Thrombotic Microangiopathies (TTP/HUS)

Ang Li, MD, MS

Assistant Professor

Hematology Oncology

Baylor College of Medicine

Relevant Disclosure

- None

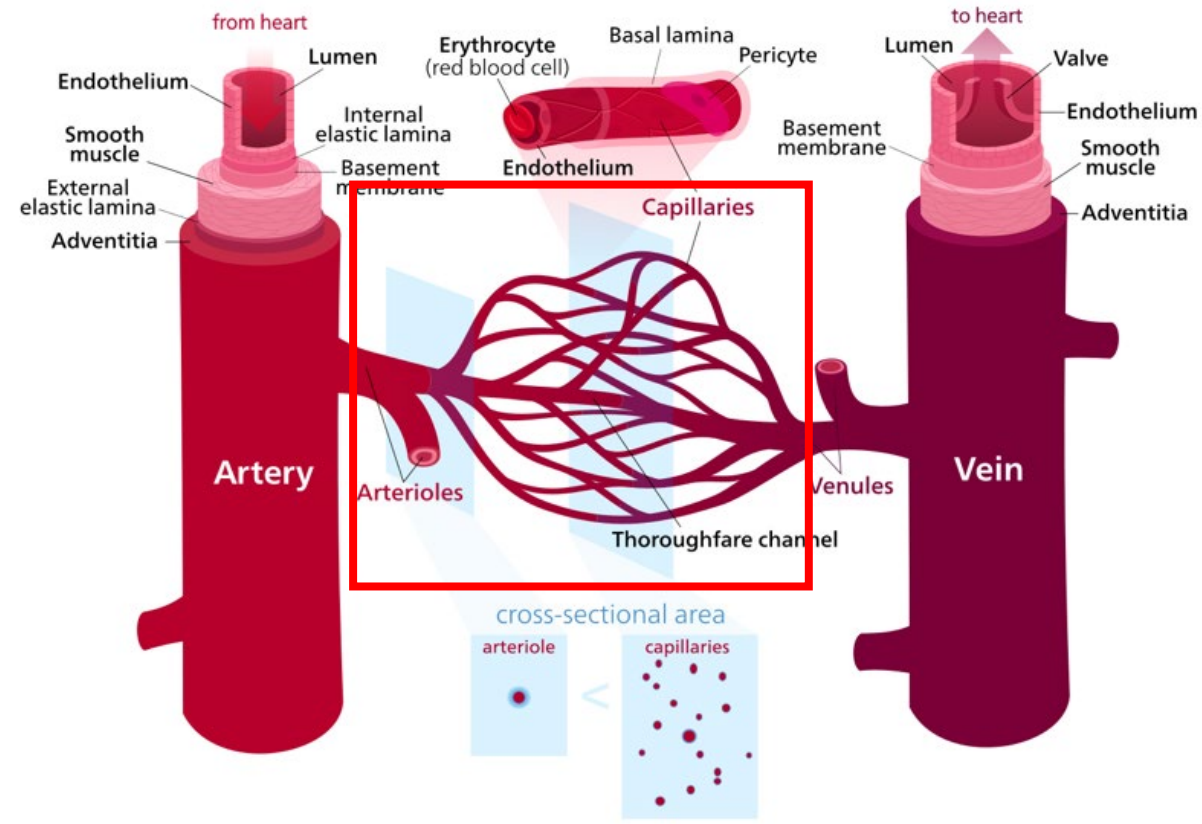
Outline

1. To be able to distinguish TMA from other types of hemolytic anemia
2. To be able to diagnose iTTP, HUS, aHUS and distinguish from other secondary TMAs
3. To be able to formulate initial treatment plans for iTTP and aHUS

Defining & Differentiating TMA

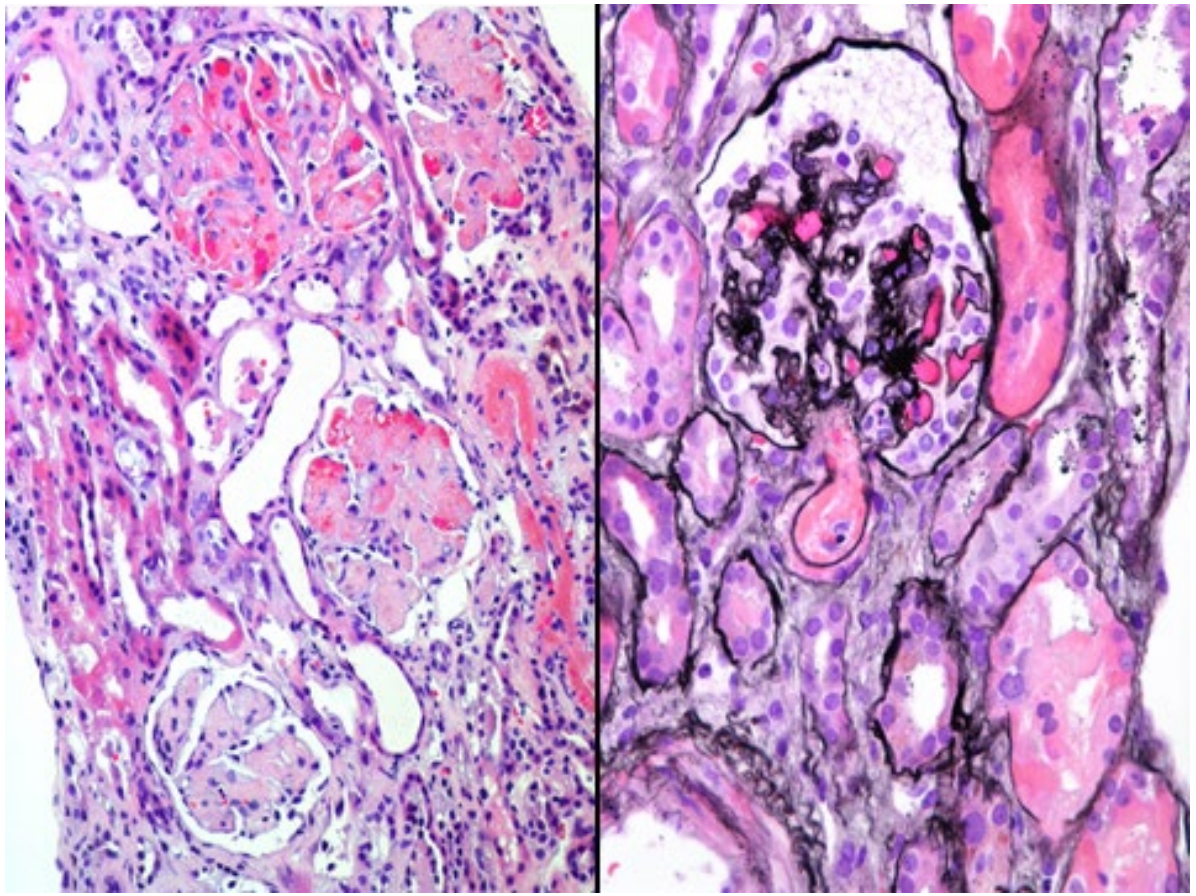
Thrombotic microangiopathy (TMA)

- Thrombotic = clot
- Micro = small, Angio = vessel
- Pathy = disease

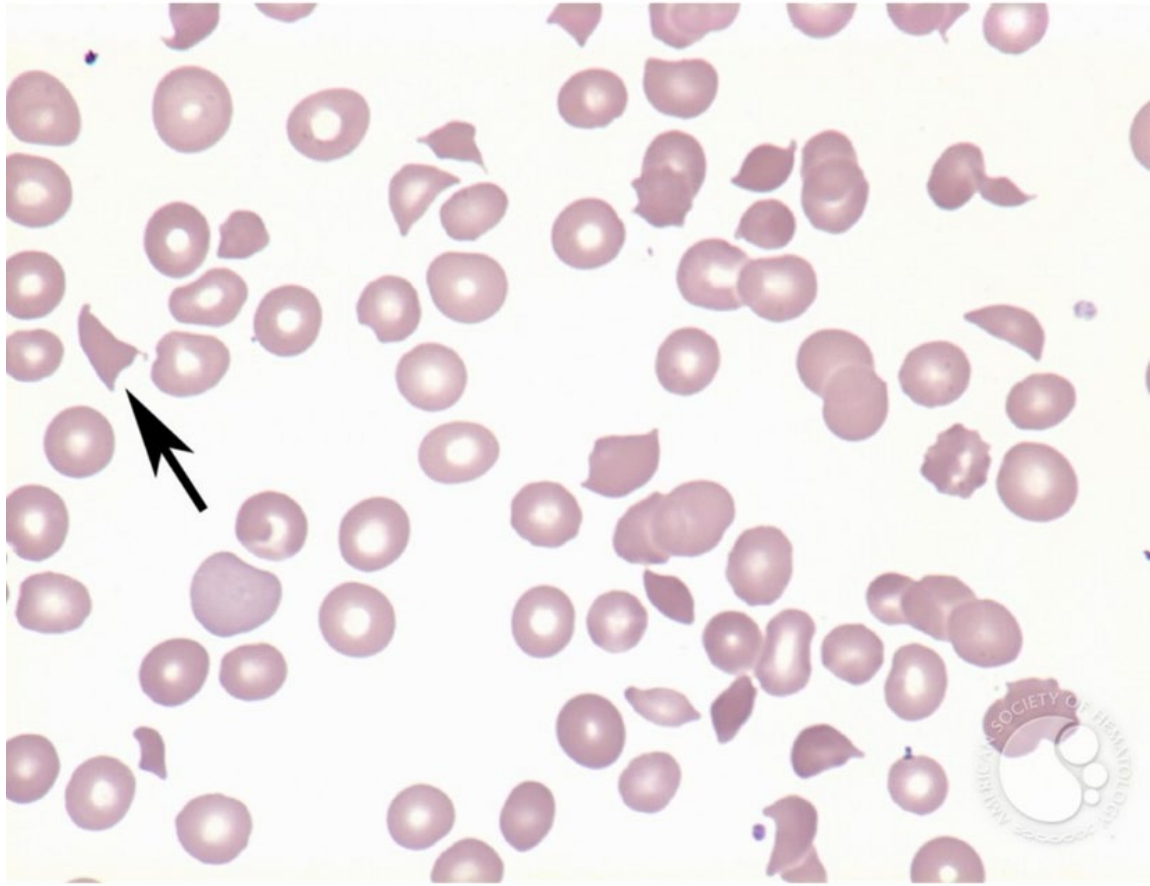


Google Image

Pathologic Diagnosis



Thrombotic Microangiopathy (TMA)
Microvascular thrombosis

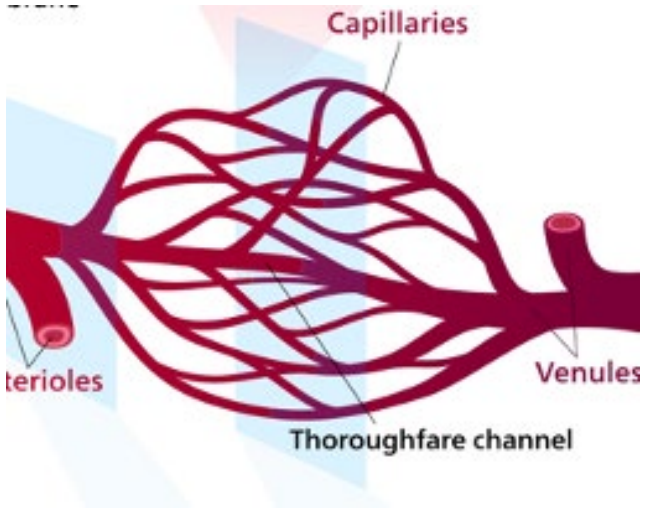


Microangiopathic Hemolytic Anemia (MAHA)
Schistocytosis

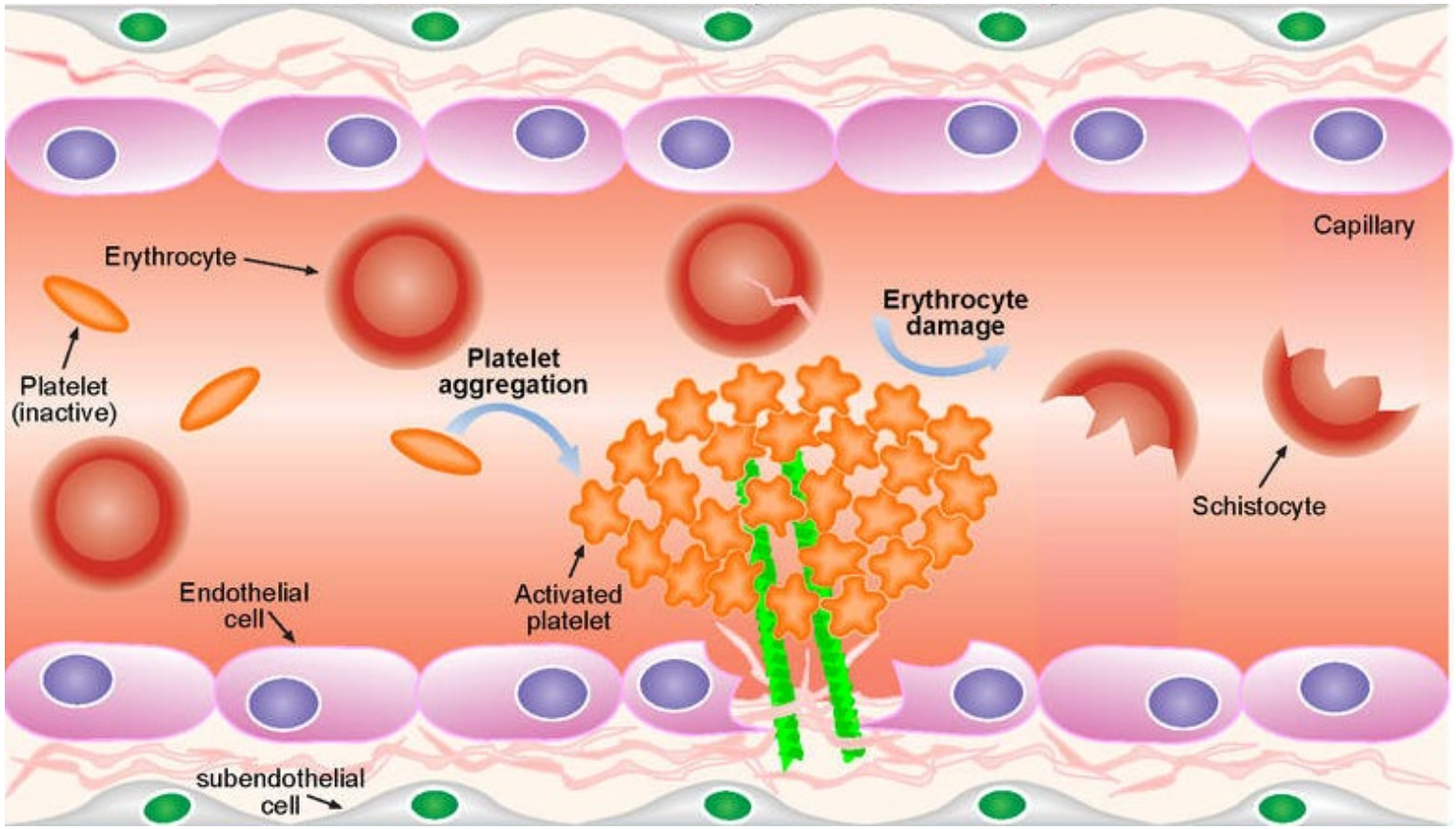
Hingorani (left). ASH Image Bank (right)

Non-Hematologic Manifestations of TMA

- Damage occurs in end-organs rich with <u>small</u> vessels:
  - Kidney => acute kidney injury, proteinuria, hypertension
  - Brain => stroke, seizure, coma
  - Heart => chest pain, elevated troponin
  - Gut => abdominal pain, bloody diarrhea



Hematologic Manifestations of TMA



Platelet clumping / consumption:
- Low platelet

RBC shearing / intravascular hemolysis:
- Anemia
- Schistocyte / fragment

Released by RBC:
- LDH, indirect bilirubin
- Low haptoglobin (binds hemoglobin)

Immunopaedia.org

Pathogenesis & Work-Up for TMA

- Primary TMA
  - ADAMTS13 abnormalities
    - Hereditary ADAMTS13 deficiency (Upshaw-Schulman)
    - **Acquired ADAMTS13 antibody (iTTP)**
  - Disorder of complement regulation
    - **Hereditary complement disorders (e.g. factor H, factor I, factor B, CD46, C3) (aHUS)**
    - Acquired complement antibody (e.g. factor H antibody)
  - Infection induced
    - **E. coli O157:H7 Shiga toxin (HUS)**
    - Strep pneumoniae
- Pseudo-TMA
  - **Defective cobalamin (B12) metabolism (low retic)**
- Autoimmune
  - Severe SLE flare
  - Catastrophic APS
- Drugs
  - Quinine
  - Ticlopidine
  - Clopidogrel
  - Cyclosporine
  - Tacrolimus
  - Gemcitabine
  - Mitomycin C
- Pregnancy
  - Severe preeclampsia
- Cancer
  - Disseminated cancer (advanced stage)
  - Bone marrow transplant (GVHD)
- Infection
  - Advanced HIV
  - Severe sepsis (DIC)

Simplifying TMA

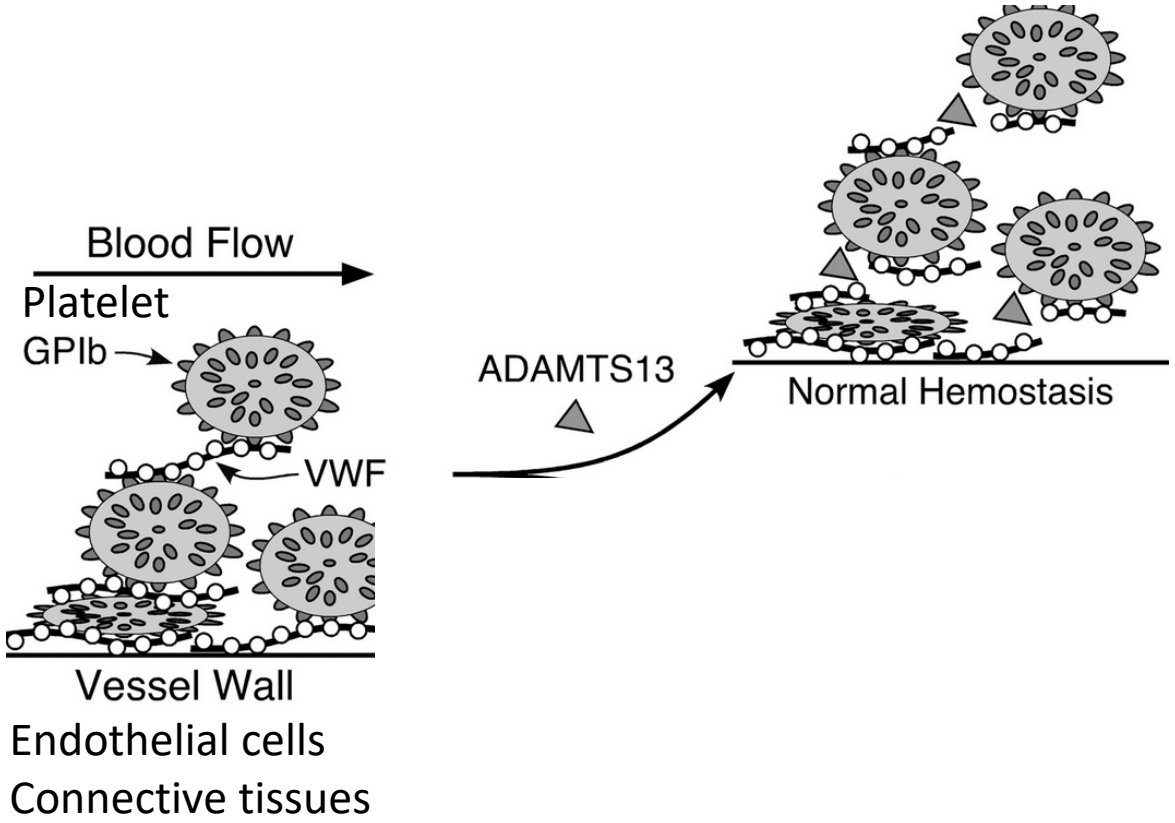
Diagnosis	Platelet	Hemolysis	Renal failure	Key features	Therapy
iTTP	<30k	Yes	Mild	ADAMTS13 deficiency	Plasma Exchange+
aHUS	>30k	Yes	Severe	Uncontrolled complement activation	Eculizumab
HUS	>30k	Yes	Severe	E. Coli O157:H7	Supportive
Other TMA	Variable	Yes	Variable	Heterogeneous	Supportive

The classic “pentad” for iTTP is present only in 5% of true TTP patients

Immune TTP

Pathophysiology of iTTP

- Pathognomonic with ADAMTS13 deficiency <5-10%
- May take days to result
- High mortality >90% without treatment
- Low mortality <20% with immediate plasma exchange



Sadler, Blood 2006

On Friday night 10 pm, you receive a call from a stand-alone ED from 3 hours away, that he needs to urgently transfer a 60 yo male patient with minimal PMH for the treatment of suspected TTP. Patient presented with epigastric pain and altered mental status. Initial labs showed a platelet count of 12×10^9/L, hemoglobin 10 g/dL, creatinine 1.3 mg/dL. What additional information should you ask the ED physicians to obtain while you discuss bed situation with the transfer center?

A. Blood smear to look for schistocytes
B. LDH, haptoglobin, retic %, direct/indirect bilirubin
C. MCV, INR
D. History of active cancer or transplant
E. All of the above

Diagnostic Accuracy of the PLASMIC Cut-Off

Systematic review and meta-analysis

- Patients with suspected iTTP
- Compared by PLASMIC score vs reference ADAMTS13
- 13 studies with 970 assessed patients & 330 true iTTP

High probability PLASMIC score (≥6)

- Sensitivity = 85% (67-94)
- Specificity = 89% (81-94)

Author Interpretation

- 15% of patients with iTTP have a score <6
- Not acceptable for screening

High probability PLASMIC score (≥5)

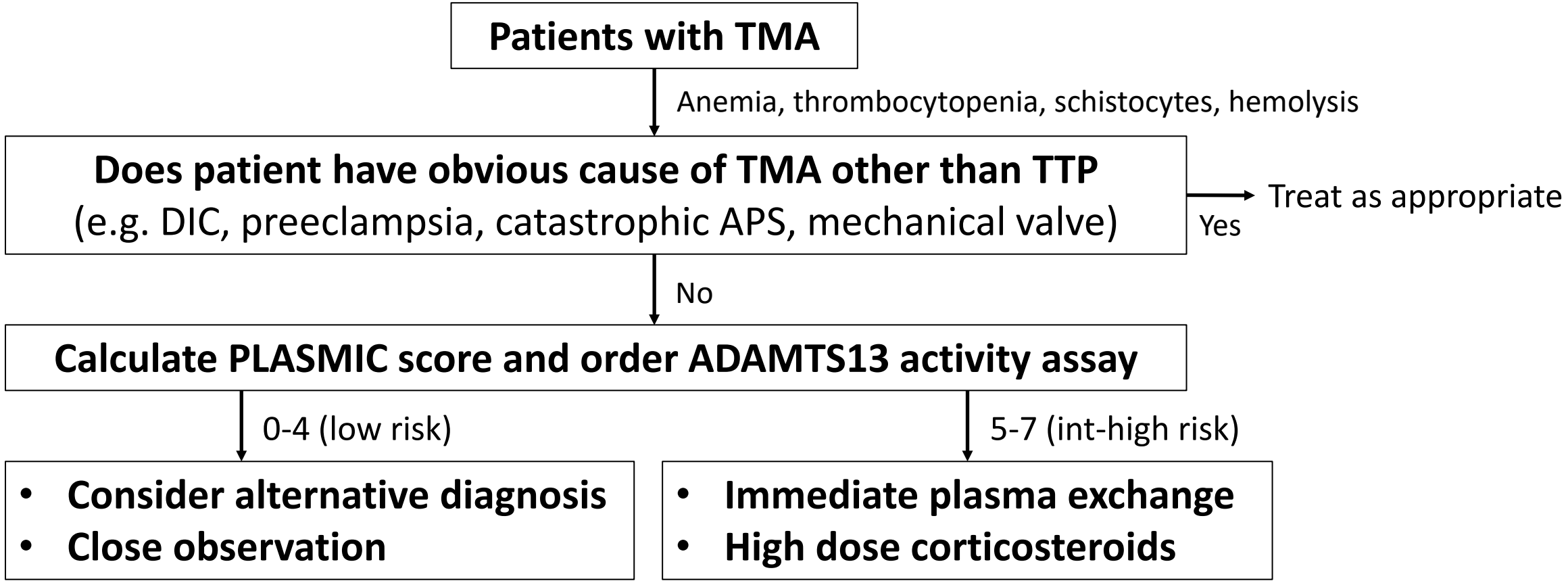
- Sensitivity = 99% (91-100)
- Specificity = 57% (41-72)

Author Interpretation

- 1% of patients with iTTP have a score <5
- Acceptable for screening

Paydary, Transfusion 2020

Initial Diagnosis and Treatment Algorithm



Chiasakul, Hematology Am Soc Hematol Educ Program 2018

The patient had 4 schistocytes per high power field and a calculated PLASMIC score of 6. You ask the ED physician to send out ADAMTS13 activity assay. There may or may not be a bed available in the next 24 hours, what should you advise the ED physician to do if there is no bed availability?

A. Watchful waiting
B. Start high-dose steroid
C. Start high-dose steroid and give 4-8 units of FFP over the next 24 hr
D. Start high-dose steroid and give 1-2 units of FFP over the next 24 hr

Standard Treatment for Acute iTTP

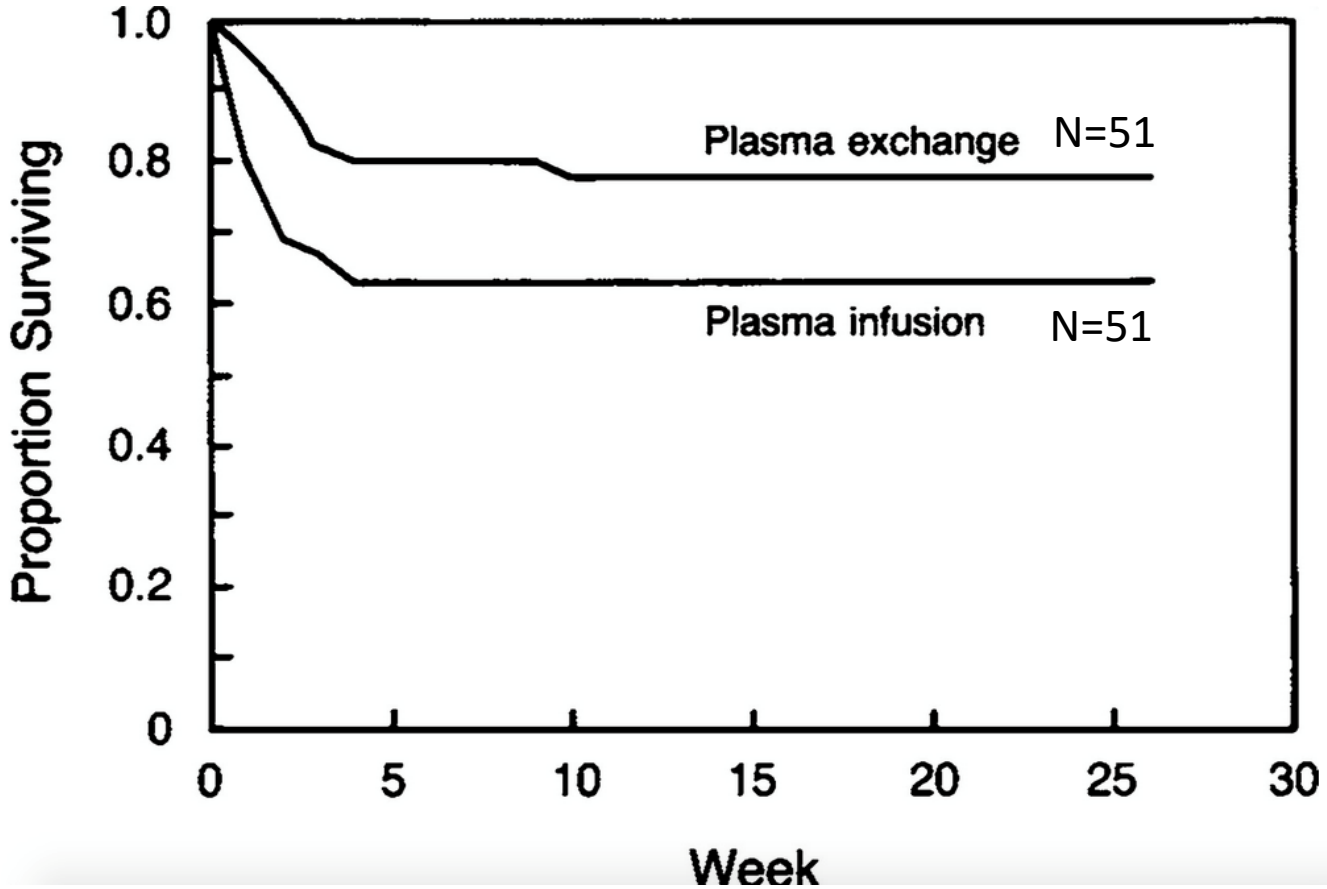
- Plasma exchange (PEX)
- High-dose steroid
- Upfront rituximab

Plasma Exchange (PEX) vs. Plasma Infusion (FFP)

Patients with TTP clinical Dx
- Platelet < 100×10^9/L
- Microangiopathic hemolytic anemia (MAHA)
- Red-cell fragmentation
- No identifiable cause for MAHA (e.g., DIC, cancer, or eclampsia)
- ADAMTS13 activity not required (available)

PEX 1.5 PV x3d
PEX 1.0 PV after

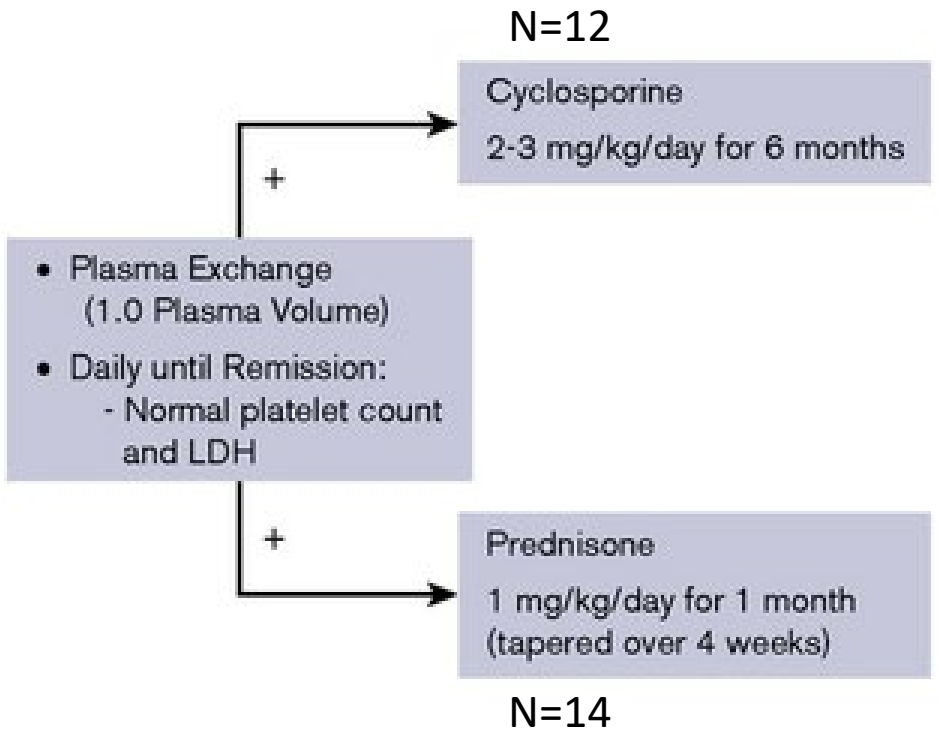
FFP 30 cc/kg x1d
(~8 units)
FFP 15 cc/kg after
(~4 units)

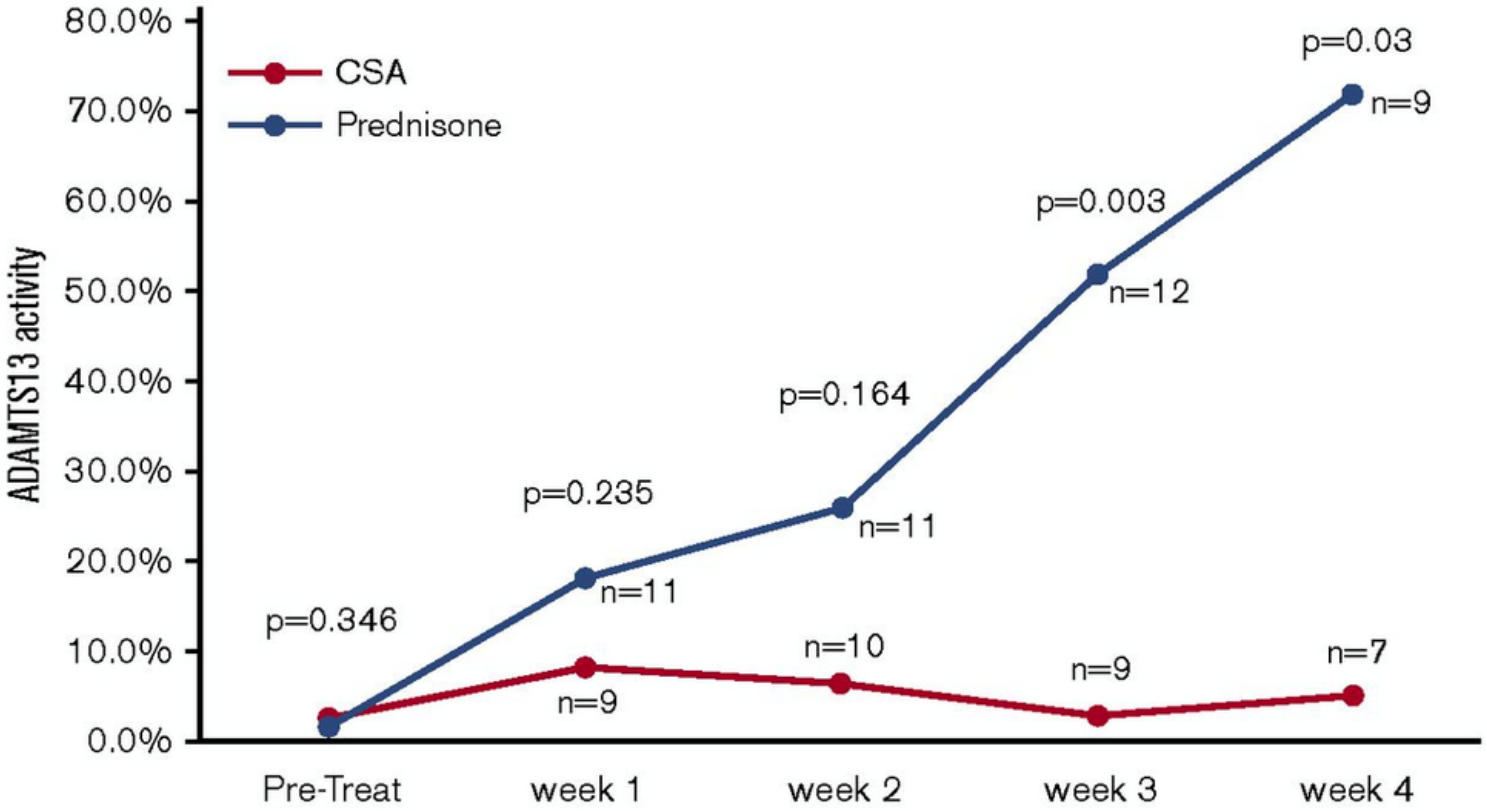


Rock, NEJM 1991

Prednisone vs. Cyclosporine (CSA) as Adjuncts to PEX

iTTP patients with ADAMTS13<10% (25/26)





Cataland, Blood Adv, 2017

Summary

- PLASMIC score (0-5 vs. 6-7) may help triage the initiation of plasma exchange while waiting for ADAMTS13 activity assay
- PLASMIC score should be calculated using the earliest lab available within 3 days of admission, in patients with thrombocytopenia + microangiopathic hemolytic anemia + schistocytosis
- Plasma exchange (PEX) and high-dose steroid are the standard of care for patients with acute iTTP
- Plasma infusion at high-dose should be considered if PEX cannot be initiated rapidly

The patient was transferred 12 hours later. He responded to daily plasma exchange and prednisone at 1 mg/kg with improvement in platelet count and normalization of hemolysis markers after 7 days. Pre-treatment ADAMTS13 activity was confirmed to be <5% and a strong inhibitor was detected. What would you do next?

A. Recheck ADAMTS13 after completion of steroid taper
B. Add rituximab 375 mg/m2 weekly x4 (lymphoma dose)
C. Add rituximab 100 mg weekly x4

Benefits of Adding Rituximab to Initial Therapy

Study arm	Treatment	Median Response Time	Median LOS	Exacerbation	Relapse
Rituximab 375 mg/m2 weekly x4 N=40	PEX + Steroid + Rituximab within 3d of admission	12 days	16.5	0%	0% at 12 months 3% at 24 months
Historical Control N=40	PEX + Steroid	Not reported	20	Not reported	16% at 12 months 34% at 24 months

Study arm	Treatment	Median Response Time	Median LOS	Exacerbation	Relapse
Rituximab 100 mg weekly x4 N=19	PEX + Steroid + Rituximab within 4d of PEX	5 days	Not reported	5%	5% at 12 months 16% at 24 months

NOT randomized controlled studies – difficult to compare results across different trials and time periods

Scully, Blood 2011. Zwicker, Blood 2019

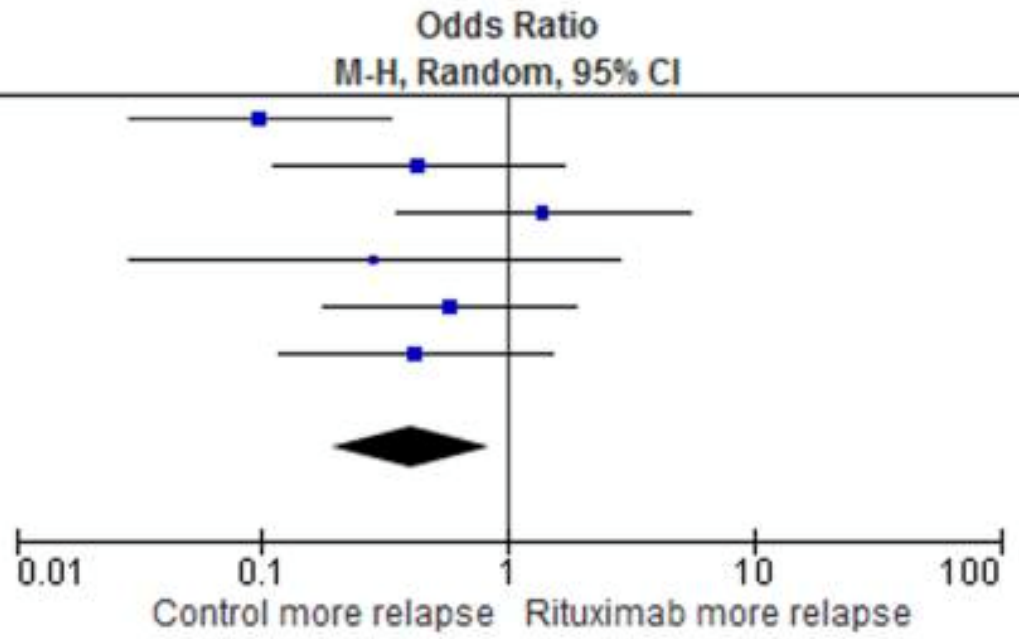
Upfront Rituximab Effect on Relapse Differs by Study

A

Study or Subgroup	Rituximab Events	Rituximab Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Scully 2011	4	37	21	38	19.3%	0.10 [0.03, 0.33]	2011
Froissart 2012	3	19	16	53	17.1%	0.43 [0.11, 1.70]	2012
Rinott 2015	4	14	9	40	16.9%	1.38 [0.35, 5.46]	2015
Page 2016	1	16	4	21	8.3%	0.28 [0.03, 2.82]	2016
Uhl 2017	5	36	10	46	20.0%	0.58 [0.18, 1.88]	2017
Falter 2018	5	17	14	28	18.3%	0.42 [0.12, 1.50]	2018
Total (95% CI)		**139**		**226**	**100.0%**	**0.40 [0.19, 0.85]**	
Total events	22		74				

Heterogeneity: $Tau^2 = 0.36$; $Chi^2 = 8.72$, $df = 5$ ($P = 0.12$); $I^2 = 43\%$

Test for overall effect: $Z = 2.39$ ($P = 0.02$)



Very heterogeneous population with different follow-up and mixed control group

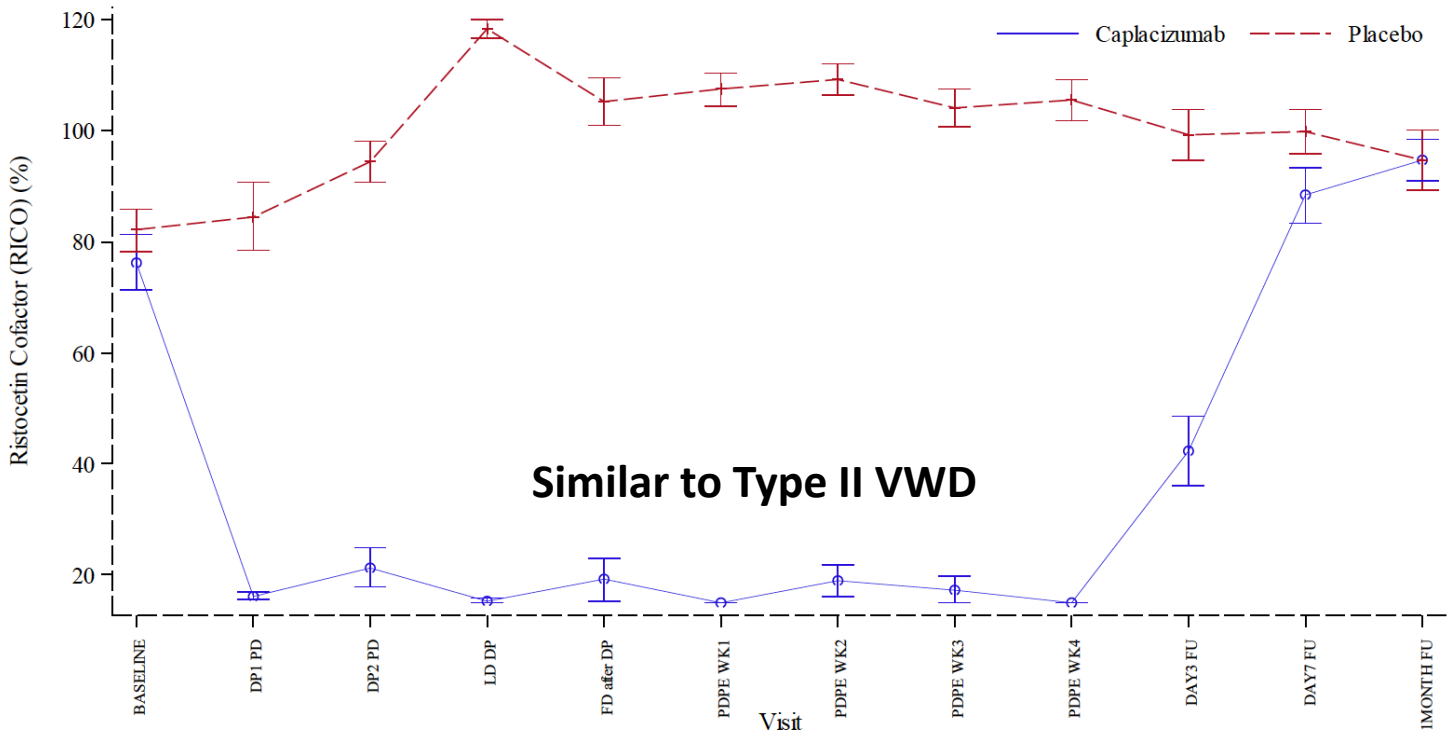
Owattanapanich, Clin Appl Thromb Hemost 2019

Summary

- Rituximab is frequently used off-label in both initial and refractory setting for treatment of iTTP
- Rituximab is beneficial for refractory iTTP and reduces iTTP relapse
- Rituximab is likely beneficial for a significant majority of patients
- Exact timing and dosing of rituximab administration is debated
  - Upfront low dose for all patients
  - Standard dose for refractory or high-risk patients for relapse
- Rituximab may have a time-varying / time-weaning effect observed in other autoimmune / lymphoma studies
  - Careful long-term surveillance is needed

Caplacizumab

- Humanized immunoglobulin nanobody targeting A1 domain of VWF, preventing interaction with platelet glycoprotein Ib-IX-V receptor
- Phase II TITAN trial
- Phase III HERCULES trial
- Approved by EMA 9/2018
- Approved by FDA 2/2019



<20% RICO represents the threshold for pharmacological activity of caplacizumab; values

Peyvandi, NEJM 2016

Summary

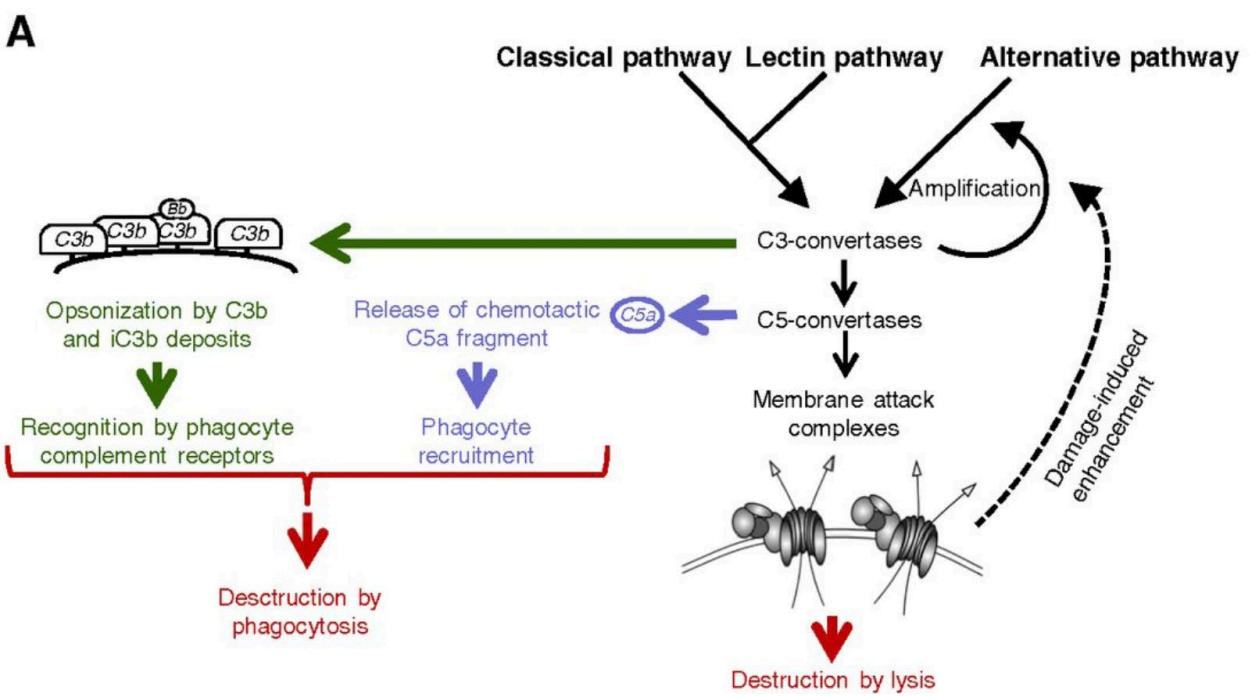
- Caplacizumab is the newest approved drug for iTTP when used together with plasma exchange
- Caplacizumab shortens time to platelet normalization by ~1 day, decreases exacerbation but increases bleeding as long as patient takes the drug (acquired VWD), increases long-term relapse, no difference on thrombosis or mortality
- Caplacizumab has been advocated for but has unclear benefit for patients with severe iTTP (more data needed)
- Caplacizumab reduces the number of plasma exchange sessions and hospital days at a significantly increased healthcare cost
- Routine addition of caplacizumab to the standard of care does not appear to be clinically significant or cost effective (personal opinion)

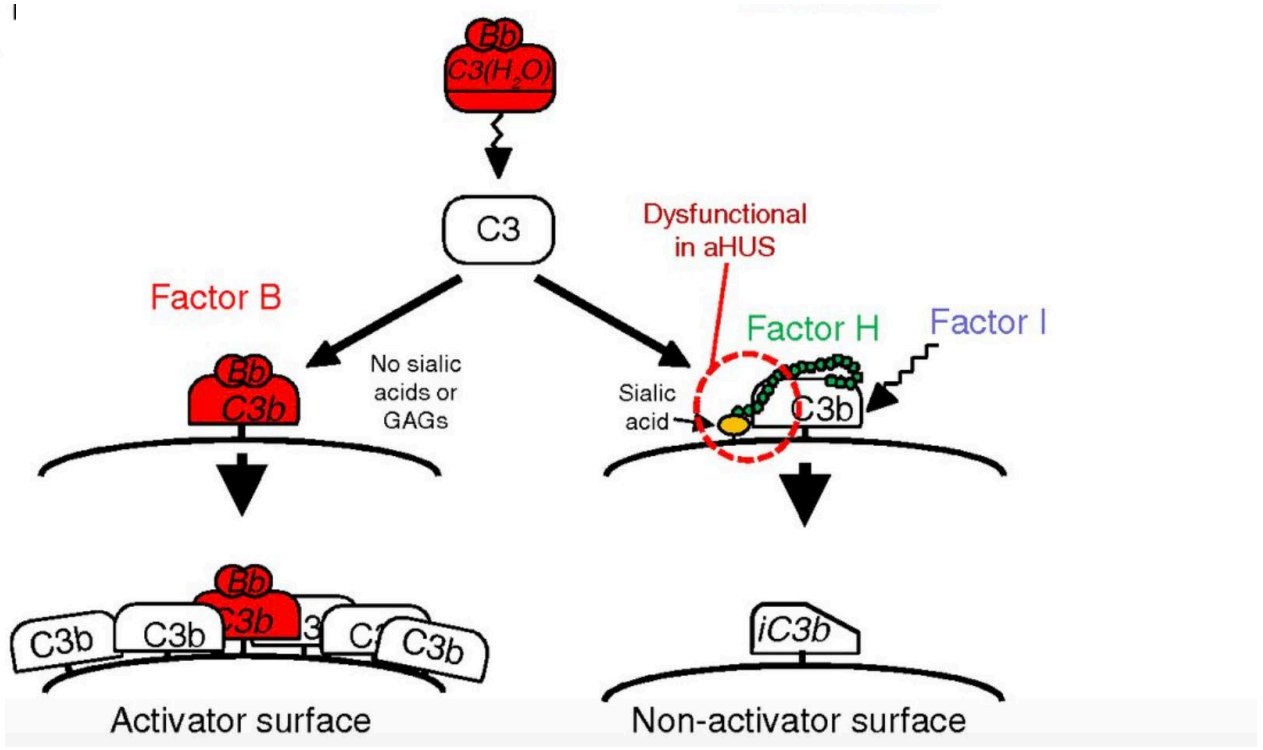
Take Home Points

- PLASMIC score, when applied correctly, is useful to triage plasma exchange decision while waiting for ADAMTS13 level
- Initial treatment of iTTP remains daily plasma exchange and corticosteroid
- Addition of rituximab to initial treatment may reduce time to response and relapse in a time-dependent fashion
- Pre-emptive rituximab given to patients with severe ADAMTS13 in remission reduces relapse
- Addition of caplacizumab to initial treatment reduces time to response, number of plasma needed, and exacerbation after plasma exchange cessation; however, possibly increases relapse long-term and definitely increases bleeding and healthcare cost

Immune HUS (aHUS)

Pathogenesis of aHUS





Jokiranta, Blood 2017

Genetic Defects in aHUS

Frequencies **of the most common mutations identified in aHUS patients**

Mutated gene/protein	**Type**	**Frequency (%)***	**Death or end-stage renal disease 3-10 y after onset (%)†**
Factor H (including *CFH/CFHR1* hybrid genes)	Loss of complement regulation	24-28	70-80
MCP (CD46)	Loss of complement regulation	5-9‡	<20
Factor I	Loss of complement regulation	4-8	60-70
C3	Gain of complement activation	2-8	60-70
Factor B	Gain of complement activation	0-4	70
Thrombomodulin	Possibly loss of complement regulation and procoagulative state	0-5	50-60
CFHR1/3 deficiency with anti-factor H autoantibodies	Loss of complement regulation	3-10§	30-70
Diacylglycerol kinase ε	Prothrombotic	0-3‖	46
None identified		30-48	50

Work-up for aHUS

- Functional Panel (quicker)
  - CH50
  - AH50
  - C3
  - C4
  - C4d
  - SC5b9
  - CFB
  - CFBb
  - CFH & anti-CFH antibody
- Gene mutation/deletion (slower)
  - C3
  - CD46 (MCP)
  - CFB
  - CFH
  - CFHR1
  - CFHR3
  - CFHR4
  - CFHR5
  - CFI
  - Plasminogen
  - Thrombomodulin

Specialty lab needed: Cincinnati Children, Iowa, Mayo, etc

Treatment of aHUS

- Eculizumab: antibody against complement C5, approved in 2011
  - Maintenance dose every 2 weeks
- Ravulizumab: antibody against complement C5, approved in 2019
  - Maintenance dose every 8 weeks
- Vaccination against encapsulated organisms and anti-meningococcal prophylaxis is needed
- Duration is under study, may be safe to discontinue with close surveillance in a subset of patients