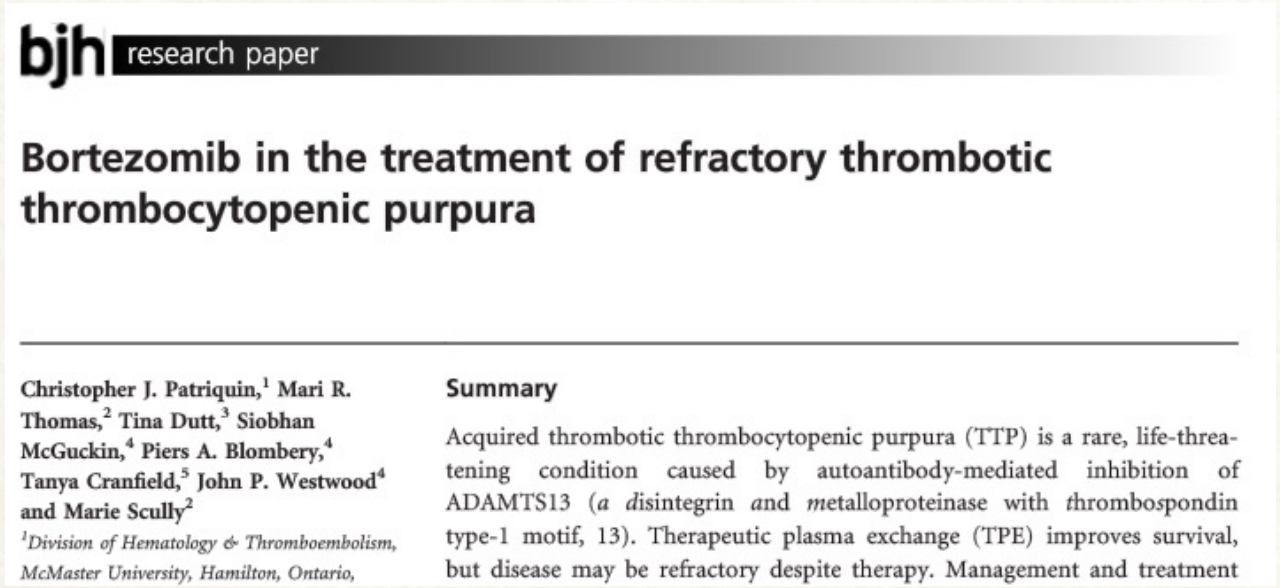
N-acetylcysteine



- N-acetylcysteine reduces size and activity of von Willebrand factor in human plasma and mice.[1]
- Inhibits platelet adherence to endothelial cell-anchored soluble ULVWF multimers by reducing their size
- Case reports of NAC as adjunctive therapy in severe refractory TTP
- Cheap, readily available, limited toxicity

Chen *et al,* JCI 2011

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. Westwood[4] and Marie Scully[2]

[1]*Division of Hematology & Thromboembolism, McMaster University, Hamilton, Ontario,*

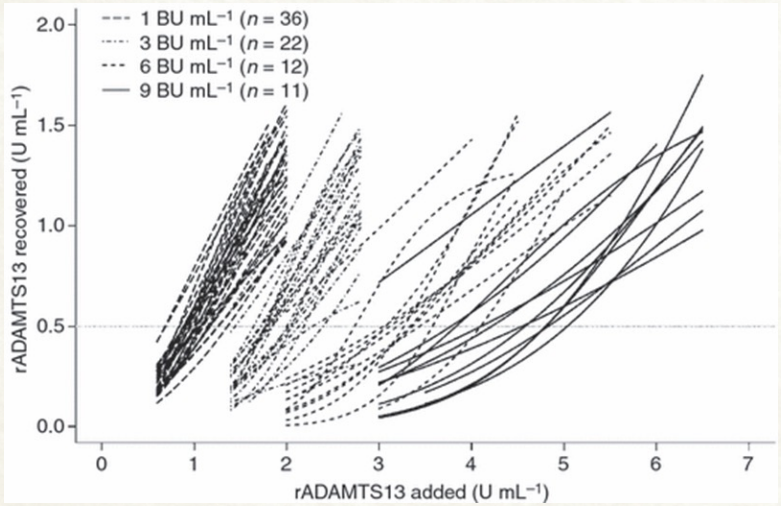
Summary

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

Phase 2 rADAMTS13 for acquired TTP

- RCT of supplementing PEX with rADAMTS13
- ?may need higher doses to overcome inhibitory antibodies

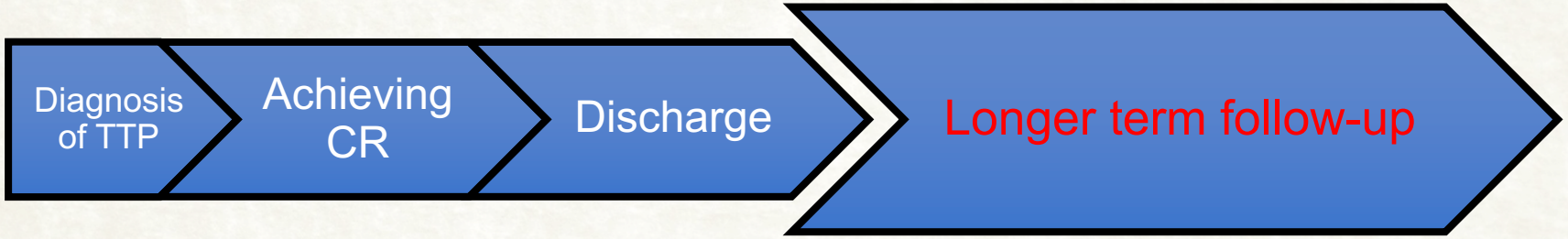


Plasma samples from 36 different TTP patients with neutralizing anti-ADAMTS13 antibodies adjusted to 1, 3, 6 and 9 BU / mL.
Effective concentration to restore 0.5 U/mL ADAMTS13 activity (EC50) shown by horizontal line.

Plaimauer *et al,* JTH 2011

The TTP Pathway – lifelong care

48–96 hours	10+ days	30 days	Months/years
Highest mortality and morbidity	Risk of exacerbation, infection, reactions eg anaphylaxis, new or progressive symptoms	Risk of exacerbation and readmission	Risk of relapse 30–50% Dictated by ADAMTS13 levels Medical/psychological impact



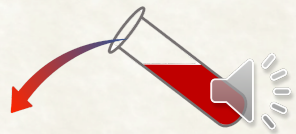
Plasma exchange, Steroids, Caplacuzimab	Anti-CD20 therapy ASAP OR wait until platelet counts drop, ie, refractory/exacerbation	Anti-CD20 therapy/ preferred immunosuppression/ additional therapy if refractory	Scenarios: 1. Discharge 2. 2. Monitor platelet counts 3. Monitor ADAMTS13 levels

CR, complete response

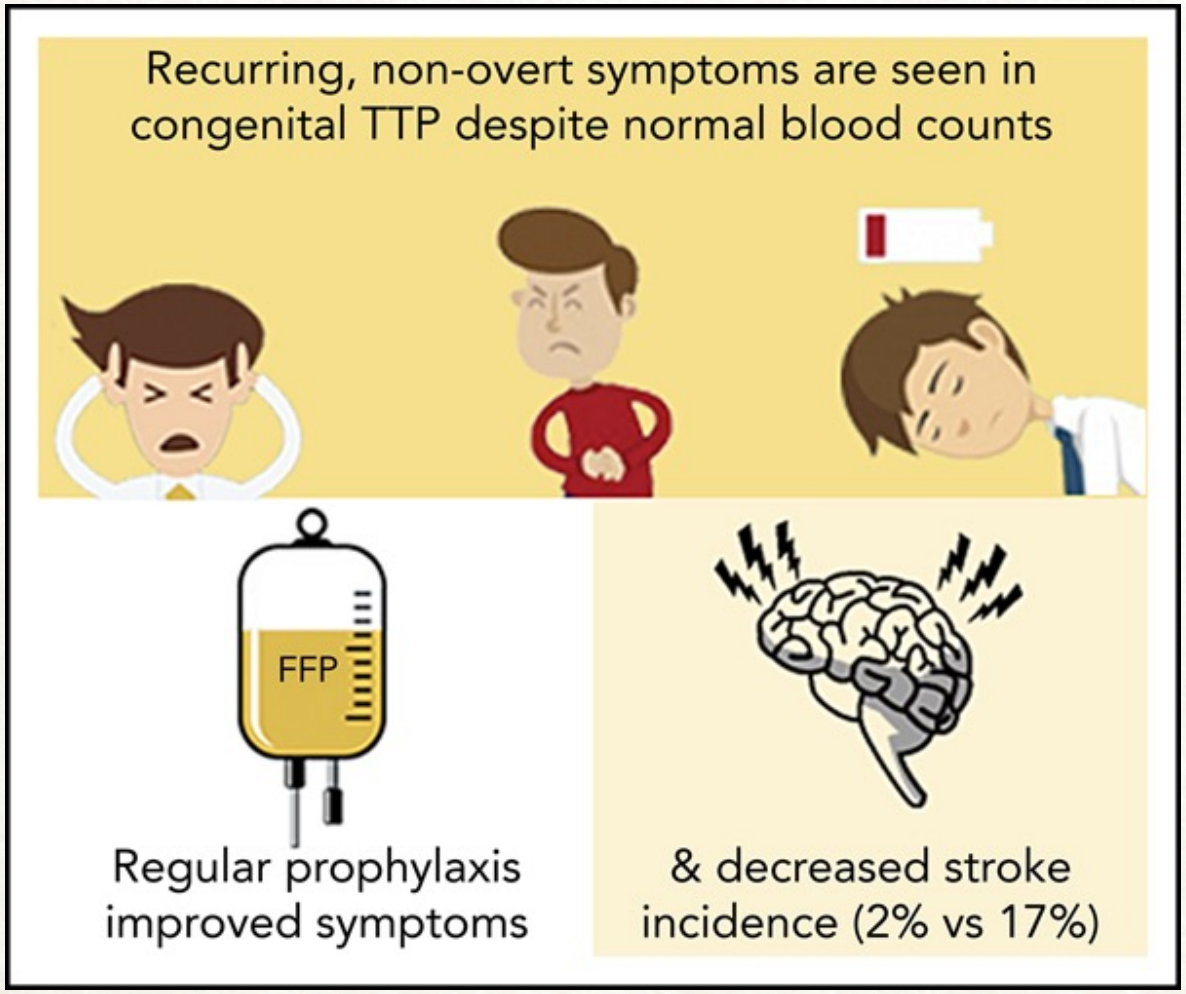
What is the impact of acute TTP ?

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 TTP ….**The **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.



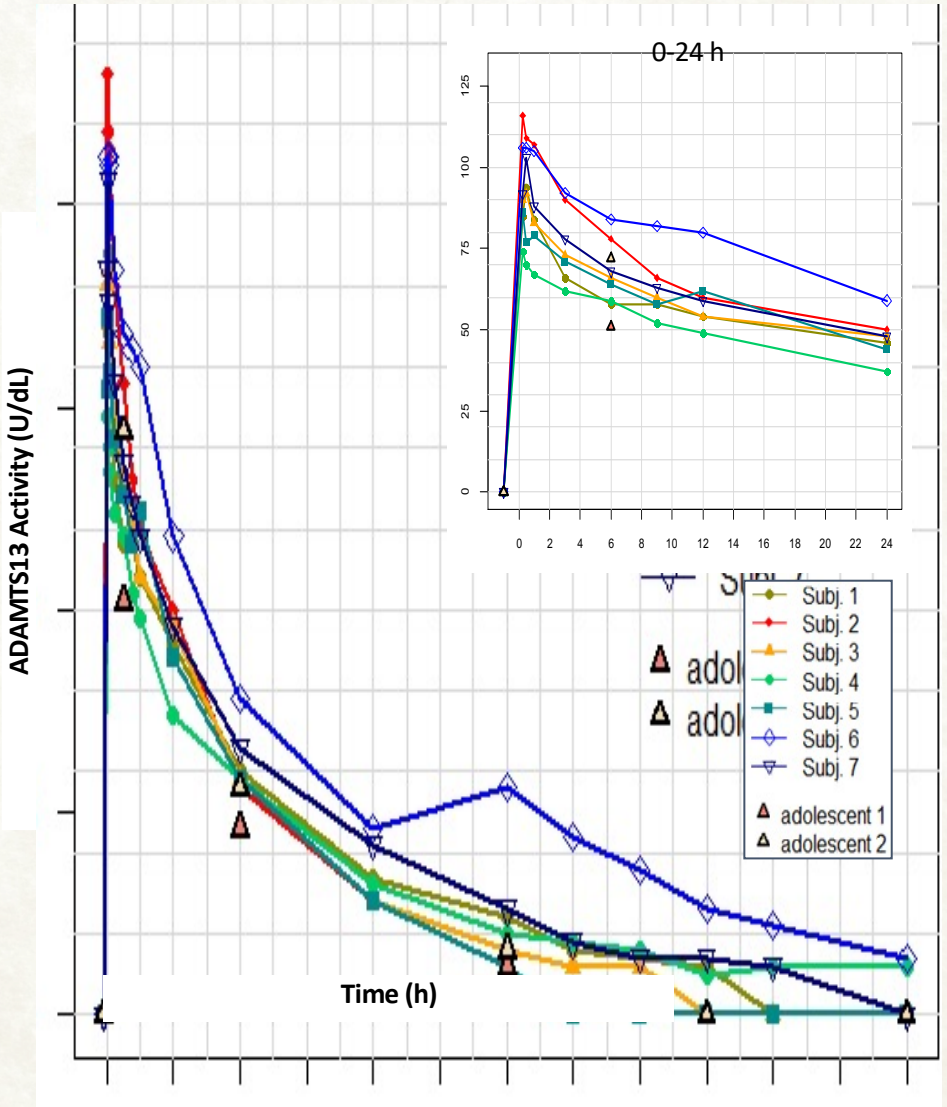
Congenital TTP



Alwan et al Blood 2019

Recombinant ADAMTS 13: (40U/Kg)

Subject #	AUC (h x U/dL)	IR (U/dL x kg/U)	Cmax (U/dL)
1	5137.7	2.1	85.0
2	4337.2	2.7	107.8
3	4468.3	2.2	88.1
4	3220.1	1.7	67.4
5	4016.4	2.1	85.0
6	9203.9	2.8	113.3
7	5767.0	1.9	92.0
Geom. Mean	4965	2.1	86.7
Geom. CV	32.1%	18.3%	18.1%
Min	3220	1.7	66.6
Median	4468	2.1	86.6
Max	9204	2.8	113.3



Scully et al, Blood 2017

rADAMTS13 for congenital TTP

Phase 3 study open

Recombinant ADAMTS13 prophylaxis instead of regular plasma infusions

So what ADAMTS13 level should we be aiming for?

Diabetologia (2017) 60:280–286
DOI 10.1007/s00125-016-4139-5

ARTICLE

ADAMTS13 activity as a novel risk factor for incident type 2 diabetes mellitus: a population-based cohort study

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

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.

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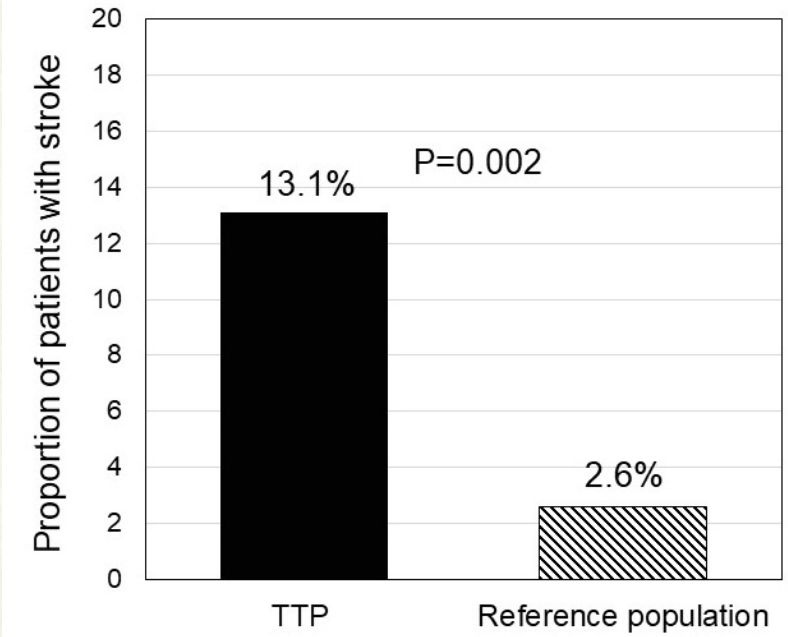
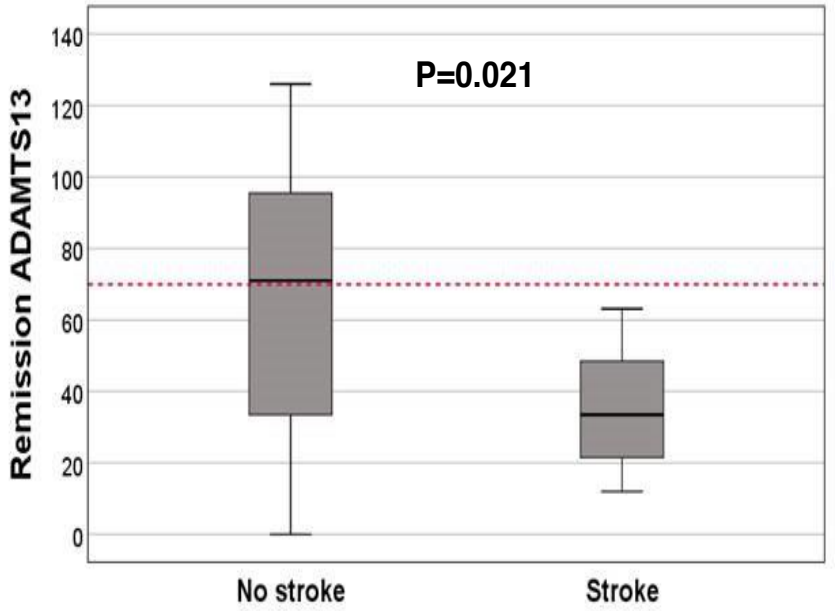
Reduced ADAMTS13 activity during TTP remission is associated with stroke in TTP survivors

Tracking no: BLD-2019-001056R3

Harshvardhan Upreti (University of Delhi, India) Jamil Kasmani (Johns Hopkins University, United States) Kathryn Dane (Johns Hopkins Hospital,





Proportion of patients developing stroke compared to a reference population

ADAMTS 13 activity in stroke vs no stroke TTP patients

CM-HUS

HUS and TTP are Thrombotic Microangiopathies with similar features

Microangiopathic haemolytic anaemia
Thrombocytopaenia
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

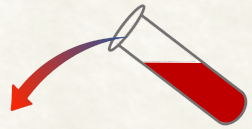
- Commonest form
- Accounts for 90-95% cases in children
- Abrupt onset following diarrhoea (e.g. E.Coli) in preceding weeks
- Supportive treatment alone
- Good prognosis
- 5% die or ESRF
- Recurrence rare post transplant

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)

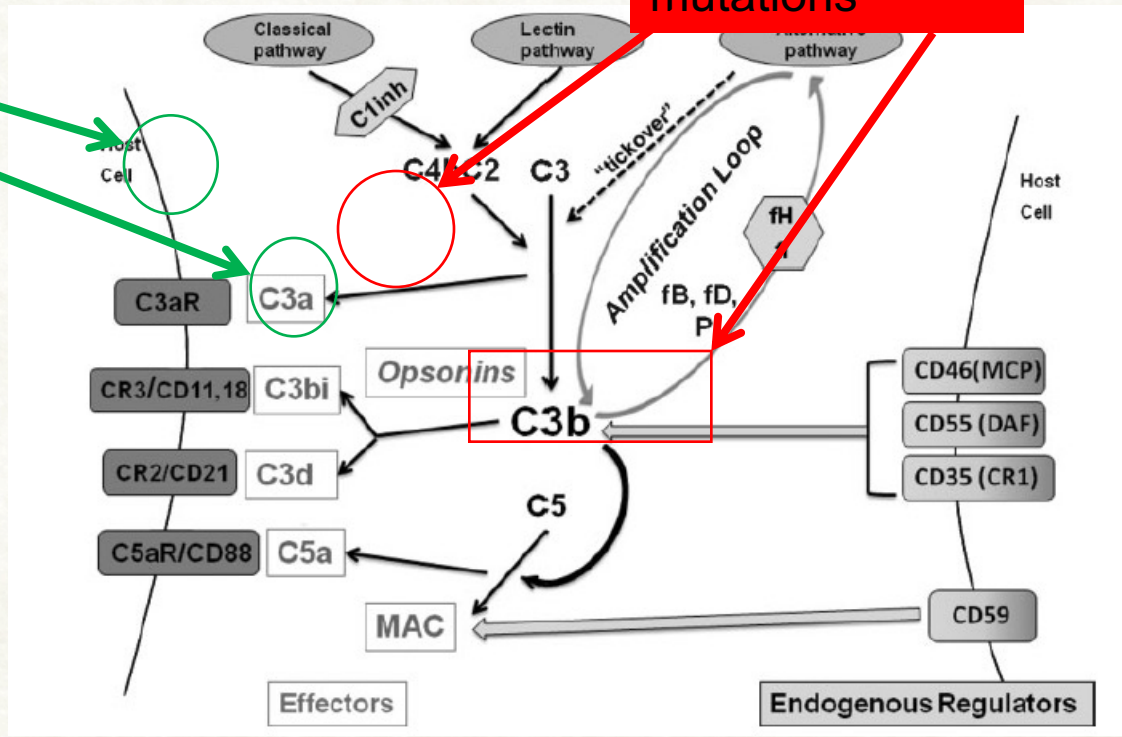
- Can be familial and sporadic
- Mutations or polymorphisms (or both) in genes for **Complement proteins**
- ? Triggered by infection, pregnancy
- Likely multifactorial



CM-HUS & Complement

Gain of function mutations

Loss of function mutations



Emlen et al, 2010

Genotype:

Mutations and polymorphisms affecting complement proteins

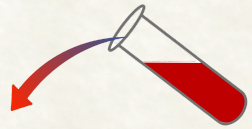
Dysregulation **Excessive activation**

Act on C3 convertase

Activation of Alternative pathway and C5

Phenotype

MAHA, Renal failure, Thrombocytopaenia



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 1st episode or within < 1 y	Risk of relapses	Risk of recurrence after renal transplantation	Plasma therapy indicated
		Children	Adults				
CFH	20-30%	Birth	any age	50-70%	50%	75-90%	Yes
CFI	4 -10%	Birth	any age	50%	10-30%	45-80%	Yes
MCP	5 -15%	> 1 y	any age	0-6%	70-90%	< 20%	Questionable
C3	2 -10%	7 m	any age	60%	50%	40-70%	Yes
CFB	1-4%	1 m	any age	50%	3/3 not in ESRD	100%	Yes
THBD	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)

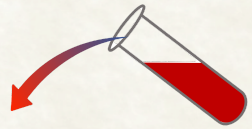
CFH: factor H; CFI: factor I; MCP: membrane cofactor protein; CFB: factor B; THBD: thrombomodulin; Ab, antibodies; ESRD: end stage renal disease; IS: immunosuppressive treatment.

- 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

Kavanagh & Goodship, 2010

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

- aHUS affects patients of all ages
  - **Perception**: child ▸ “it’s aHUS”; adult ▸ “it’s TTP”
  - **Medical evidence**: 40% of aHUS patients are adults
- aHUS patients frequently demonstrate CNS involvement
  - **Perception**: patient has neurological symptoms ▸ “it’s TTP”
  - **Medical evidence**: up to 48% aHUS cases reported to have neurological dysfunction
- ADAMTS13 activity differentiates between aHUS and TTP
  - **Perception**: clinical symptoms direct the differentiation between aHUS and TTP
  - **Medical evidence**: severe ADAMTS13 activity separates TTP (≤10%)



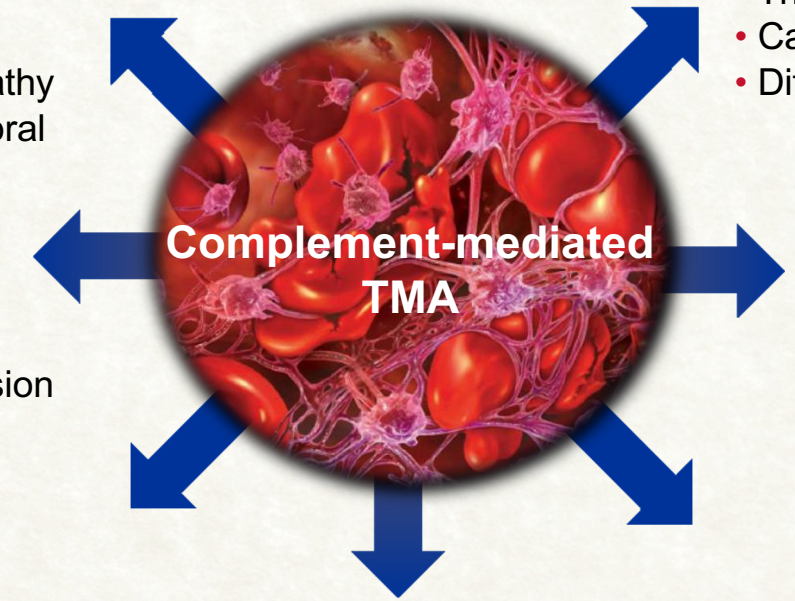
Clinical presentation alone does not fully differentiate CM-HUS from TTP

CM-HUS	TTP
Well-recognised aHUS signs: • Decreased platelet count • Microangiopathic haemolysis • Renal insufficiency	**Well-recognised TTP signs:** • Decreased platelet count • Microangiopathic haemolysis • Neurological dysfunction
Under-recognised aHUS signs: • Neurological dysfunction (up to 48%) • Cardiac symptoms (up to 43%)	**Under-recognised TTP signs:** • Renal pathology (96%) • Renal insufficiency (47%)

CM-HUS is a multisystem disorder

CNS
- Confusion
- Seizures
- Stroke
- Encephalopathy
- Diffuse cerebral dysfunction

Cardiovascular
- Myocardial infarction
- Thromboembolism
- Cardiomyopathy
- Diffuse vasculopathy



Renal
- Elevated creatinine
- Oedema
- Malignant hypertension
- Renal failure
- Dialysis
- Transplant

Gastrointestinal
- Liver necrosis
- Pancreatitis
- Diabetes mellitus
- Colitis
- Diarrhoea
- Nausea and vomiting
- Abdominal pain

Pulmonary
- Dyspnoea
- Pulmonary haemorrhage
- Pulmonary oedema

Blood[1],
- Haemolysis
- Decreased platelets
- Fatigue
- Transfusions

Impaired quality of life
- Fatigue
- Pain and anxiety
- Reduced mobility

Complement analysis does not support diagnosis of CM-HUS

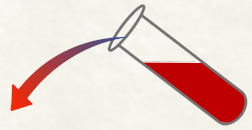
- Levels of complement proteins and inhibitors are sometimes measured to look for evidence of complement activation or dysfunction

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

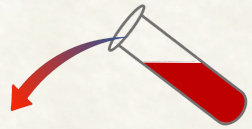
- Most aHUS patients (including patients with identifiable mutations) have normal C3 and C4 levels
- Factor H levels – normal in up to 87% of aHUS patients with identified CFH mutation



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

- Genetic mutation cannot be identified in 30–50% of patients with aHUS
- Absence of identifiable genetic mutations does not exclude aHUS
- 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 aHUS 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

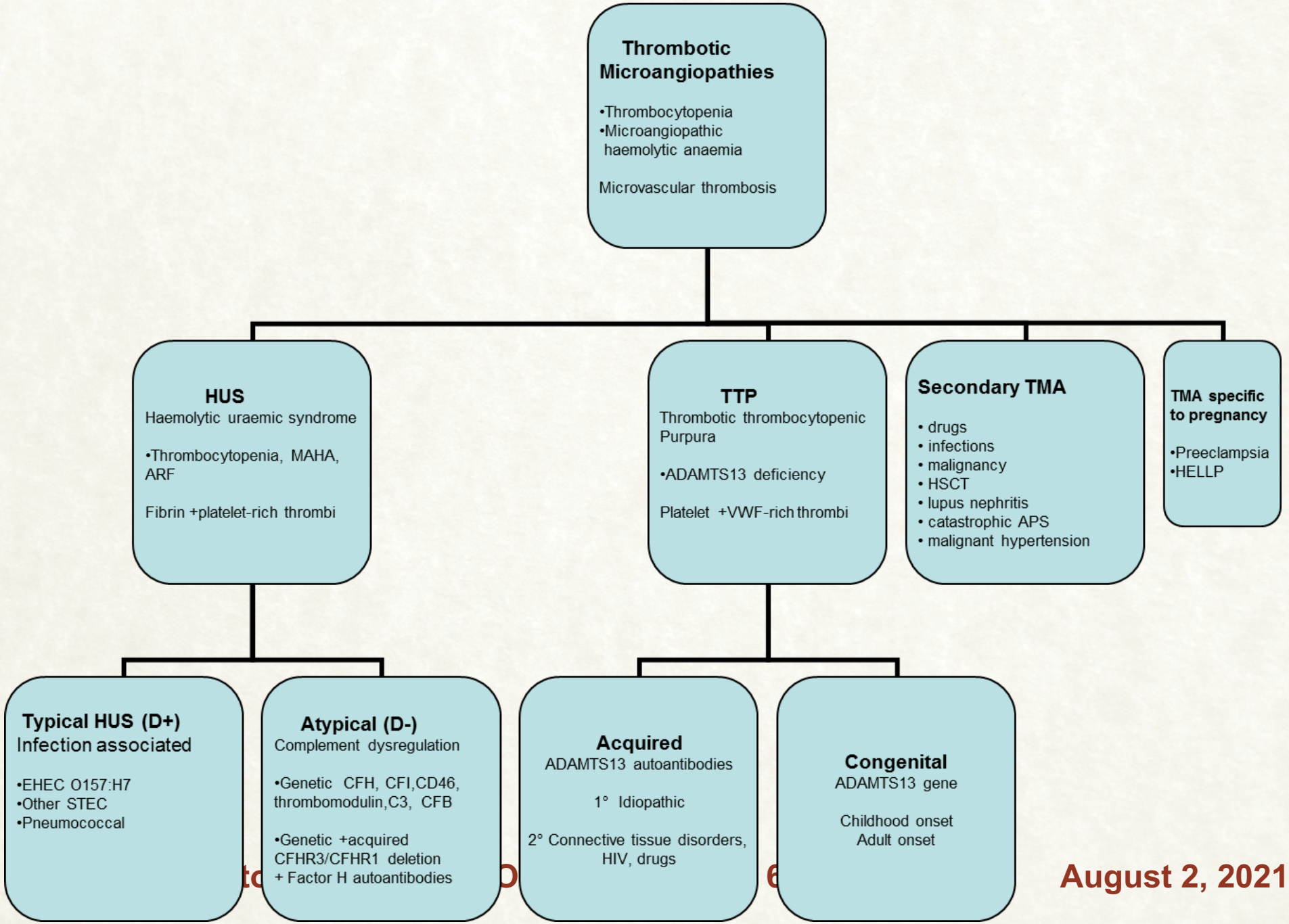
Vaccinate against meningococcus
Prophylactic antibiotics

Clinical efficacy and safety profile of eculizumab

Improvements in key renal and haematologic parameters

- 80% of patients discontinued dialysis
- Earlier initiation of treatment led to greater improvement in eGFR
- >95% achieved platelet count normalisation at 1 yr

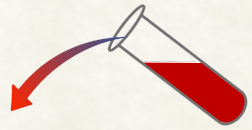
Secondary TMAs


Thrombotic Microangiopathies
•Thrombocytopenia
•Microangiopathic haemolytic anaemia
Microvascular thrombosis
HUS
Haemolytic uraemic syndrome
•Thrombocytopenia, MAHA, ARF
Fibrin +platelet-rich thrombi
TTP
Thrombotic thrombocytopenic Purpura
•ADAMTS13 deficiency
Platelet +VWF-rich thrombi
Secondary TMA
• drugs
• infections
• malignancy
• HSCT
• lupus nephritis
• catastrophic APS
• malignant hypertension
TMA specific to pregnancy
•Preeclampsia
•HELLP
Typical HUS (D+)
Infection associated
•EHEC O157:H7
•Other STEC
•Pneumococcal
Atypical (D-)
Complement dysregulation
•Genetic CFH, CFI,CD46, thrombomodulin,C3, CFB
•Genetic +acquired CFHR3/CFHR1 deletion + Factor H autoantibodies
Acquired
ADAMTS13 autoantibodies
1° Idiopathic
2° Connective tissue disorders, HIV, drugs
Congenital
ADAMTS13 gene
Childhood onset
Adult onset

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

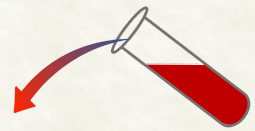


Drug-Induced TMA

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



DDx pregnancy TMAs

- Disseminated Intravascular Coagulation
- Acute fatty liver of pregnancy
- Association with anti-phospholipid antibodies
- Pre-eclampsia
- HELLP syndrome
- Thrombotic Thrombocytopenic Purpura
- Haemolytic-Uraemic Syndrome

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 erythematosis APS:
±: possibly occurs.
+++: definitive feature. HBP: high blood pressure.

Pregnancy-associated TMA

TTP

HELLP/Pre-eclampsia
3rd Trimester

- Reduced ADAMTS 13 activity-31% (12- 43%).
- No anti ADAMTS 13 antibodies
- High vWF:Ag
- No ULvWF multimers

HUS- 90% post partum

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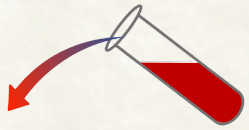
Mutations in Complement Regulatory Proteins Predispose to Preeclampsia: A Genetic Analysis of the PROMISSE Cohort

Jane E. Salmon[1]*, Cara Heuser[2], Michael Triebwasser[3], M. Kathryn Liszewski[3], David Kavanagh[4], Lubka Roumenina[5], D. Ware Branch[2], Tim Goodship[4], Veronique Fremeaux-Bacchi[5], John P. Atkinson[3]

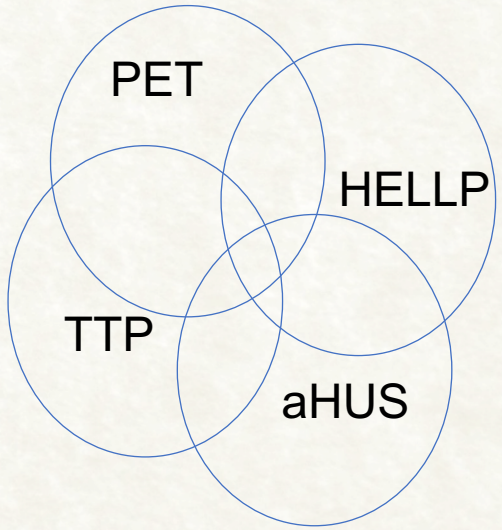
August 2, 2021



When to treat obstetric TMAs?

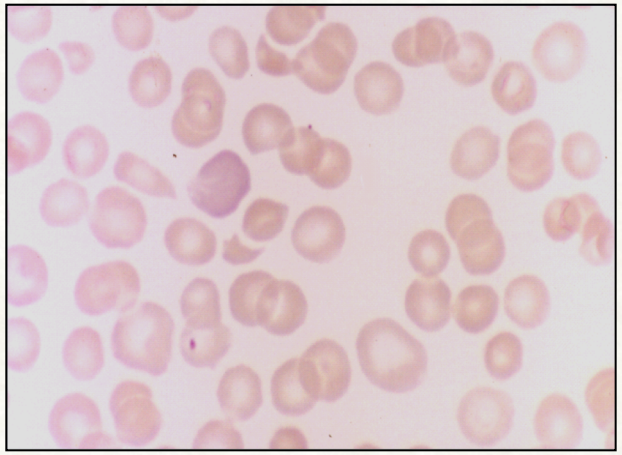
Deliver or exchange?

- **TTP**: PEX asap!
- **PET/HELLP**: difficult
- Monitor/supportive care
  - Delivery
    - Deterioration clinically
    - Exclude TTP/aHUS
  - PEX Decreasing platelet count (especially <50)
- **HUS**
  - PEX
  - Eculizumab



Differential diagnosis of TMAs: summary

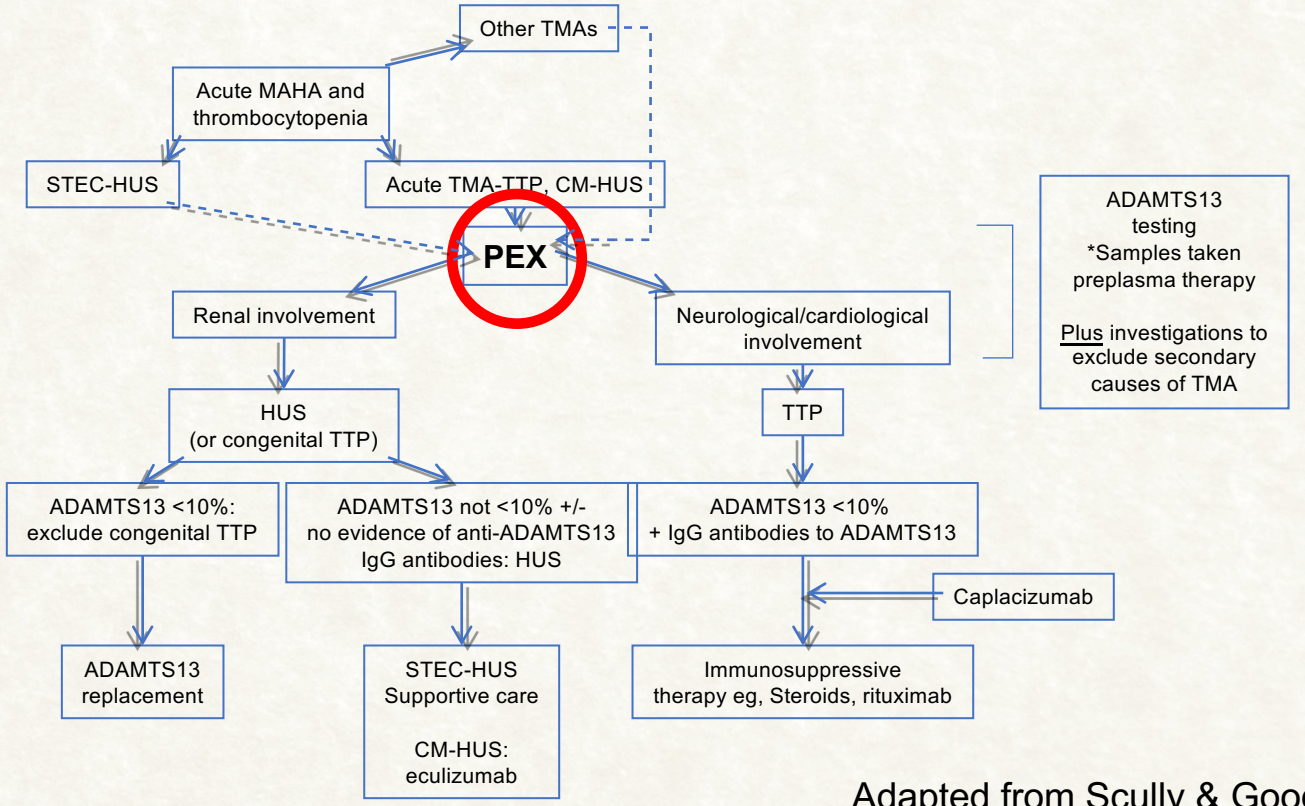
- MAHA
- Thrombocytopenia
- Absence of underlying cause



Assume TTP
Commence PEX urgently

Haematological emergency

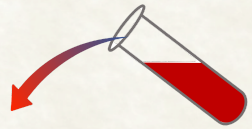
Summary of treatment of TMAs



Adapted from Scully & Goodship, Br J Haematol 2014;

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 is an acute life threatening illness associated with severe deficiency of 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

- Prof Marie Scully
- Dr JP Westwood
- Dr Chiara Vendramin
- Dr Ferras Alwan
- Dr Matt Stubbs
- Dr Lucy Naeve
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- Apheresis Team - UCLH
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- Collaborators & Investigators of the UK TTP regis
- National and International Collaborators