Why Does My Patient Have Thrombocytopenia?

And what should I do about it?

Keith McCrae, M.D.
Cleveland Clinic
mccraek@ccf.org

Disclosures

- Dova: Advisory Board
- Argenex: Data Safety Monitoring Board
- Halozyme: Data Safety Monitoring Boards (2)
- Rigel: Advisory Board
- Sanofi-Genzyme: Advisory Board

Goals

- Approach to the patient with thrombocytopenia
- Specific Disorders
  - ITP
  - Thrombocytopenia during pregnancy
  - Inherited thrombocytopenias
  - Heparin-induced thrombocytopenia
  - ICU thrombocytopenia
  - Thrombotic microangiopathies

Approach to Thrombocytopenia

Pseudothrombocytopenia

Platelets < 150 x 10^9/L

- Chronicity
- Family history
- Severity
- Bleeding

Medical History
Physical Exam

Adenopathy
Splenomegaly
Other

Sequestration

Other cytopenias?

Peripheral blood film?

- ITP (1°/2°)
- Drugs (DITP)
- MAHAT (TMA; TTP, HUS)
- DIC
- Sepsis
- PTP
- Mechanical (heart valve, bypass, etc)

Increased Platelet Destruction

- Infection (EBV, HIV, CMV, etc)
- Medication (chemotherapy, abx, alcohol)
- Radiation
- Nutritional (B12, folate)
- Liver disease
- BM failure (AA, Fanconi, DBA, Schwachman-Diamond)
- Malignant (leukemia, MDS, MF)
- Myelopthistic
- Inherited

Decreased Platelet Production

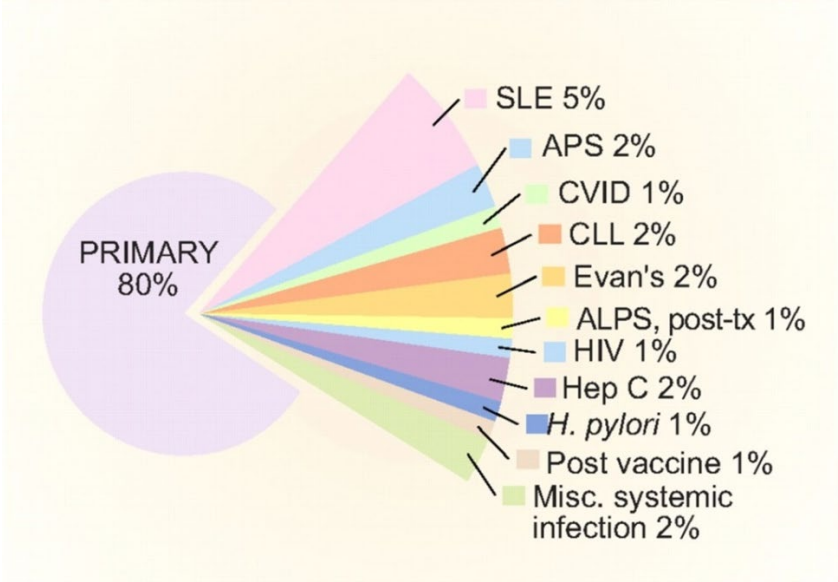
Immune Thrombocytopenia (ITP)

ITP Terminology: International Working Group

- Primary ITP
  - Isolated thrombocytopenia (not caused by or associated with another disorder)
  - Platelet count <100,000/µl
  - Comprises 80% of all cases

Rodeghiero F, et al. Blood. 2009

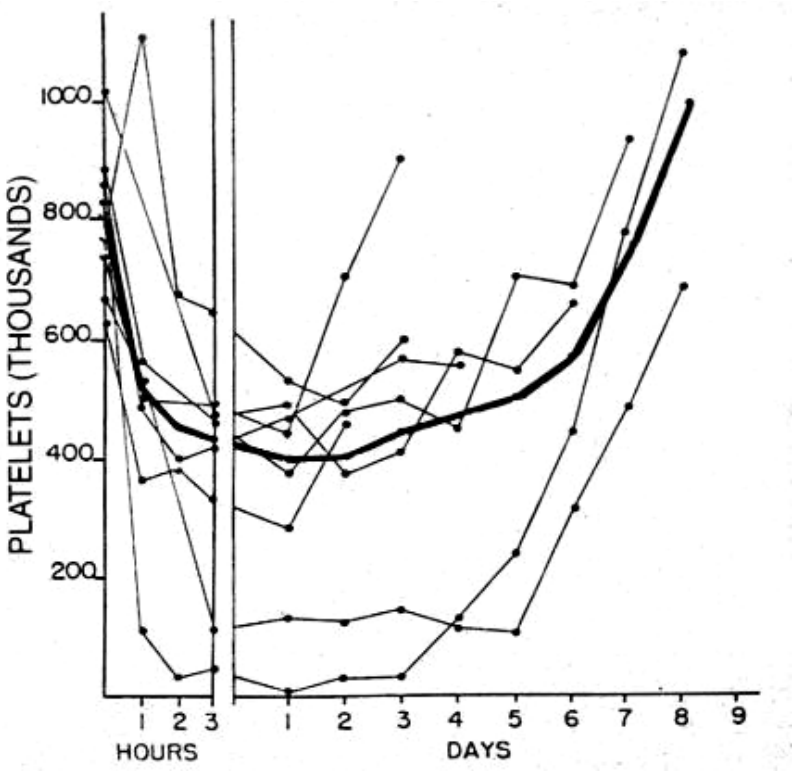
- Secondary ITP
  - All other immune-mediated thrombocytopenia
    - Infection-associated (HCV, HIV, H. Pylori, CMV)
    - Immunodeficiency
      - CVID, WAS
    - Autoimmune disorders
      - SLE, others
    - Lymphoproliferative
      - CLL, others
    - Drug-induced



Cines DB, et al. Blood 2009

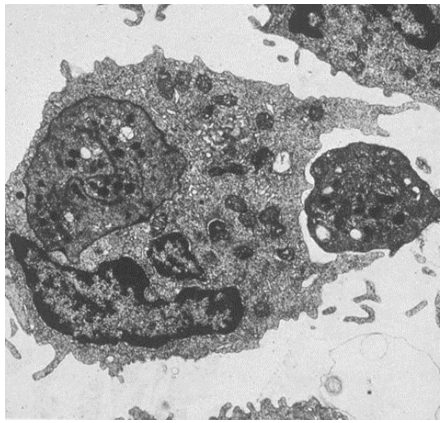
- There are no clinical or laboratory tests that establish this diagnosis with certainty
- ITP is diagnosed by excluding other causes of thrombocytopenia
- Best diagnostic parameter is response to therapy

Platelet Antibodies



Harrington WJ, et al. J Lab Clin Med. 1951;38:1-10.

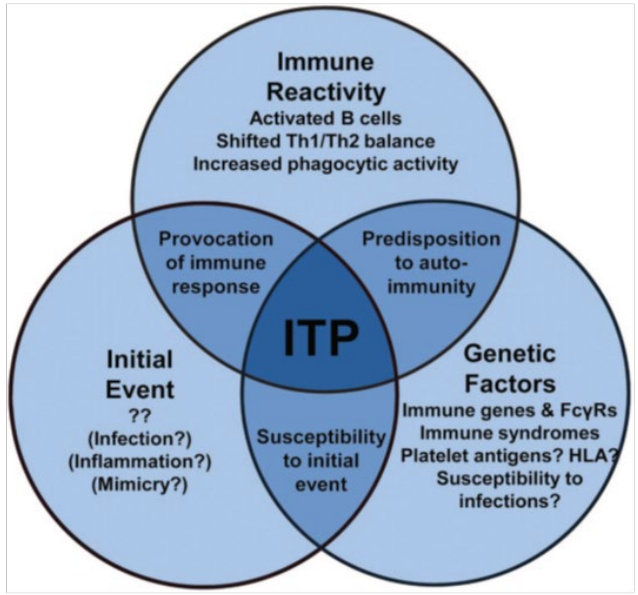
- Accelerated clearance caused by anti-platelet antibodies
- IgG antibodies to GPIIb/IIIa most common
- Many patients have antibodies to multiple platelet glycoproteins (GP Ib/IX)-epitope spreading?
- Antibody-coated platelets cleared by phagocytosis by splenic macrophages via Fcγ receptors



Karpatkin S. Lancet. 1997;349:1531-1536.

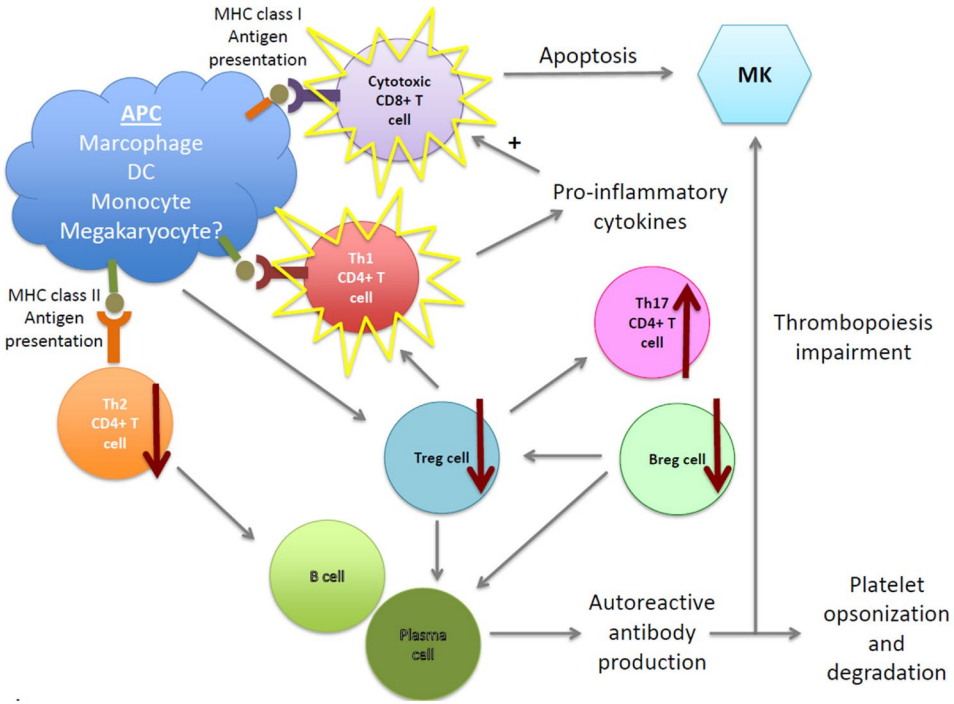
Pathogenesis of ITP: Overview

- *Predisposing factors*
- *Secondary ITP may be less responsive*



HIV
HCV
EBV
H. Pylori
CMV

Johnsen J, Hematology, 2012

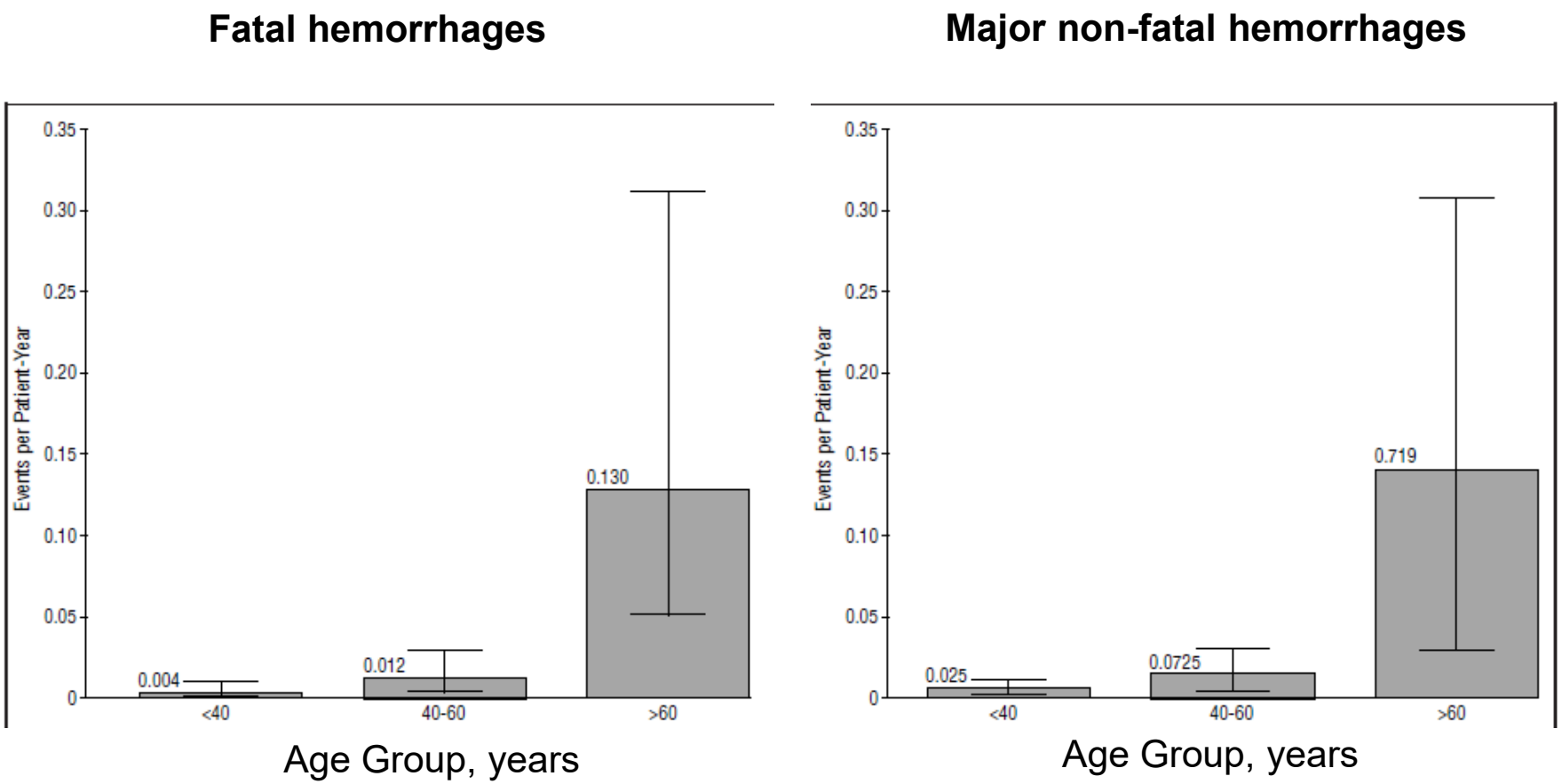


Zufferey et al, J Clin Med 2017

It's a lot more complicated than just anti-platelet antibodies!

- *Broad immune dysregulation—deeper in secondary ITP*
- *T cells, dendritic cells, plasma cells are all involved*
- *Decreased T reg cells is a common finding*
- *Splenic plasma cells may account for resistance to therapy*

Estimated Annual Bleeding Incidence in ITP by Age



Cohen YC, et al. Arch Intern Med. 2000;160:1630-1638.

Impact of ITP on Health-Related Quality of Life

HR-QoL Parameter, n (%)	ITP Pts (N = 15)
Signs and symptoms	**14 (93)**
▪ Fatigue	14 (93)
▪ Bleeding	8 (53)
▪ Bruising	8 (53)
▪ Other	8 (53)
Treatment Effects	**13 (87)**
▪ Steroids	13 (87)
▪ Other treatments	8 (53)
Emotional health	**11 (73)**
▪ Fear, stress, anxiety	11 (73)
▪ Relationships	7 (47)
▪ Depression, isolation, loss of control	7 (47)
▪ Mood, self-consciousness	7 (47)

HR-QoL Parameter, n (%)	ITP Pts (N = 15)
Functional health	**13 (87)**
▪ Daily activities	11 (73)
▪ Sleep	9 (60)
▪ Changes in lifestyle	7 (47)
Work	**13 (87)**
▪ Absences	10 (67)
▪ Changes in attitudes	5 (33)
▪ Career advancement	3 (33)
▪ Productivity	4 (27)

Mathias SD, et al. Health Qual Life Outcomes. 2008;6:13.

Therapeutic Approach to ITP

1st line

Corticosteroids
------IVIg
----------Anti-D

2nd line?

Rituximab
TPO-RA
Splenectomy
----------fostamatinib
----------MMF
----------CyA

3rd line?

Splenectomy
--fostamatinib
--combination therapy
--------Azathioprine
----------Vinca alkaloids
----------Cyclophosphamide
----------Danazol
----------Dapsone

- First, second and third line therapies not well defined
- Role of intensive initial therapy?
- Combination therapy for resistant disease

Recommended “Safe” Platelet Ranges

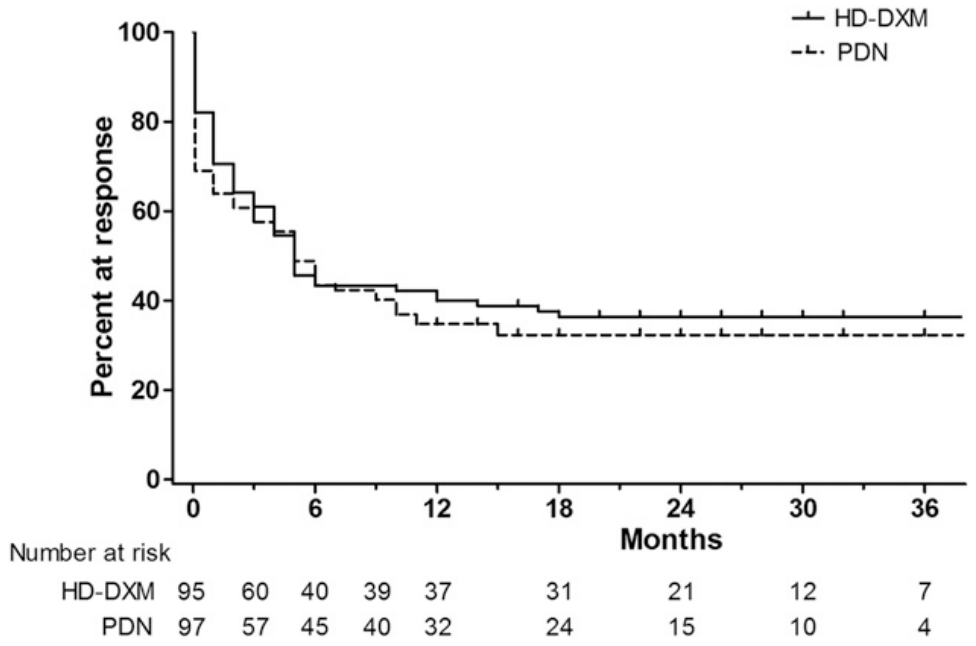
Clinical Situation	Platelets
General dentistry	≥ $10x10^9$/L
▪ Extractions	≥ $30x10^9$/L
▪ Regional dental block	≥ $30x10^9$/L
Surgery	
▪ Minor	≥ $50x10^9$/L
▪ Major	≥ $80x10^9$/L
Pregnancy	
▪ Vaginal delivery	> $50x10^9$/L
▪ Caesarean section	> $80x10^9$/L
▪ Spinal/epidural anesthesia	> $80x10^9$/L

British Committee for Standards in Haematology General Haematology Task Force. Br J Haematol. 2003;120:574-596.

Initial Therapy of ITP: Corticosteroids

Dexamethasone vs Prednisone

- Dexamethasone 40 mg/d x 4 days, x 1-2 cycles
- Prednisone 1 mg/kg for 4 weeks, then taper
- Dexamethasone
  - Higher initial response rate (82.1% vs 67.4%)
  - Higher CR (50.5% vs 26.8%)
  - Shorter time to response
- But no difference in sustained response (40% dexamethasone vs 41.2% prednisone)
- Extent of initial response correlates with sustained response



- Dexamathasone might be a better choice for a severely thrombocytopenic patient
- Otherwise, no efficacy advantage of one over the other

Wei et al, Blood 2016

Rituximab in ITP

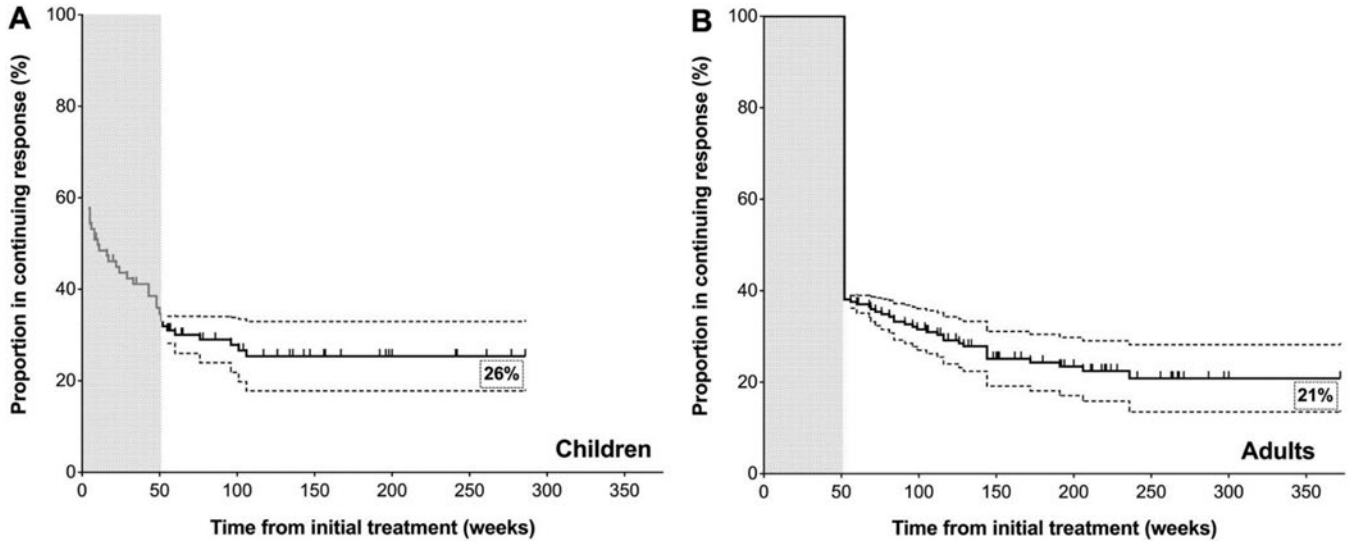
Systematic analysis

Table 2. **Overall, Complete, and Partial Platelet Count Response after Treatment with Rituximab in Adults with Idiopathic Thrombocytopenic Purpura according to Studies Enrolling at Least 5 Patients Each***

Platelet Count Response, × 10^9 cells/L	Pooled Estimate (95% CI), %	Contributing Reports (Patients), *n* (*n*)
Overall response (>50)	62.5 (52.6–72.5)	19 (313)
Complete response (>150)	46.3 (29.5–57.7)	13 (191)
Partial response (50–150)	24.0 (15.2–32.7)	16 (284)

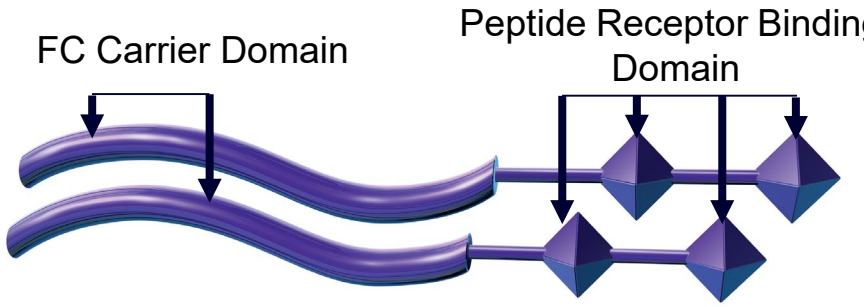
Arnold DM. Ann Int Med. 146:25, 2007

- *Retrospective analysis*
- *376 adults, 116 children*
- *Baseline platelet counts < 30,000*
- *Patients with complete or partial response to initial course of rituximab (>150,000 or >50,000, respectively) maintained for 1 year were followed for total of 5 years*
- *Durable remissions in 21-26%*



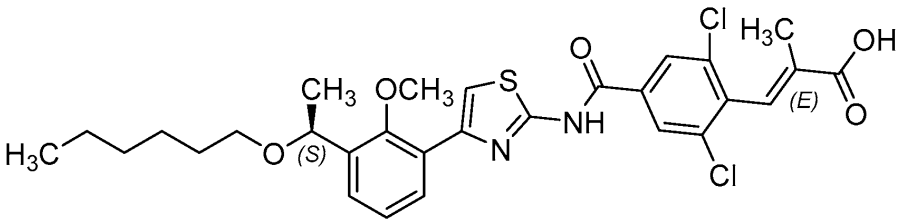
Patel et al Blood 119:5989, 2012

TPO-Receptor Agonists (TRAs)



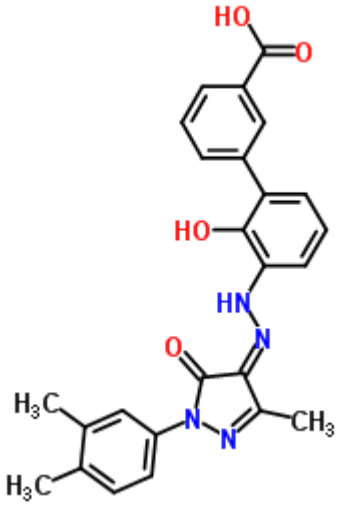
Romiplostim[1]

- ITP with insufficient response to a previous treatment



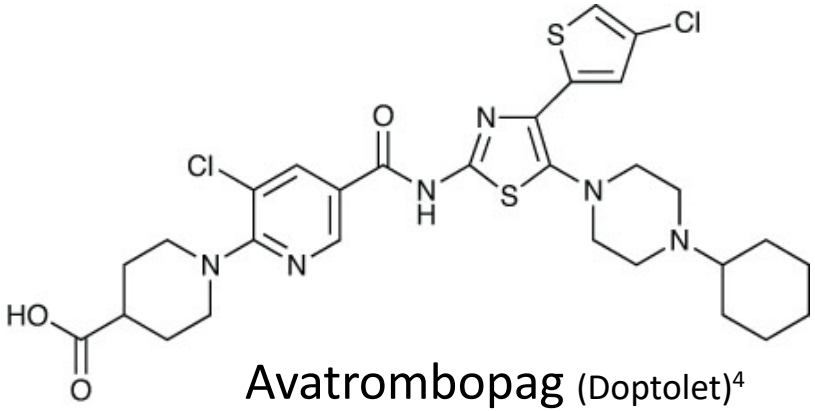
Lusutrombopag (Mulpleta)[3]

- thrombocytopenia in adults with chronic liver disease scheduled to undergo an invasive procedure



Eltrombopag[3]

- ITP with insufficient response to a previous treatment
- Thrombocytopenia with chronic hepatitis C
- Severe aplastic anemia (first line)
- Pediatric ITP

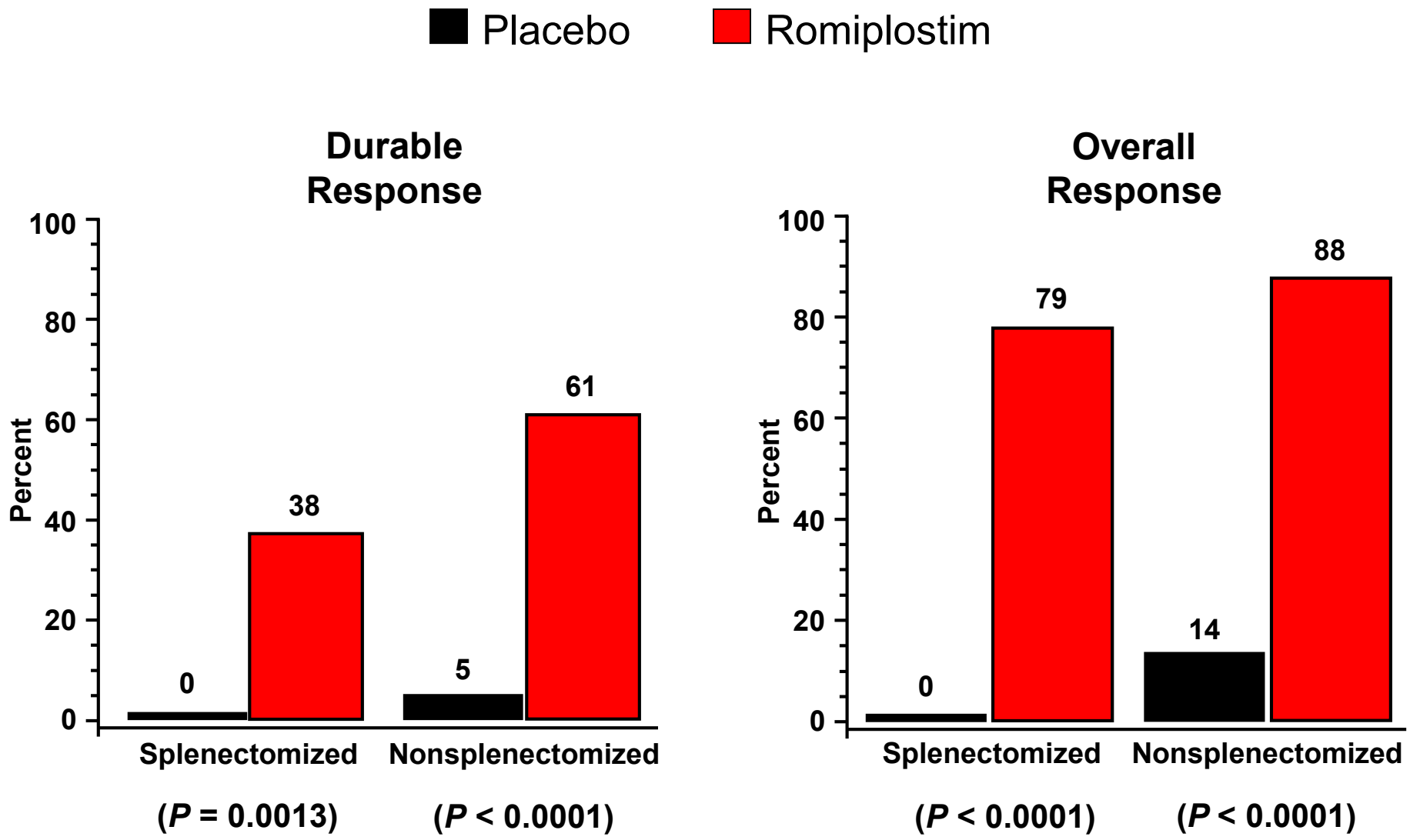


Avatrombopag (Doptolet)[4]

- thrombocytopenia in adults with chronic liver disease scheduled to undergo an invasive procedure
- ITP with insufficient response to a previous treatment

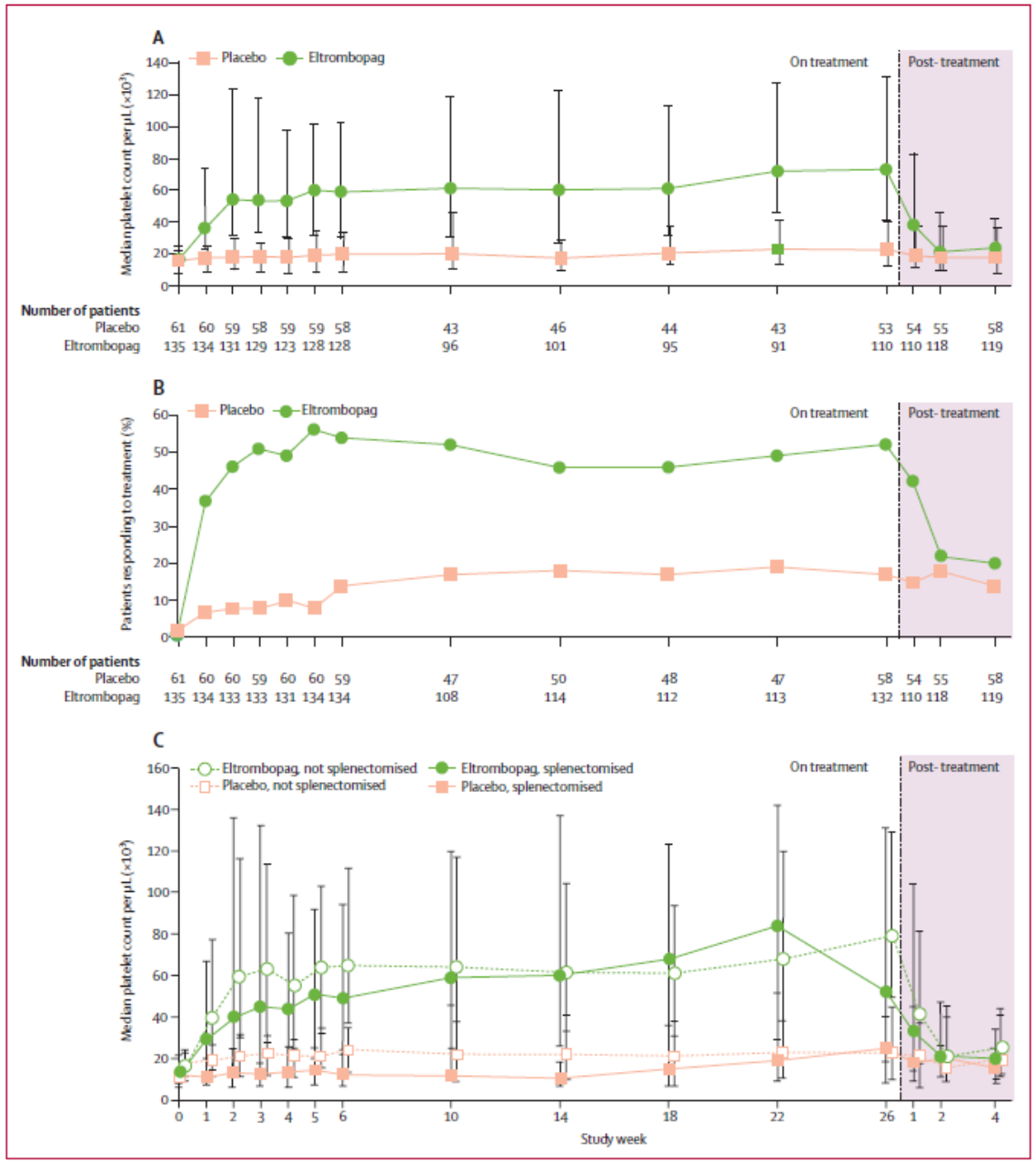
1. Bussel JB, et al. N Engl J Med. 2006;355:1672. 2. www.chemspider.com 3. https://www.hpcimedia.com/images/website/ManChemTechnical/DIR_10/F_16166.jpg. 4. Clemons-Bangston, Int J Mol Sci 2019

Platelet Responses: Romiplostim Phase 3



From Kuter DJ, et al. *Lancet.* 2008;371:395-403.

Eltrombopag: Phase 3 (RAISE) Study



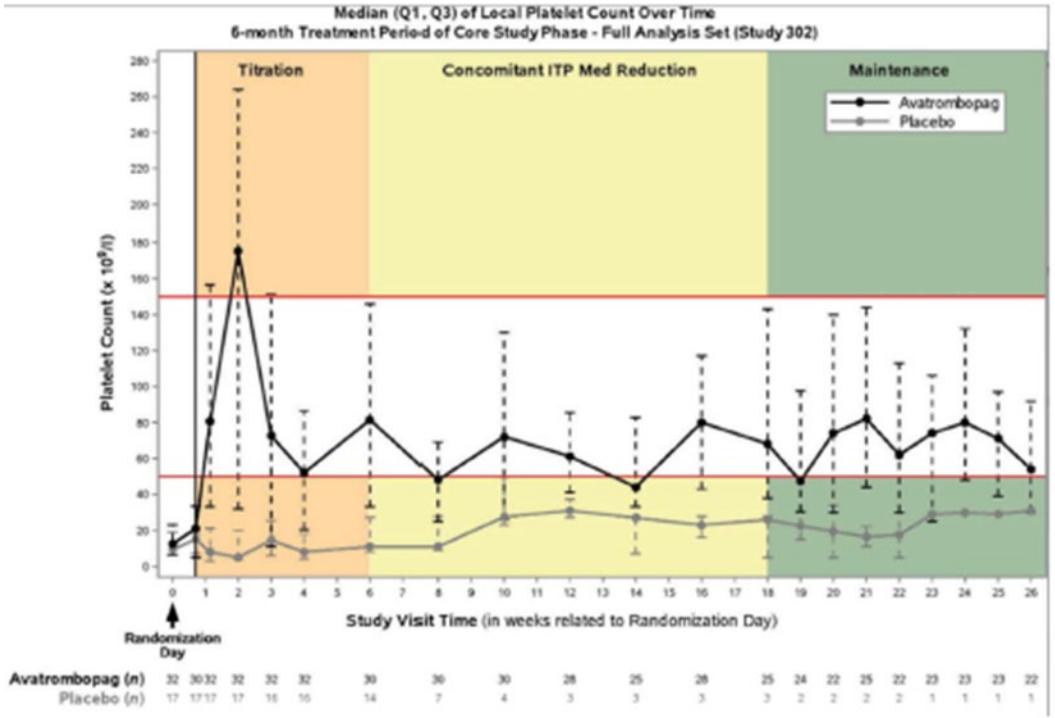
- *197 patients*
- *Baseline platelet counts < 30,000/μl*
- *6 month, 2:1 randomization, placebo-controlled*
- *79% response rate in treatment arm (platelet count 50-400,000/μl) at least once, vs 28% placebo*
- *OR for response eltrombopag = 8.2*
- *Splenectomy status had no effect on response*
- *2% (eltrombopag) vs no thromboembolic events (NS)*
- *7% (eltrombopag) vs 3% increased ALT*
- *<1% (eltrombopag) vs 7% serious bleeding events*

Cheng G et al. Lancet 377:393, 2011

Phase III Study of Avatrombopag in ITP

	Placebo (N=17)	Avatrombopag (N=32)	
Platelet Count ≥50 x 10^9/L at Day 8 n/N (% [95% CI])	0/17 (0.0 [-,-])	21/32 (65.6 [49.2, 82.1])	***P* < 0.05**
Reduction of Concomitant ITP Medication n/N (% [95% CI])	0/7 (0.0 [-,-])	5/15 (33.3 [9.5, 57.2])	***P* - NS**
Durable Platelet Response[a] n/N (% [95% CI])	0/17 (0.0 [-,-])	11/32 (34.4 [17.9, 50.8])	***P* < 0.05**

CI, confidence interval.
[a]The proportion of participants who had a platelet response for ≥6 of the last 8 weeks of treatment.



- 49 patients, 2:1 randomization
- Starting dose of avatrombopag: 20 mg (adjust to 5-40)
- 26 week study

Jurczak et al, BJH, 2018; Dlugosz-Danecka et al Exp Rev Clin Immunol, 2019

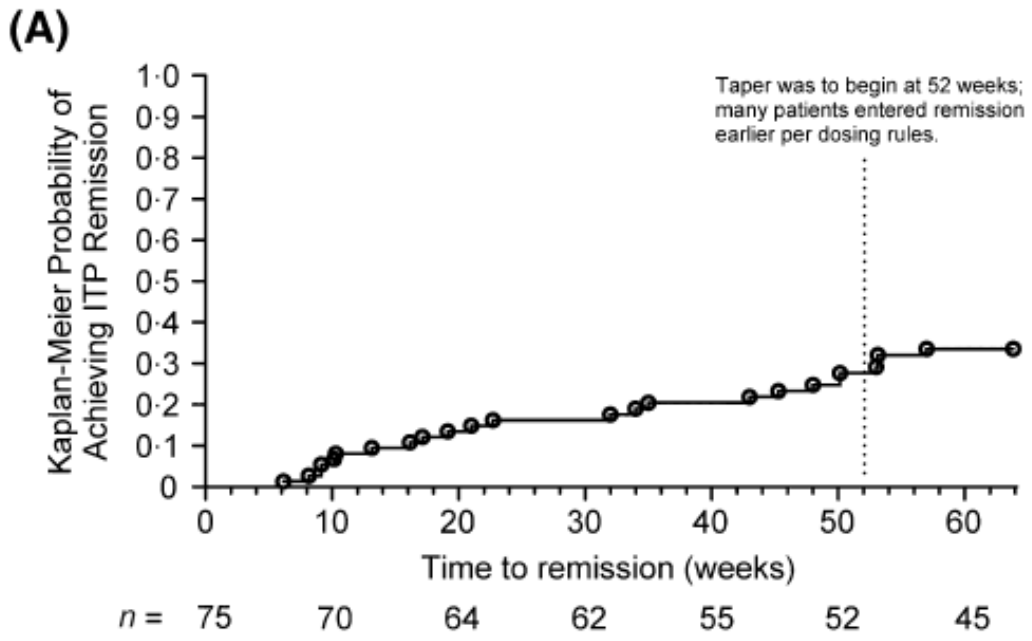
TRAs Are Safe

Table 2 Adverse events (AE)

	Romiplostim			PBO/SOC		
	$N = 994$; pt-yr = 1520			$N = 138$; pt-yr = 110		
	#	*r*	95 % CI	#	*r*	95 % CI
All AE	17,129	1127.1	1110–1144	1268	1152.3	1090–1218
Serious AE	910	60	56–64	107	97	80–118
Fatal AE	40	2.6	1.9–3.6	8	7.3	3.1–14.3
Treatment-related AE[a]	1739	114.4	109–120	168	152.7	131–178
Treatment-related serious AE[a]	118	7.8	6.4–9.3	18	16.4	9.7–25.9
Treatment-related fatal AEs[a]	5	0.3	0.1–0.8	0	0	0.0–2.7
AE leading to D/C IP (treatment-related)	83 (40)	5.5 (2.6)	4.4–6.8 (1.9–3.6)	8 (4)	7.3 (3.6)	3.1–14.3 (1.0–9.3)
AE leading to D/C study (treatment-related)	65 (35)	4.3 (2.3)	3.3–5.5 (1.6–3.2)	4 (0)	3.6 (0)	1.0–9.3 (0.0–2.7)
Haemorrhage						
Any grade	3115	205	198–212	289	263	233–295
Grade 3 or greater	182	12	10–14	19	17	10–27
Serious haemorrhage	151	9.9	8.4–11.7	15	13.6	7.6–22.5
Thrombotic/thromboembolic events	83	5.5	4.4–6.8	6	5.5	2.0–11.9
Serious thrombotic/thromboembolic events	61	4.0	3.1–5.2	2	1.8	0.2–6.6
Bone marrow reticulin/collagen[b]	18	1.3	0.8–2.1	1	0.9	0.0–5.1
Non-haematological tumours	34	2.2	1.6–3.1	4	3.6	1.0–9.3
Haematological malignancies/MDS	7[c]	0.5	0.2–1.0	3[d]	2.7	0.6–8.0
Cataracts	34	2.2	1.6–3.1	1	0.9	0.0–5.1

Cines et al. Int J Hematol, 2015

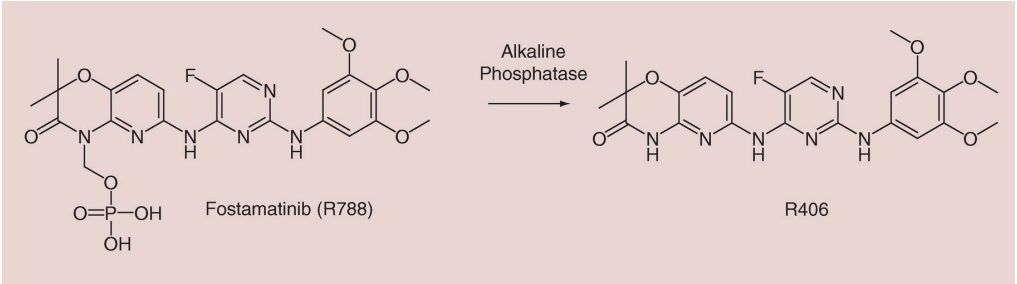
Some Patients Treated with TRA May Achieve Remission

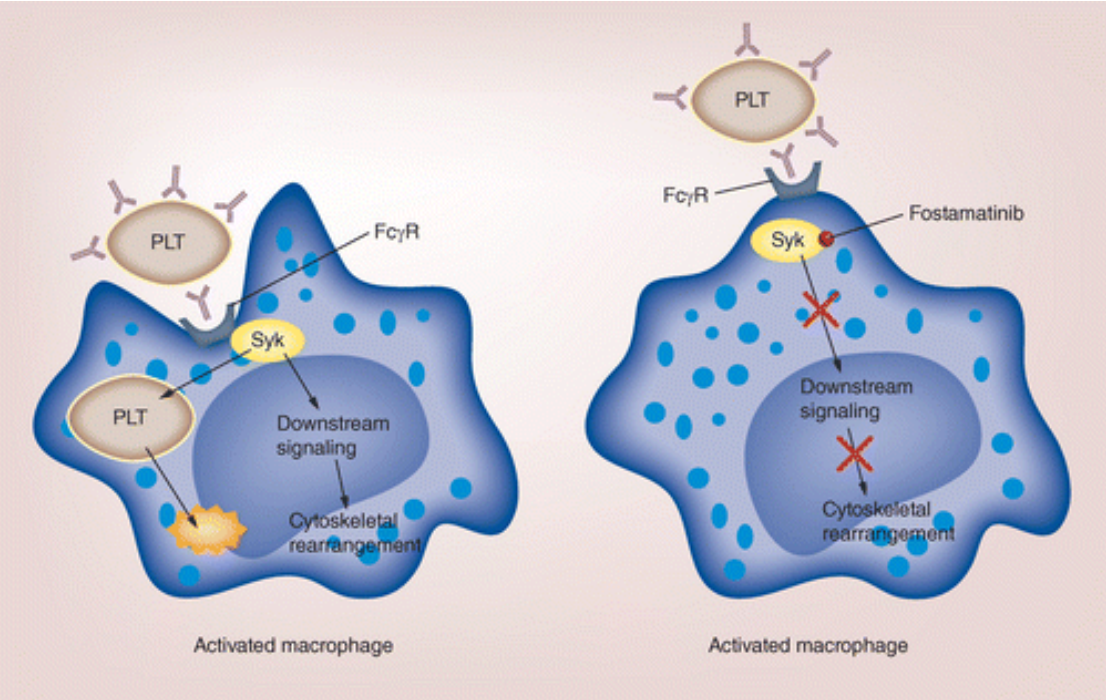


Newland et al BJH 2015

- *75 patients with primary ITP*
- *Median duration of ITP before enrollment 2.2 months*
- *57% had received only first-line therapy*
- *Primary endpoint (number of months in the 12 month study in which a platelet response occurred) = 11*
- *24/75 (32%) of patients who discontinued romiplostim maintained platelet count ≥ 50,000/µl without any additional treatment for 24 weeks*
- *Median time to onset of ITP remission = 27 (6-57) weeks*

Fostamatinib (Tavalisse)

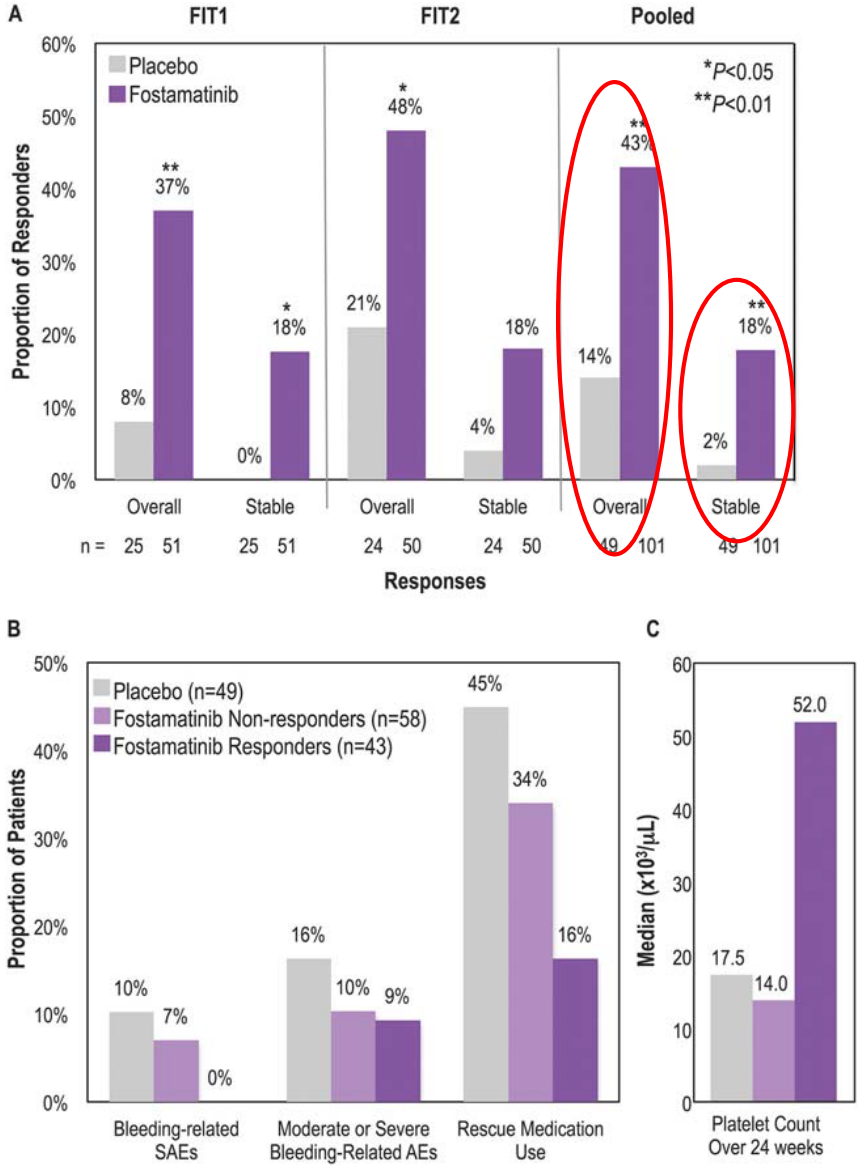




- Orally available, small molecule
- Mechanism—inhibition of spleen tyrosine kinase (Syk), resulting in impaired macrophage phagocytosis
- Converted to active form R406 by alkaline phosphatase
- FDA approved in April 2018 for treatment of chronic ITP that has had an insufficient response to previous treatment

Newland et al, Immunotherapy 2017

Fostamatinib: FIT1 and FIT2 Studies



- Randomized (2:1), placebo-controlled studies
- 24 week duration
- Stable response: 4 of the last 6 weeks of the study with platelet count > 50,000
- Overall response: 1 platelet count >50,000 within first 12 weeks of treatment
- Toxicity generally mild
  - Diarrhea-31% vs 15%,
  - Hypertension-28% vs 13%
  - Nausea-18% vs 9%
  - ALT increase-11% vs 0%
- Place in overall ITP therapy has yet to be determined

Bussel et al, AJH 2018

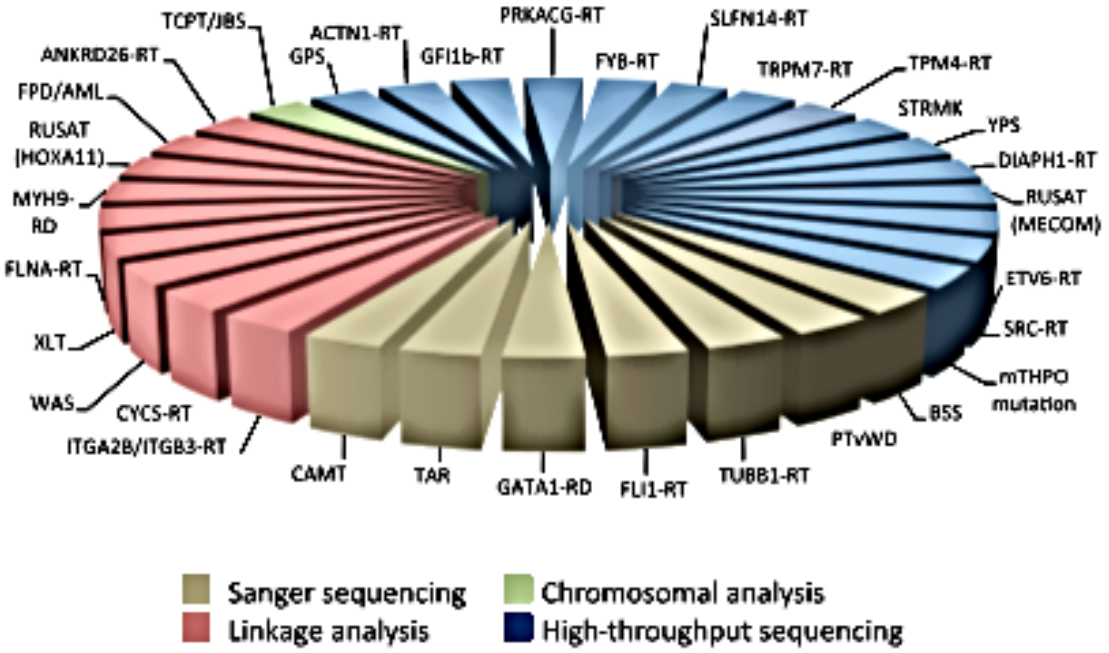
Therapies for Relapsed or Resistant ITP

Therapy	Response rate	Time to response	Toxicity	Response Duration
Splenectomy	80% initial 66% stable	1-24 d	Surgical complications Infection Thrombosis	2/3 require no additional therapy
Ritiximab	60% overall 40% stable	1-12 wk	First infusion reactions Serum sickness Hep B reactivation Immune suppression	20-25% sustained at 5 yr
TPO mimetics	>80% overall 40-60% stable	1-3 wk	Rebound thrombocytopenia Hepatoxicity (eltrombopag) Increased marrow reticulin (1-5%)	Continuous with drug administration, 90% of responses durable
Fostamitinib	43% overall 18% stable	2-8 wk	Hypertension Diarrhea, nausea Neutropenia	Continuous with drug administration

Connell and Berliner, Blood 2019

Inherited Thrombocytopenia

Inherited Thrombocytopenias



Noris and Pecci, Hematology 2017

Molecular defects

- Transcription factors
- Cytoskeletal components
- Regulation of gene splicing
- Signal transduction pathways
- Protein trafficking
- Mitochondrial function
- Endoribonucleases

Inherited Thrombocytopenias

Red = syndromic disorders

blue = at risk for additional manifestations

- **Defects in megakaryocyte differentiation**
  - CAMT (MPL)
  - TAR syndrome (RBM8a)
  - Radioulnar synostosis with AMT (HOXA11, MECOM)
- **Defects in megakaryocyte maturation**
  - Familial platelet disorder with propensity to AML (RUNX1)
  - ANKRD26 related thrombocytopenia (ANKRD26)
  - Paris-Trousseau/Jacobsen syndrome (11q23 deletions, FLI1)
  - FLI1-related thrombocytopenia (FLI1)
  - ETV6-related thrombocytopenia (ETV6)
  - GATA1-related thrombocytopenia (GATA1)
  - GFI1b-related thrombocytopenia (GFI1b)
  - Grey platelet syndrome (NBEAL2)
  - SLFN14-related thrombocytopenia (SLFN14)
  - FYB-related thrombocytopenia (FYB)
  - Src-related thrombocytopenia (SRC)
- **Defects in platelet release**
  - MYH9-related syndromes (MYH9)
  - ACTN1-related thrombocytopenia (ACTN1)
  - FLNA-related thrombocytopenia (FLNA)
  - Bernard-Soulier syndrome (GPIBA, GPIBB, GP9)
  - ITGA2B/ITGB3-related thrombocytopenia (ITGA2B, ITGB3)
  - TUBB1-related thrombocytopenia (TUBB1)
  - TRPM7-related thrombocytopenia (TRPM7)
  - TPM4-related thrombocytopenia (TPM4)
  - CYCS-related thrombocytopenia (CYCS)
  - DIAPH1-related thrombocytopenia (DIAPH1)
  - PRKACG-related thrombocytopenia (PRKACG)
- **Shortened platelet survival**
  - Type II VWD (GP1BA)
  - Wiscott-Aldrich syndrome (WAS)
  - X-linked thrombocytopenia
- **Unknown**
  - Stormorken defect/York platelet syndrome

Defects Associated with Syndromic IT

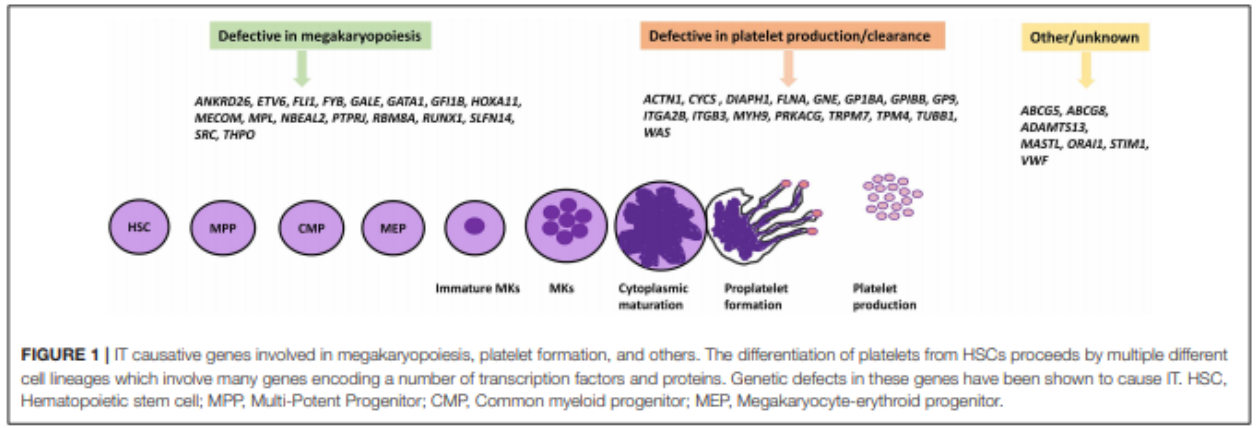
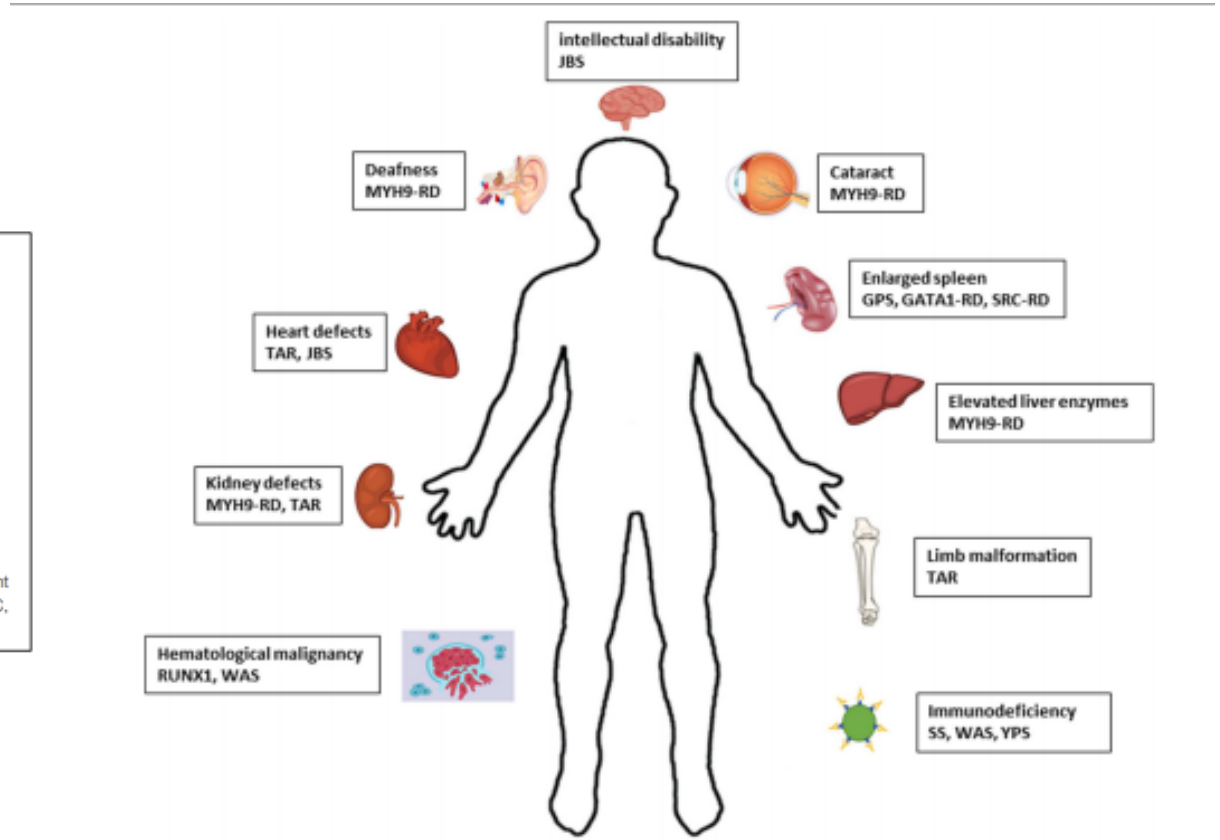
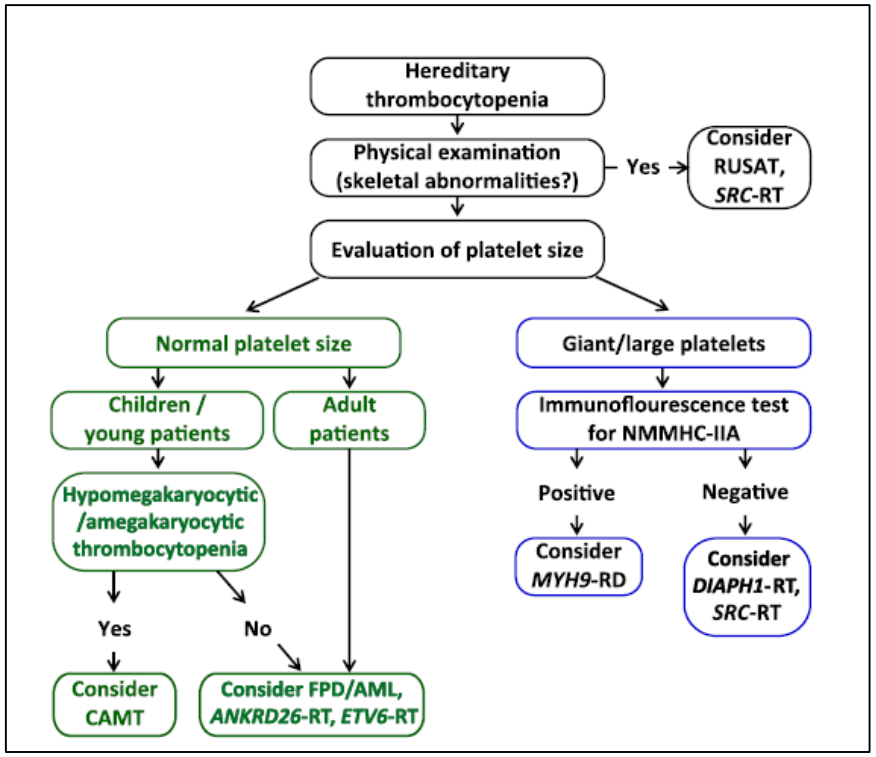


FIGURE 1 | IT causative genes involved in megakaryopoiesis, platelet formation, and others. The differentiation of platelets from HSCs proceeds by multiple different cell lineages which involve many genes encoding a number of transcription factors and proteins. Genetic defects in these genes have been shown to cause IT. HSC, Hematopoietic stem cell; MPP, Multi-Potent Progenitor; CMP, Common myeloid progenitor; MEP, Megakaryocyte-erythroid progenitor.



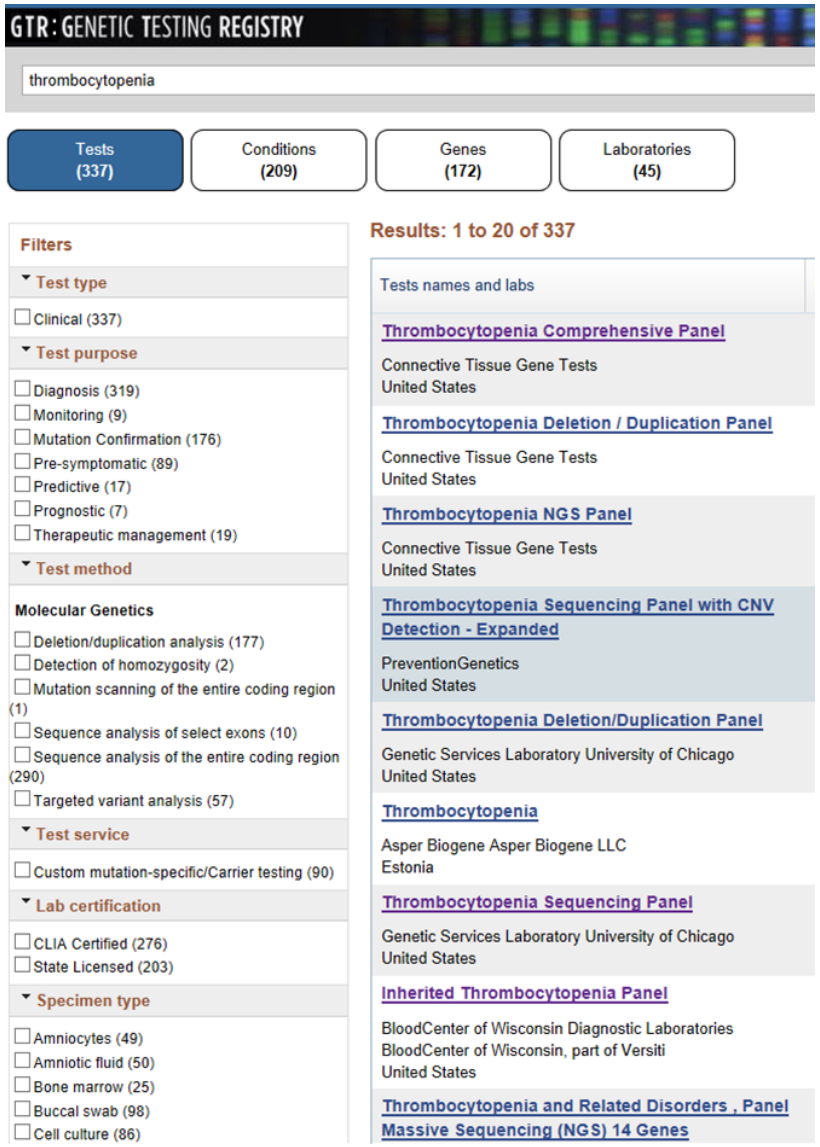
Almazni et al. Front Cardiov Med, 2019

Diagnosis of Inherited Thrombocytopenias



Noris and Pecci, Hematology 2017

- *Syndromic features*
- *Lifelong thrombocytopenia*
- *Bleeding worse than expected*
- *Dysmorphic (large) platelets*
- *Failure to respond to ITP therapy*

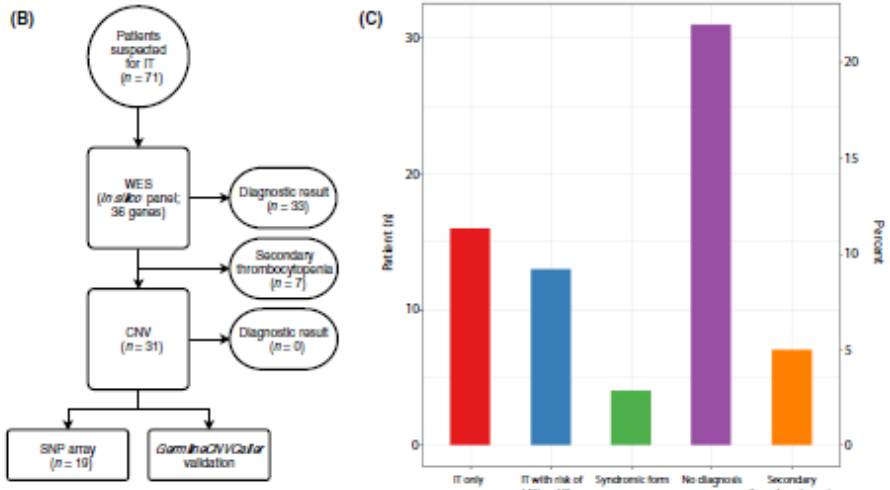


https://www.ncbi.nlm.nih.gov/gtr/

Diagnostic Pipeline for Patients with Suspected IT

(A)

IT only	Syndromic forms of IT (congenital)	IT with increased risk of additional illnesses
ACTN1	*ABCA1* (Cardiovascular disease)	*ABCG5/ABCG8* (Premature coronary atherosclerosis, xanthomas)
ANKRD18A	*ADAMTS13* (Thrombotic thrombocytopenic purpura)	*ANKRD26* (Myeloid malignancy)
CYCS	*ARPC1B* (Immunodeficiency)	*DIAPH1* (Sensoneuronal deafness)
FLI1	*FLNA* (Periventricular nodular heterotropia)	*ETV6* (Haematological malignancies)
FYB	*GATA1* (Thalassaemia)	*HOXA11* (Bone marrow aplasia, radioulnar synostosis)
GFI1B	*MPIG6B* (Anaemia, myelofibrosis)	*MPL* (Bone marrow aplasia)
GP1BA / GP1BB / GP9	*ORAI1* (Immunodeficiency, myopathy)	*MYH9* (Deafness, cataract, nephropathia)
ITGA2B / ITGB3	*STIM1* (Immunodeficiency, myopathy)	*NBEAL2* (Myelofibrosis)
PRKACG	*WAS* (Eczema, Immunodeficiency)	*RUNX1* (MDS, AML)
SLFN14		*SRC* (Osteoporosis, edentulism)
THPO		
TPM4		
TUBB1		



- 71 patients with suspected IT
- No platelet phenotyping-direct assessment of 36 genes by WES
- Median age at time of study = 34 years
- Results
  - 33/71 (46%) patients received immediate diagnosis based on identification of rare variants in IT related genes and explorative screen among genes associated with specific phenotypes
    - 20 patients had previously reported mutations
    - 13 patients had 14 novel causative variants
  - Platelet counts normalized in 7 patients = secondary thrombocytopenia
  - No CNV in patients with normal sequencing results—correlated with SNP analysis

Leinoe et al, BJH 2019

Management of Inherited Thrombocytopenias

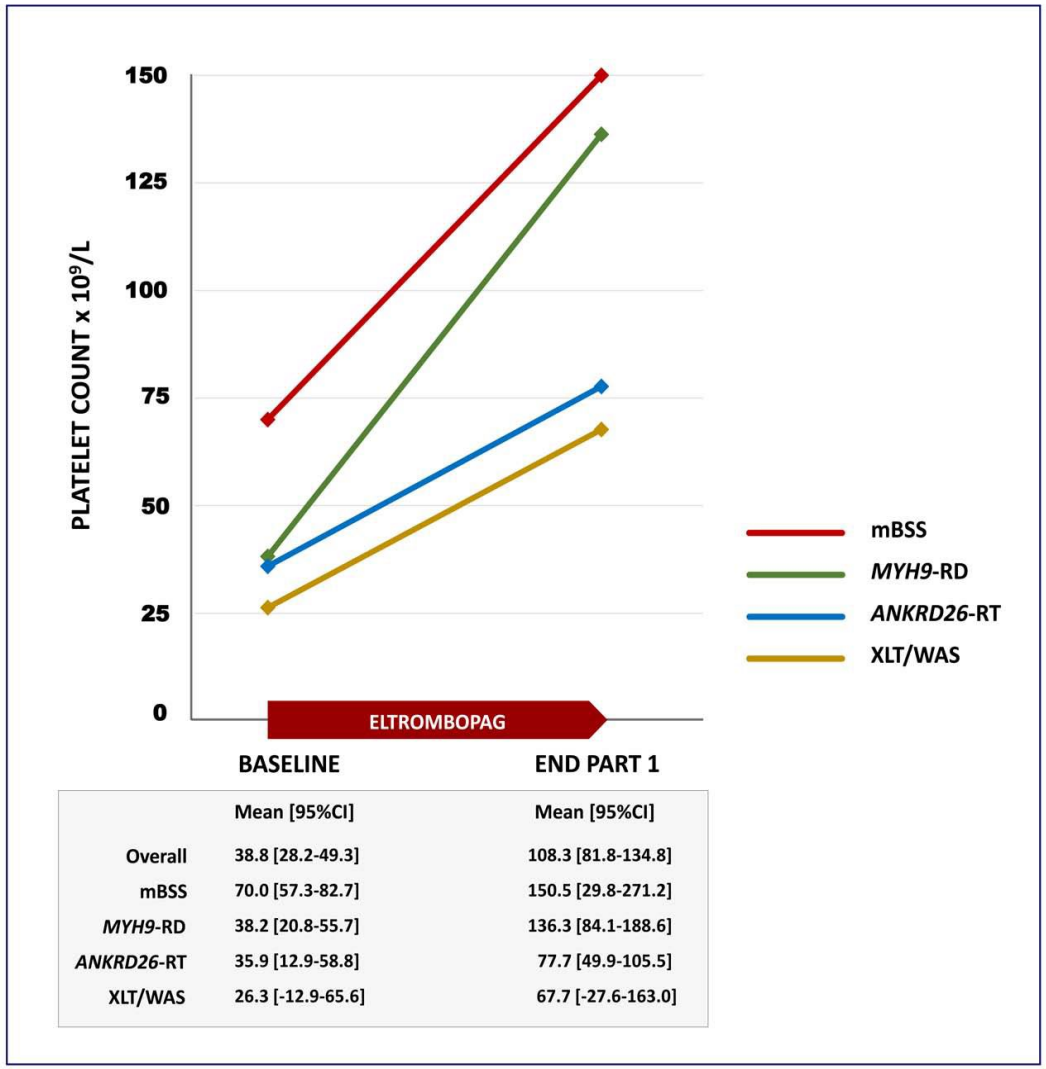
Stopping bleeding/hemostasis

- Platelet transfusions
- Antifibrinolytic agents (tranexamic acid)
- DDAVP
- rVIIa
- Short term eltrombopag (MYH9, ANKRD26)

Long-term management

- Eltrombopag (WAS/XLT)
- Splenectomy (WAS/XLT, but increased infection risk)
- HSCT (WAS/XLT treatment of choice)
- Gene therapy (experimental)

Phase 2 Trial of Eltrombopag in IT



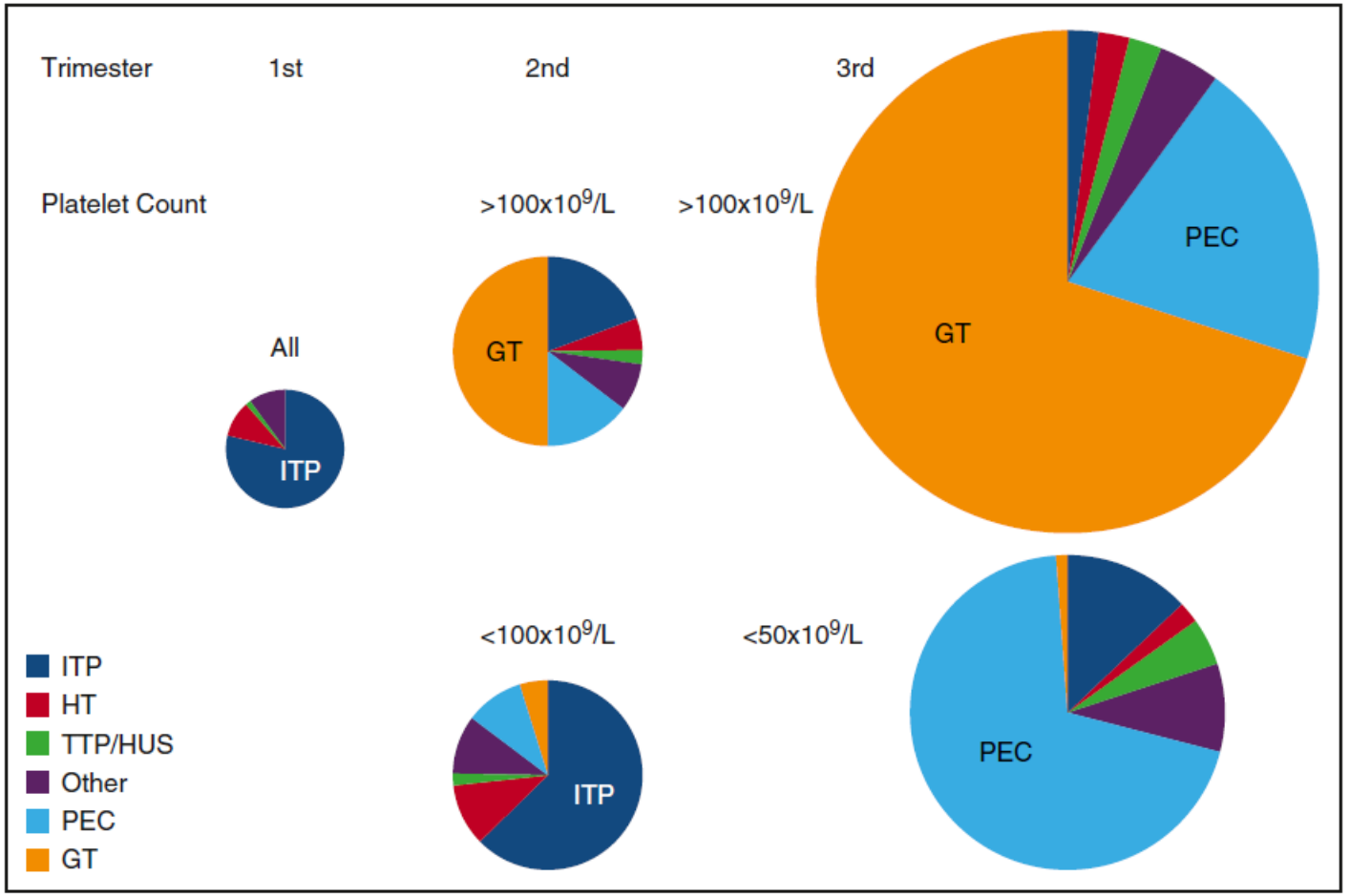
	Mean [95%CI]	Mean [95%CI]
Overall	38.8 [28.2-49.3]	108.3 [81.8-134.8]
mBSS	70.0 [57.3-82.7]	150.5 [29.8-271.2]
MYH9-RD	38.2 [20.8-55.7]	136.3 [84.1-188.6]
ANKRD26-RT	35.9 [12.9-58.8]	77.7 [49.9-105.5]
XLT/WAS	26.3 [-12.9-65.6]	67.7 [-27.6-163.0]

- Most patients with IT respond to eltrombopag
- Degree of response depends on subtype of IT
- Glanzmann's do not respond

Zaninetti et al, Haematologica, 2019

Pregnancy-Associated Thrombocytopenia

Causes of Thrombocytopenia in Pregnancy



- *Platelet count declines by ~10% in normal pregnancy*
- *Most likely cause of thrombocytopenia depends on stage of pregnancy and severity*
- *Gestational thrombocytopenia (GT) is the most common cause of thrombocytopenia in pregnancy, and requires no specific treatment*
- *GT may be hard to distinguish from ITP, but the platelet count in GT usually remains above 80 x 10^9/L*
- *Preeclampsia is a common cause of third trimester thrombocytopenia*
- *TTP may occur in the 2^{nd} or 3^{rd} trimester, while HUS is usually post-partum*

Cines and Levine, Blood 2017

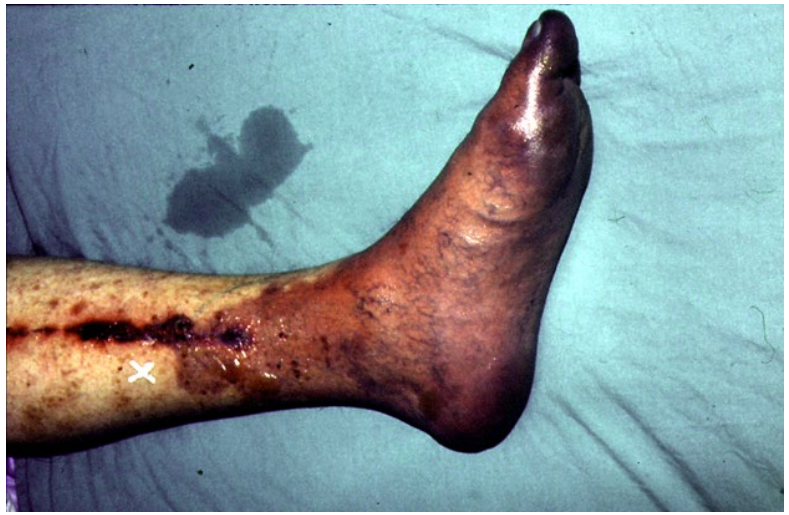
Maternal Management of Pregnancy-Associated ITP

- No need for platelet count higher than ~30 x 10^9/L until near delivery
- ITP responds to treatment in a similar fashion as in the non-pregnant patient
- Corticosteroids increase risk for several pregnancy-specific complications, so use lowest dose possible for minimum time needed
  - May supplement with or substitute IVIg
- Other treatments
  - Safe use of anti-D reported in a small number of patients
  - Splenectomy (if required) should be in early 2nd trimester
  - Rituximab: effective but causes delayed development of neonatal B cells
  - Thrombopoietic agents: class C
- Thrombocytopenia may occur in offspring
  - Only predictor—previous history of thrombocytopenic neonate
  - Risk of invasive testing exceeds that of delivering thrombocytopenic neonate
  - Incidence: 15% overall, 10% < 50K, 5% < 20K
  - Since mode of delivery does not affect risk of neonatal ICH, mode of delivery should be dictated by maternal factors

Heparin Induced Thrombocytopenia(HIT/HIT-T)

Heparin-Induced Thrombocytopenia (HIT)

- Terminology
  - HIT (asymptomatic thrombocytopenia)
  - HITT (with thrombosis)
- Occurs in 1-3% of patient treated with UFH, 0.2% with LMWH
  - Overall, thrombosis develops in 30-50% of patients with thrombocytopenia
- More common in patients undergoing cardiac/orthopedic surgery, trauma, or with cancer
- 4T scoring system used to assess pretest probability of HIT
- Laboratory studies
  - Heparin-PF4 antibodies, if negative, have high negative predictive value, but low positive predictive value if positive
  - Functional studies more specific
- Treatment of acute HIT requires discontinuation of heparin and institution of alternative anticoagulant (argatroban, bivalirudin, fondaparinux)
- Avoid warfarin in acute HIT due to risk of skin necrosis



Courtesy of Douglas Cines, M.D.

HIT is a profoundly hypercoagulable state

HIT is an iatrogenic disorder mediated by IgG antibodies that bind **PF4-heparin** complexes

These antibodies cause a **hypercoagulable state** by activating platelets and other vascular cells

One-third to one-half of patients with HIT develop venous, arterial, or microvascular thrombosis

Case: Medical Inpatient Admission

82 year old male

Past Medical History: Diabetes, Hypertension, Heart Failure

Medications: Metformin, Ramipril, Aspirin, Furosemide

Admitted to: Internal Medicine with heart failure exacerbation secondary to poor compliance with diet/diuretics

Treated with:

- Intravenous Furosemide, Nitroglycerin patch
- ***Subcutaneous unfractionated heparin (UFH)*** 5,000 IU Q12H started on admission for DVT prophylaxis

- No fever or signs of infection. No other new medications. No signs or symptoms of thromboembolism.
- No exposure to heparin in the 3 months prior to this admission
- **Bloodwork: Day 0 is admission date**

Date	**Day 0**	**+1**	**+2**	**+3**	**+4**	**+5**	**+6**	**+7**
Platelets (x 10^9)	200	220	206	210	220	230	150	67
Hemoglobin (g/dL)	13.5	13.1	13.3	13.0	13.0	13.3	13.1	13.3

Considering your patient's progressive thrombocytopenia and heparin exposure, you are concerned about the possibility of HIT.

Which of the following most accurately describes his clinical probability of HIT?

A. Probably low probability, given overall clinical context
B. Probably high probability, given overall clinical context
C. Low probability, based on 4Ts score
D. Intermediate probability, based on 4Ts score
E. High probability, based on 4Ts score

Recommendation.

- In patients with **suspected HIT**, the panel recommends using the **4Ts score** to estimate the probability of HIT **rather than a gestalt approach** *(strong recommendation, moderate certainty)*

REMARKS:

- Missing or inaccurate information may lead to a faulty 4Ts score and inappropriate management decisions
- Every effort should be made to obtain ***accurate and complete information*** necessary to calculate the 4Ts score. If key information is missing it may be prudent to err on the side of a higher 4Ts score.
- Reassess frequently. If there is a change in clinical picture, the 4Ts score should be recalculated.

4T Score Clinical Probability Model

Our patient:
Platelets 67, > 50% drop.
Onset of drop on day +6.
No thrombosis.
No other cause for thrombocytopenia.

HIGH probability:
6-8 points

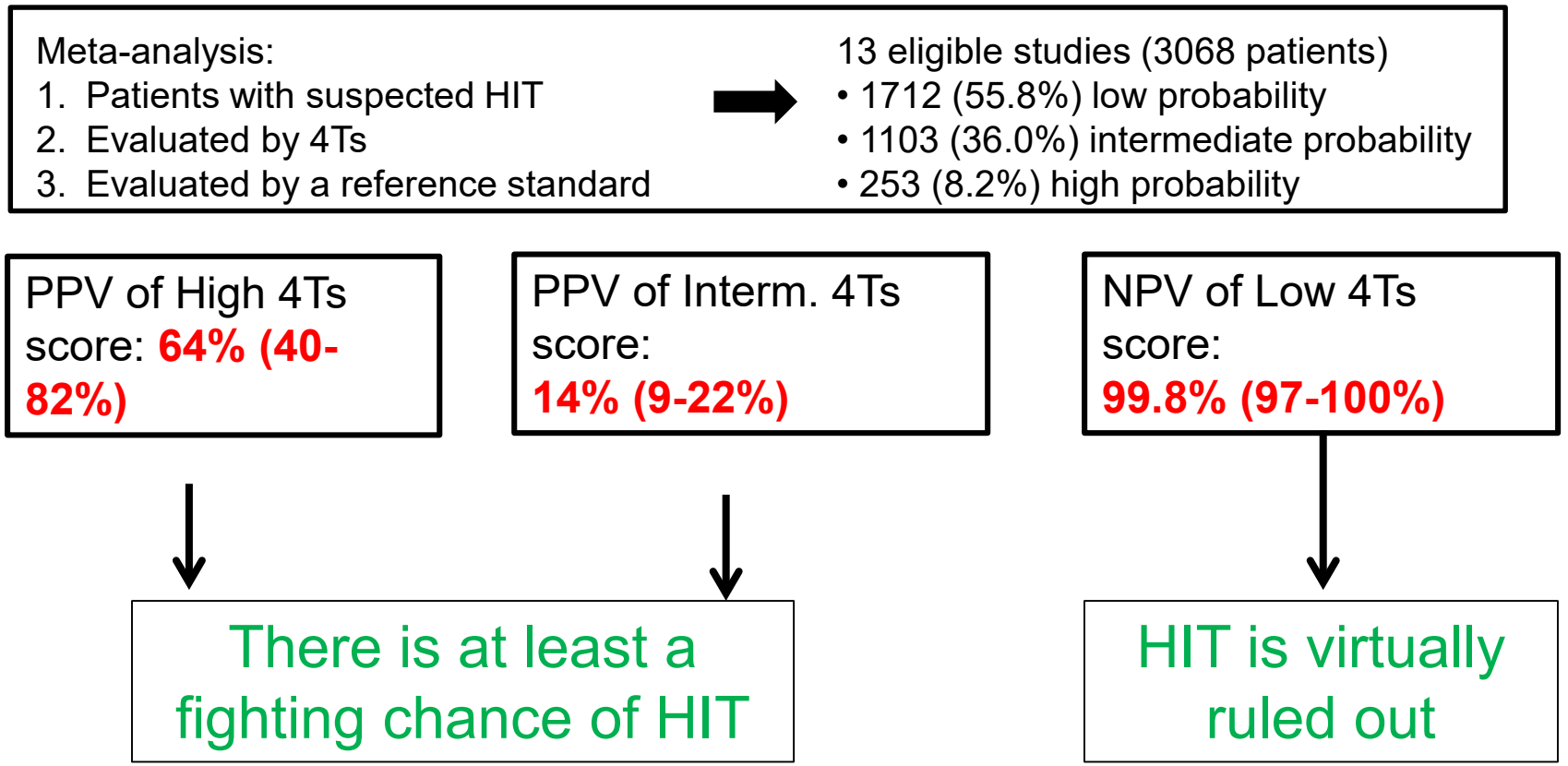
INTERMEDIATE probability:
4-5 points

LOW probability:
≤ 3 points

4T's	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count fall > 50% and platelet nadir ≥ 20 x 10^9/L	Platelet count fall 30-50% or platelet nadir 10-19 x 10^9/L	Platelet count fall < 30% or platelet nadir < 10 x 10^9/L
Timing of platelet count fall	Clear onset between days 5-14 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5-14 fall, but not clear (e.g. missing platelet counts) or onset after day 14 or fall ≤ 1 day (prior heparin exposure 30-100 days ago)	Platelet count fall ≤ 4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis at heparin injection sites; anaphylactoid reaction after IV heparin bolus	Progressive or recurrent thrombosis; Non-necrotizing (erythematous) skin lesions; Suspected thrombosis (not confirmed)	None
oTher causes of thrombocytopenia	None apparent	Possible	Definite

Lo *J Thromb Haemost* 2006
ASH 2009 Clinical Guide

How should the 4Ts score be interpreted?



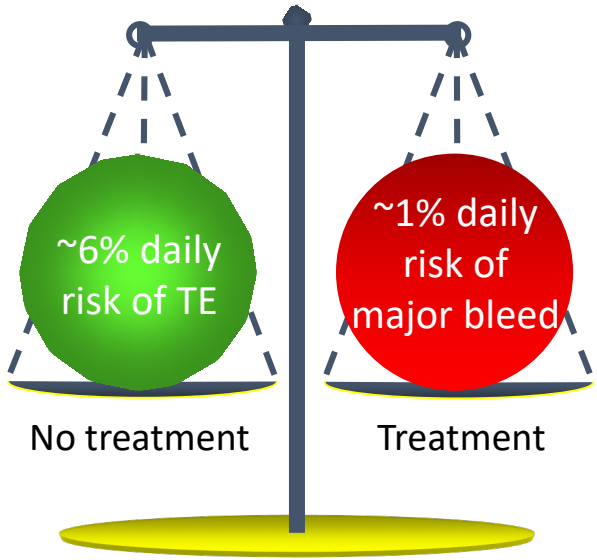
Cuker et al., Blood 2012;120:4160

Your patient's 4Ts score indicates high probability for HIT, and you have sent off the HIT ELISA (result is pending). Currently, your patient is receiving subcutaneous UFH 5,000 units twice daily.

How should you manage his anticoagulants while you are waiting for diagnostic test confirmation?

A. Continue heparin as the diagnosis of HIT is not confirmed
B. Stop heparin, wait for ELISA result
C. Stop heparin, start non-heparin anticoagulant at prophylactic intensity
D. Stop heparin, start non-heparin anticoagulant at therapeutic intensity
E. Stop heparin, provide a platelet transfusion as platelet count is only 67

To treat or not treat for HIT: A high-stakes decision



Greinacher et al., Blood 2000:96;846; Lubenow et al., JTH 2005:3;2428; Lewis et al., Chest 2006:129;1407

Recommendation.

In patients with suspected HIT and HIGH PROBABILITY 4Ts score:

- The panel recommends discontinuation of heparin and initiation of a non-heparin anticoagulant at **therapeutic intensity** *(strong recommendation, moderate certainty)*

Which of the following non-heparin anticoagulants would be appropriate at this point?

A. Argatroban
B. Rivaroxaban
C. Fondaparinux
D. Danaparoid
E. Any of the above

Recommendation.

- In patients with acute HIT, the panel *suggests* treatment with **argatroban, bivalirudin, danaparoid, fondaparinux or a direct oral anticoagulant (DOAC)**

Duration of Anticoagulation for HIT

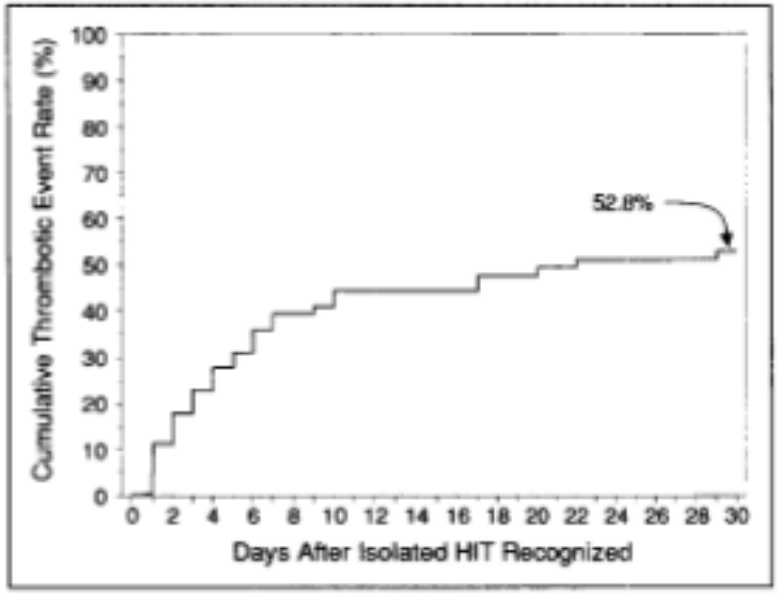


TABLE II

Thrombotic Complications of Heparin-induced Thrombocytopenia

Thrombosis Associated with Heparin-Induced Thrombocytopenia	Group I Presenting with Thrombosis (n = 65)	Group II Presenting with Isolated Thrombocytopenia (n = 62)
Patients with any venous thrombosis (n = 78)	54	24
Deep vein thrombosis (n = 61)*	40	21
New	35	21
Progression	4	0
Recurrence	1	0
Pulmonary embolism (n = 32)†	26	6
New	25	5
Recurrence	1	1
Patients with any arterial thrombosis (n = 18)	12	6
Limb artery thrombosis	7	2
Myocardial infarction	3	1
Thrombotic stroke	2	3
Other (n = 3)	1	2
Sudden death (no postmortem)	0	1
Adrenal hemorrhagic infarction‡	1	1
No thrombosis (n = 30)	Not applicable	30

Warkentin and Kelton, AJM 1996

- Procoagulant state of HIT may last 30 days or more
- Multiple guidelines (2016) suggest 4 weeks of anticoagulation for isolated HIT
- Anticoagulate for three months if thrombosis present
- Four-extremity US may diagnose unsuspected thrombosis
- Overlap non-warfarin anticoagulant with warfarin for at least 5 days if switching to warfarin to avoid warfarin-induced skin necrosis

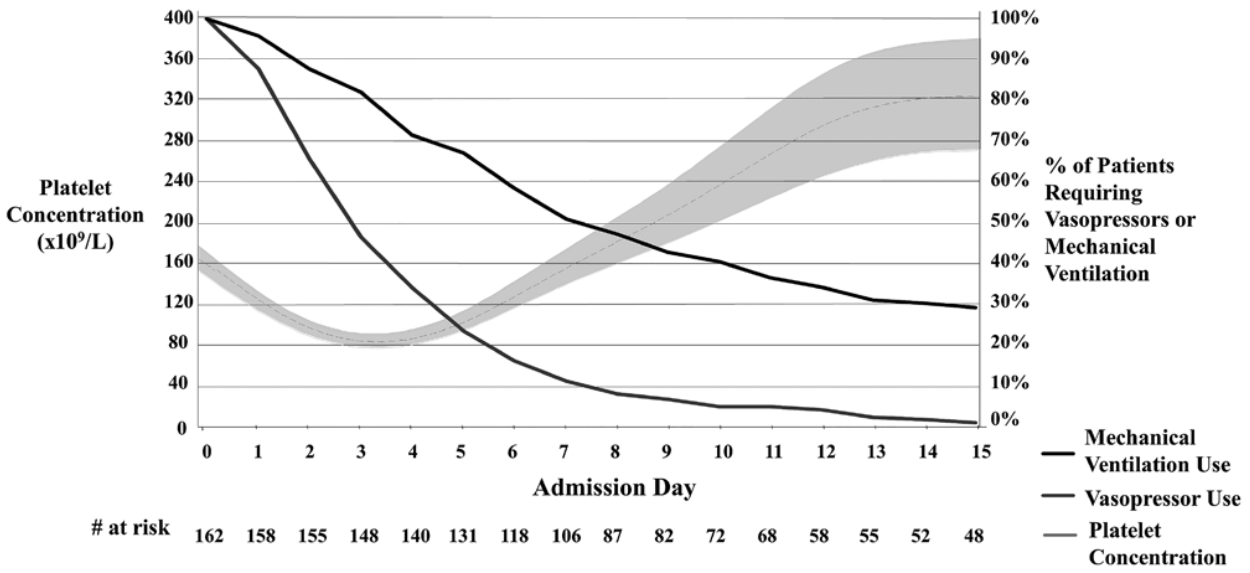
ICU Thrombocytopenia

ICU Thrombocytopenia

- Thrombocytopenia occurs in >25-65% of ICU patients
- Degree of thrombocytopenia is a major predictor of ICU mortality
- Multiple causes, usually multifactorial
  - Pseudothrombocytopenia
  - Increased platelet consumption (blood loss, massive blunt trauma, DIC, sepsis, extracorporeal)
  - Inflammatory disorders
    - Platelet aggregation due to high VWF
    - Histone mediated thrombocytopenia
    - Accelerated platelet clearance on activated vasculature
  - Platelet sequestration (spleen, liver)
  - Decreased platelet production (viruses, drugs, radiation, bone marrow infiltration, nutrient deficiency)
  - Hemodilution, massive transfusion
  - Clot thrombocytopenia
  - Platelet destruction (ITP, DITP, HIT, TMA, PTP, passive alloimmune thrombocytopenia)

Adapted from Greinacher and Selling, Blood 2007; Thachil and Warkentin, BJH 2016; Menard et al Crit Care Med, 2019

Thrombocytopenia and Sepsis Outcomes

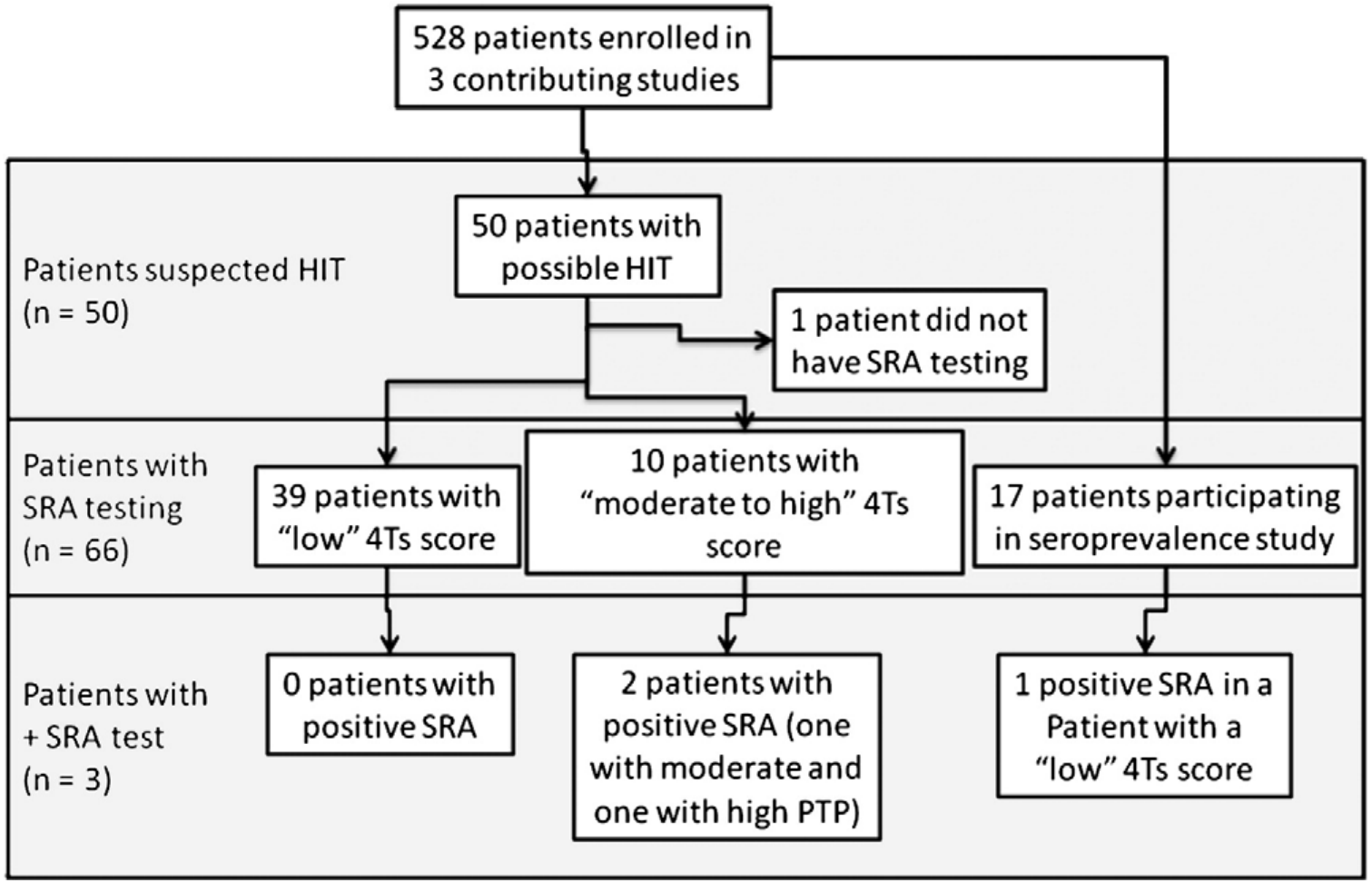


Mortality	Hazard Ratio (95% CI)	p
Hospital mortality	1.93 (1.48–2.51)	< 0.01
Hospital mortality stratified by severity of thrombocytopenia		
Mild thrombocytopenia (51–100 × 10⁹/L)	1.77 (1.31–2.39)	< 0.01
Moderate thrombocytopenia (20–50 × 10⁹/L)	2.01 (1.38–2.92)	< 0.01
Severe thrombocytopenia (< 20 × 10⁹/L)	3.49 (1.81–6.72)	< 0.01
ICU mortality	1.99 (1.51–2.63)	< 0.01
ICU mortality stratified by severity of thrombocytopenia		
Mild thrombocytopenia (51–100 × 10⁹/L)	1.83 (1.32–2.54)	< 0.01
Moderate thrombocytopenia (20–50 × 10⁹/L)	2.04 (1.38–3.00)	< 0.01
Severe thrombocytopenia (< 20 × 10⁹/L)	3.55 (1.81–6.95)	< 0.01

Cox proportional hazard model adjusted for adjusted for age, sex, Acute Physiology and Chronic Health Evaluation II score, duration of hospitalization prior to the onset of shock, number of new organ failures on day 1 of ICU admission, baseline laboratory results, preexisting comorbidities (chronic obstructive lung disease, diabetes, New York Heart Association class IV heart failure, or dialysis dependence), primary infectious organism, and the time to appropriate antibiotics.

Menard et al Crit Care Med 2019

Prevalence of HIT in Patients with ICU Thrombocytopenia



- Patients derived from three ICU thromboprophylaxis studies
- 17 patients from one study used for seroprevalance study
- Patients investigated for HIT if they had a platelet count drop to <50,000, >50% drop in platelet count, or high suspicion of clinical team
- ELISAs performed in local hospital, SRA in referral lab
- 50/528 prompted evaluation for HIT
- Overall incidence of HIT, based on SRA positivity was 2/527 (0.4%), or 2/49 suspected cases (4%)
- HIT is a rare cause of thrombocytopenia in ICU settings

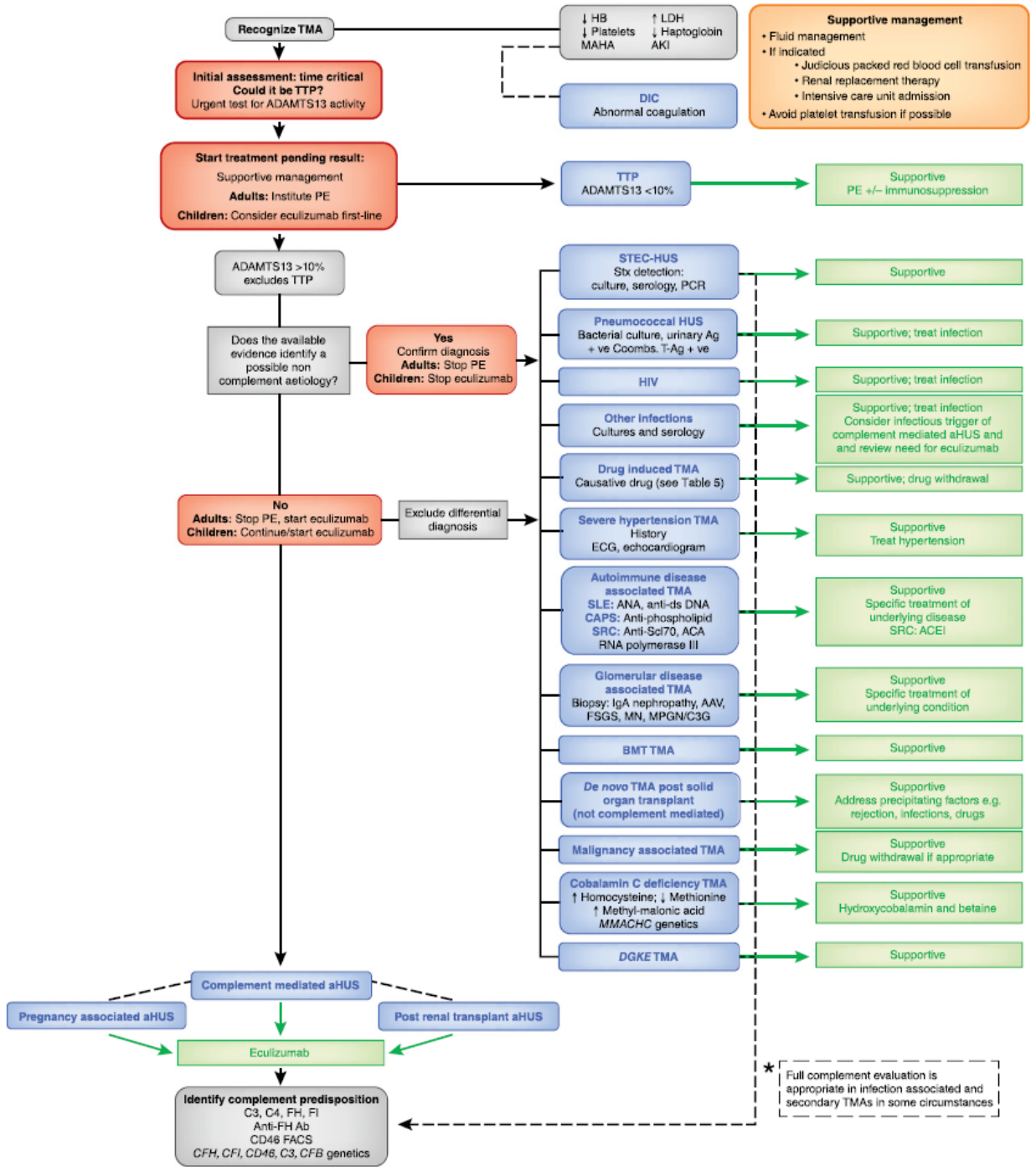
Crowther et al, J Crit Care 2010

Thrombotic Microangiopathies

Diagnosis of TMA

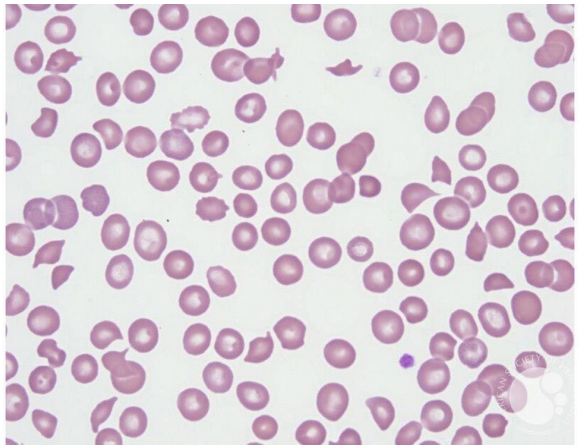
General Approach to TMA Diagnosis and Treatment

- Recognize TMA
- Send ADAMTS13 studies
- Start treatment-usually PLEX in adults
- Review ADAMTS13 results when available; if > 10%...
  - Secondary TMA—identify primary cause
  - IA-HUS
  - CM-HUS
- Alter therapy if appropriate

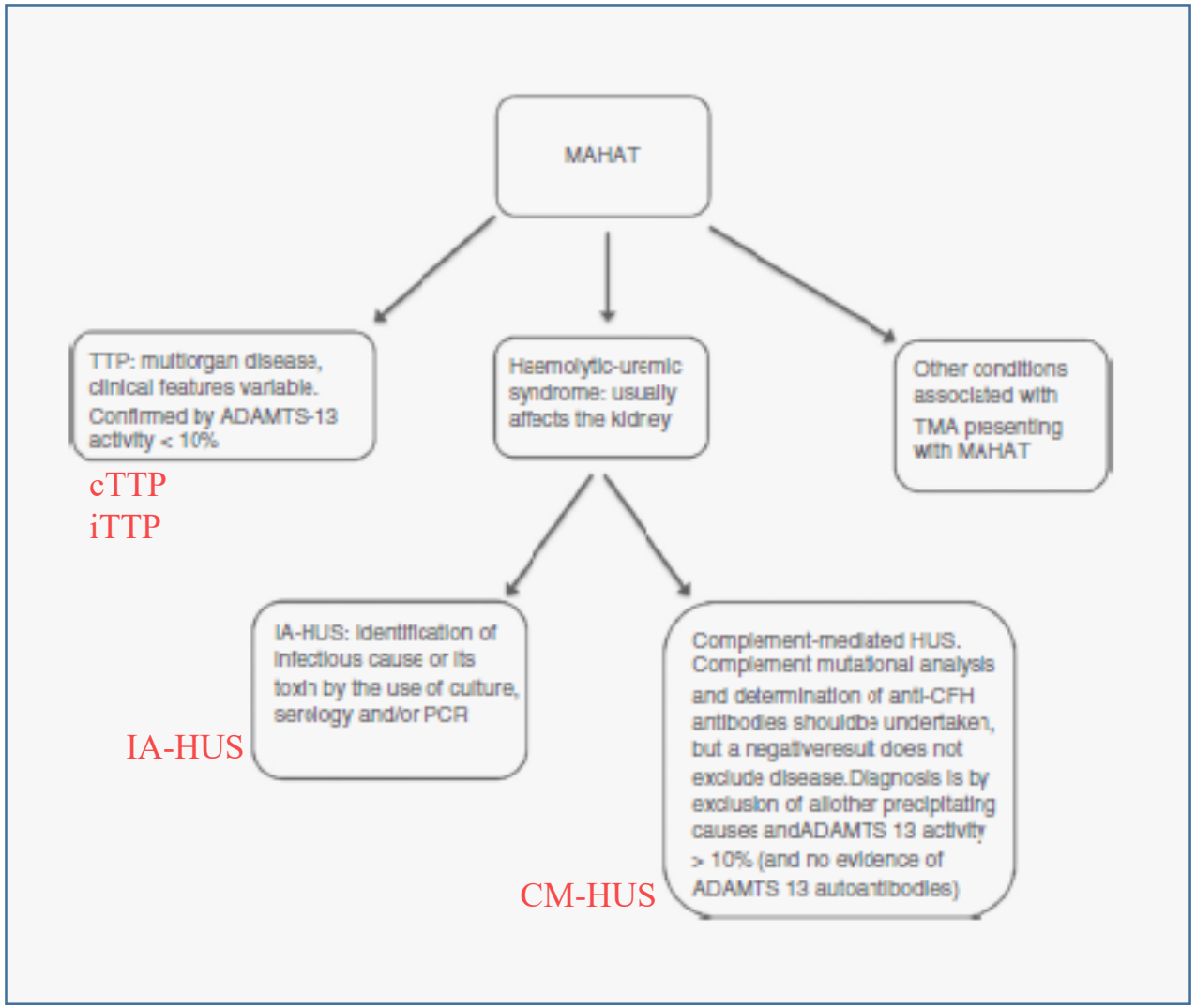


Brocklebank et al, CJASN, 2018

ISTH IWG: Terminology for TMAs



ASH Image Bank 00060307; Teresa Scordino

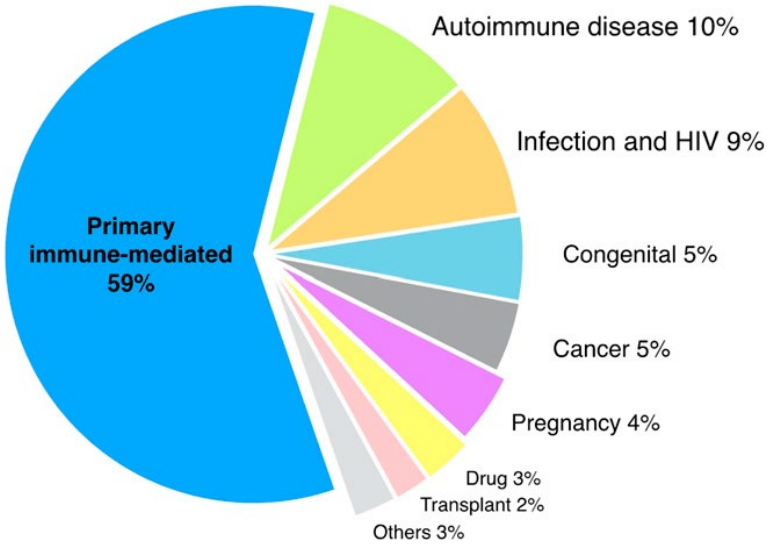


Scully et al JTH 15:312, 2017

- *TTP = immune (iTTP) or congenital (cTTP)*
- *Shigatoxin-associated HUS (IA-HUS)*
- *Atypical (aHUS) = complement-mediated (CM-HUS)*

Thrombotic Thrombocytopenic Purpura (TTP)

- Epidemiology
  - Prevalence = 10 cases per million
  - Incidence = 1-2 new cases per million (immune), < 1 per million (inherited)
- Milestones
  - First described by Moschowitz in 1924
  - Efficacy of plasma exchanged noted in 1977 by Bukowski
  - UL-VWF described in 1982 by Moake
  - 1996-VWF cleaving protease isolated from plasma
  - 2001-VWF cleaving protease identified as ADAMTS13
- Three broad categories
  - Inherited (cTTP)—due to biallelic mutations of ADAMTS13 gene (5%)
  - Primary immune (iTTP, aTTP)—due to autoantibodies to ADAMTS13 (60%)
  - Multiple secondary forms associated with other disorders
- Pathogenesis involves multi-organ dysfunction due to microvascular ischemia
  - Brain, heart, pancreas, kidneys
  - Significant diversity among patients
  - Triggering factors implicated but not well characterized



Chiasakul and Cuker, Hematology 2018

Clinical and Laboratory Findings in TTP

Table 2. Clinical and laboratory findings in TTP[2-7,12]

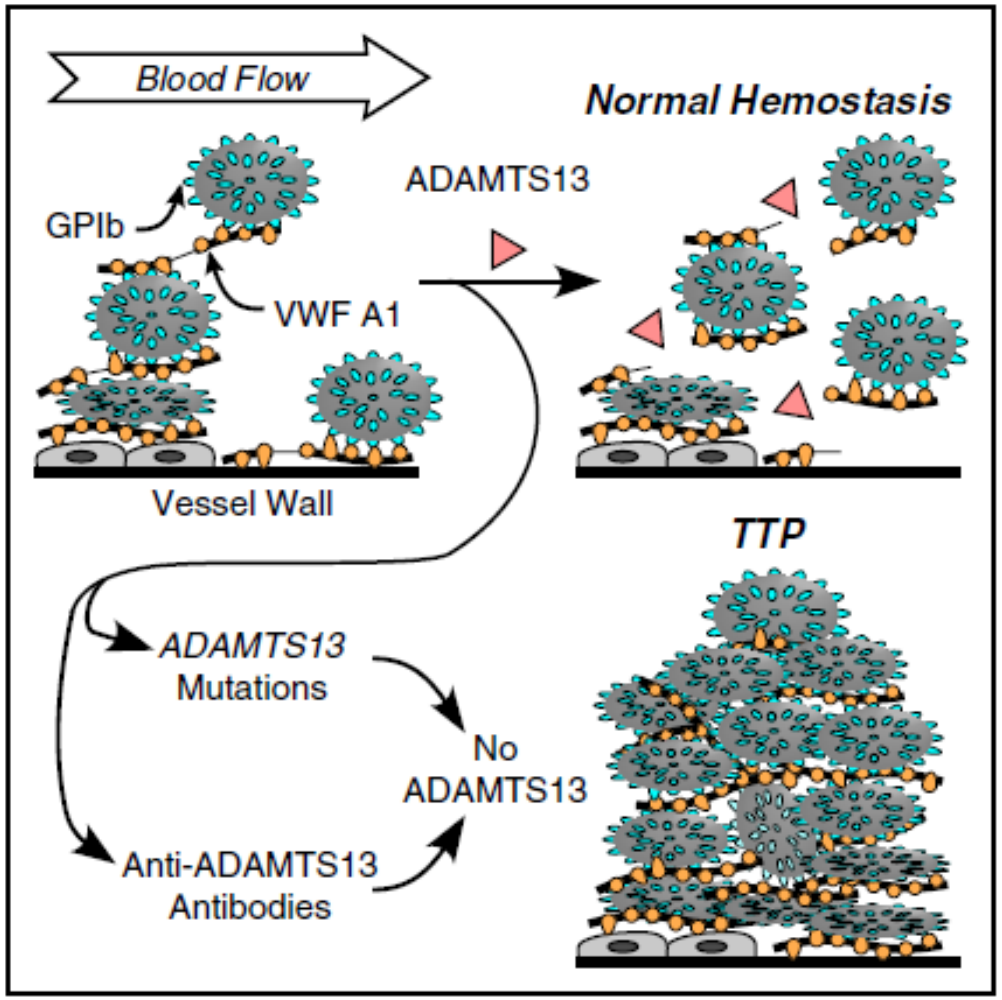
	Frequency (%)
Clinical presentation, %	
MAHA with thrombocytopenia	100
Neurological abnormalities	39-80
Major	18-53
Minor	27-42
Fever	10-72
Gastrointestinal symptoms	35-39
Renal involvement	10-75
Classic pentad*	7
Laboratory findings	
Median platelet count, $\times 10^9$/L	10-17
Median creatinine, μmol/L	0.96-1.42
Median LDH, U/L	1107-1750
Median hematocrit, %	20-27

LDH, lactate dehydrogenase.
*MAHA, thrombocytopenia, neurological abnormalities, fever, and renal dysfunction.

MAHA and thrombocytopenia without another apparent cause is sufficient to make the diagnosis

Chiasakul and Cuker, Hematology 2018

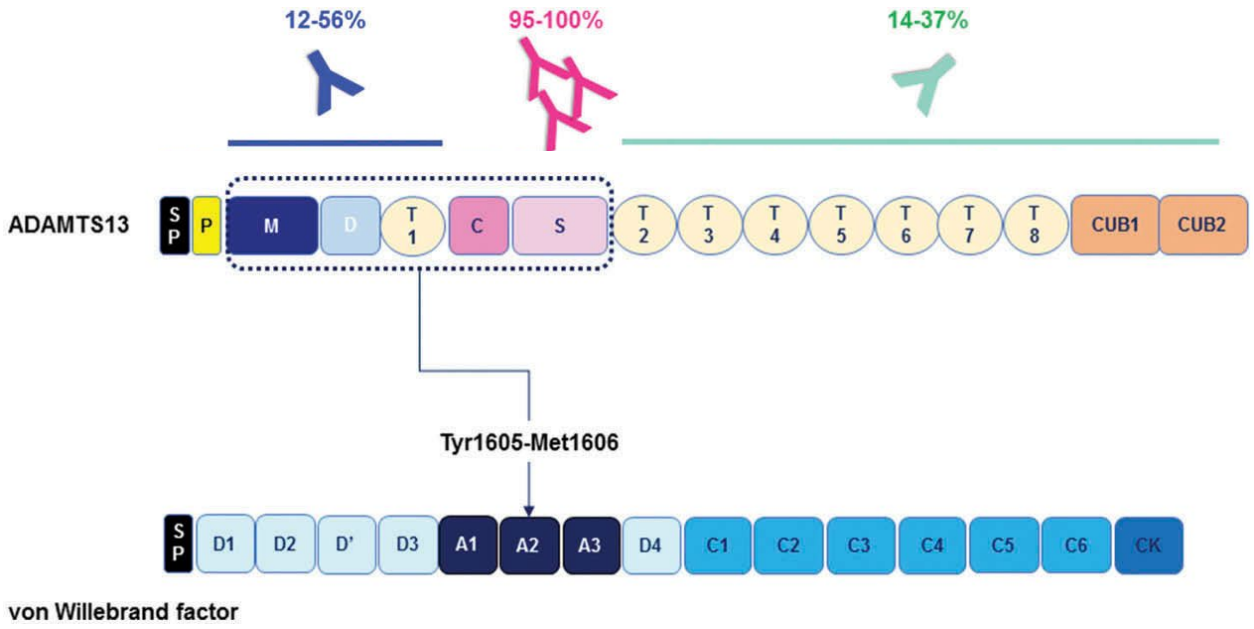
TTP: Pathogenesis



- *ULVWF normally cleaved by ADAMTS13 upon secretion for the endothelial cell*
- *Lack of ADAMTS13, either through inhibition or inherited deficiency, allows VWF-induced platelet agglutination and microvascular thrombosis*
- *Additional triggers of an acute TTP are needed, but these have not been well characterized*

Sadler JE. Blood 130:1181, 2017

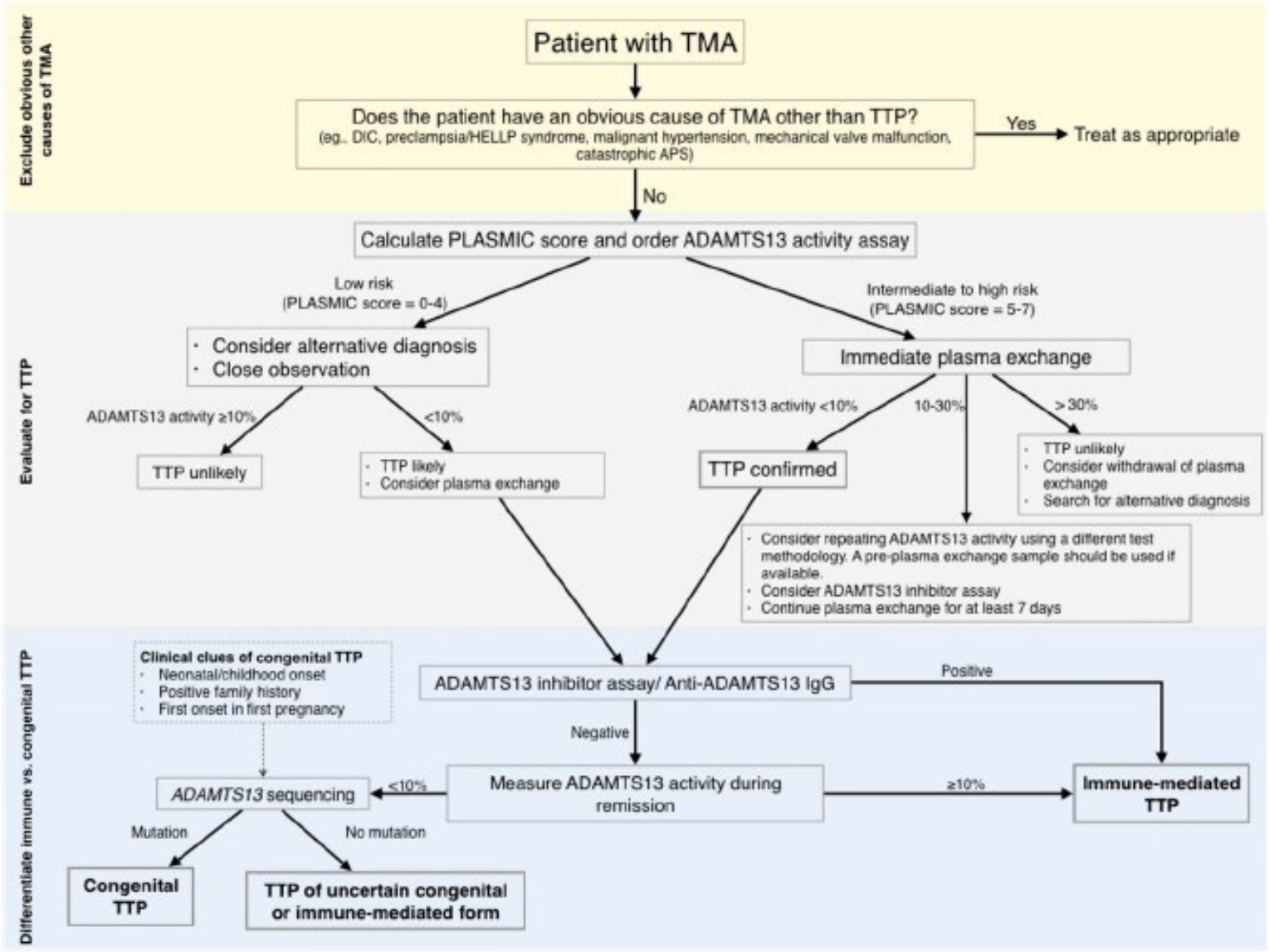
ADAMTS13 VWF Interactions/Autoantibodies



Modified from Joly Exp Rev Hematol, 2019

- Most commonly IgG, some may be IgA or IgM
- IgG subclasses 1 and 4
- IgG1 and IgA associated with higher death rate, IgG4 with higher risk of relapse
- May be neutralizing or non-neutralizing
- 95% of patients have anti-spacer domain antibodies
- 20-25% of patients do not have detectable in acute phase (sensitivity, IgA isotype, other)

Approach to Diagnosis of TMA/TTP



Chiasakul and Cuker, Hematology 2018

The Plasmic Score Predicts ADAMTS13 Activity

MAHA
Thrombocytopenia
~~**Neurologic dysfunction**~~
~~**Fever**~~
~~**Renal disease**~~

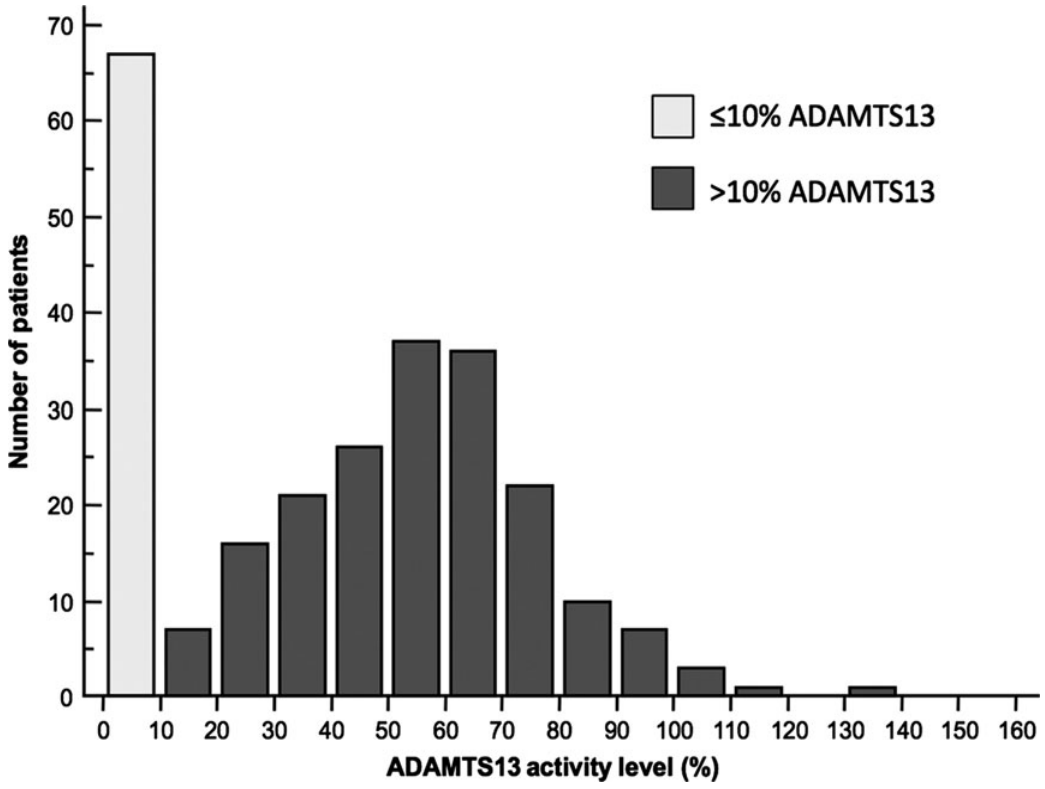
*The PLASMIC Score for TTP Prediction	
Component	**Point**
Platelet count <30 x 10^9 per L	1
HemoLysis (indirect bilirubin >2 mg/dL, uncorrected reticulocyte > 2.5%, OR undetectable haptoglobin)	1
No Active cancer in previous year	1
No history of Solid-organ or Stem-cell transplant	1
MCV <90 fL	1
INR <1.5	1
Creatinine <2.0 mg/dL	1

Score	Risk Category	ADAMTS13 ≤ 10%
0-4	Low	4.3%
5-6	Intermediate	56.8%
7	high	96.2%

- TTP working definition = MAHAT with no other apparent cause
- ADAMTS13 ≤ 10% drawn prior to PLEX is diagnostic

Bendapudi et al Lancet Haem 4:e157, 2017

Harvard TMA Research Collaborative:ADAMTS13 Testing

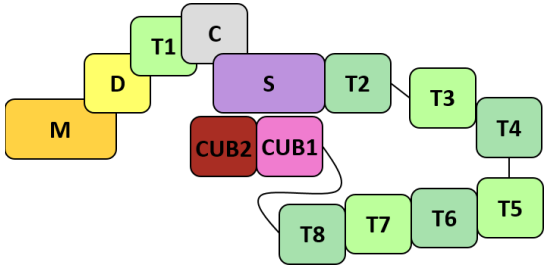


Bendapudi et al, BJH 2015

- 254 patients with ADAMTS13 testing for suspected TTP at three Harvard hospitals
- ADAMTS13 level < 10% in only 68 (27%)
- Higher incidence of <10% in younger, female, non-Caucasian
- Sensitivity 97%, specificity 100% based on response to PLEX
- Diagnoses in patients with ADAMTS13 >10%
  - DIC--40% (sepsis, cancer, pancreatitis, other)
  - Transplant-related--14%
  - Drug-associated--8.1%
  - Multifactorial—7.5%
  - Autoimmune—7%
  - HUS—6.5%
  - Hypertensive emergency—5.4%
  - Other TMA—4.8%
  - Pregnancy related—1.6%
  - Autoimmune TTP—1.1% (two patients, 15% and 92%)
  - Disseminated cancer—1.1%
- Outcomes
  - <10%: shorter hospitalization, more rapid platelet recovery, better survival (90 day-95% vs 57%; 360 day 93% vs 47.5%)

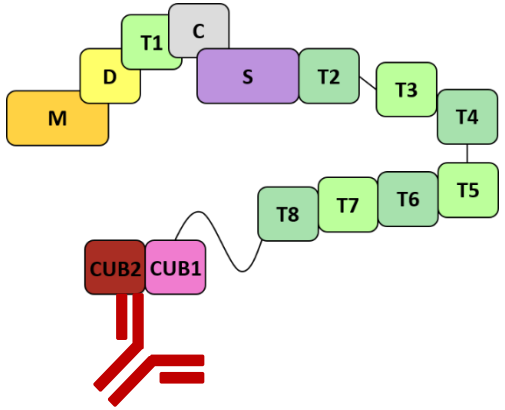
iTTP patient in acute phase

Folded ADAMTS13



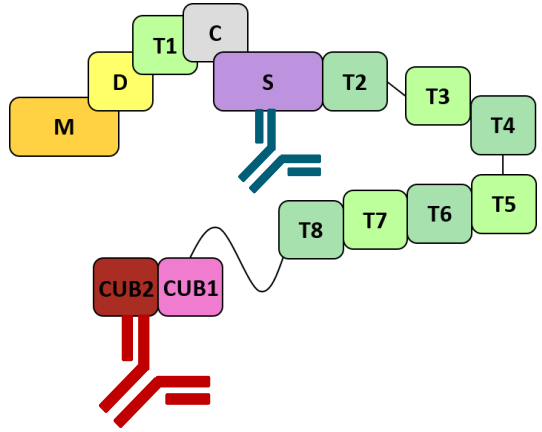
Opening Abs

Open ADAMTS13



Cryptic Abs

Inhibition/clearance of ADAMTS13

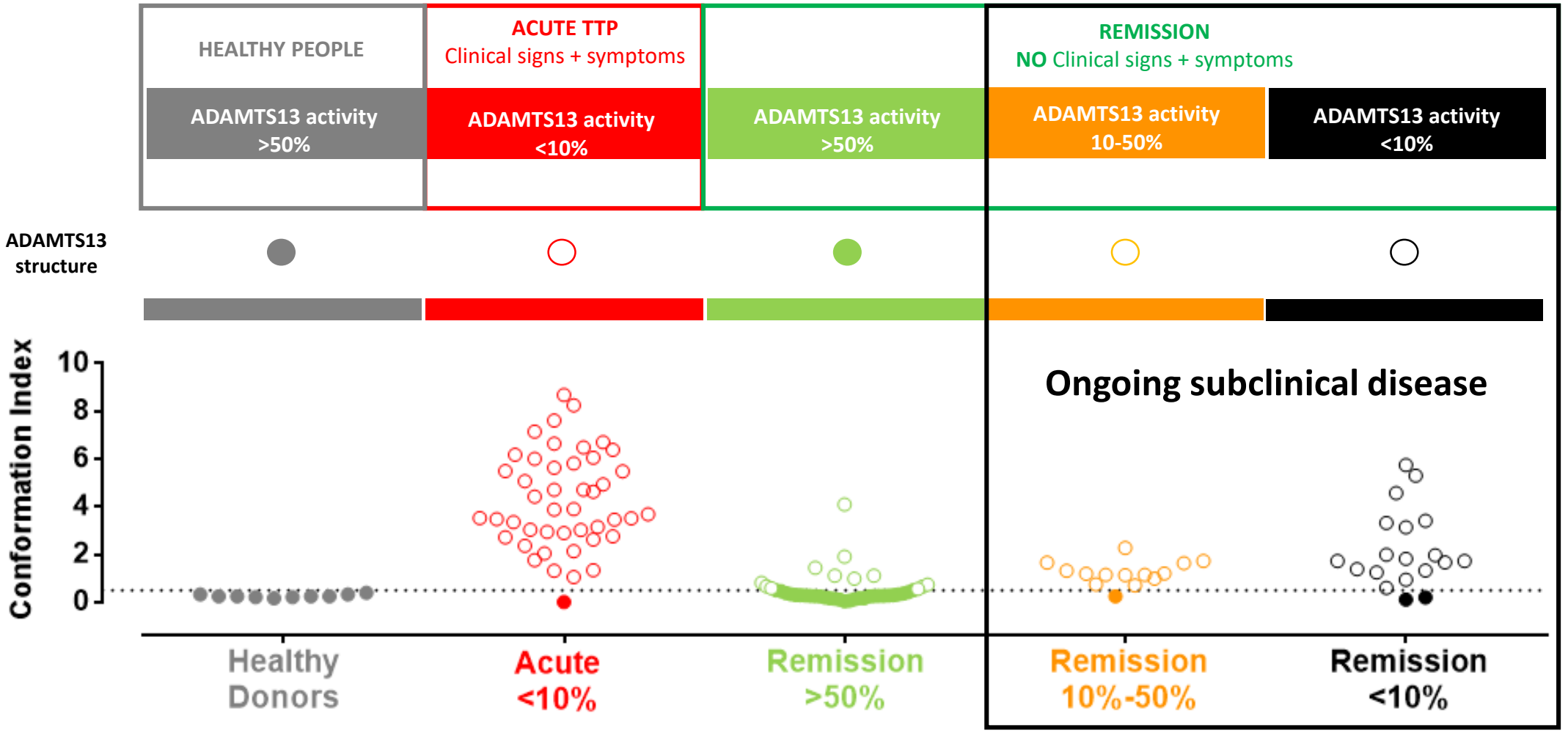


→ Explains how cryptic antibodies can inhibit ADAMTS13 activity
→ Explains formation of immune complexes and clearance of ADAMTS13
→ Rationale for targeted therapy: blocking opening antibodies

ADAMTS13 Conformation in iTTP

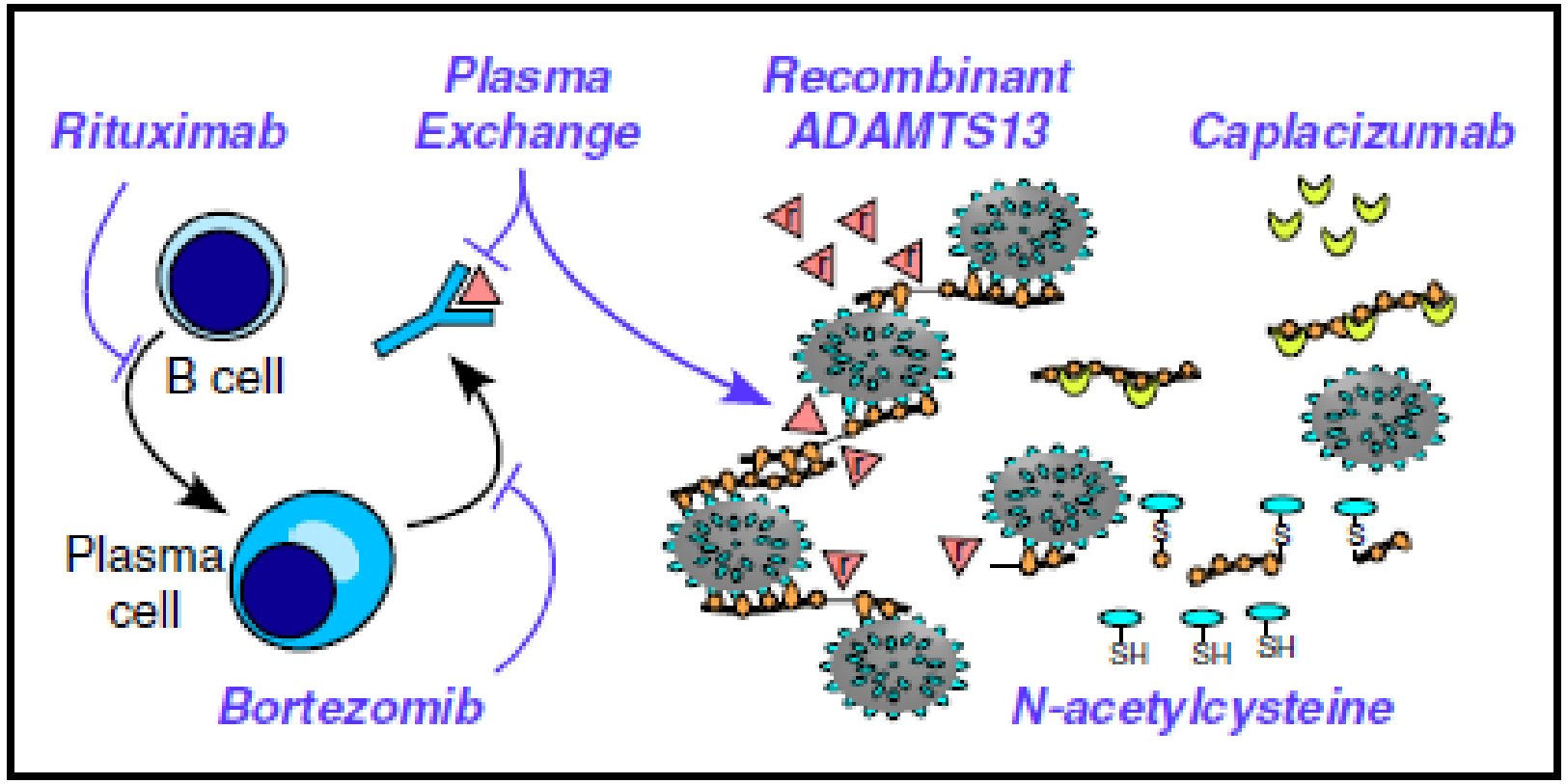
Folded ADAMTS13 ●

Open ADAMTS13 ○



Roose, Schelpe et al., unpublished

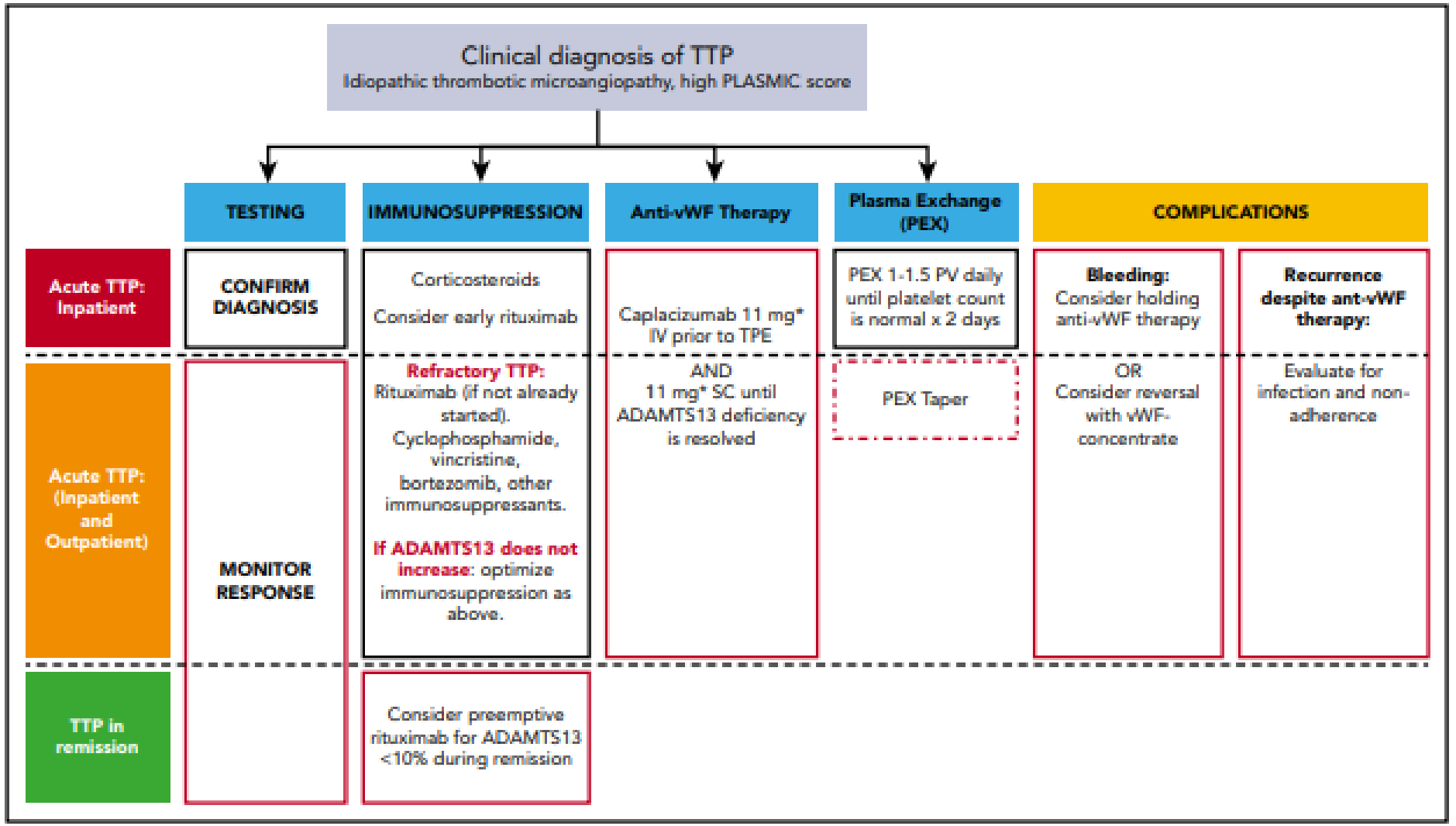
Mechanism-based therapy of iTTP



- *PLEX: remove autoantibody, provide ADAMTS13*
- *Rituximab: removes antibody-producing B cells*
- *Bortezimib: removes antibody-producing plasma cells*
- *Caplacizumab: nanobody that binds VWF A1 domain and blocks interaction of VWF with platelets (GPIbα)*
- *N-acetylcysteine: reduces disulfide bonds in VWF and prevents assembly of ULVWF*

Sadler JE. Blood 130:1181, 2017

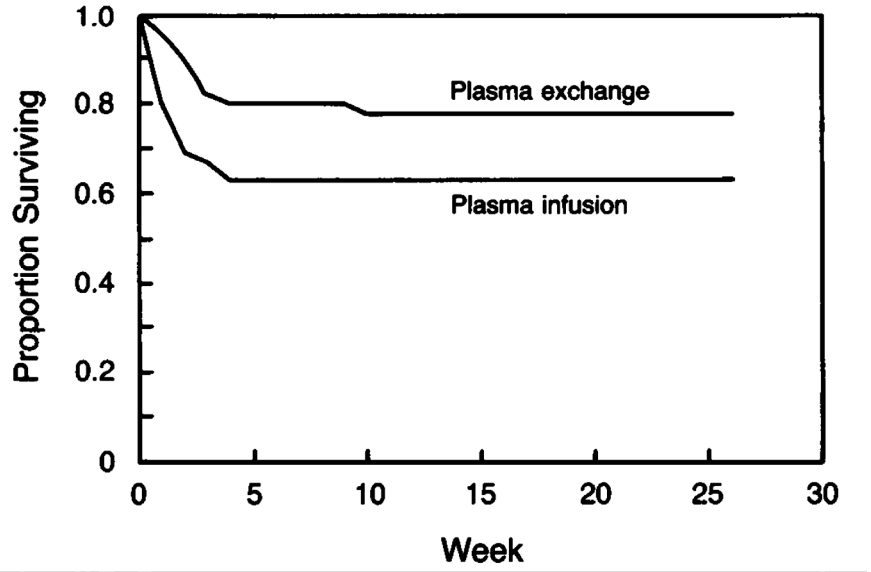
Approach to the Treatment of TTP



Mazepa and Chaturvedi, Blood 2019

Plasma Exchange in TTP

- Efficacy of plasma therapy first noted in 1977
- Plasma exchange remains first line treatment for TTP (with steroids)
- Increases survival rates to >80%
- Mechanism: removal of ADAMTS13 inhibitors, replacement of ADAMTS13
- Rock et al (NEJM 1991): Compared to plasma infusion, increases response rates and significantly increases survival (78% vs 50% at six months)
- Standard of care not well established
  - Optimal regimen not established—no direct comparative studies
  - Most continue for two days after platelet count normalization
  - Superiority of tapering versus abrupt discontinuation not proven
  - FFP, SD-treated plasma, psoralens-treated plasma all effective
  - Cryo-poor plasma may be tried in refractory patients, but no conclusive data as to whether it is more efficacious than FFP
- Increased use of rituximab, caplacizumab, rADAMTS13 likely to reduce duration and use of PLEX in future
- Plasma alone may be used to temporize when PLEX not available



Rock et al NEJM, 1991

Hercules Trial

- Eligibility: Clinical diagnosis of TTP with one plasma exchange performed
- Randomized, double-blind placebo-controlled: PLEX + caplacizumab vs PLEX + placebo
- Dosing: Caplacizumab 10 mg IV prior to first PLEX after randomization, then 10 mg subq daily until 30 days after last PLEX
- Primary endpoint: Time from first treatment with caplacizumab or placebo to first normal platelet count
- Four key secondary outcomes:
  - Composite of TTP-related death, recurrence of TTP or major thromboembolic event during trial period
  - Recurrence of TTP at any point during the trial, including the follow up period
  - Refractory TTP: lack of doubling of the platelet count within four days of starting treatment and LDH above ULN
  - Time to normalization of three organ damage markers: cardiac troponin, LDH, creatinine

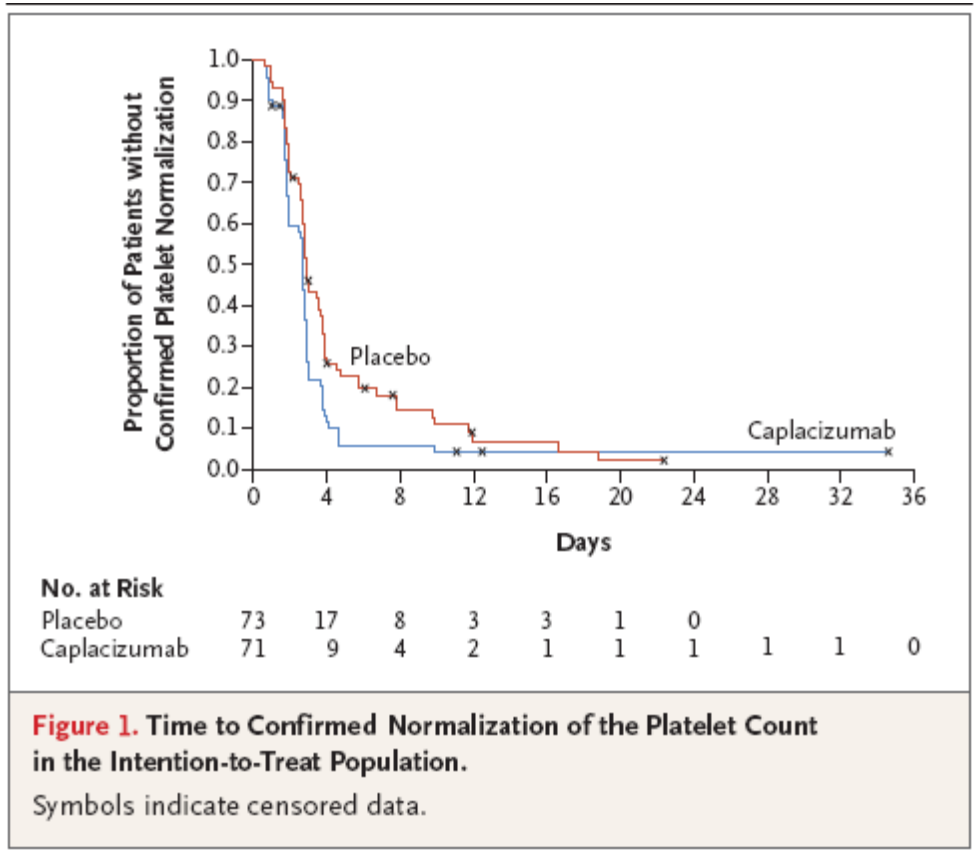


Figure 1. Time to Confirmed Normalization of the Platelet Count in the Intention-to-Treat Population.

Symbols indicate censored data.

HR 1.55; 95% CI 1.09-2.19; P = 0.01

Scully et al, NEJM 2019

Hercules Trial

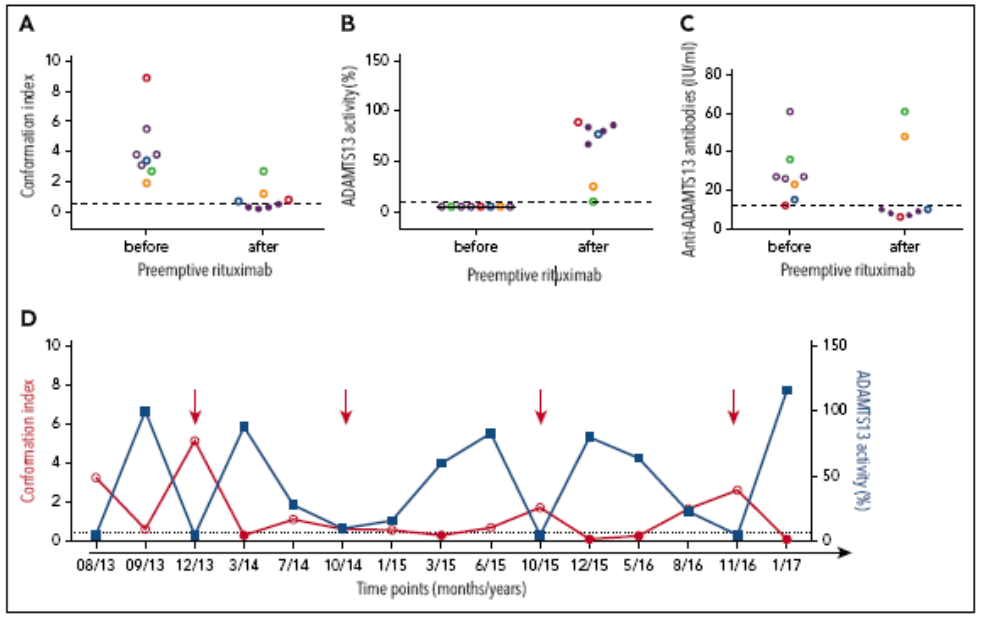
Table 2. Primary and Secondary Efficacy Outcomes in the Intention-to-Treat Population.

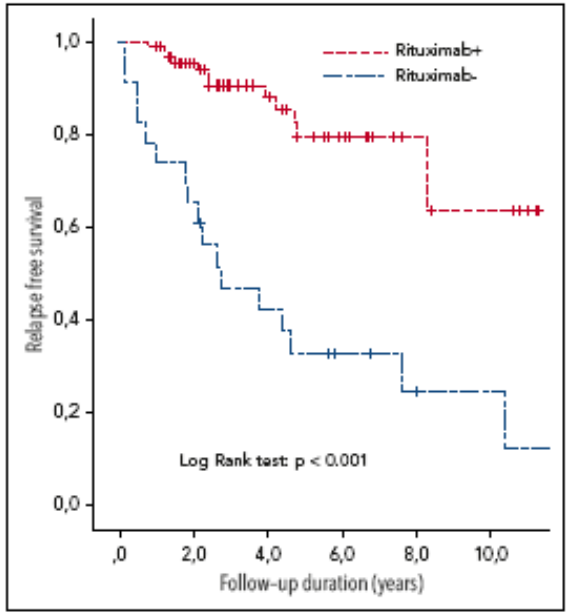
Outcome	Caplacizumab (N=72)	Placebo (N=73)	P Value
Primary outcome			
Time to normalization of platelet count			
25th Percentile (95% CI) — days	1.75 (1.65–1.87)	1.94 (1.70–2.64)	
50th Percentile (95% CI) — days	2.69 (1.89–2.83)	2.88 (2.68–3.56)	
75th Percentile (95% CI) — days	2.95 (2.85–3.81)	4.50 (3.78–7.79)	
Rate ratio for normalization of platelet count, caplacizumab vs. placebo (95% CI)*	1.55 (1.09–2.19)		0.01
Key secondary outcomes			
Composite of TTP-related death, recurrence of TTP, or major thromboembolic event during the double-blind treatment period — no. (%)	9 (12)	36 (49)	<0.001
TTP-related death	0	3 (4)	
Recurrence of TTP: exacerbation†	3 (4)	28 (38)	
Major thromboembolic event	6 (8)	6 (8)	
Recurrence of TTP at any time during the trial — no. (%)†	9 (12)	28 (38)	<0.001
During the double-blind treatment period: exacerbation	3 (4)	28 (38)	
During the follow-up period: relapse‡	6 (8)	0	
Refractory TTP — no. (%)§	0	3 (4)	0.06
Median time to normalization of organ-damage markers (95% CI) — days	2.86 (1.93–3.86)	3.36 (1.88–7.71)	
Other secondary outcomes¶			
Number of days of plasma exchange			
Mean (95% CI)	5.8 (4.8–6.8)	9.4 (7.8–11.0)	
Median (range)	5.0 (1.0–35.0)	7.0 (3.0–46.0)	
Volume of plasma exchanged — liters			
Mean (95% CI)	21.3 (18.1–24.6)	35.9 (27.6–44.2)	
Median (range)	18.1 (5.3–102.2)	26.9 (4.0–254.0)	
No. of days of hospitalization			
Mean (95% CI)	9.9 (8.5–11.3)	14.4 (12.0–16.9)	
Median (range)	9.0 (2.0–37.0)	12.0 (4.0–53.0)	
Patients admitted to the intensive care unit — no. (%)‖	28 (39)	27 (37)	
No. of days in the intensive care unit			
Mean (95% CI)	3.4 (2.6–4.2)	9.7 (5.3–14.1)	
Median (range)	3.0 (1.0–10.0)	5.0 (1.0–47.0)	

Major toxicity = bleeding

- Placebo = 35 (48%), caplacizumab = 46 (65%)
- 4 severe, 3 in caplacizumab, 1 placebo
- Bleeding SAEs in 11% caplacizumab, 1% placebo

Preemptive Rituximab Prevents TTP Relapse



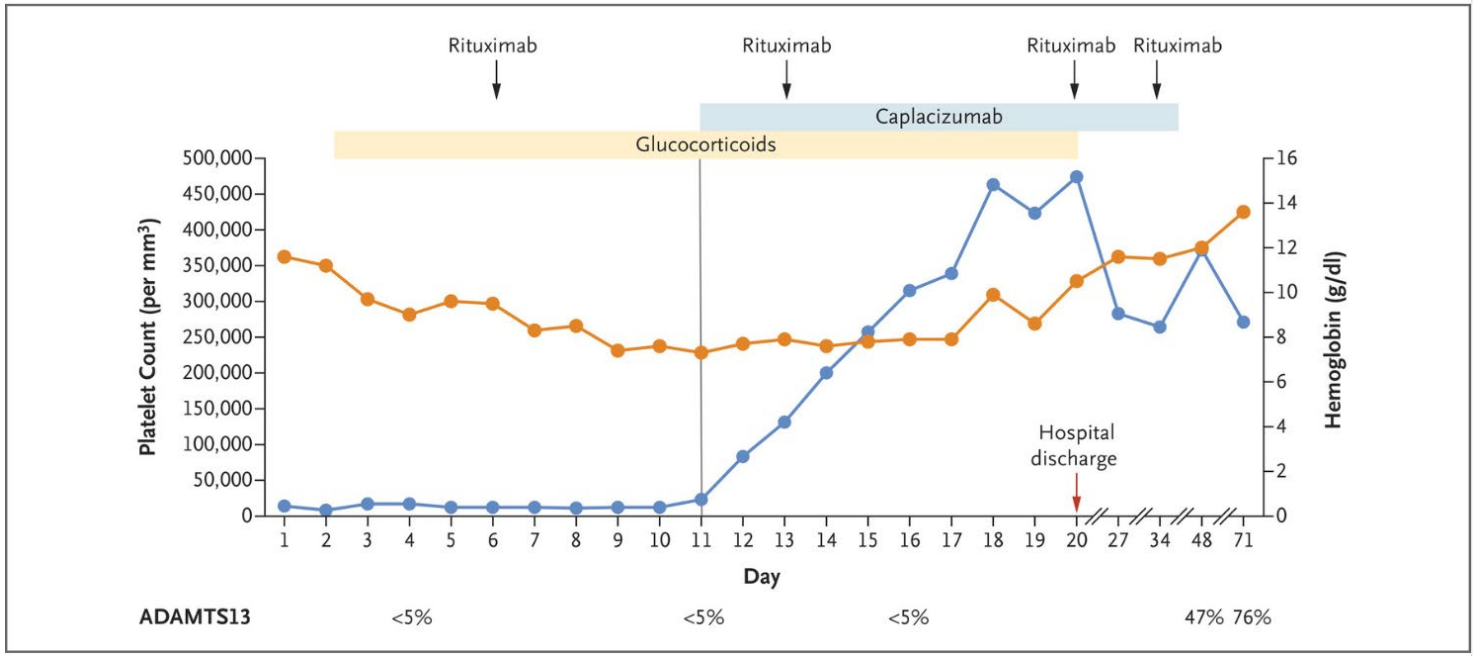


Jestin et al, Blood 2018

Measure	Total (N = 76)			Standard dose (n = 24)			Reduced dose (n = 19)			Intermediate dose (n = 17)			Other doses (n = 16)		
	n/N	%	Months (range)	n/N	%	Months (range)	n/N	%	Months (range)	n/N	%	Months (range)	n/N	%	Months (range)
No. of patients in CR (ADAMTS13 ≥60%)	60/76	78.9		18/24	75		16/19	84.2		12/17	70.6		14/16	87.5	
No. of patients in PR (ADAMTS13 30%-59%)	10/76	13.2		3/24	12.5		2/19	10.5		4/17	23.5		1/16	6.25	
No. of patients achieving at least a PR (ADAMTS13 ≥30%)	70/76	92.1		21/24	87.5		18/19	94.7		16/17	94.1		15/16	93.4	
Time to ADAMTS13 recovery			1 (<1-5)			1 (<1-5)			2 (<1-4)			1 (<1-3)			2 (<1-4)
Median overall follow-up			15 (1-141)			17.5 (1-141)			25 (9-43)			10 (3-20)			21 (3-112)
No. of patients requiring re-treatment	38/76	50		12/24 *	50		14/19 *	73.7		3/17	17.6		10/16	62.5	
Re-treatment episodes per year	0.25			0.17†			0.38†			0.20			0.29		

Westwood et al, Blood Adv 2017

Treatment of Acute TTP without PLEX



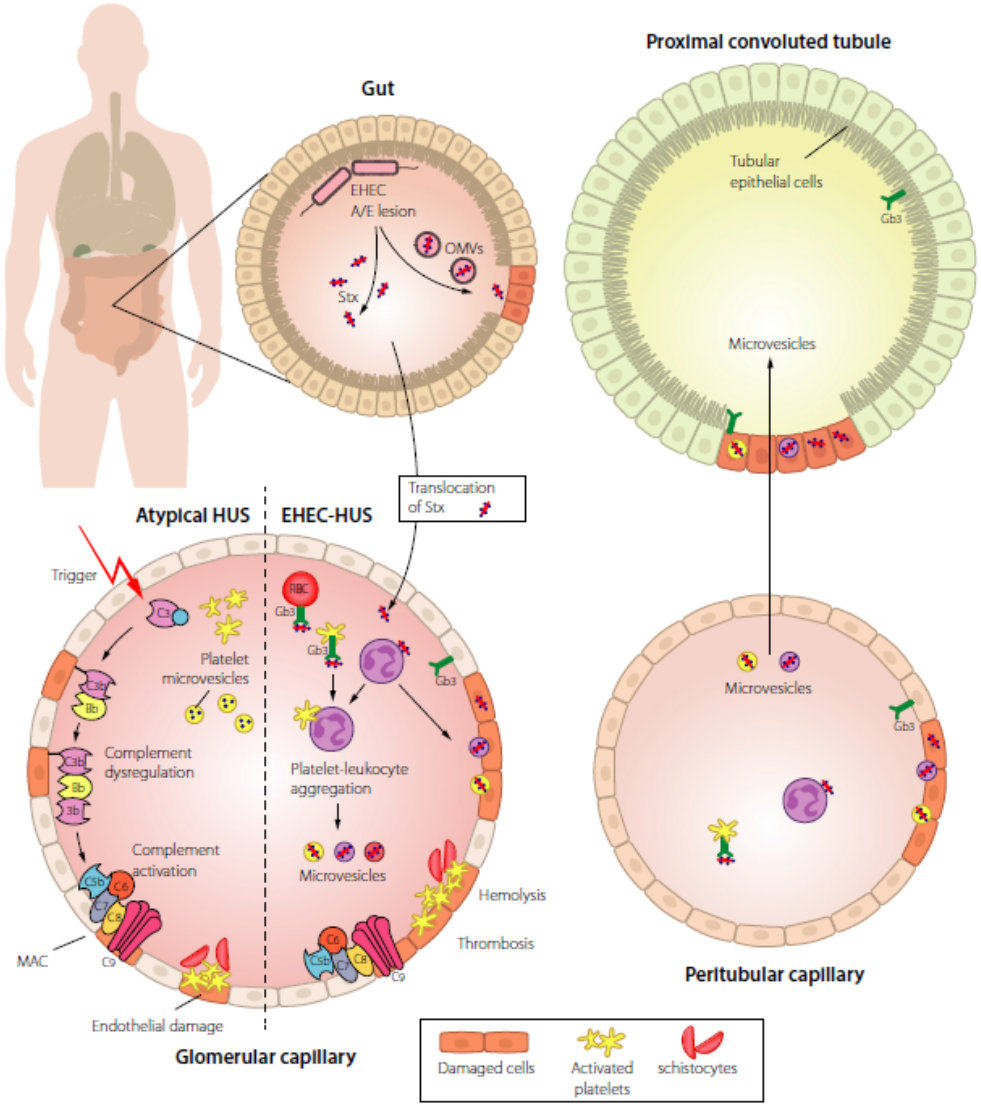
- 63 yo woman (Jehovah's witness) with new onset purpura and platelet count 14,000
- Initially treated for ITP with dexamethasone: no response
- Day 2: haptoglobin < 30, LDH 605
- Day 4: ADAMTS13 < 5%,
- Treated with corticosteroids, rituximab, Koate DVI
- Continued progressive neurologic symptoms, facial droop: caplacizumab requested on day 7, approved on day 11 (platelet count 23,000)
- Day 12: resolution of neurologic symptoms, platelet count 83,000
- Afterward-continued rise in platelet count, discharge on day 20, total 40 days of caplacizumab
- Recovery of ADAMTS13 activity by day 34

Chander et al NEJM, 2019

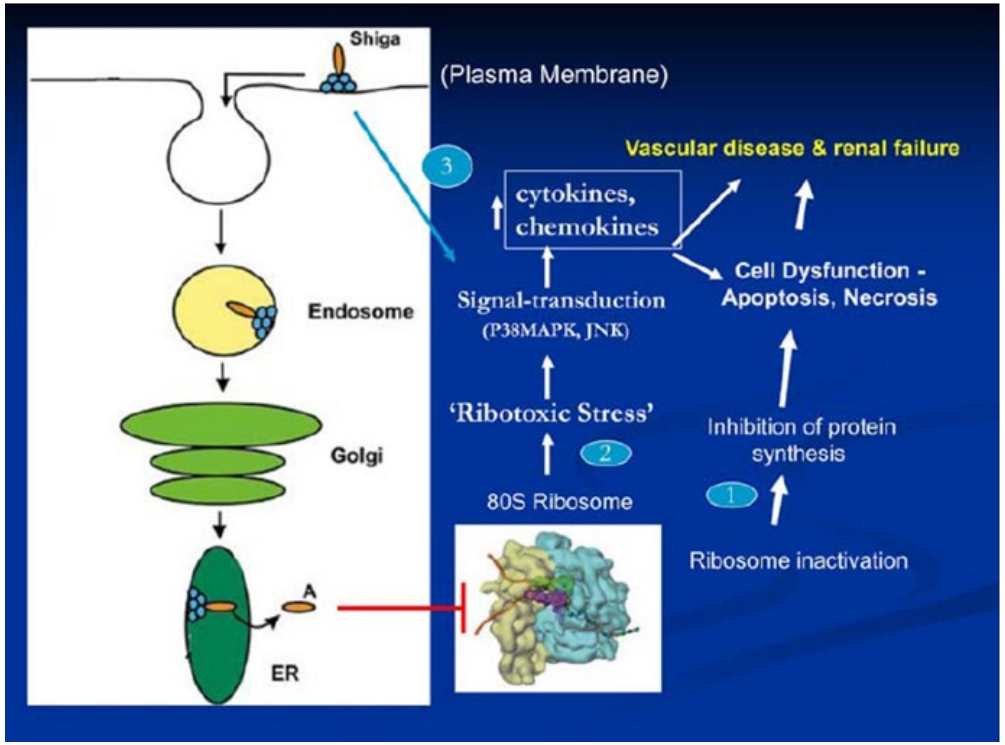
IA HUS (STEC HUS)

- Occurs following exposure to shigatoxin producing organisms (e.g. E. Coli O157:H7)
  - Enterohemorrhagic E. Coli (EHEC) most common, including O157:H7, 026, 0104, 0111, 0103, 0145, 0121, 0145
  - Also Shigella dysenteriae type I, Citrobacter
- Other agents, different mechanisms
  - *S pneumoniae*
  - Influenza A (H1N1)
  - Enteroviruses (Coxsackie A, B, Echo), HIV
  - *Pseudomonas aeruginosa*
- Epidemiology
  - Large or small outbreaks, or sporadic; overall incidence 2/100,000
  - Most common in children < 5 y.o, or elderly
  - Sources: uncooked meat, vegetables, unpasteurized juice or milk, water, person to person, animals
- Disease course
  - EHEC infection followed by 4 day incubation period
  - Onset of diarrhea, often bloody
  - Development of HUS within 2-12 days after diarrhea onset
- Dx: stool culture, stool toxin, PCR for EHEC virulence genes, serology (LPS/adhesins)
- Treatment
  - Supportive care, dialysis may be needed
  - Antibiotic therapy-not recommended
  - Plasma exchange--no change in CKI or survival
  - Eculizumab—generally no response, but anecdotal improvement in certain extrarenal manifestations

Pathogenesis of IA-HUS

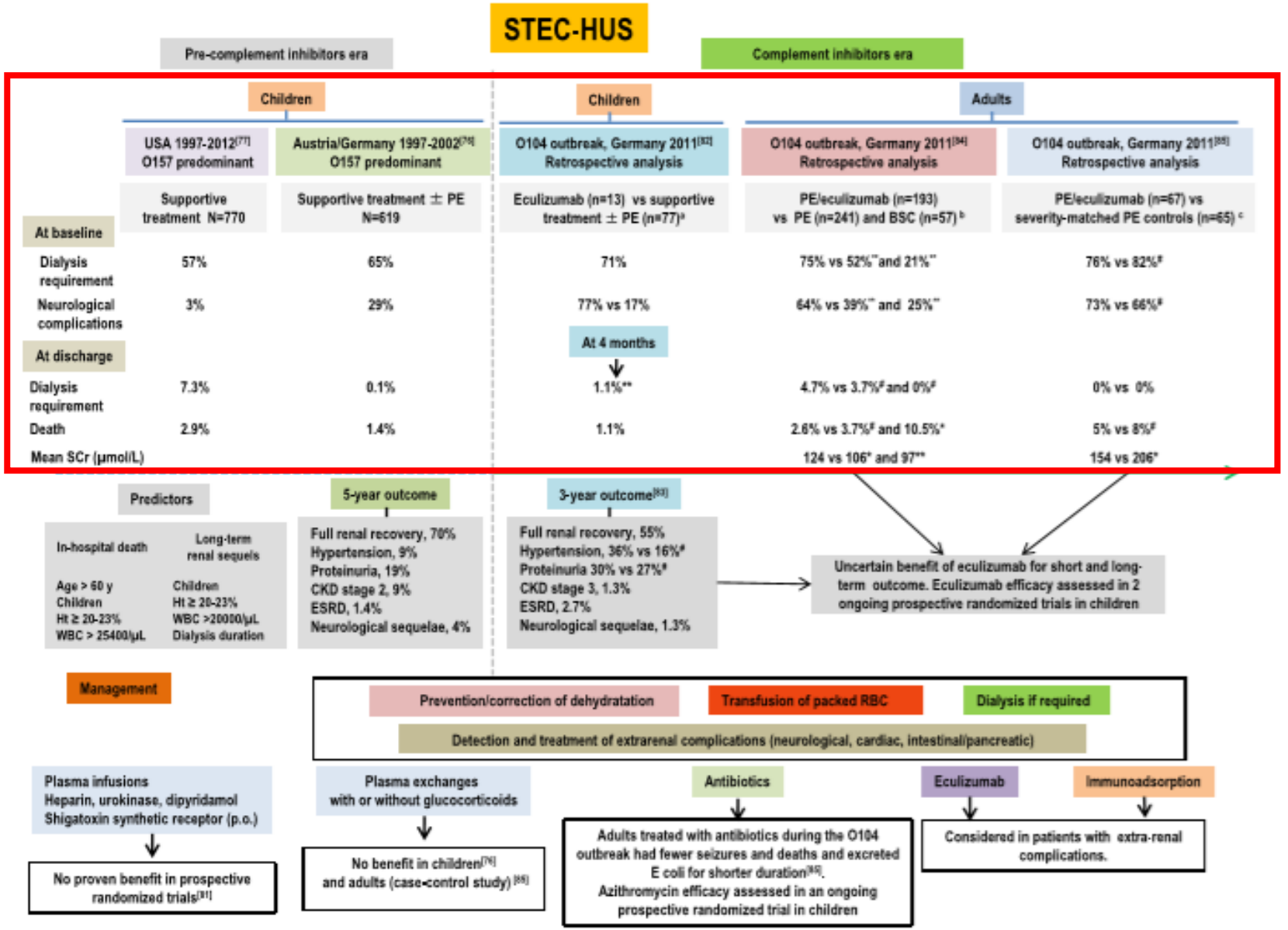


Karpman et al. J. Int Med, 2017



Obata and Obrig, Microbiol Spectrum, 2014

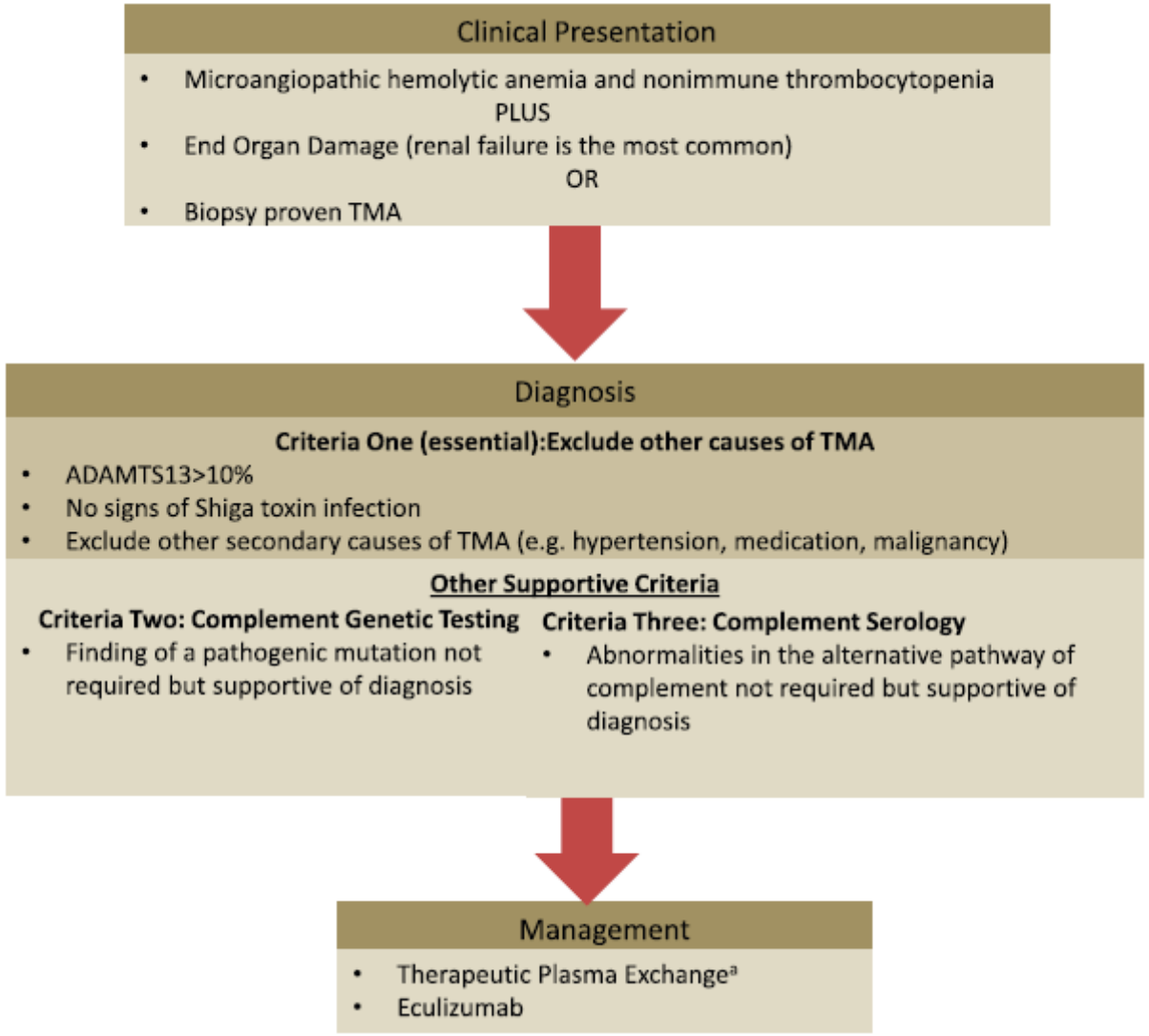
Outcomes of IA-HUS Before and After Eculizumab



Fakhouri and Loirat, Sem Hematol, 2018

- *Eculizumab does not appear to increase survival or improve renal outcomes in IA-HUS in retrospective analyses*
- *Randomized trials in progress*

Approach to CM-HUS (aHUS)



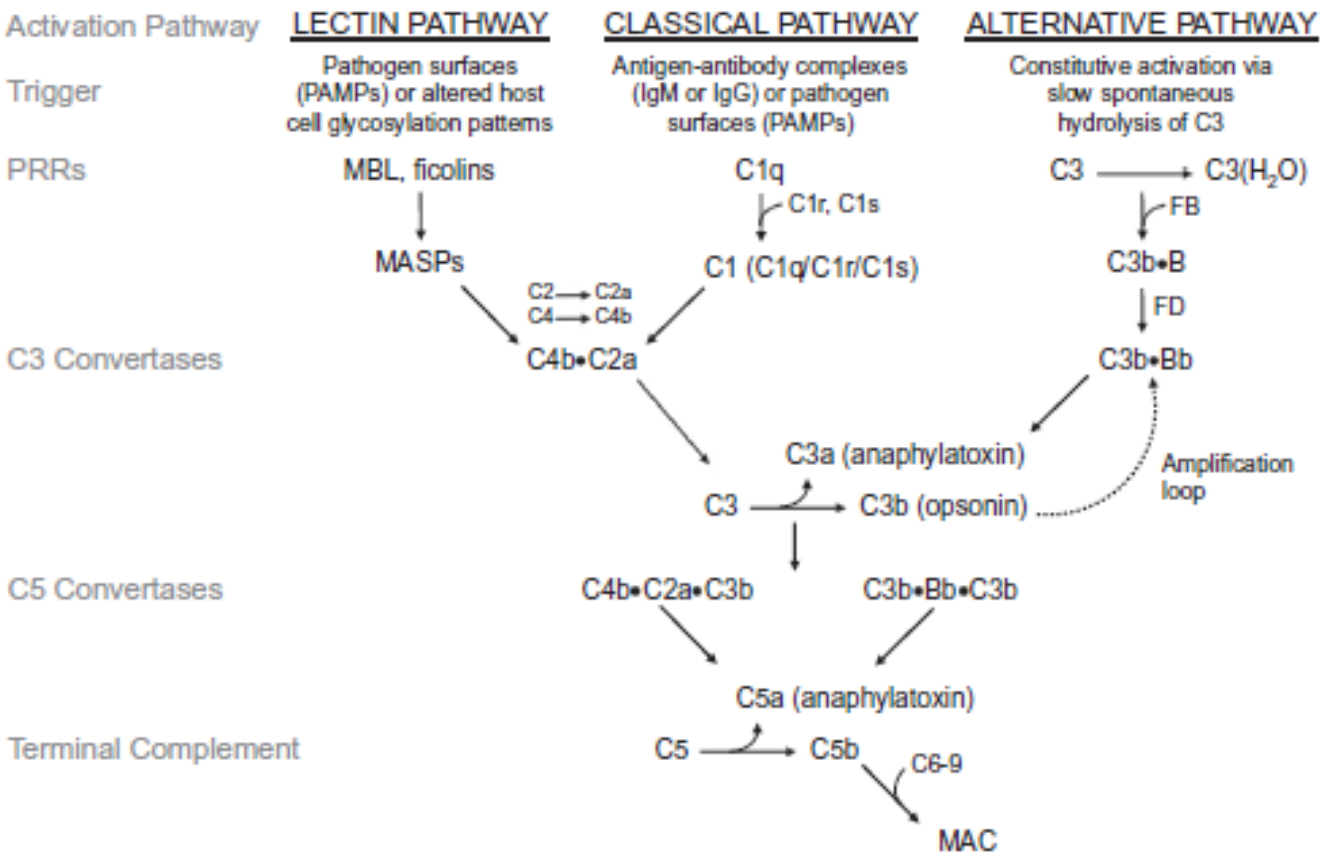
- *MAHA not always apparent*
- *Thrombocytopenia may be mild*
- *Dx may be revealed by renal biopsy*

- *Genetic testing is essential*

- *Response to anti-complement therapy may aid dx*

Sridharan J Imm Meth 2018

The Complement Cascade



Alternative pathway dysregulation underlies aHUS-through inactivating mutations in regulatory proteins or activating mutations in proteases

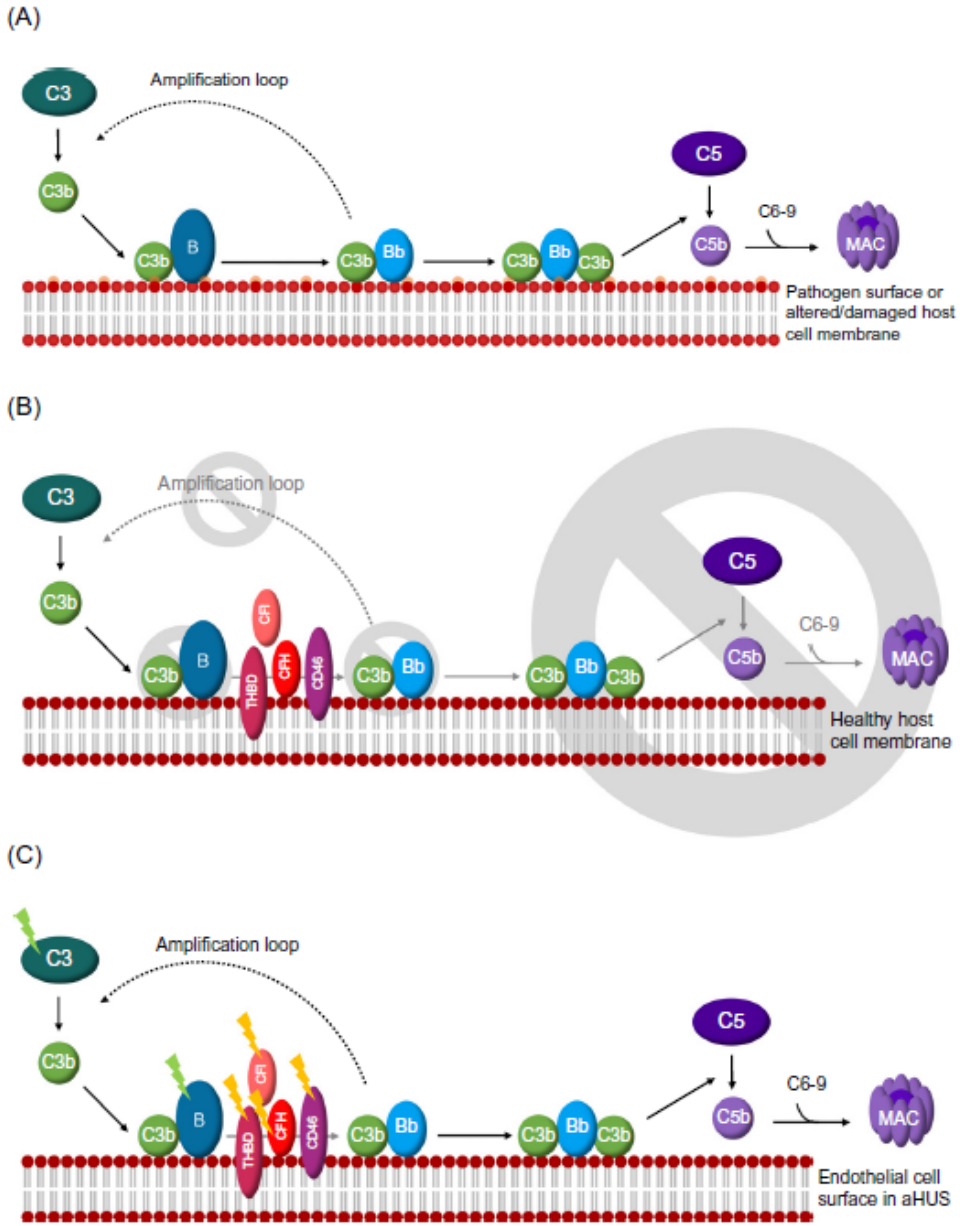
Baines and Brodsky Blood Rev 2017

Mutated Complement Genes in CM-HUS

Mutated Gene/Protein	Type	Frequency	Death or ESRD 3-10 years after onset	Soluble/ membrane
CFH (including CFH/CFHR1 hybrid genes)	Loss of complement regulation	24-28	70-80	soluble
CFHR1/3 deficiency with FH antibodies	Loss of complement regulation	3-10	30-70	soluble
FI	Loss of complement regulation	4-8	60-70	soluble
MCP (CD46)	Loss of complement regulation	5-9	<20	membrane
THBD	Loss of complement regulation/procoagulant state	0-5	50-60	membrane
C3	Gain of function	0-4	60-70	soluble
Factor B	Gain of function	2-8	70	soluble
None		30-48	50	
Diacyglycerol kinase ε	Prothrombotic	0-3	46	intracellular

Modified from Jokiranta et al, Blood 2017

Complement Activation in CM-HUS

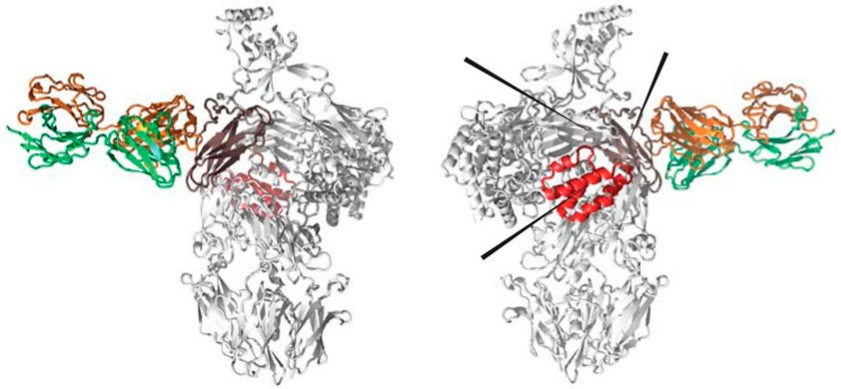


Effects of complement activation

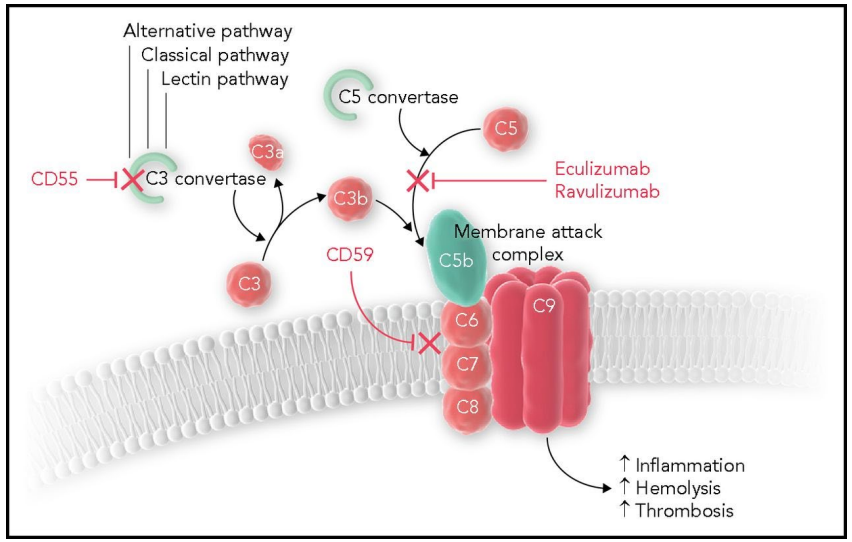
- Vascular wall damage/activation
- Platelet activation/thrombocytopenia
- Hemolysis with free Hgb release
- Immune cell chemoattraction and activation

Baines and Brodsky Blood Rev 2017

Eculizumab (Soliris)/Ravulizumab (Ultomiris)



Schatz-Jakobsen, J Imm 2016



Connell NT, Blood 2019

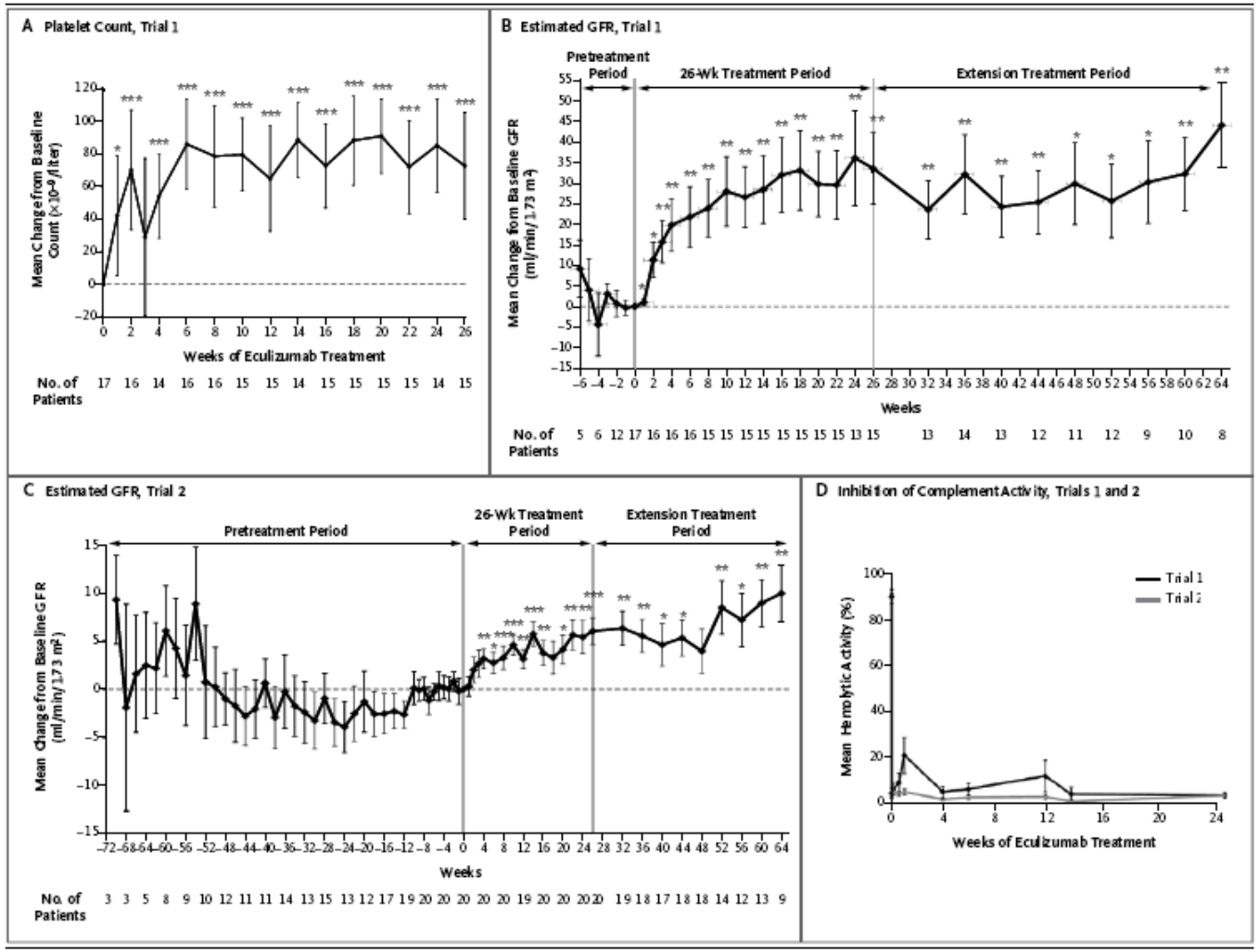
Ravulizumab vs Eculizumab

- Both are engineered, humanized mAb to C5
- Eculizumab indications: PNH, CM-HUS, GMG
- Ravulizumab indications: PNH (CM-HUS expected soon)
- *T1/2 =11 hrs vs 49 hours*
- Mechanism: site specific amino acid changes in ravulizumab allow dissociation of antibody:C5 complex in early endosome after uptake by FcRn--C5 is degraded and ravulizumab recycled
- Both have black box warnings re: meningococcal infection
  - Immunization two weeks before treatment with MenACWY, MenB (BexSero, 2 doses, or Trumenba, 3 doses)
  - If urgent use needed, prophylaxis with Cipro, ceftriaxone
- Cost
  - Soliris ~$500,000/year
  - Ultomiris ~$458,000/year

Eculizumab in CM-HUS

Table 1. Baseline Demographic and Clinical Characteristics in the Intention-to-Treat Population.*

Variable	Trial 1 (N=17)	Trial 2 (N=20)
Age — yr		
Median	28	28
Range	17–68	13–63
Female sex — no. (%)	12 (71)	12 (60)
White race — no.†	15	17
Time from diagnosis of atypical HUS to screening — mo		
Median	9.7	48.3
Range	0.3–235.9	0.7–285.8
Time from current clinical presentation of atypical HUS to screening — mo		
Median	0.8	8.6
Range	0.2–3.7	1.2–45.0
First clinical manifestation of atypical HUS — no. (%)	7 (41)	5 (25)
History of kidney transplantation — no. (%)	7 (41)	8 (40)
Dialysis before the first dose of eculizumab — no. (%)	6 (35)‡	2 (10)§
Sessions of plasma exchange or infusion during current clinical presentation — no./patient		
Median	17	62
Range	2–35¶	20–230
Duration of plasma exchange or infusion treatment — mo		
Median	0.7	10.1
Range	0.1–3.2	2.4–47.0



Key result summary

	Trial 1		Trial 2	
Intervention rate	.88	0	.23	0
Complete TMA response	65%		25%	
↓ Cr ≥ 25%	65%		15%	

Legendre et al NEJM 2013

Eculizumab Reduces the Incidence of ESRD in CM-HUS

	Children			Adults				
	Pre-eculizumab era		Eculizumab	Pre-eculizumab era		Eculizumab		
	French cohort[2] (n=89)	Italian cohort[3] (n=149)	Trial 3[139,140] (n=22)	French Cohort[2] (n=89)	Italian cohort[3] (n=149)	Trial 1[141,142] (n=17)	Trial 2[141,142] (n=20)	Trial 4[143,144] (n=41)
First episode	16%	..	..	46%	..	..	..	..
6-month follow-up	..	..	9%	..	..	6%	10%	15%
1-year follow-up	29%	..	9%	56%	..	6%	10%	15%
2-year follow-up	..	..	..	..	..	12%	10%	..
3-year follow-up	..	48%	..	..	67%	..	..	..
5-year follow-up	36%	..	..	64%	..	..	..	..

For a detailed table legend see the appendix (pp 27,28). HUS=haemolytic uraemic syndrome.

Table 2: **Percentage of patients with atypical HUS who progressed to end-stage renal disease or who died in four prospective trials of eculizumab compared with the Italian and French registries of the pre-eculizumab era**

Fakhouri et al Lancet 2017

- *Plasma therapy may induce hematologic remission in aHUS in up to 75% of cases, but does not affect long-term outcomes or progression to end-stage renal disease*

Discontinuation of Eculizumab in Patients with CM-HUS

Variants	Published case reports and series[a]		French retrospective study[b]	
	Patients who discontinued, *N*	Patients with relapse after discontinuation, *N* (%)	Patients who discontinued, *N*	Patients with relapse after discontinuation, *N* (%)
CFH and CFH/CFHR1 hybrid	15	9 (60)	11	8 (72.7)
MCP	8	3 (37.5)	8	4 (50)
C3	7	3 (42.8)	1	0
CFI	4	0	/	/
CFB	1	0	/	/
No variant identified	25	2 (8)	17	0
Total	60	17 (28.3)	37	12 (32.4)

CFHR1 = complement factor H related protein 1; CFI = complement factor I.

[a] Thirteen case reports (see references in Supplemental data on eculizumab discontinuation), and 5 cases series [7,36-38,40].

[b] Ref. [39].

Fakhouri and Loirat, Sem Hematol, 2018

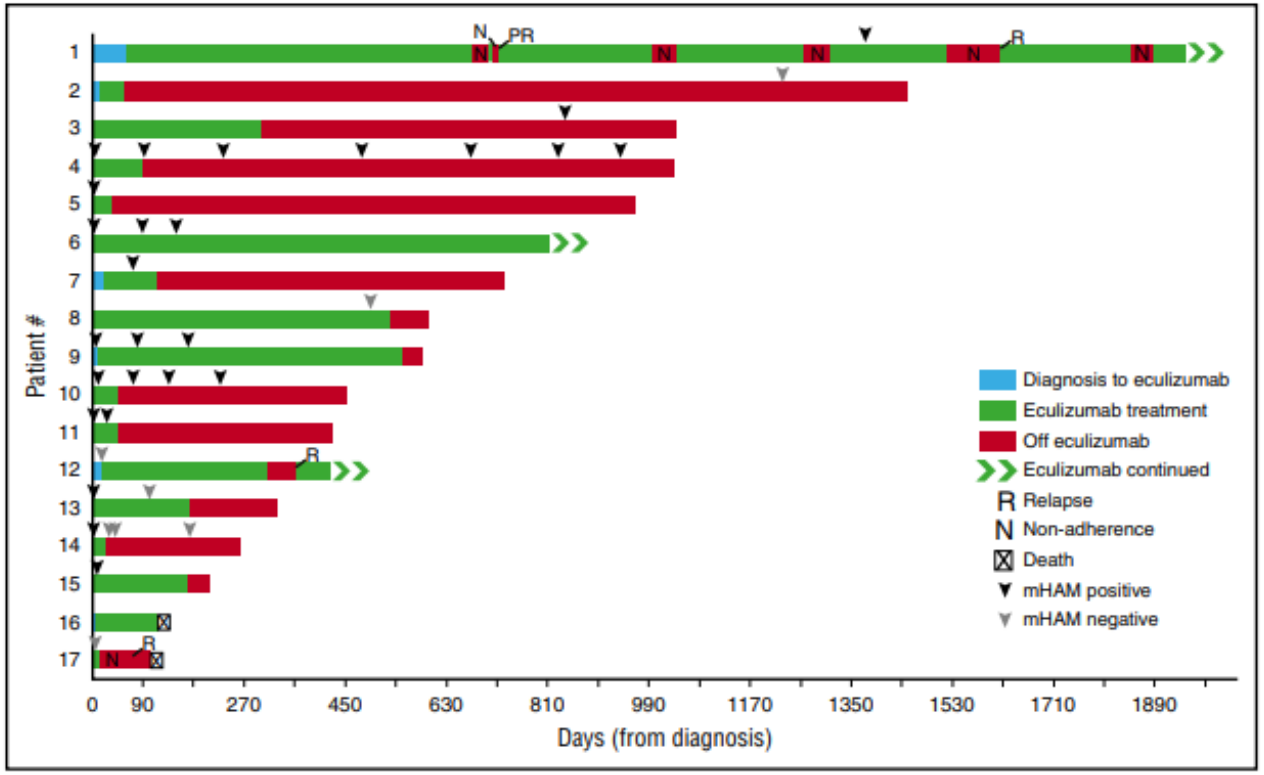
Table 3 Genetic and autoimmune complement abnormalities in patients in the study

Complement Abnormality by Risk Level,[a] n (%)	Never Discontinued (*n* = 51)	Discontinued (*n* = 42)	
		Reinitiated (*n* = 21)	Not Reinitiated (*n* = 21)
High risk	25 (49)	8 (38)	6 (29)
CFH	14 (27)[b]	6 (29)	3 (14)[c]
C3	6 (12)	1 (5)	1 (5)[d]
CFH autoantibodies	5 (10)	1 (5)	1 (5)
CFB	0 (0)	0 (0)	1 (5)
Low/moderate risk	6 (12)	6 (29)	3 (14)
CD46 (MCP)	3 (6)[e]	3 (14)	2 (10)
CFI	3 (6)[f]	3 (14)	1 (5)
Deletions	0 (0)	0 (0)	1 (5)
CFHR1, CHFR3	0 (0)	0 (0)	1 (5)
No identified abnormality	20 (39)	7 (33)	11 (52)

Menne et al BMC Nephrology, 2019

- *Eculizumab can be safely stopped in some patients with CM-HUS*
- *Highest recurrent rates in CFH mutant patients*
- *No measures of ongoing complement activation in these studies*

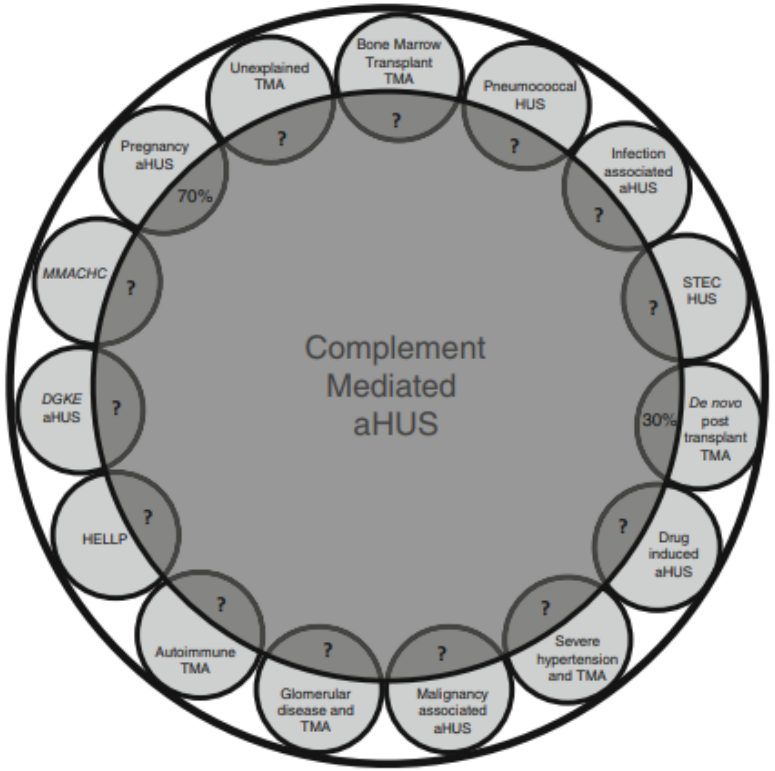
Discontinuation of Eculizumab in CM-HUS



- *Most patients may have eculizumab discontinued safely even with evidence of ongoing complement activation*

Merrill et al Blood, 2017

Other TMAs



Wong et al Sem Immunopath 2018

Type	Pathogenesis	Complement	Eculizumab
Malignancy	Intravascular tumor emboli	unknown	Anecdotal responses
Drugs: anti-VEGF cyA, tacrolimus, everolimus, gemcitabine, mitomycin	Endothelial cell toxicity	unknown	Anecdotal responses
HSCT	Endothelial toxicity	Anti-CFH ab, increased C5-b9 and arteriolar C4d staining	Hematologic response in >50% and potential decreased mortality
Solid organ transplant	CNI, mTOR toxicity, HLA mismatch	Rare variants in CFH, CFI described	Anecdotal
Autoimmune disease—SLE, APS, SS, PM/DM	Multifactorial, Ics, anti-EC ab,	Uncertain, DM is C-mediated	Anecdotal reports in CAPS, SLE
Malignant hypertension	EC damage	Activated, but cause or effect	Uncertain
Pregnancy (mostly post-partum)-HUS	Uncertain	Complement gene mutations in >80%	Several responses reported
HELLP	Placental ischemia,	Mutations in ~25%	unknown
Infection-HIV, parvovirus, CMV, influenza H1N1, malaria	EC damage, Thomson-Freidrich antigen exposure by neuraminidase	Uncertain	Uncertain
DGKE aHUS	Prothrombotic EC phenotype	Not complement mediated	Unknown
Cobalamin C aHUS	Mutation in MMAHC	Not complement mediated	Unknown

Summary

- Thrombocytopenia may be primary or secondary, and a variety of causes exist
- Appropriate treatment depends on accurate diagnosis that considers past history, drug exposure, status of other hematopoietic lineages, etc.
- Inherited thrombocytopenias should be considered in patients with the appropriate history, or if their “ITP” does not respond as expected.
- Better outcomes in HIT are obtained through use of the 4T score
- There are many causes of TMAs, but proper diagnosis can usually be reached by following a diagnostic pathway