Thrombocytopenia

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Conflicts of interest disclosure

- NIH Clinical Center - Transfusion Medicine – Senior clinical advisor (contractor)
- Dova/Sobi – research, consulting
- Sanofi- research, consulting

Approach to thrombocytopenia

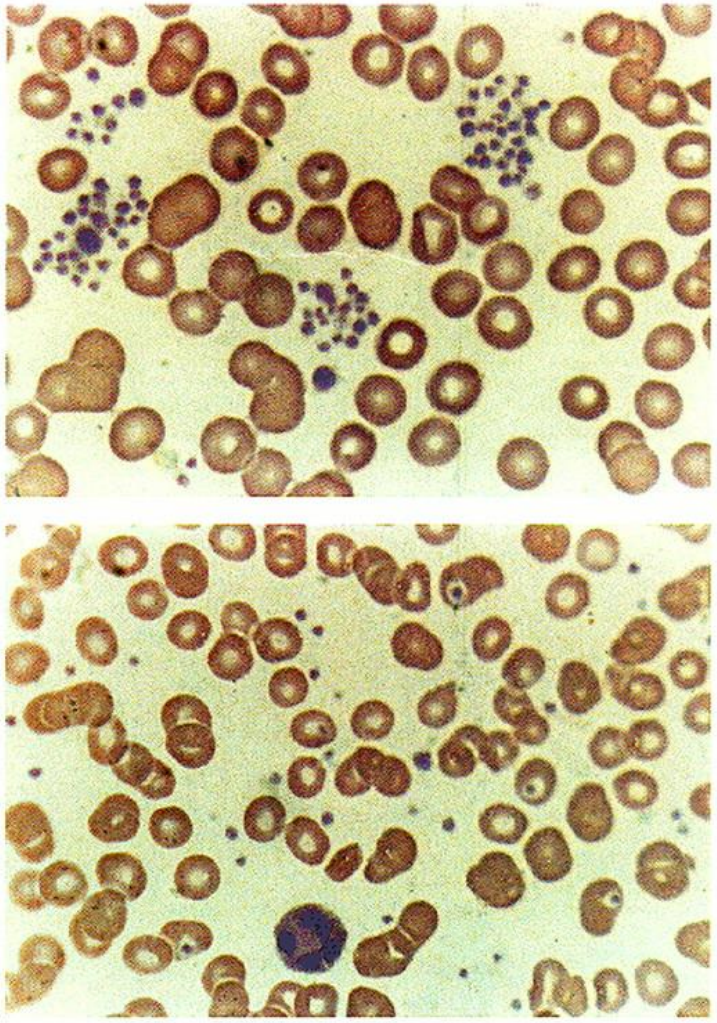
Thrombocytopenia: below 2.5th lower percentile of normal distribution (<150X10^{9}/L)

Platelet counts between 100-150X10^{9}/L may not pathological especially if present chronically

- History
- Physical examination
- Complete blood count
- **Peripheral blood smear**

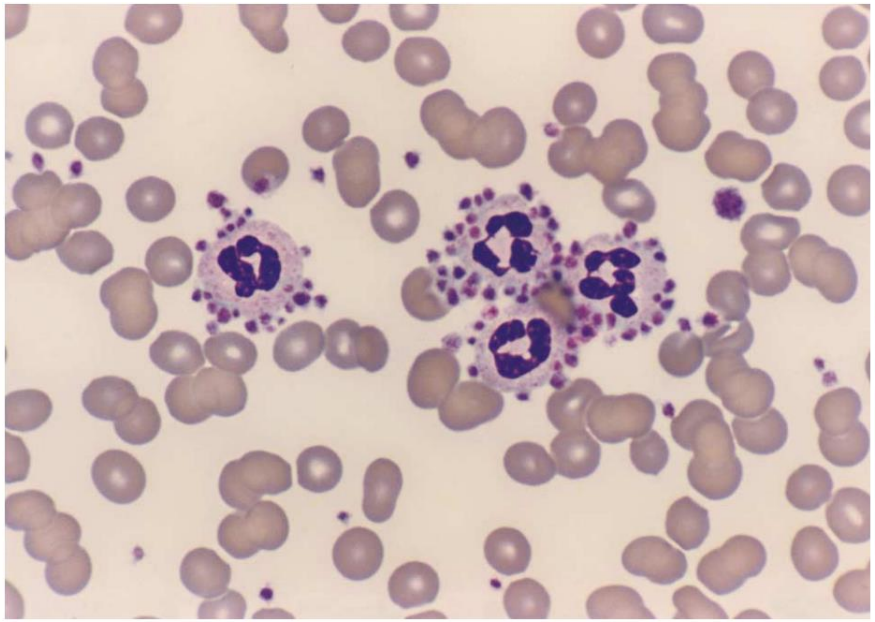
Pseudo-thrombocytopenia

Clumping



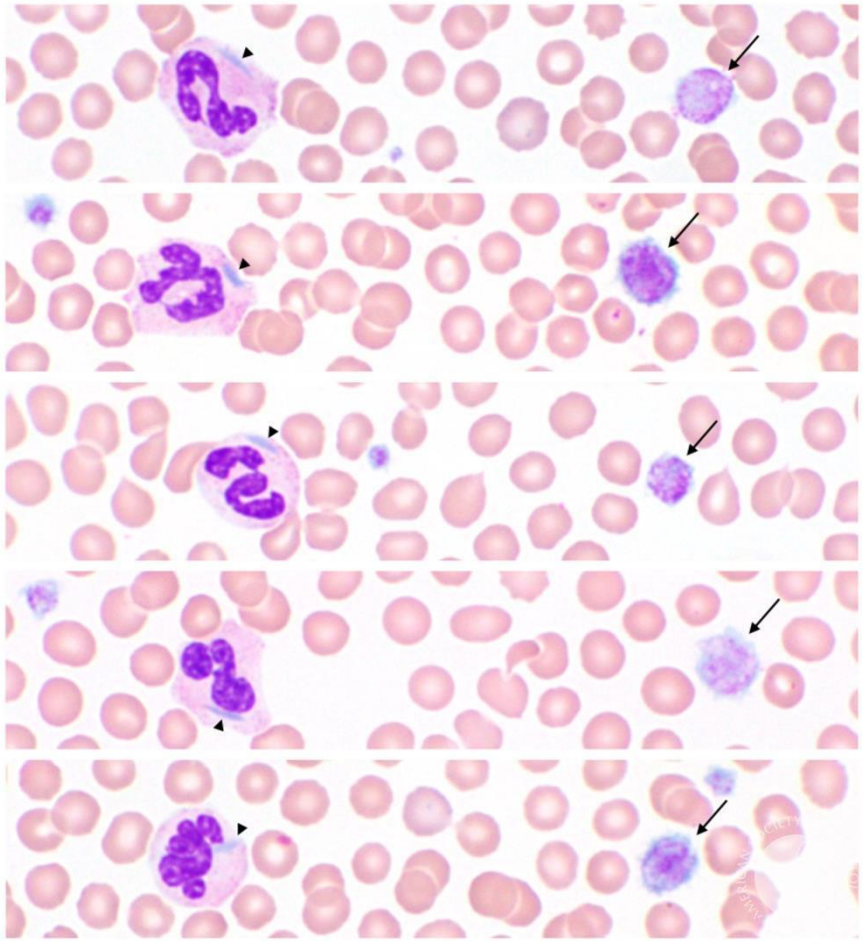
Shalev, O. et. al. N Engl J Med 1993

Satellitism

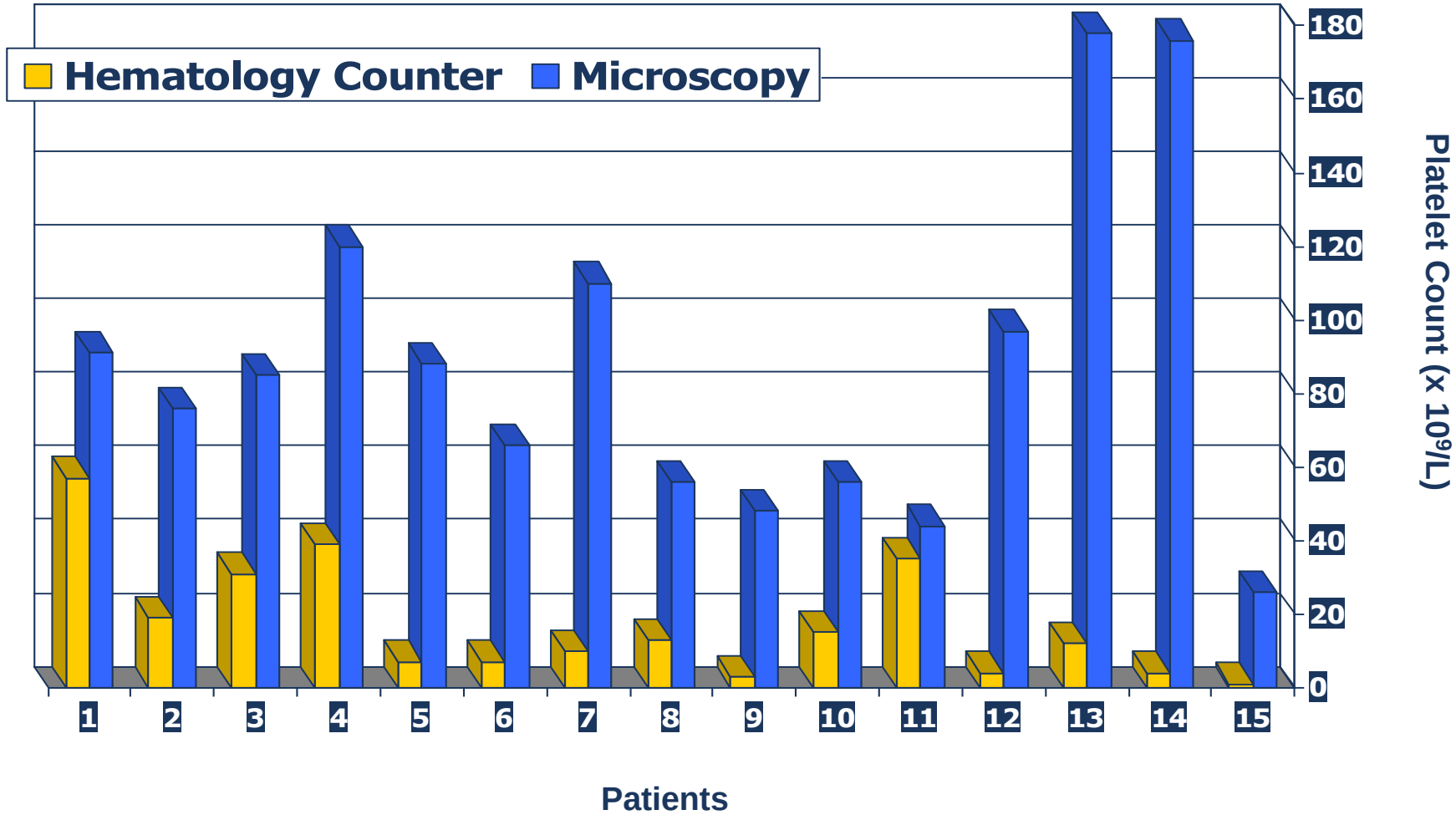


Shahab, N. et al. N Engl J Med 1998

Macrothrombocytopenia



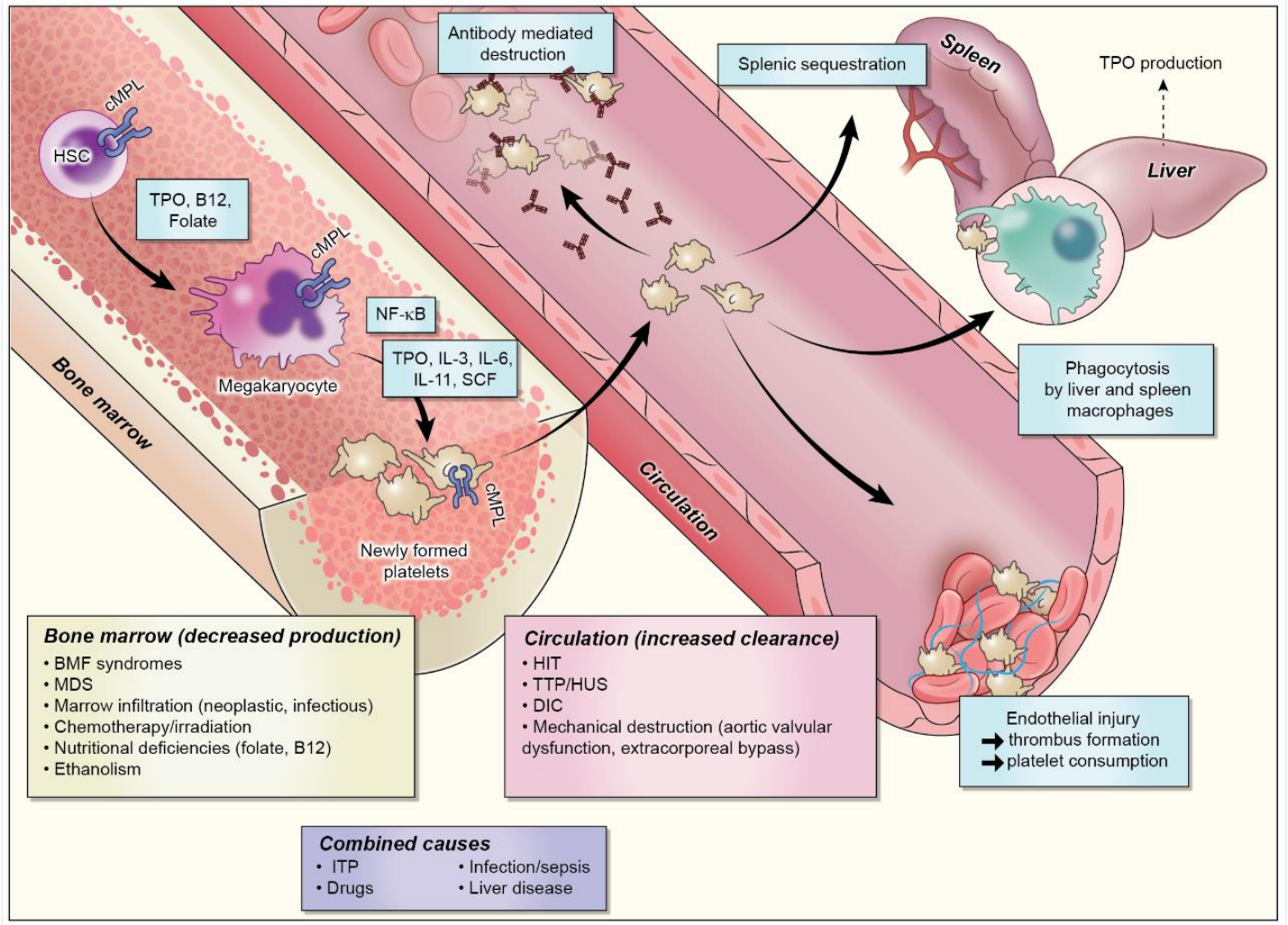
Platelet count errors in macrothrombocytopenia



Noris, P. et al., Am. J. Medicine, 1998

Mechanisms of thrombocytopenia

- Normal blood platelet concentration: 150-400 billion/L
- Healthy adults produce 100 to 300 billion platelets per day
- The average platelet life span is 7 to 10 days
- Platelet production: TPO-cMPL
- Platelets loss: senescence, activation, consumption, etc



Panch SR & Dunbar CE, "Thrombocytopenia" Bethesda Handbook of Hematology 4th Ed;

Mechanisms of thrombocytopenia

Decreased Production	Increased Destruction / Consumption	Combination
Marrow failure	**Heparin induced thrombocytopenia; Vaccine induced thrombotic thrombocytopenia**	**Immune Thrombocytopenia**
Inherited thrombocytopenia	**Thrombotic thrombocytopenic purpura/ atypical HUS,** DIC	Other autoimmune conditions
Myelodysplasia	**Pre-eclampsia, HELLP syndrome, AFLP**	Infection/sepsis
Marrow infiltration	**Post transfusion purpura**	Liver disease
Irradiation	Neonatal alloimmune thrombocytopenia	**Drugs**
Chemotherapy/drugs	vWD Type IIB	Cyclic thrombocytopenia
Nutritional deficiencies (Vit B12, folate, severe iron deficiency)	Mechanical destruction (valvular dysfunction, cardio-pulmonary bypass, LVADs)	*OTHER: pseudothrombocytopenia, gestational/dilutional*
Alcohol	Hypersplenism (sequestration)	***Qualitative platelet disorders***

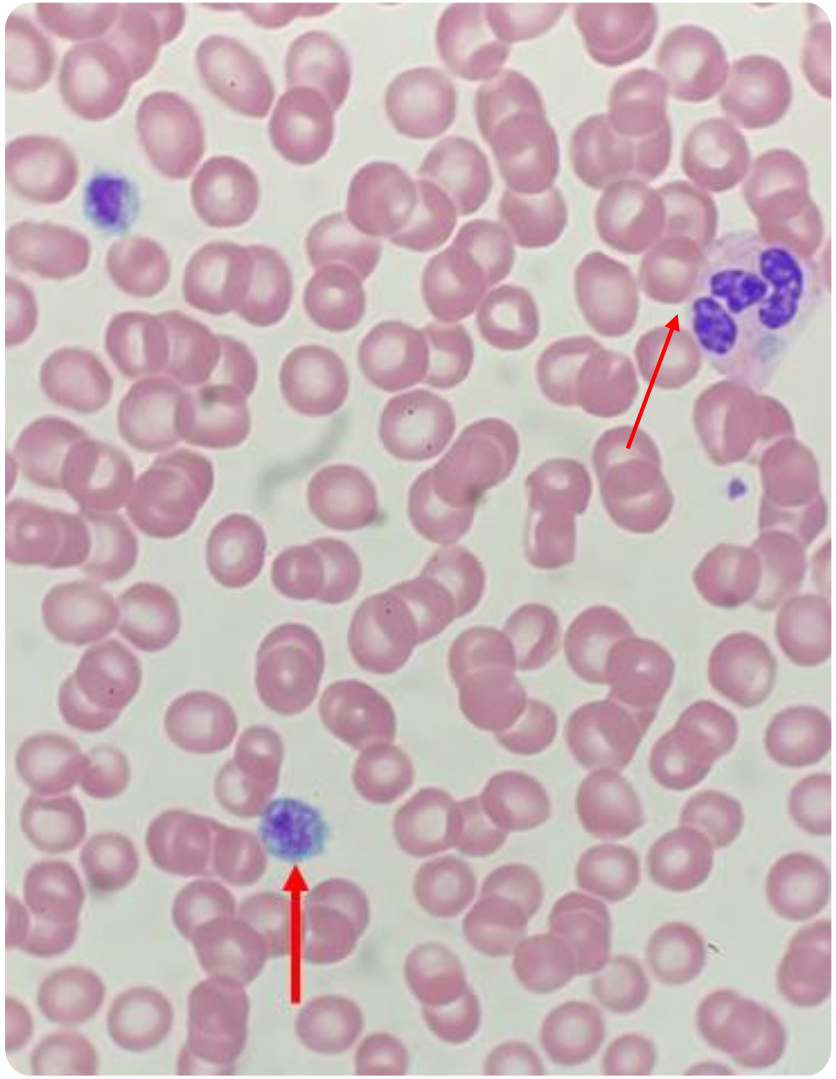
Thrombocytopenia: Question 1

A 28yo female presents to hematology clinic. She has a family history of easy bleeding/ bruising in her father and brother. She has a personal history of frequent and prolonged episodes of epistaxis and heavy menstrual periods. Patient is also noted to have a family history of hearing loss. Previous steroid treatment failed to demonstrate response.

- Mild microcytic anemia
- Iron deficiency
- Significantly decreased platelets (15-40X10^9/L)
- Peripheral smear : Large platelets and inclusion bodies in WBCs

What is the most likely diagnosis?

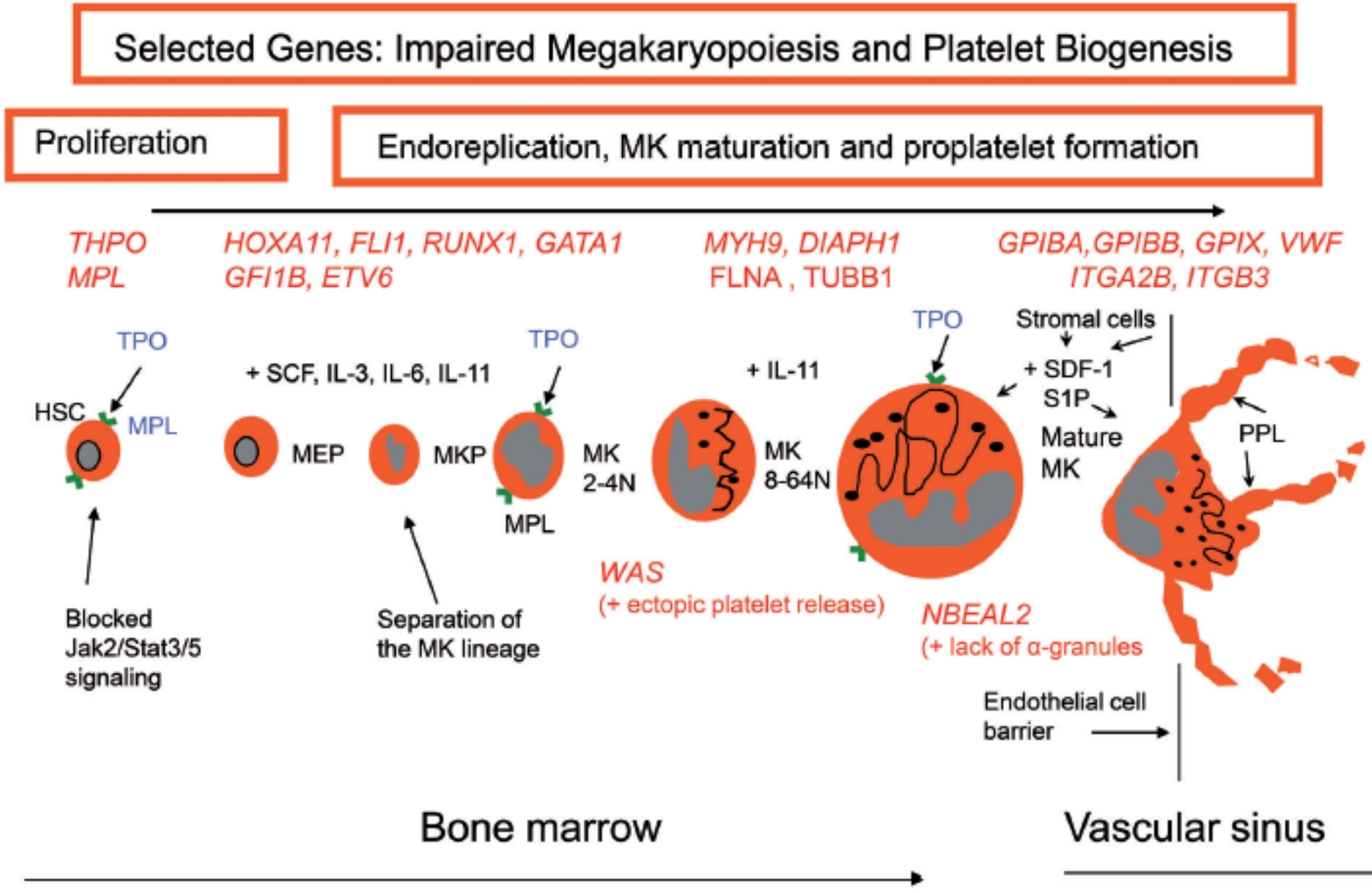
A. Bernard Soulier Syndrome
B. Glanzman's thrombasthenia
C. MYH9-related thrombocytopenia
D. Immune thrombocytopenia (ITP)



Inherited Thrombocytopenia

- Inherited thrombocytopenia (IT): Uncommon but advance understanding of genetic disorders, megakaryopoiesis, platelet biogenesis, structure and function
- Professors Bernard and Soulier described Bernard-Soulier syndrome (BSS) in 1948
- Many platelets enlarged, some giant
- Absence of platelet surface GP1 → defined molecular landscape of ITs
- Diagnoses not to be missed- a recent investigation (Norris, 2014)
  31% misdiagnosed with ITP
  25% received undue immunosuppression
  8% underwent unnecessary splenectomy
- Several recessive forms present in adulthood when co existing conditions develop

Inherited thrombocytopenia



Nurden et al. Haematologica. 2020

Inherited macrothrombocytopenia

Syndromic and non-syndromic MTP

Non-syndromic

Cytoskeletal genes

TUBB1,
ACTN1
TPM4

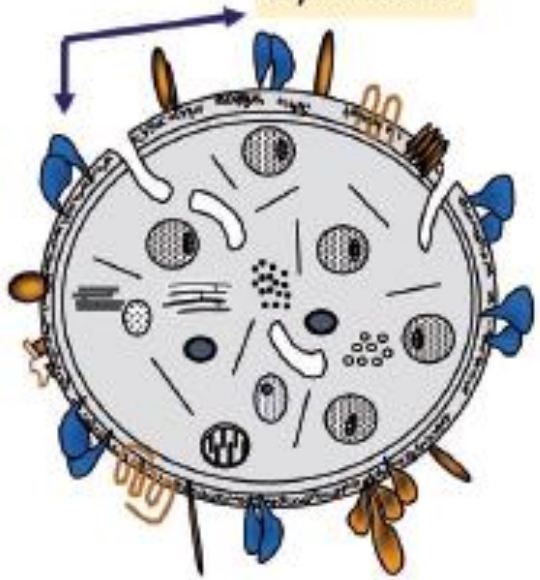
Receptors/ligands signaling genes

GPIBA, GPIBB, GP9 (BSS)
ITGA2B, ITGB3,
VWF (Plt-type VWD + VWD2B)
PRKACG
SLFN14

Sialylation defects

GNE, SLC351, GALE

Syndromic

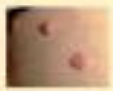


Ion channel genes

STIM1 (Stormorken), *TRPM7*

Metabolic genes

ABCG5, ABCG8 (sitosterolemia)



Other genes

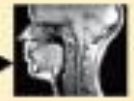
G6B: Myelofibrosis + anemia
SRC: Myelofibrosis + bone pathology

Cytoskeletal genes

MYH9

DIAPH1

FLNA



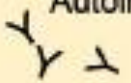
CDC42

α-Granule biogenesis genes

NBEAL2,
(GPS)

Myelofibrosis

Autoimmunity



Transcription factors

GATA1

α-granule deficiency

GFI1B

αδ-granule deficiency

red cell defects

Nurden et al. Haematologica. 2020

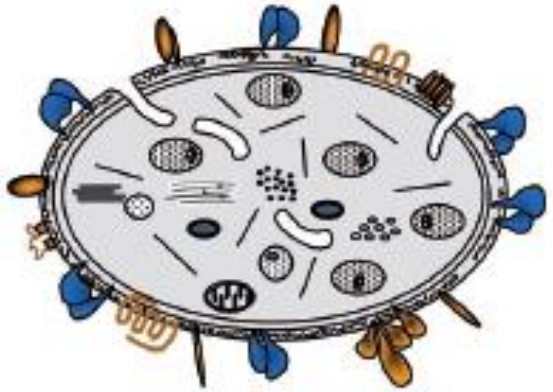
Inherited thrombocytopenia with small/normal platelet size

Thrombocytopenia with normal sized or small platelets

Non-syndromic

CYCS, MASTL
IKZF5

Syndromic



Predisposition to leukemia

RUNX1 (FPD/ AML)	*ETV6*	*ANKRD26* (THC2)
Myeloid malignancies	Lymphoid malignancies	Myeloid malignancies

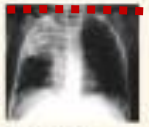
Platelet
MYH10

Skeletal defects

HOXA11	*MECOM* (*EVI1*)	*RBM8A*
Radioulnar synostosis	Radioulnar synostosis. BM failure	Absent radius

Small platelets

WAS
(Wiskott-Aldrich syndrome



severe infections

eczema

+ *ARPC1B (syndromic)*
FYB, PTPRJ (non-syndromic)

Ion sensor gene

STIM1 (Stormoken syndrome)
Tubular aggregate myopathy

Others

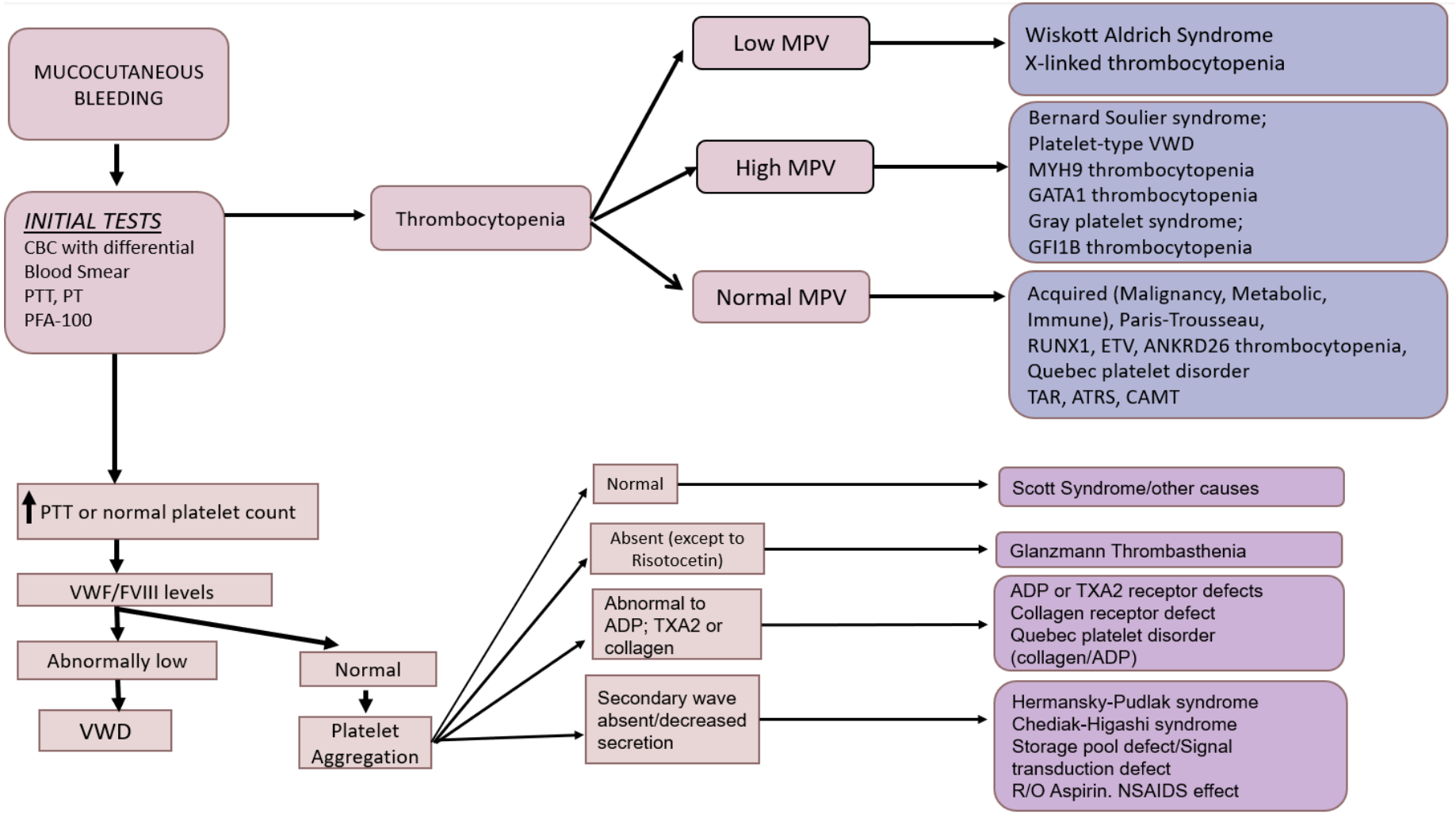
KDSR (severe skin disorder)
RNU4ATAC (RNA nuclear gene)

Early megakaryopoiesis

MPL/THPO
Low numbers of stem cells; aplasia

Nurden et al. Haematologica. 2020

Diagnosing inherited platelet disorders



Jobe, S. M. and J. Di Paola (2019)

Inherited thrombocytopenia

Inherited TCP	Inheritance	Salient features
Bernard Soulier	AR/AD	Prevents platelet binding (via GP1b-IX) to VWF; No ristocetin-induced platelet agglutination BSS-like picture in 22q11 del. velocardiofacial syndromes
VWD Type IIB	AD	Platelet aggregates in blood smear. Absence of HMW multimers (as in VWD type 2B).
MYH9-related disease	AD	Macrothrombocytopenia, basophilic neutrophilic inclusions (Döhle bodies), hearing loss, kidney disease, liver disease, cataracts (previously known as May-Hegglin, Sebastian, Fechner, Epstein)
Gray platelet syndrome	AR; NEALB2	Absent α-granules, Impaired platelet function with weak agonists. Elevated serum B12. Early myelofibrosis; occasional splenomegaly; autoimmune diseases. Moderate to severe bleeding
CAMT	AR; MPL	Severe neonatal thrombocytopenia, amegakaryocytic; progression to aplastic anemia; Severe bleeding
Wiskott-Aldrich	XL; WAS	Microthrombocytopenia, severe thrombocytopenia. Immunodeficiency, eczema, lymphoproliferative, autoimmune disorders. Severe bleeding
Familial TCP		*predisposition to myeloid or lymphoid malignancies

IT with predisposition to malignancies

Inherited TCP	Inheri-tance	Salient features
GATA1	XL	Mild to severe thrombocytopenia. Dyserythropoiesis with or without anemia, thalassemia, neutropenia, splenomegaly, congenital erythropoietic porphyria; Dysplastic megakaryocytes. Platelets granule deficiency and functional defect. Rarely Lu a- b- (Lu null). Mild-severe bleeding
GFI1b	AD/ AR	Mild to severe thrombocytopenia (monoallelic & biallelic forms). Red blood cells with anisopoikilocytosis, dysplastic megakaryocytes, emperipolesis. Platelets with granule deficiency and aggregation defect. CD34+ abnormal expression in platelets. Absent-severe bleeding.
RUNX1	AD	Predisposition to myeloid malignancies; Mild-moderate neonatal thrombocytopenia. Platelet function defect “Aspirin-like”. Platelet granule deficiency. High risk (>40%) AML, MDS at young age; ALL and solid tumors. Absent-moderate bleeding.
ETV6	AD	RBC with high MCV. Platelets show elongated granules, impaired clot retraction.- High circulating CD34 + cells. Predisposition (30%) to acquired lymphoid, myeloid, MPNs. Absent-mild bleeding.
ANKRD26	AD	Mild-moderate neonatal thrombocytopenia. Some patients with high levels of Hb, WBC ~10% develop myeloid neoplasms. Absent-mild bleeding

Inherited disorders of platelet function

Inherited platelet disorders	Inherit-ance	Salient features- Normal platelet count and morphology
Glanzmann' thrombasthenia	AR/ GP2B/3A	Absent or severely reduced LTA with all agonists except with ristocetin. Absence or decreased IIb3 expression demonstrable by flow cytometry: Type I <5%; Type II 10–20%; Variant GT with even >50% non-functional IIb3. Severe bleeding tendency
Hermansky-Pudlak Syndrome	AR/ HPS1, HPS2	Delta-granule defect. Reduced LTA, absence of second wave with weak/low dose agonists (ADP, epinephrine, collagen). CD63 release defects by flow cytometry. Oculocutaneous albinism; neutropenia, immunodeficiency, pulmonary fibrosis, granulomatous colitis. Mild to moderate bleeding
Chediak-Higashi Syndrome	AR/ LYST	Delta-granule defect. Reduced LTA and/or absence of second aggregation wave with weak/low dose agonists (ADP, epinephrine, collagen). Defect in CD63 release by flow cytometry. Oculocutaneous albinism; Immunodeficiency, In 85% evolution to HLH. Mild to moderate bleeding

Inherited thrombocytopenia: Management

	Indications	Comments
Platelet transfusions	All inherited thrombocytopenias. To stop bleedings when local measures failed. To prepare patients for surgery	Leukoreduction of platelet concentrates and HLA-matched donors reduce the risk of alloimmunization and refractoriness to platelet transfusion
Splenectomy	-Wiskott–Aldrich syndrome -X-linked thrombocytopenia	Increases platelet count but also the already high risk of infections
TPO-receptor agonists	Preparation for hemostatic challenges of patients with: - *MYH9*-related disease - Wiskott–Aldrich syndrome/X-linked thrombocytopenia - monoallelic Bernard-Soulier syndrome - *ANKRD26*-related thrombocytopenia	Efficacy in other conditions to be tested The efficacy and safety of long-term treatments (life-long?) remain to be demonstrated
	Variant of congenital amegakaryocytic thrombocytopenia (*THPO* mutation)	Restore entire hemopoiesis
Hematopoietic stem cell transplantation	-Wiskott–Aldrich syndrome -Congenital amegakaryocytic thrombocytopenia (*MPL* mutation) -Severe Bernard-Soulier syndrome -*MECOM*-associated syndrome	Can cure patients and is the first-line treatment for patients with poor prognosis
Gene therapy	-Wiskott–Aldrich syndrome	Can cure patients. Efficacy in other conditions not yet tested

Balduini Haematologica 2022

Thrombocytopenia: Question 1

A 28yo female presents to hematology clinic. She has a family history of easy bleeding/ bruising in her father and brother. She has a personal history of frequent and prolonged episodes of epistaxis and heavy menstrual periods. Patient is also noted to have a family history of hearing loss. Previous steroid treatment failed to demonstrate response.

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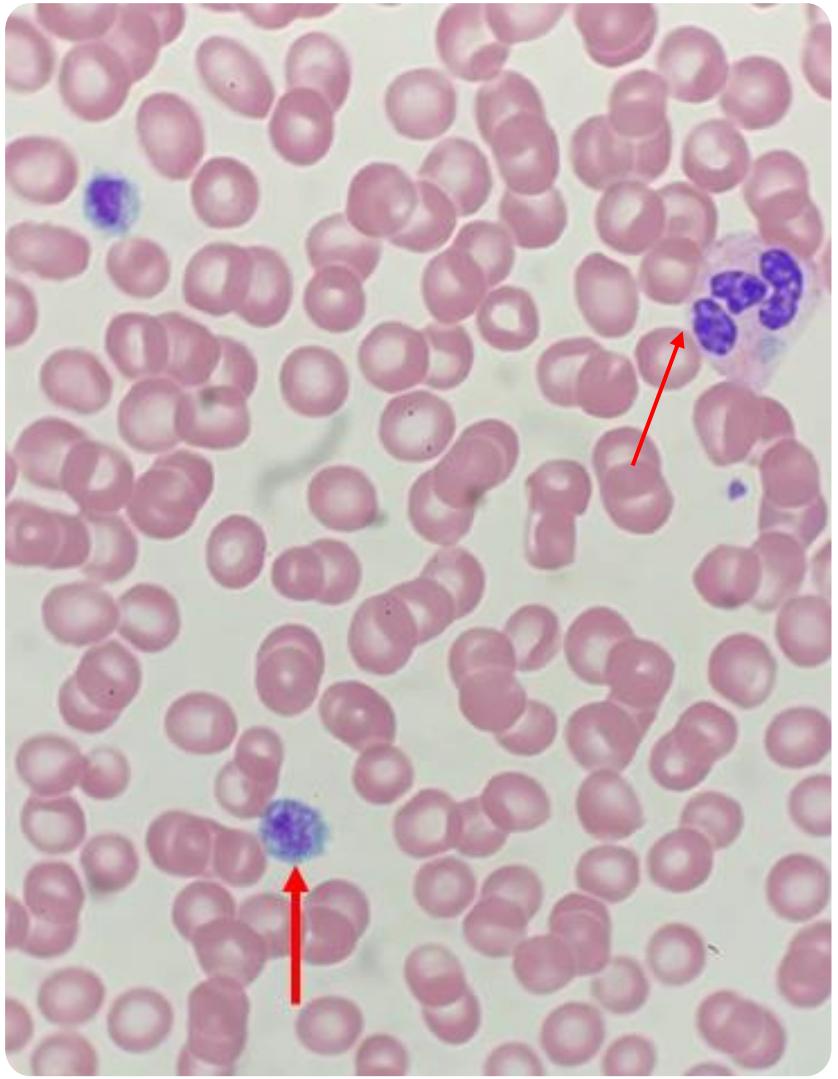
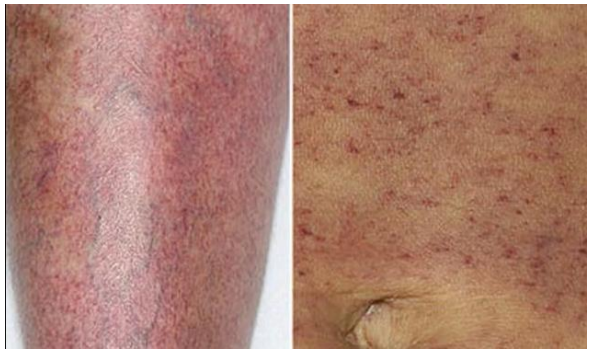


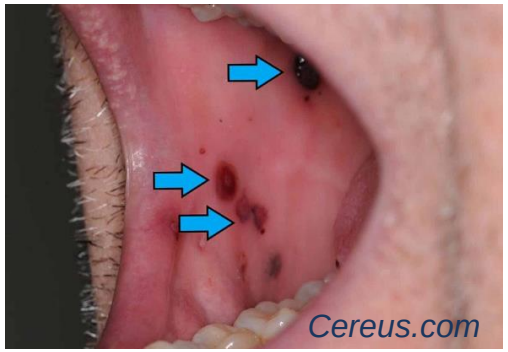
Thrombocytopenia: Question 2

42yo female with Immune thrombocytopenia (ITP) diagnosed 1 year ago (platelet nadir $3X10^9/L$) and responded to a short course of steroids ($120X10^9/L$) now presents with platelet counts of $40X10^9/L$. Counts repeated within a week are still at $40X10^9/L$. She reports no bleeding/bruising. What are her management options?

A. Initiate TPO-RA
B. Re dose prednisone +/- IVIG
C. Initiate rituximab
D. Observe
E. Refer for splenectomy

Immune Thrombocytopenia (ITP)

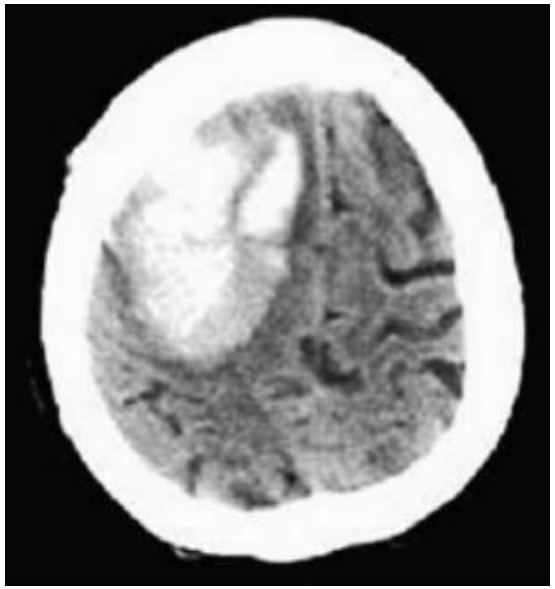




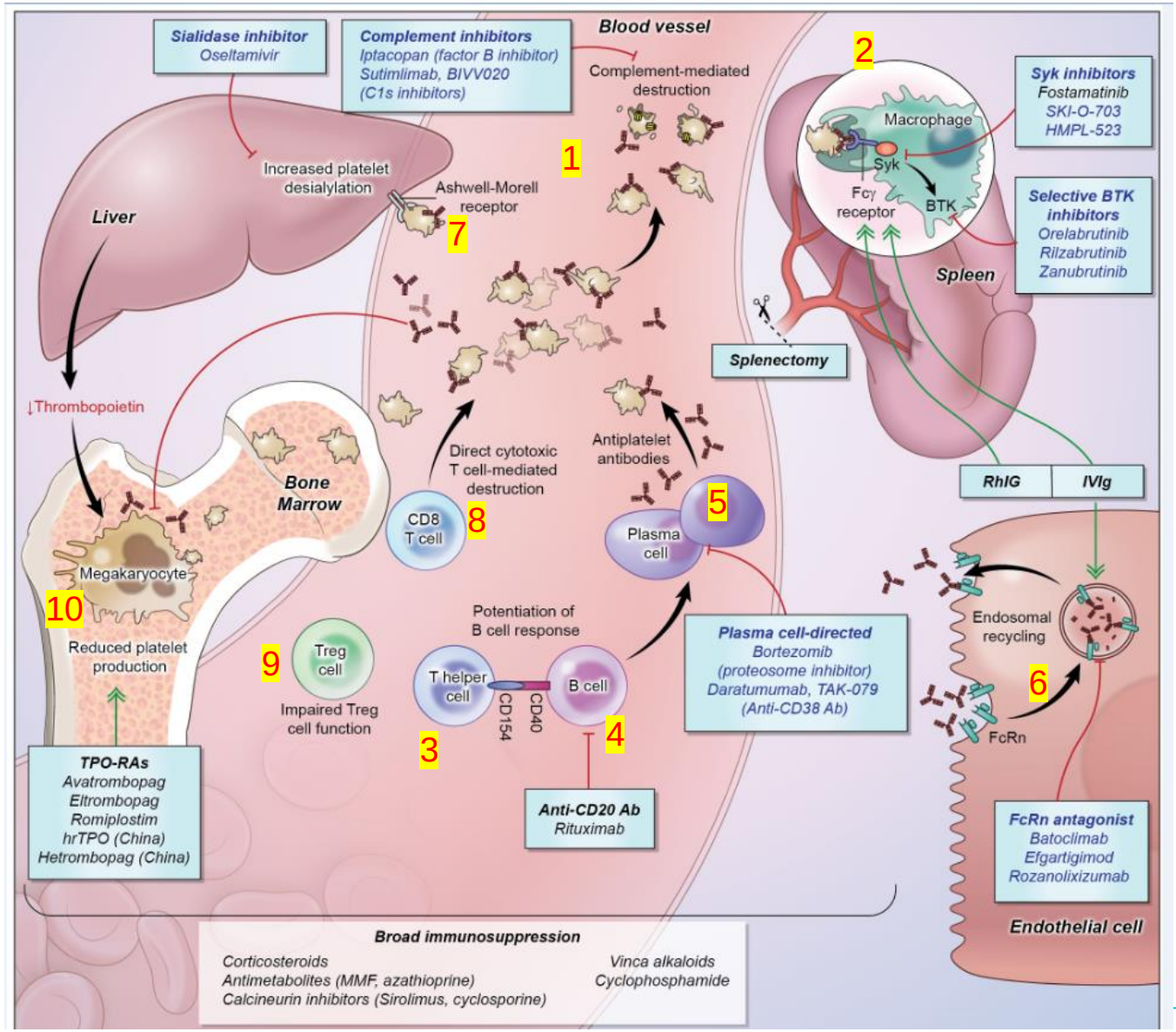
- Petechiae

Mucosal bleeding

Intracranial bleeding



ITP: Pathophysiology



Autoimmune disease due to
-Peripheral platelet destruction
-Inappropriate bone marrow production

1950s: ITP due to autoantibody mediated peripheral destruction of platelets; Rx: splenectomy!

Blood

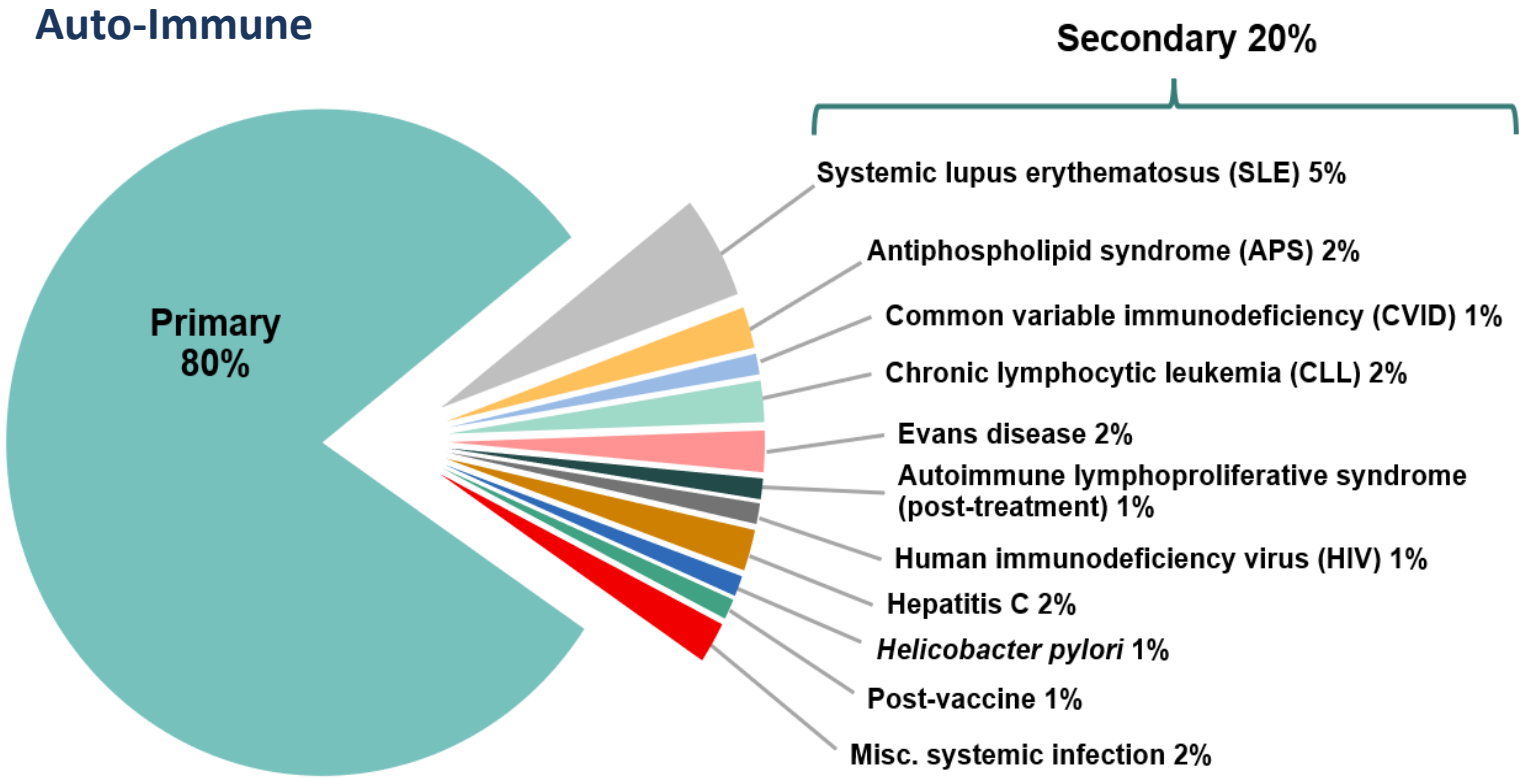
1. Abs to platelet GP → complement activation → lysis
2. Phagocytosis by splenic macrophages
3. T-helper cells→ autoreactive B cell proliferation/differentiation
4. B cells→Plasma cells →Abs→ platelet destruction
6. **Endothelial FcRn** → antibody recycling
7. Abs trigger platelet desialylation→ **liver AMR**→ removal
8. CD8 cytotoxic T cells →platelet destruction
9. Autoimmunity → loss of tolerance (Treg deficiency)

Bone marrow

10. Autoimmune response to megakaryocytes + insufficient TPO

Jiang, Al-Samkari, Panch TMR 2022

Secondary ITP, DITP, PTP



Drug induced

Quinine, sulfonamides, NSAIDs, PCNs, Vancomycin, Abciximab, Heparin

Occur 5-10 days after drug exposure, except GpIIb/IIIa antagonists which occur within hours

Allo-immune

Post-transfusion Purpura
Neonatal allo-immune thrombocytopenia (NAIT)

Cines et al. Blood 2009

ITP diagnosis

Diagnosis of exclusion

- History & PE
- Full blood count, retic & peripheral blood examination
- Helicobacter pylori infection detection by breath test or stool antigen
- HBV, HIV, HCV
- Quantitative immunoglobulins
- DAT, ANA, TSH, Anti-PL Abs
- Other testing in selected individuals (platelet-specific ab, imaging)
- Bone marrow in select individuals

Diagnosis of exclusion

- Pseudothrombocytopenia (review smear!)
- Liver/renal disease
- MDS/Leukemia/SAA(Smear, BM biopsy, Flow cytometry, cytogenetics)
- Inherited T.penia (smear, MPV, genomic testing)
- TTP (neuro/cardiac symptoms, schistocytes, ADAMTS13, DAT neg. hemolytic anemia)
- HIT/DITP (prior VTE, heparin exposure, PF-4 Ab tests, SRA)

Provan D et al. Blood Adv. 2019

Initial treatment of ITP

Treatment type/parameter	ASH 2020[1]	ICR Recommendations[2]
Platelet count threshold for treatment	≤30 × 10^9/L	<20-30× 10^9/L Individualize to patient & phase
First-line treatment	Corticosteroids (prednisone, or dexamethasone) taper off by 6 weeks	same
First-line treatment if corticosteroids are contraindicated	IVIg or anti-D	same
Emergency treatment	IVIg plus corticosteroids	High-dose IV corticosteroids plus IVIg platelet transfusions antifibrinolytic drugs

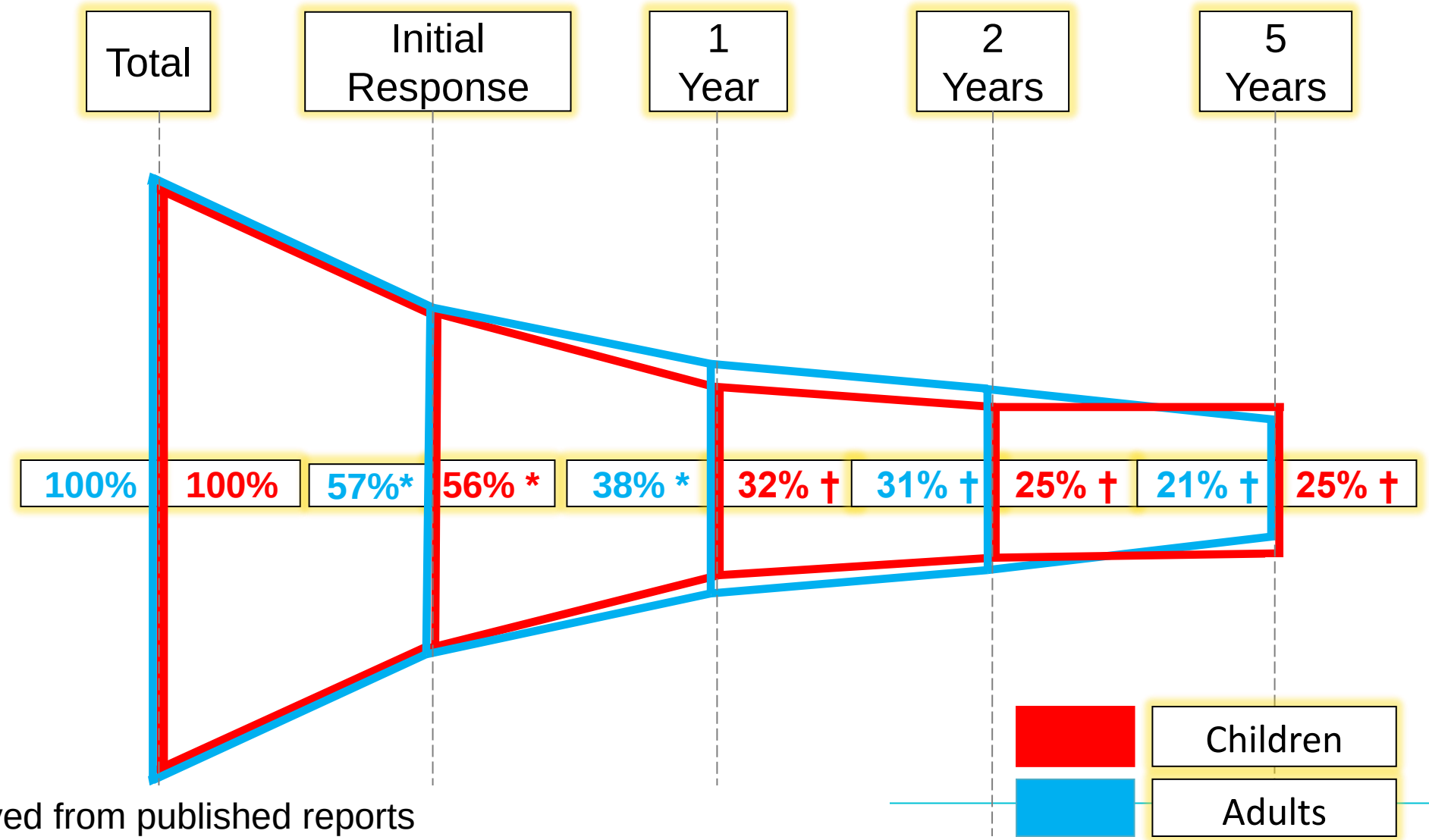
Neunert C et al. Blood Adv. 2019
Provan D et al. Blood Adv. 2019

Treatment of persistent/chronic ITP

Treatment type/parameter	ASH 2020[1]	ICR Recommendations[2]
Platelet count threshold for treatment	≤30 × 10^9/L	Treat to maintain platelet count >20-30× 10^9/L Individualize to patient & phase, minimize toxicity
Subsequent therapy	TPO receptor agonists Rituximab Splenectomy	TPO receptor agonists Rituximab Fostamatinib Splenectomy
Agents with less robust evidence /subsequent treatment	Azathioprine Cyclosporin A Cyclophosphamide Danazol	Dapsone Mycophenolate mofetil Vinca alkaloids TPO RA switch

Neunert C et al. Blood Adv. 2019
Provan D et al. Blood Adv. 2019

Summary of response to rituximab in ITP

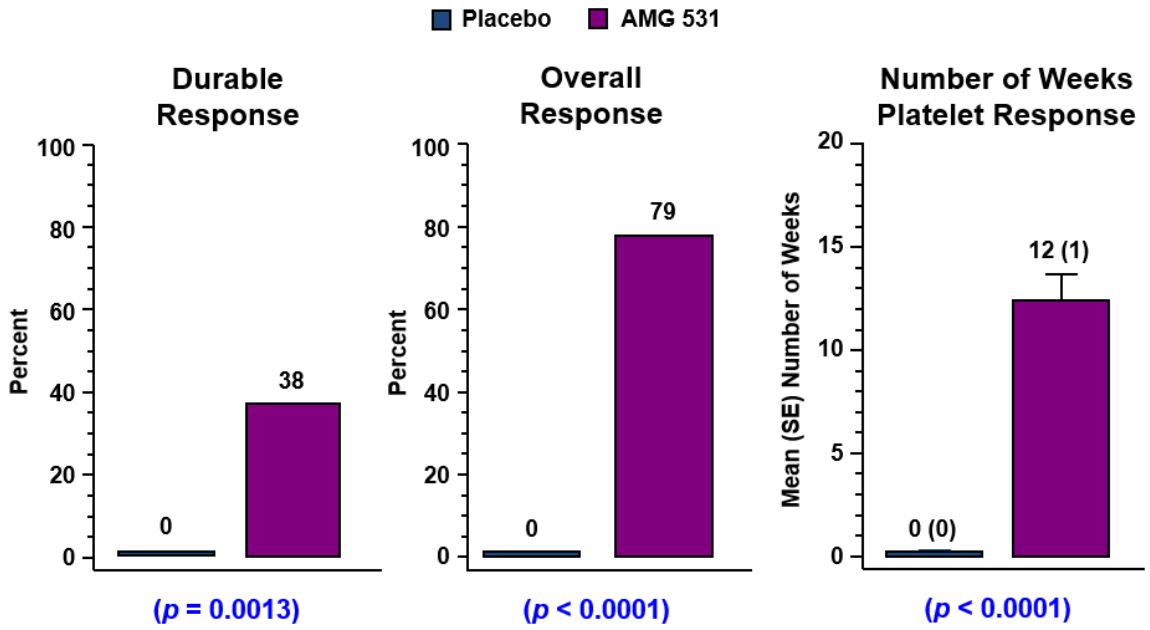


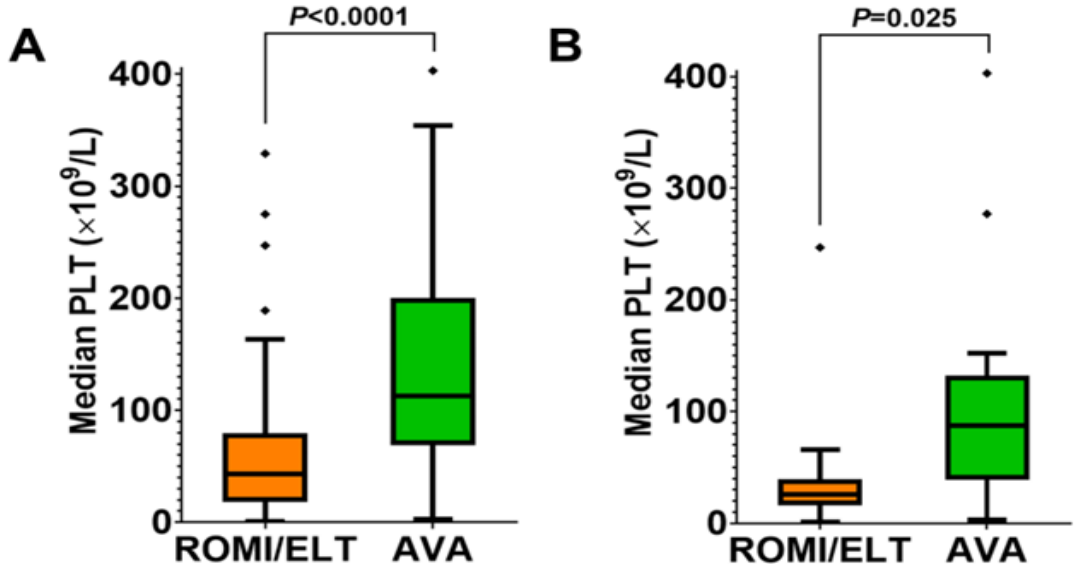
* Derived from published reports

† Long-term follow up data acquired in this study

Patel VL, et al. ASH 2010 Abstract 72

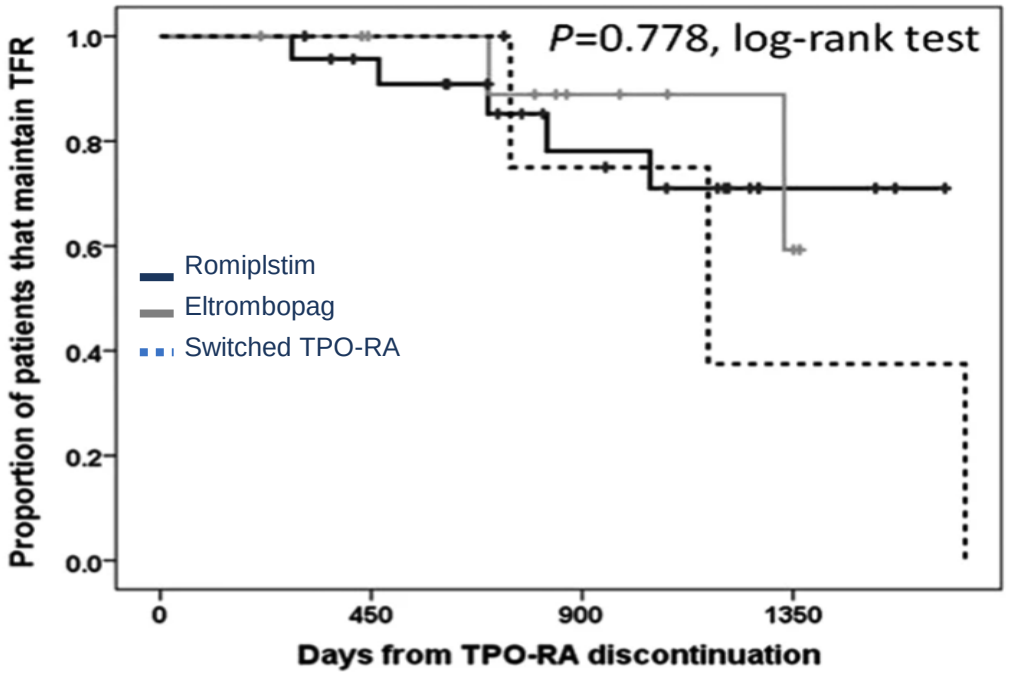
Summary of response to TPO-RAs in ITP





Al-Samkari et al. Brit. J. Heme 2022 *Gernsheimer T, et al. Blood 2007*

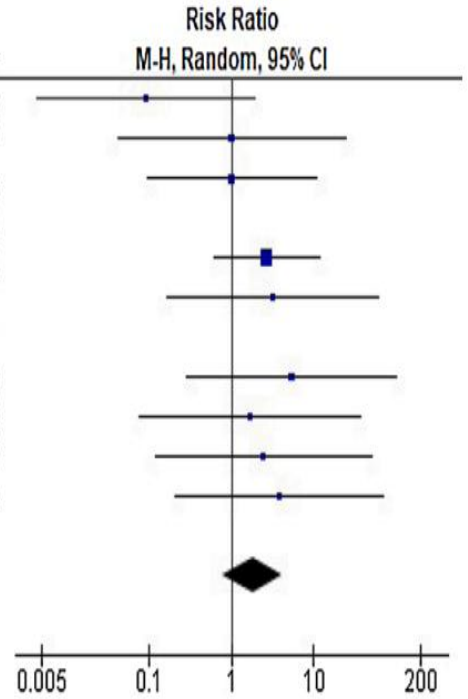
Summary of response to TPO-RAs in ITP



Study or Subgroup	TPO-RA Events	TPO-RA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Bussel et al. 2006	0	17	1	4	7.7%	0.09 [0.00, 1.94]	2006
Bussel et al. 2007	1	88	0	29	7.1%	1.01 [0.04, 24.17]	2007
Kuter et al. 2008	2	83	1	42	12.7%	1.01 [0.09, 10.84]	2008
Bussel et al. 2009	0	76	0	38		Not estimable	2009
Kuter et al. 2010	11	157	2	77	32.4%	2.70 [0.61, 11.87]	2010
Cheng et al. 2011	3	135	0	62	8.2%	3.24 [0.17, 61.84]	2011
Shirasugi et al. 2011	0	22	0	12		Not estimable	2011
Haselboeck et al. 2012	2	11	0	12	8.3%	5.42 [0.29, 101.77]	2012
Tomiyama et al. 2012	1	15	0	8	7.4%	1.69 [0.08, 37.26]	2012
Yang et al. 2016	2	104	0	51	7.8%	2.48 [0.12, 50.64]	2016
Jurczak et al. 2018	3	32	0	17	8.4%	3.82 [0.21, 69.88]	2018
Total (95% CI)		**740**		**352**	**100.0%**	**1.82 [0.78, 4.24]**	
Total events	25		4				

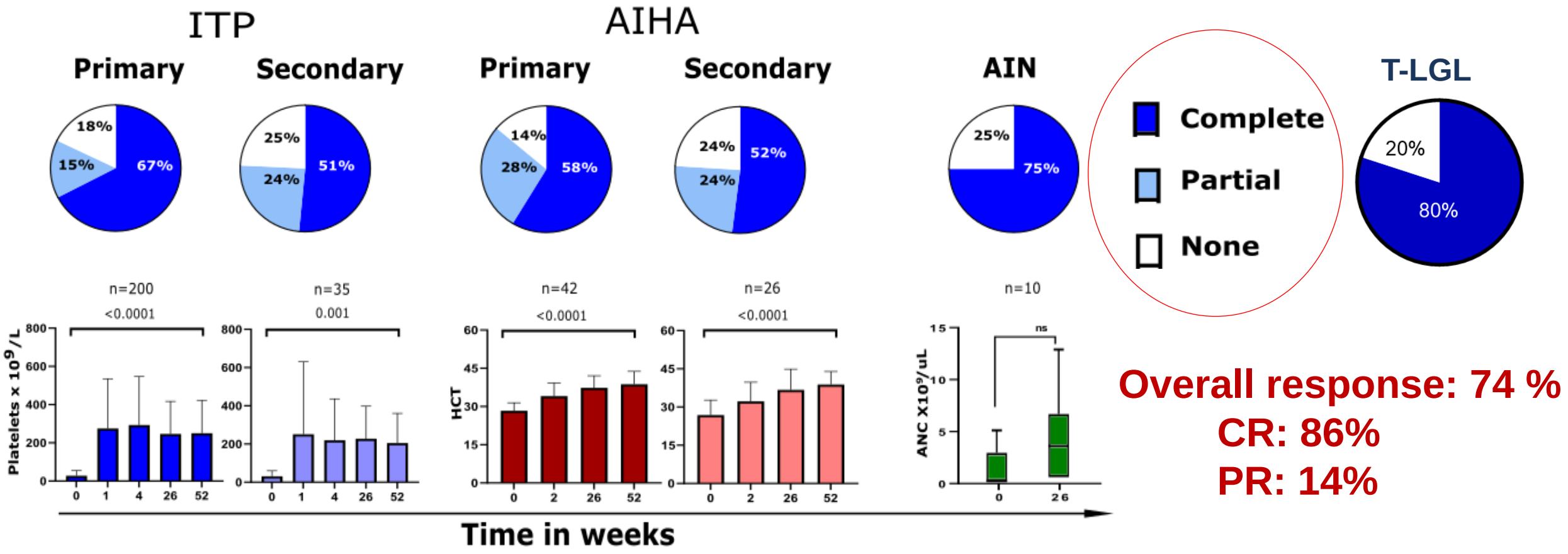
Heterogeneity: Tau² = 0.00; Chi² = 5.30, df = 8 (P = 0.73); I² = 0%

Test for overall effect: Z = 1.39 (P = 0.16)



Lozano et al. Sci Rep 2019
Tjepkema et al. Crit rev Oncol Hematol 2022

Response to splenectomy in immune cytopenia



Overall response: 74 %
CR: 86%
PR: 14%

Ogbue et al. Blood (2022) 140 (Supplement 1): 1226–1227.

Post splenectomy discordant diagnoses

20% of the cases had a post-operative diagnosis that was discordant with the original indication for splenectomy

Splenectomy indication	Post operative pathologic diagnoses	Frequency (n)
AIHA (6), ITP (7), ES (2)	B-cell lymphoproliferative disorder including DLBCL	15
AIHA (3), ITP (7), ES (2)	Chronic lymphocytic leukemia/Small lymphocytic lymphoma	12
AIN (1), ES (1)	Felty's syndrome	2
ES (4)	Hepatosplenic T-cell lymphoma	4
AIHA, ITP (4)	Non caseating granulomas	5
ES (2)	Peripheral T-cell lymphoma	2
AIHA (5), AIN (6), ES (4)	T-LGL	15

Ogbue et al. Blood (2022) 140 (Supplement 1): 1226–1227

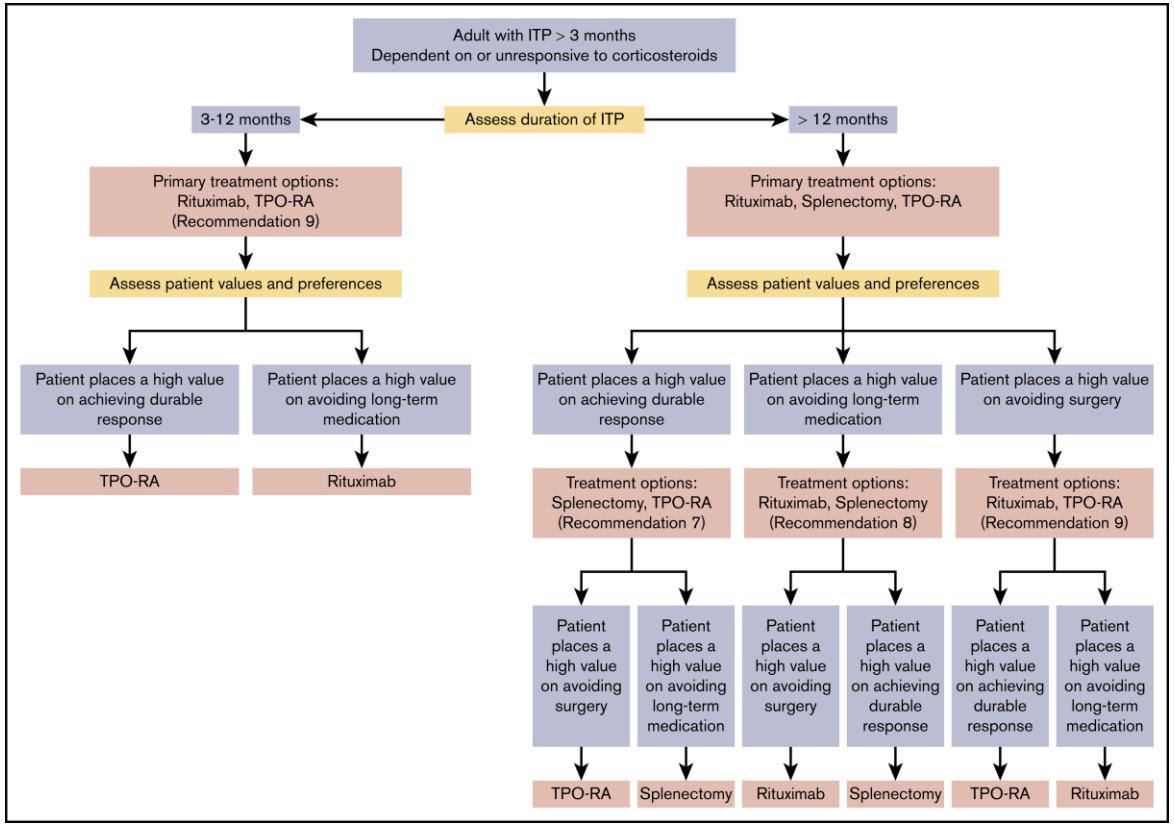
Thrombocytopenia: Question 2

42yo female with Immune thrombocytopenia (ITP) diagnosed 1 year ago (platelet nadir $3X10^9$/L) and responded to a short course of steroids ($120X10^9$/L) now presents with platelet counts of $40X10^9$/L. Counts repeated within a week are still at $40X10^9$/L. She reports no bleeding/bruising. What are her management options?

A. Initiate TPO-RA
B. Re dose prednisone +/- IVIG
C. Initiate rituximab
D. Observe
E. Refer for splenectomy

American Society of Hematology 2019 guidelines for immune thrombocytopenia

Cindy Neunert,[1] Deirdra R. Terrell,[2] Donald M. Arnold,[3,4] George Buchanan,[5] Douglas B. Cines,[6] Nichola Cooper,[7] Adam Cuker,[8] Jenny M. Despotovic,[9] James N. George,[2] Rachael F. Grace,[10] Thomas Kühne,[11] David J. Kuter,[12] Wendy Lim,[13] Keith R. McCrae,[14] Barbara Pruitt,[15] Hayley Shimanek,[16] and Sara K. Vesely[2]



Treatment of drug induced thrombocytopenia

- DITP is less likely if platelet nadir >20X10^9/L
- Stop offending agent(s)
- Severe: IVIg
- Severe refractory: Plasma exchange

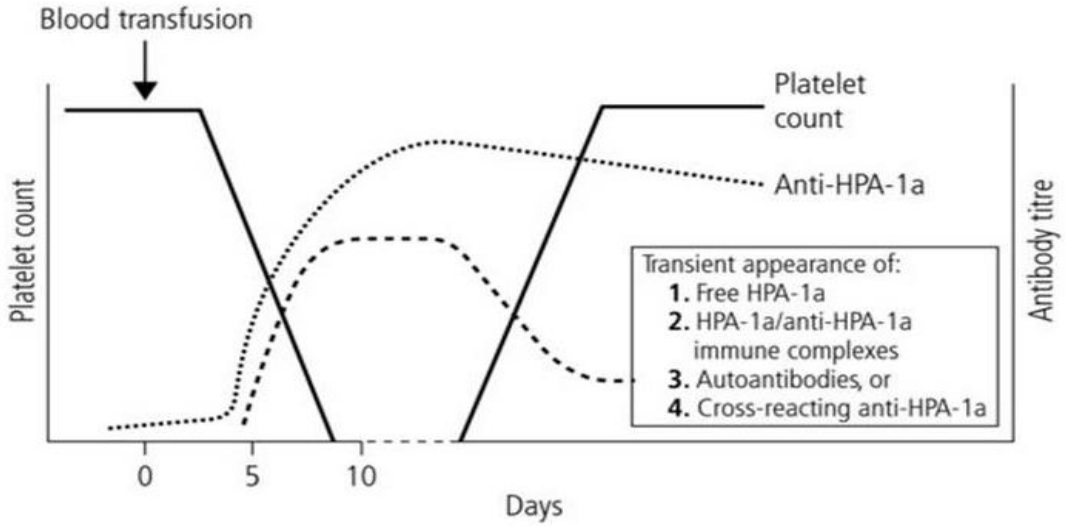
  Dialysis
- Severe adjunctive therapy
  - Platelet transfusions
  - Antifibrinolytic agents
- Testing for drug dependent antibody

Quinine, sulfonamide antibiotics, non-steroidal anti-inflammatory drugs
Penicillin, some cephalosporin antibiotics
Tirofiban, Eptifibatide
Abciximab
Gold salts, procainamide
Heparin, an as yet unidentified component of adenoviral vector-based vaccine against COVID-19

Marini et al. Haematologica 2022

Post-transfusion purpura

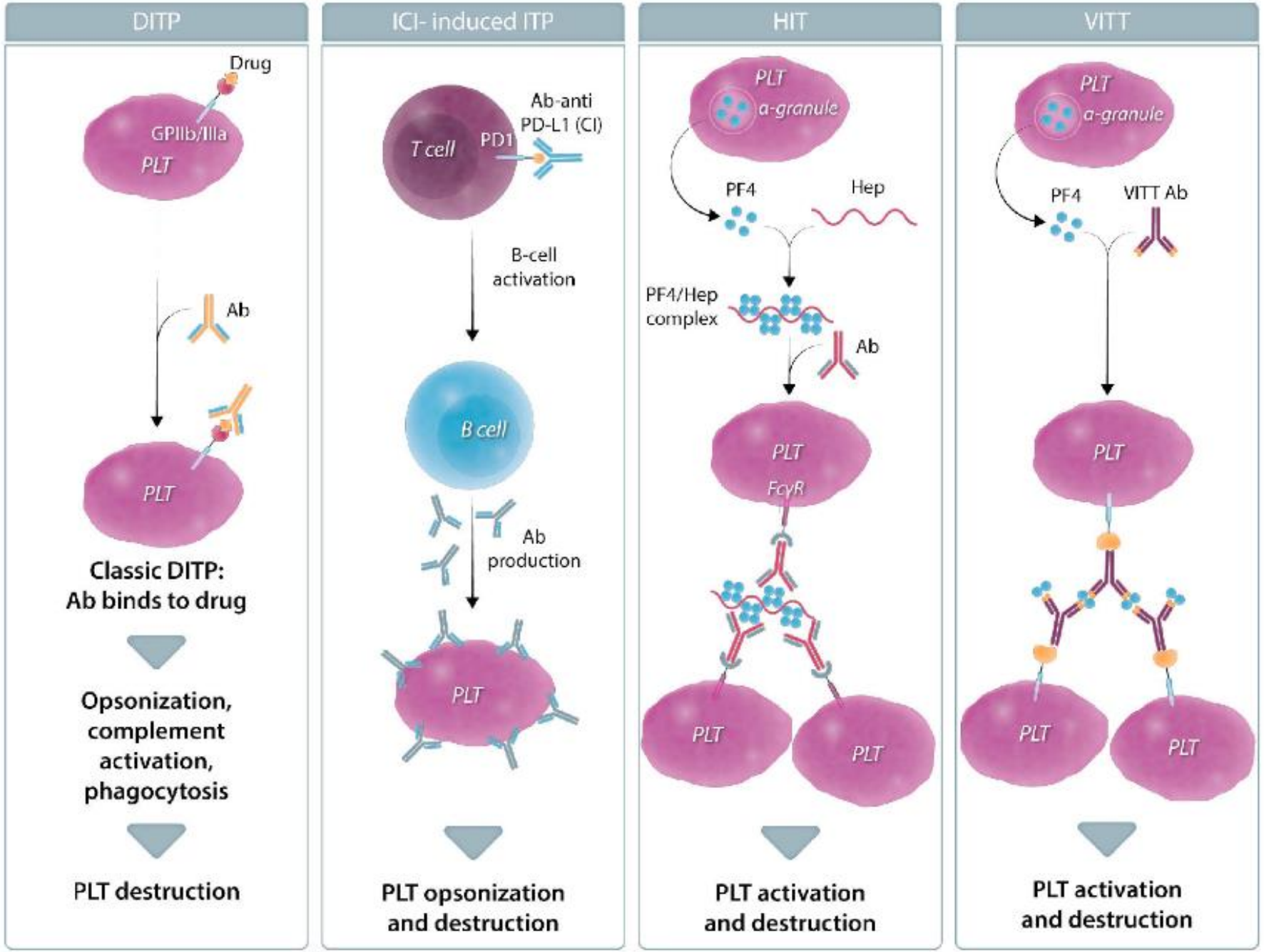
- PTP: transfusion related AE; sometimes with severe bleeding
- Symptomatic overlap with other thrombocytopenia (ITP, dITP, TTP, HIT)
- Thrombocytopenia may be severe (<10,000 K/uL)
- Incidence: 1:24,000 to 1:50,000–100,000 transfusions
- Higher in multiparous women



- Anti-HPA-1a made by HPA-1b/1b recipients, genotype in ~2% Caucasians
- Prior exposure to antigen; re-exposure of antigen through transfusion→ anamnestic alloimmune response
- Management: IVIG, steroids, PLEX; Caution with Txns.

Hawkins et al. JBM (2019)

HITT/VITT



Mirini et al. Haematologica 2022

HIT/VITT: PF4 disorders

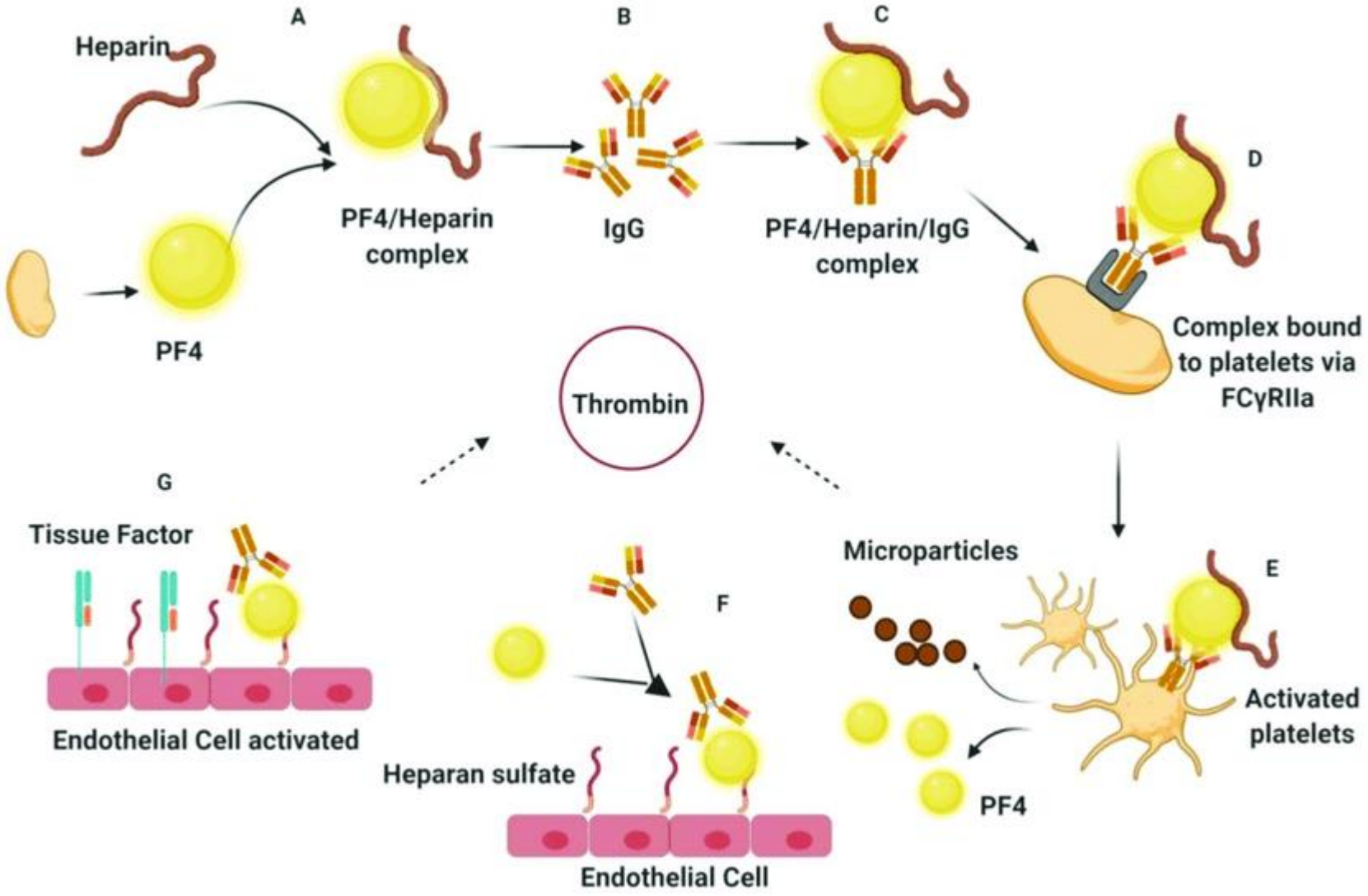
- Thrombocytopenia with or without thrombosis (“clinical” criteria)
- Detectable antibodies that recognize PF4, and that cause platelet activation (“pathological” criteria)

- Since antibody mediated, 5-10 days from the initial exposure to trigger to thrombocytopenia
- Consequences: Pan-cellular activation→ endothelial damage; PF4 binding on vWF → arterial and venous thrombosis

- VITT vs. HIT: higher CVT (30% vs 95%), higher DIC (~ 50%), ~15%-20% arterial thrombosis (similar in VITT and HIT)
- Vaccination benefits far outweigh risk of VITT (linked to the ChAdOx1 CoV-19 vaccine (AstraZeneca) and the Ad26. COV2.S vaccine (Johnson & Johnson/Janssen) adenoviral vaccines)

Warkentin Semin in Hematol. 2022

HIT: Pathophysiology



Warkentin Semin in Hematol. 2022

Clinical scoring system for HIT pretest probability: "The 4Ts"

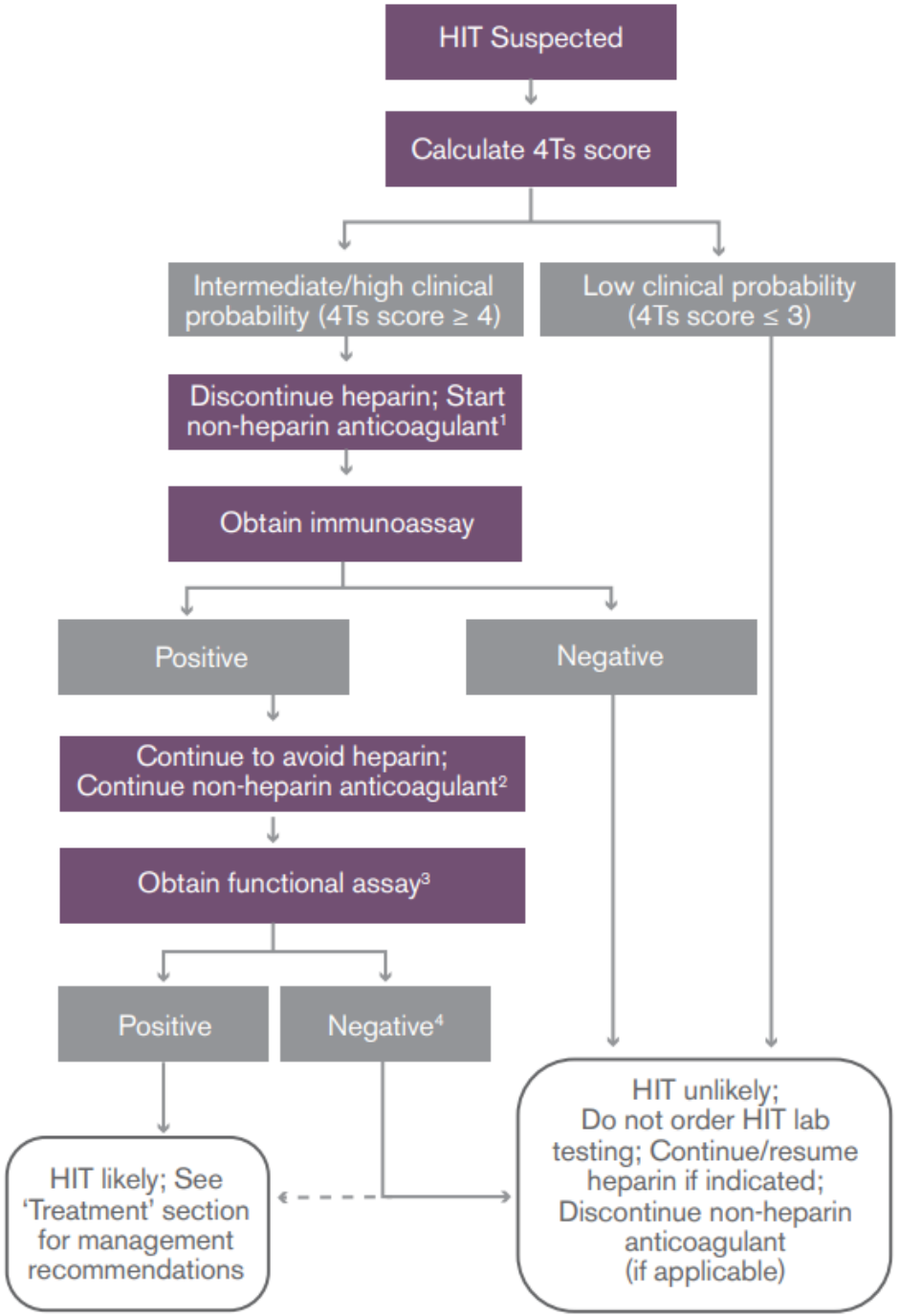
Table 1 Pretest scoring system for HIT: the 4 T's

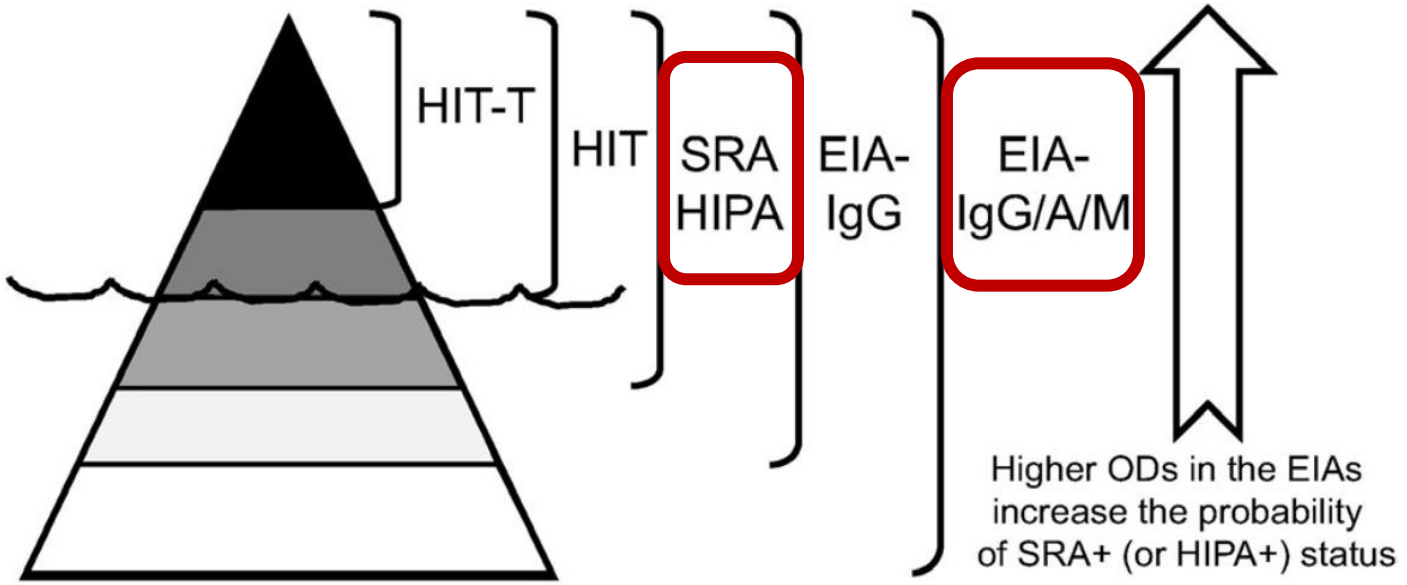
4T's	2 points	1 point	0 point
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥20*	Platelet count fall 30–50% or platelet nadir 10–19	Platelet count fall <30% or platelet nadir <10
Timing of platelet count fall	Clear onset between days 5–10 or platelet fall ≤1 day (prior heparin exposure within 30 days)†	Consistent with days 5–10 fall, but not clear (e.g. missing platelet counts); onset after day 10‡; 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§; acute systemic reaction postintravenous unfractionated heparin (UFH) bolus	Progressive or recurrent thrombosis¶; Non-necrotizing (erythematous) skin lesions§; Suspected thrombosis (not proven)**	None
Other causes for thrombocytopenia	None apparent	Possible††	Definite††

0-3 Points: Low pretest probability of HIT; lab testing not indicated; **4-5 Points: Intermediate pretest probability of HIT;**
6-8 Points: High pretest probability of HIT

Lo et al (2006) Journal of Thrombosis and Hemostasis

Diagnosis of HIT

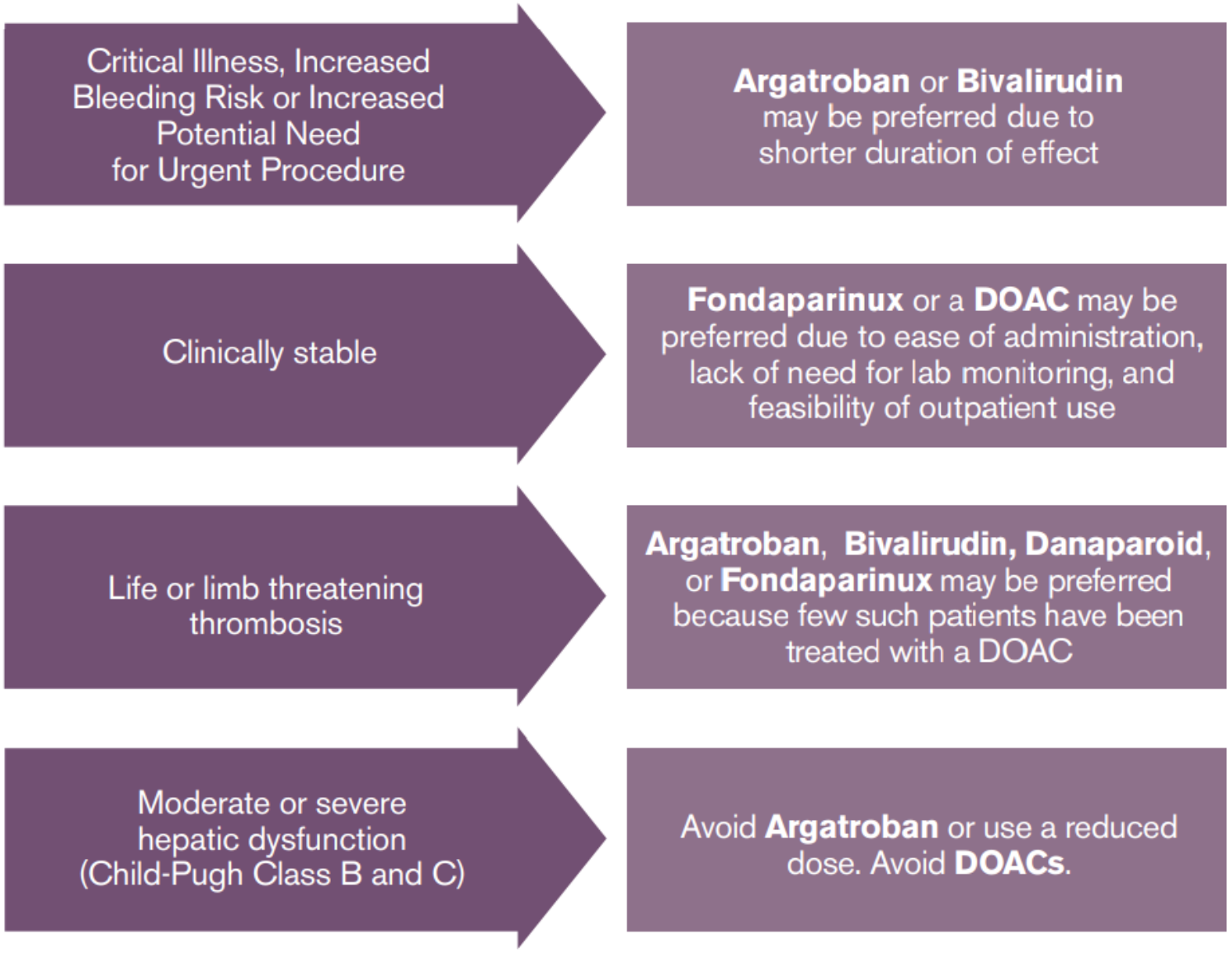




EIA-IgG/A/M result (OD units):	≤0.4	0.4-1.0	1.0-1.5	1.5-2.0	>2.0
Probability of SRA+ status:	~0%	~5%	~25%	~50%	~90%

Warkentin T.E. (2019), Int J Lab Hematol
Cuker et al, Blood Adv 2018

Management of HIT



Cuker et al, Blood Adv 2018

Management of HIT: Other considerations

Cardiac surgery if HIT positive

- Delay 3-6 months
- Antibody (ELISA) Neg
- Expose during CPB only
- Use alternate anticoagulation post-op
- Experimental:
  - Plasma Exchange
  - IVIg

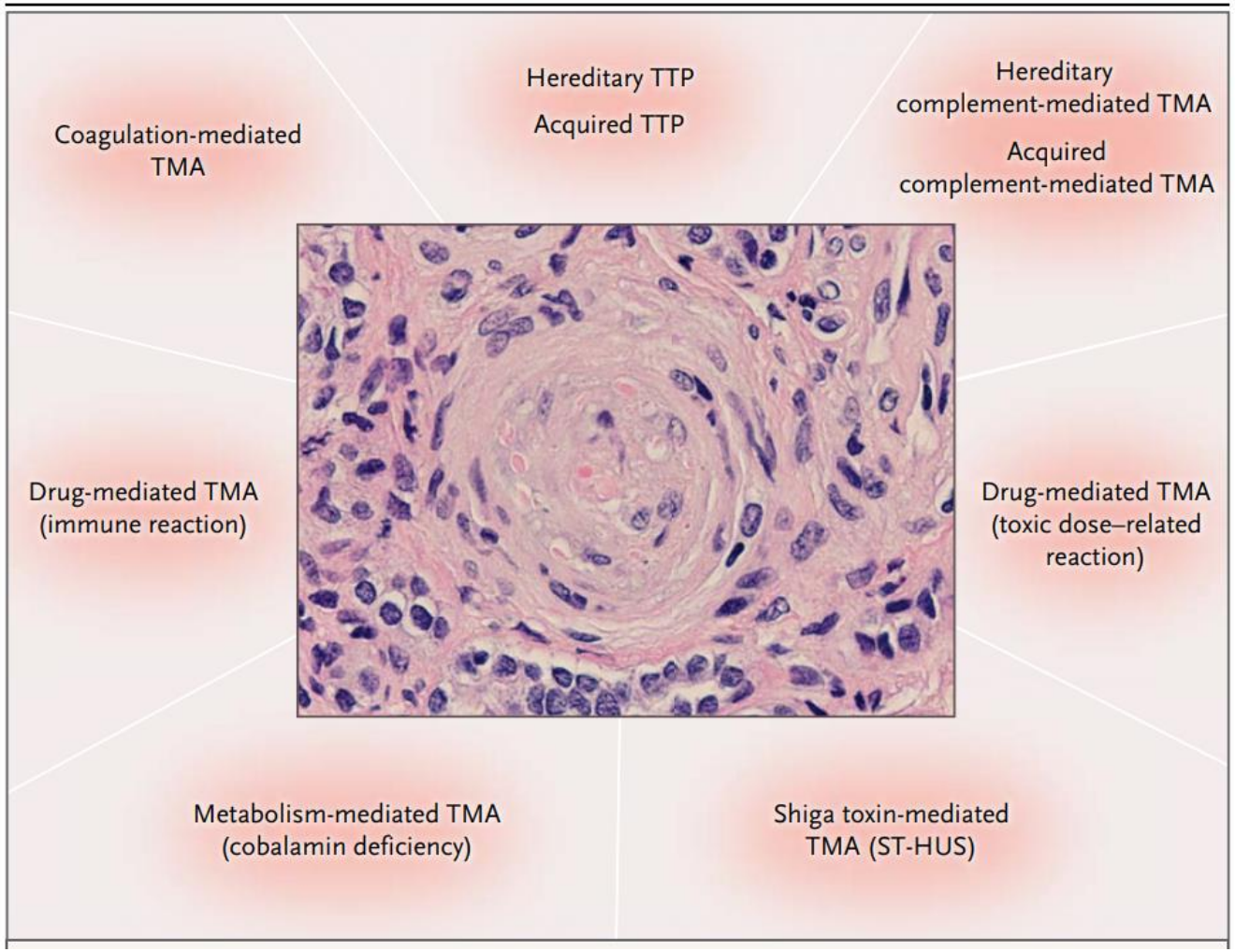
Cuker et al, Blood Adv 2018

Thrombotic Microangiopathy Syndromes

In Manhattan **1924**, **Dr. Eli Moschcowitz** described the case of a **16-year-old girl,** who died after hospitalization for an acute illness displaying **high fever, pallor, arm pain, petechiae, paralysis of the left arm and leg, and a preterminal coma.** The **autopsy revealed multiple 'hyaline' thrombi in the heart muscle vessels, the congested spleen, and kidneys**. The disease cause and right treatment remained elusive…similar cases seen by Dr. Max Lederer **had clinical improvement following blood transfusions**..

Moschcowitz E. Hyaline thrombosis of the terminal arterioles and capillaries: a hitherto undescribed disease. Proc New York Pathol Soc 1924;

Thrombotic microangiopathies



End-organ damage

- Renal
- Neurologic
- GI tract
- Cardiovascular
- Pulmonary
- Visual

Thrombocytopenia

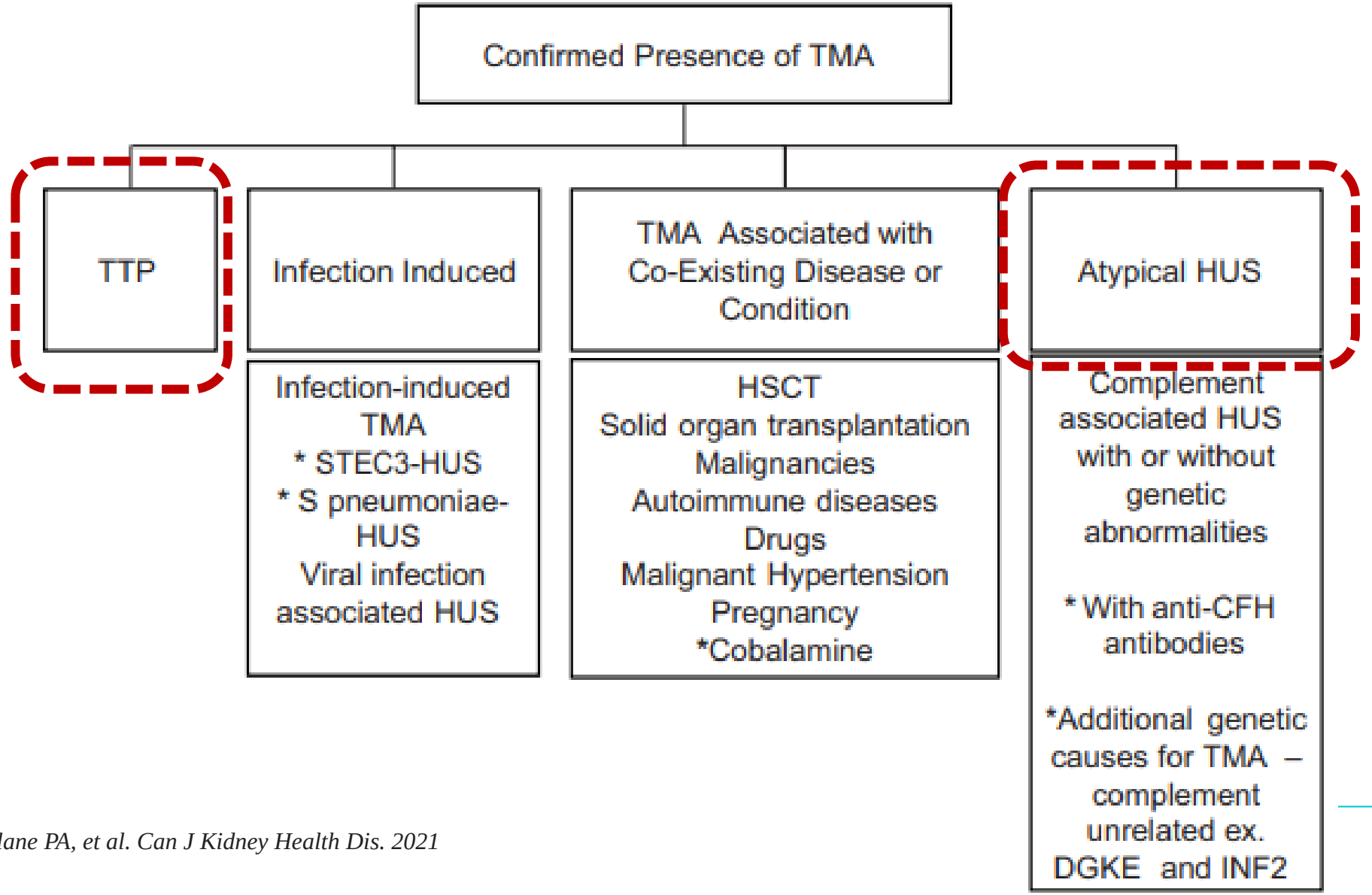
- Plts<150K/uL/ >25% decrease from baseline
- Plts <100K/uL in pregnancy

MAHA

- Anemia: Hb<10gm/dL
- Schistocytes on smear
- Elevated LDH + decreased haptoglobin
- Indirect bilirubinemia
- Hemoglobinuria

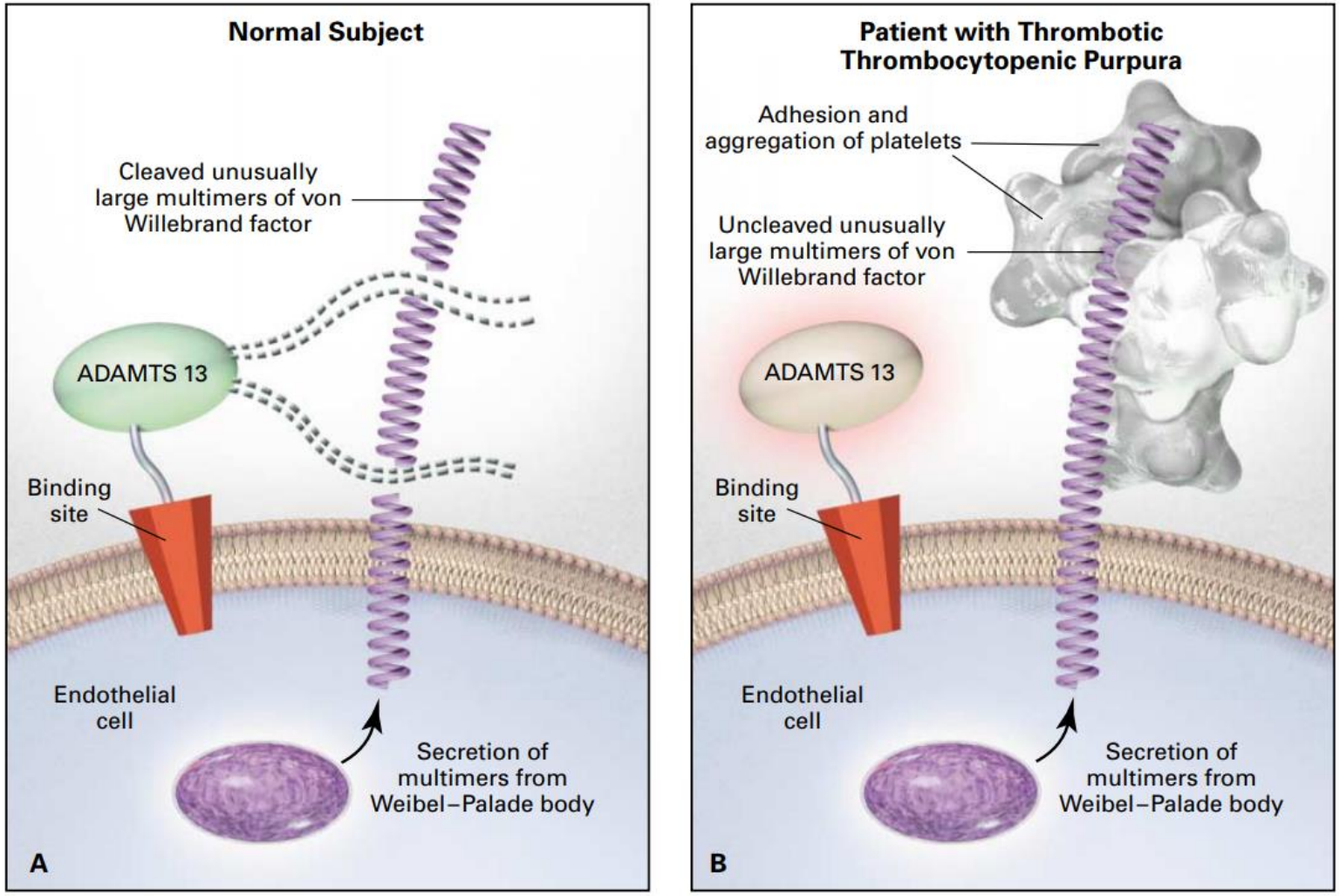
George and Nester NEJM 2014

Thrombotic microangiopathy syndromes



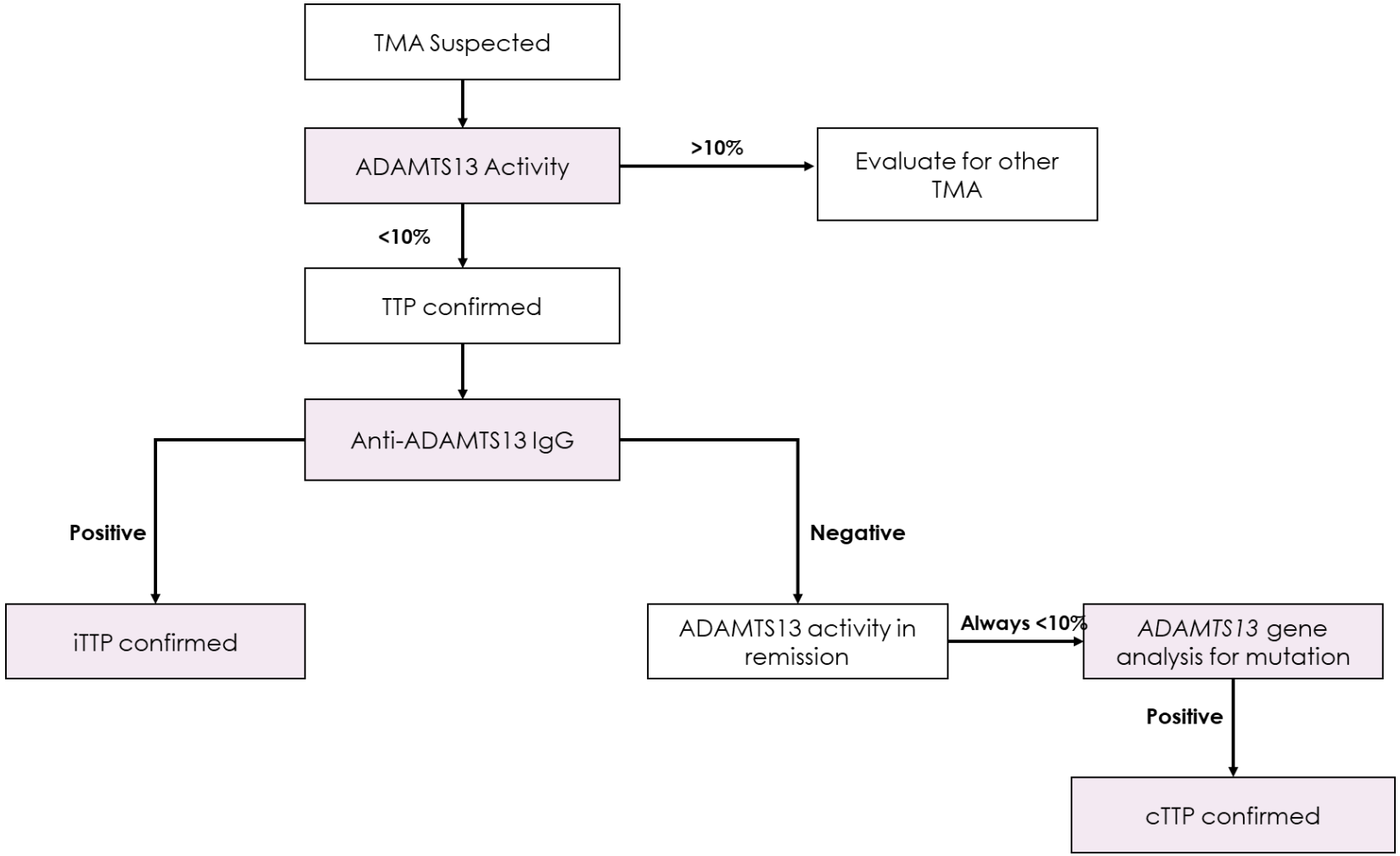
McFarlane PA, et al. Can J Kidney Health Dis. 2021

Pathophysiology of TTP



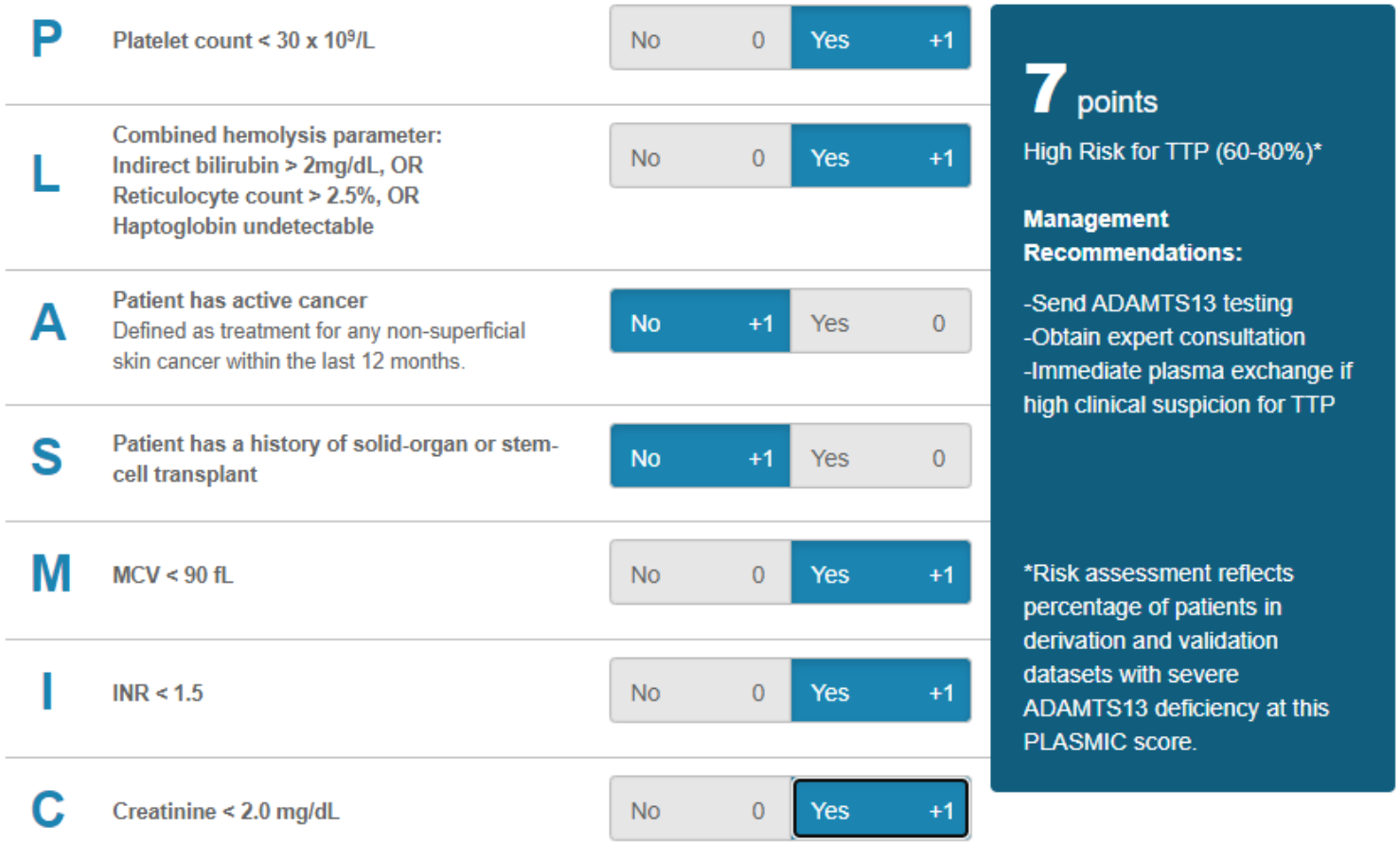
Moake NEJM 2002

TTP: Diagnosis



Adapted from Sukumar et al. J. Clin. Med. 2021

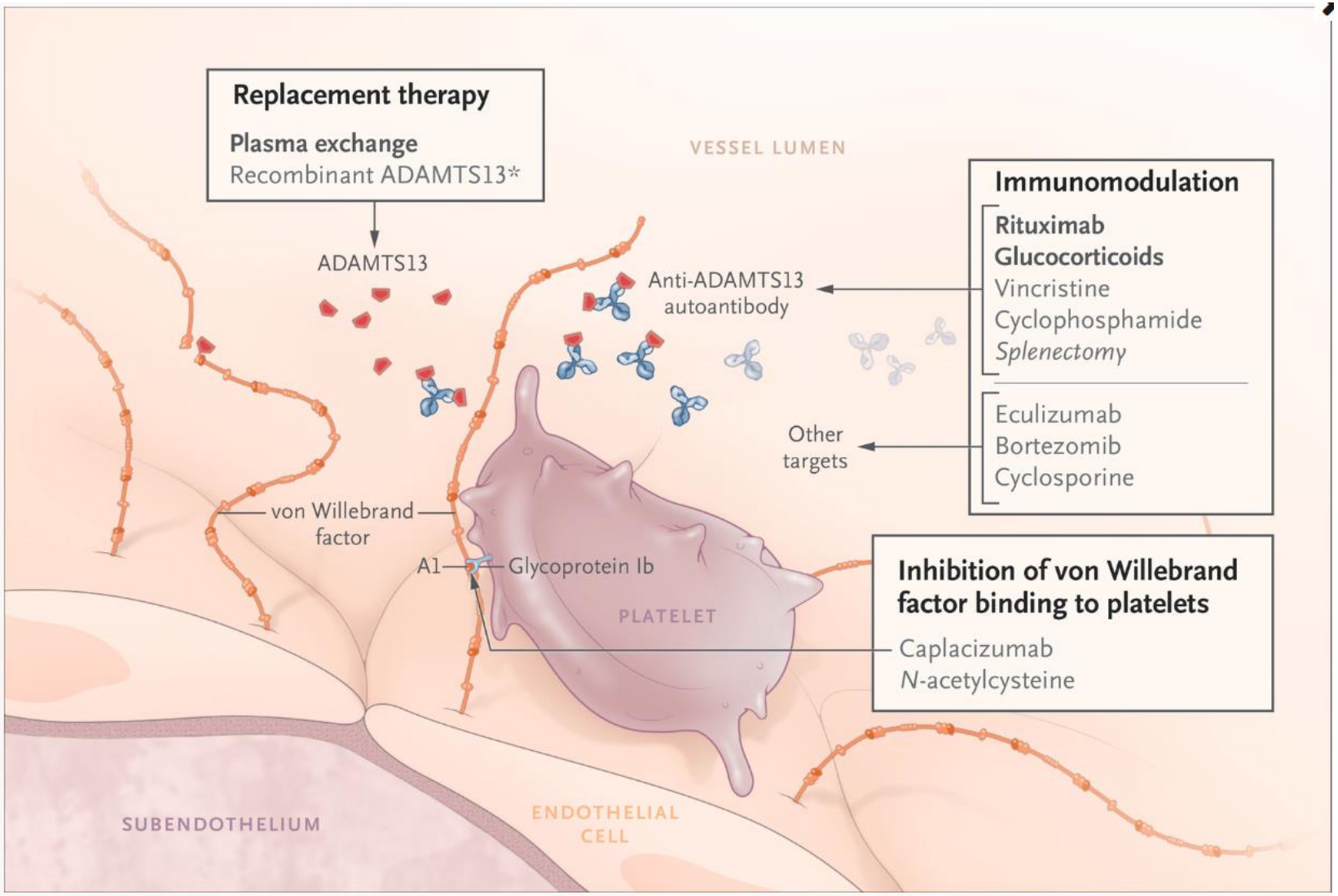
TTP: Diagnosis



>80% of patients in the derivation cohort with a PLASMIC score of 6-7 had severe ADAMTS13 deficiency, and those with confirmed TTP had a median score of 7

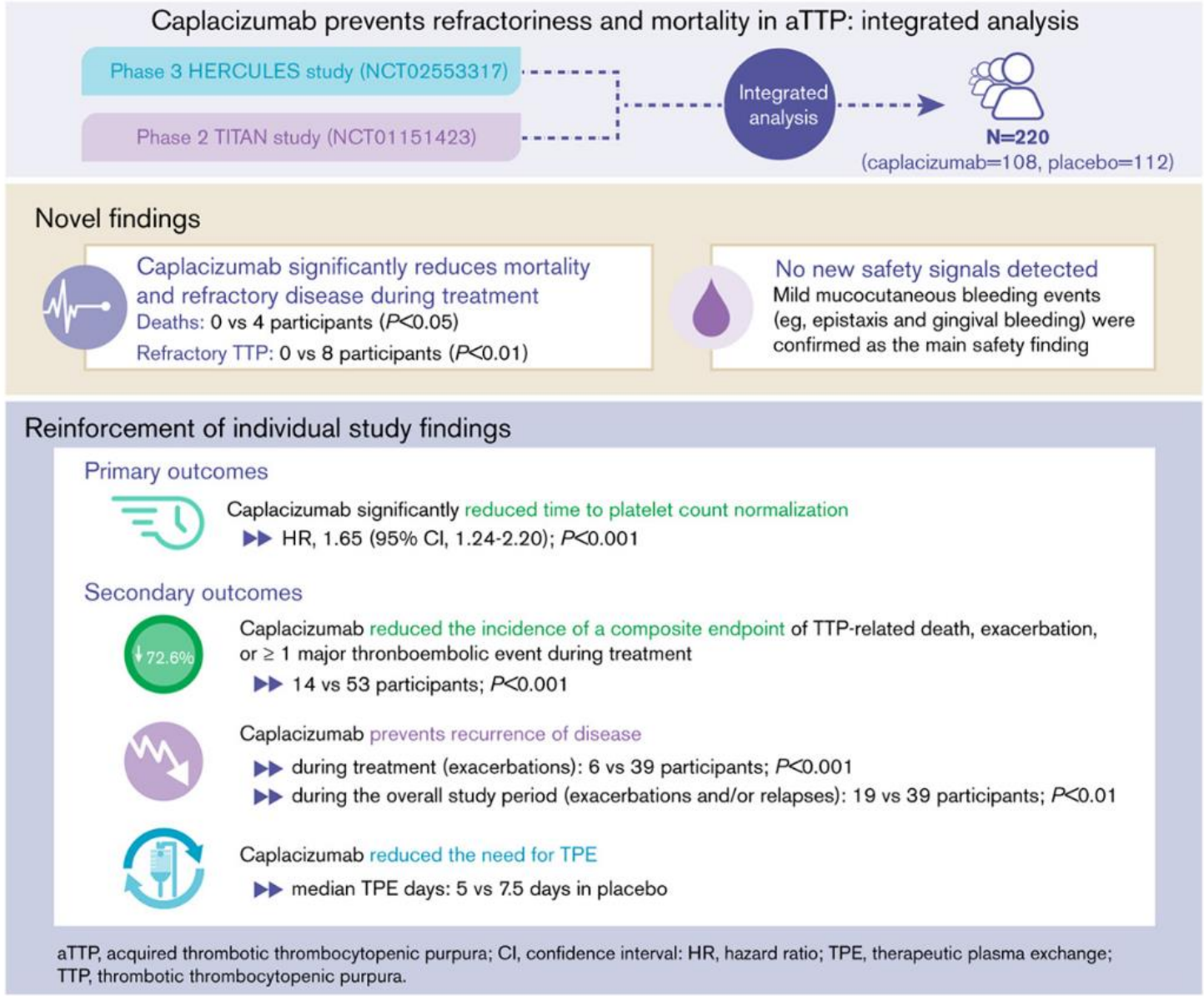
Bendapudi, Lancet Haematology (2017)

TTP: Management



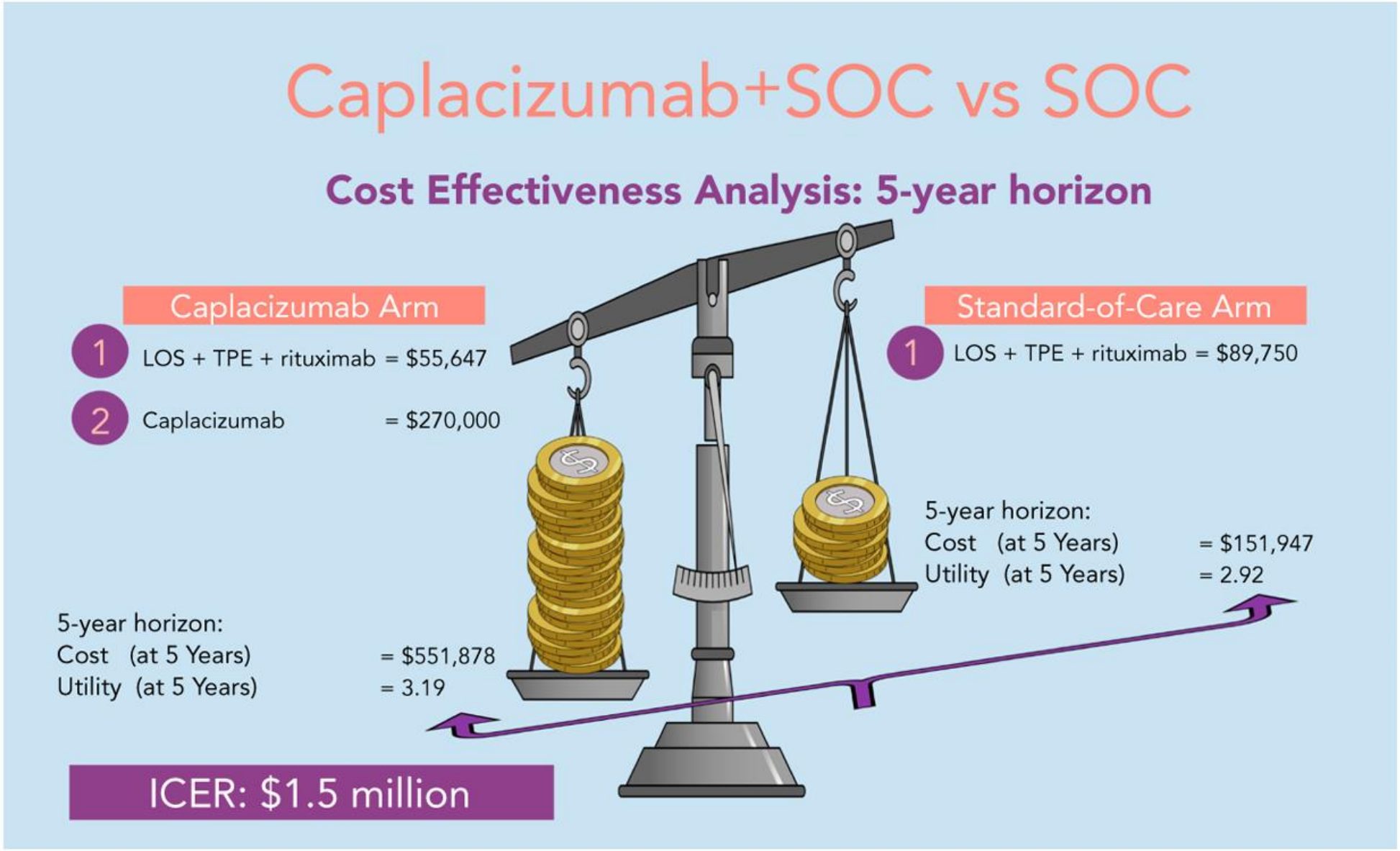
NEJM 2019

TTP: Management



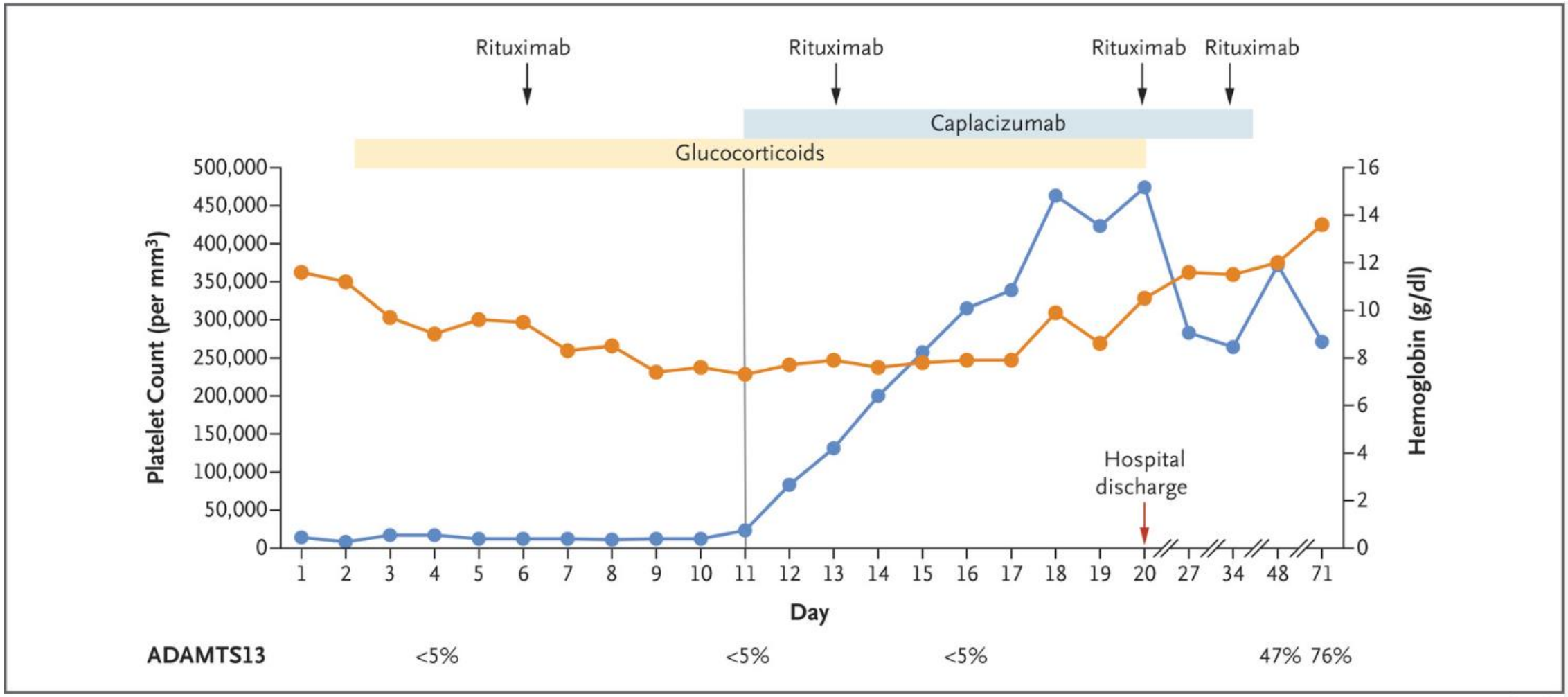
Peyvandi, F., et al. (2021). Blood Advances

TTP: Management



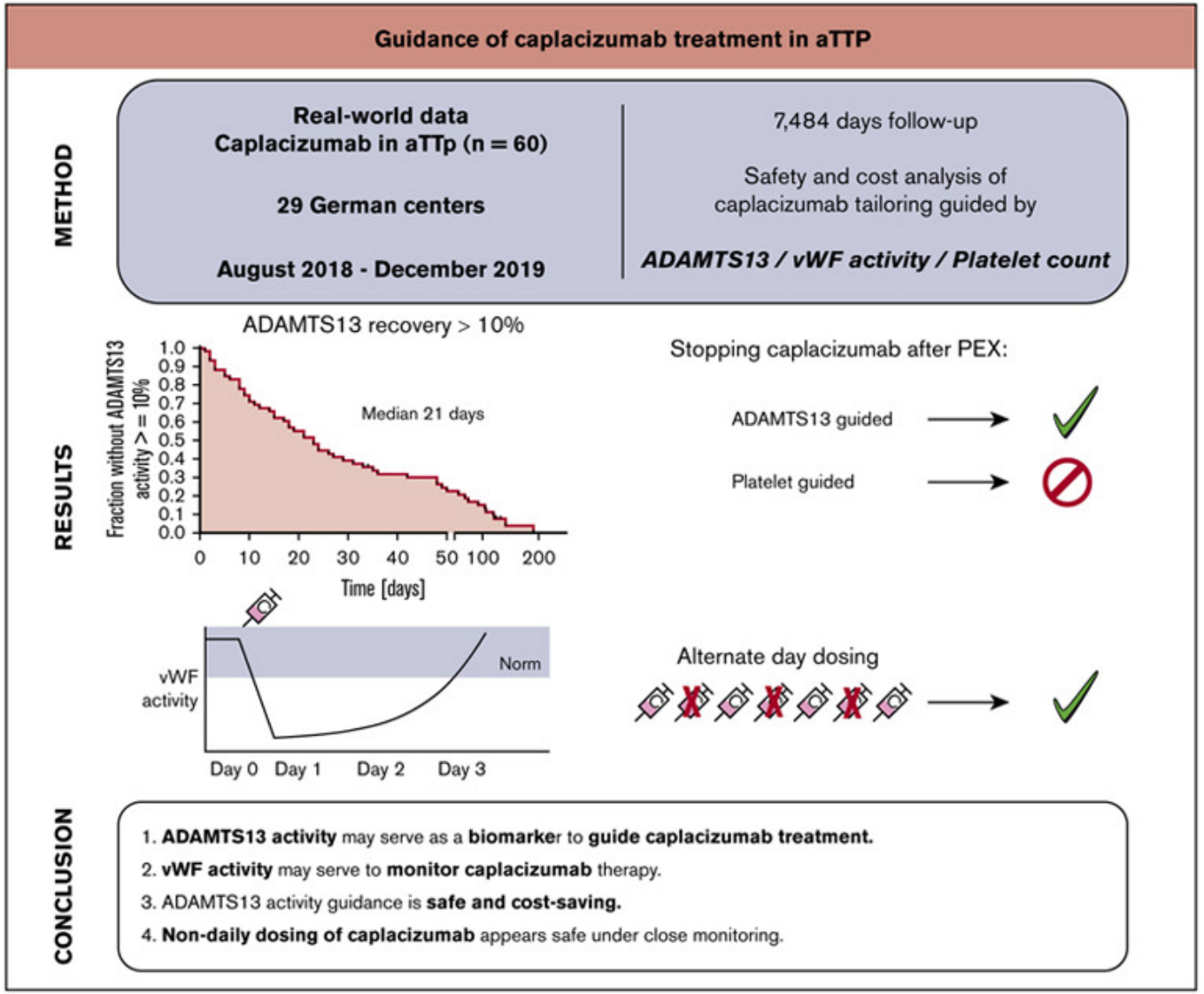
Goshua et al. Blood (2021)

TTP: Management



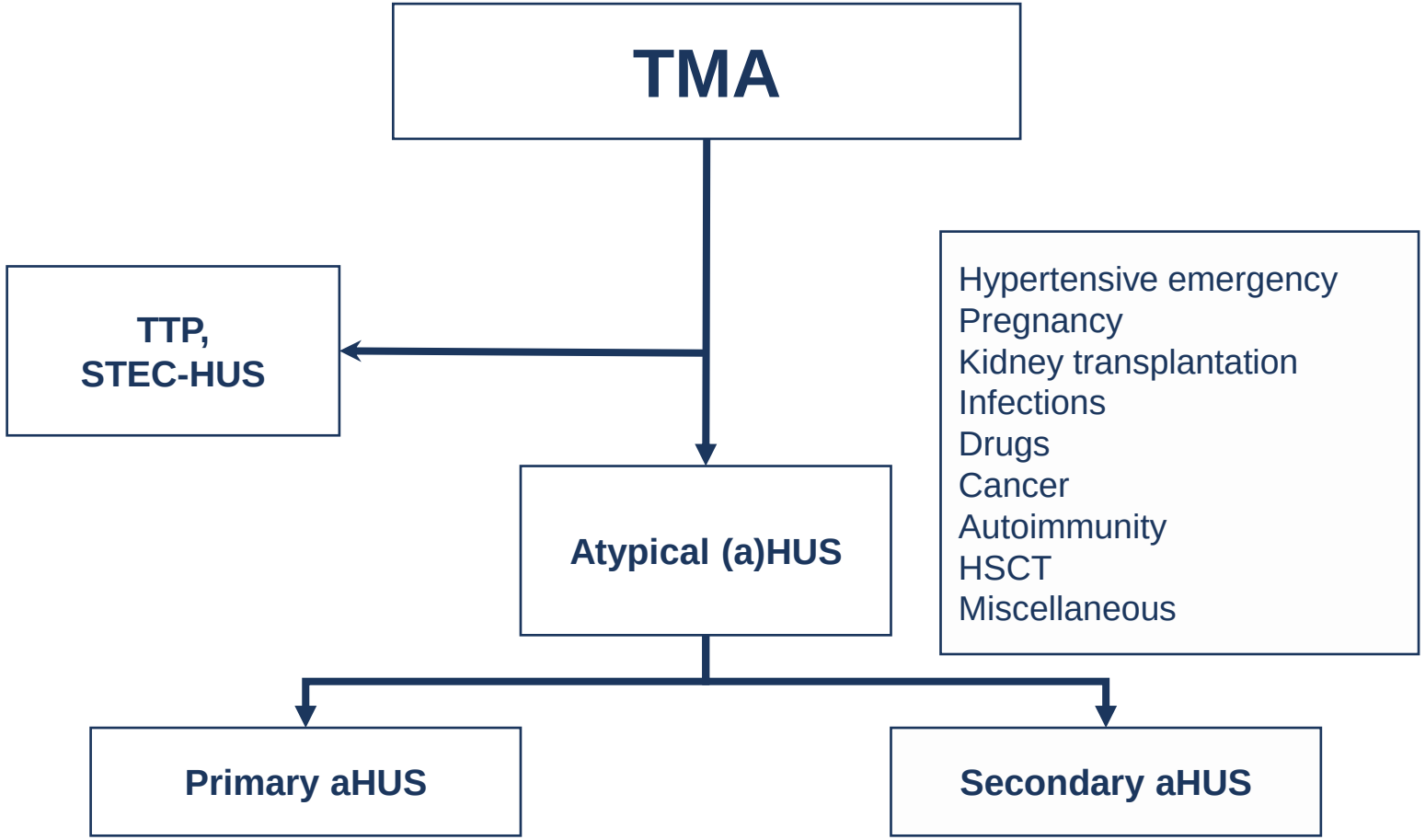
Chander, D. P., et al. (2019). NEJM

TTP: Management

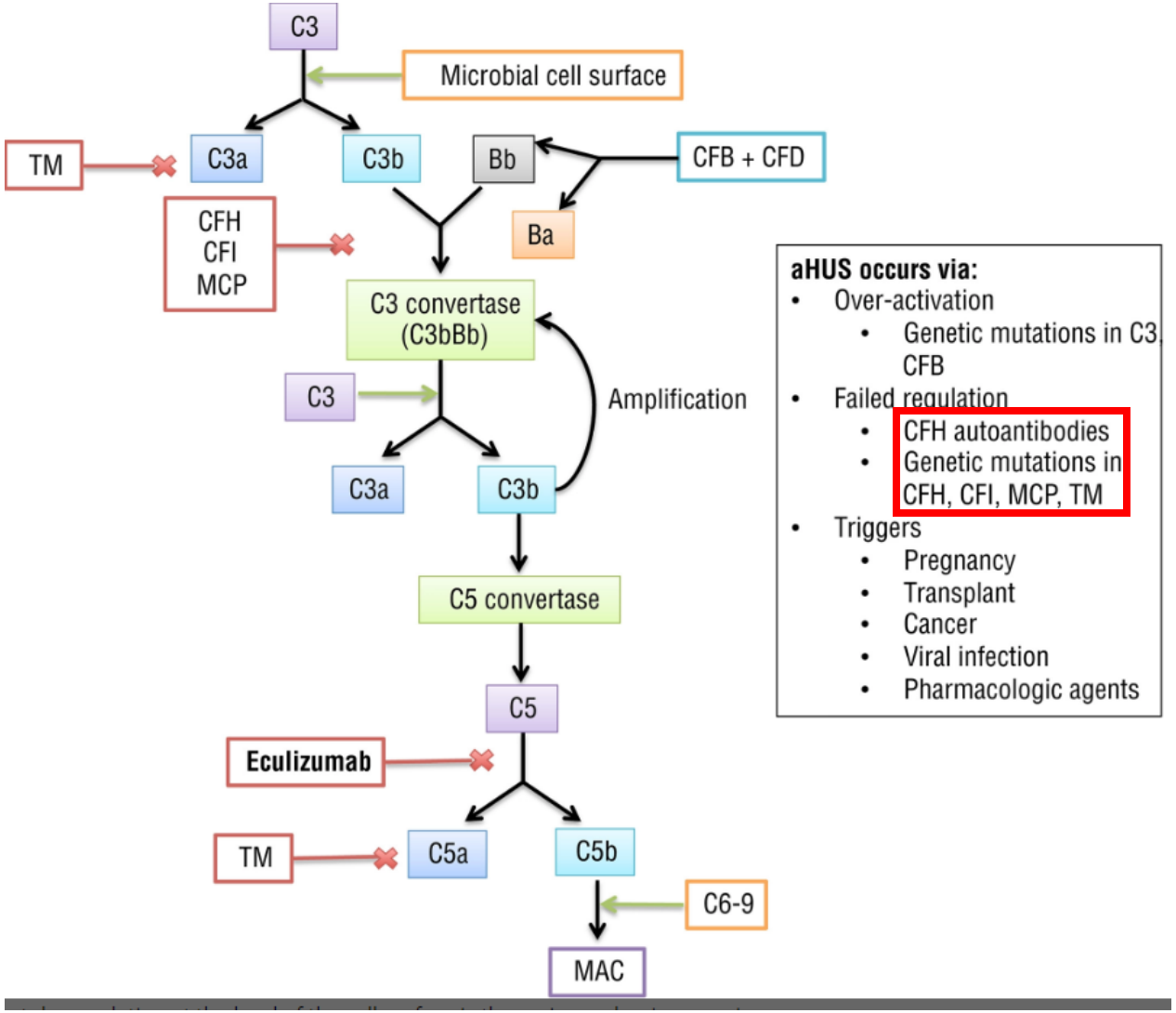


Völker, L. A., et al. (2020). Blood Advances

Atypical Hemolytic Uremic Syndrome (aHUS)

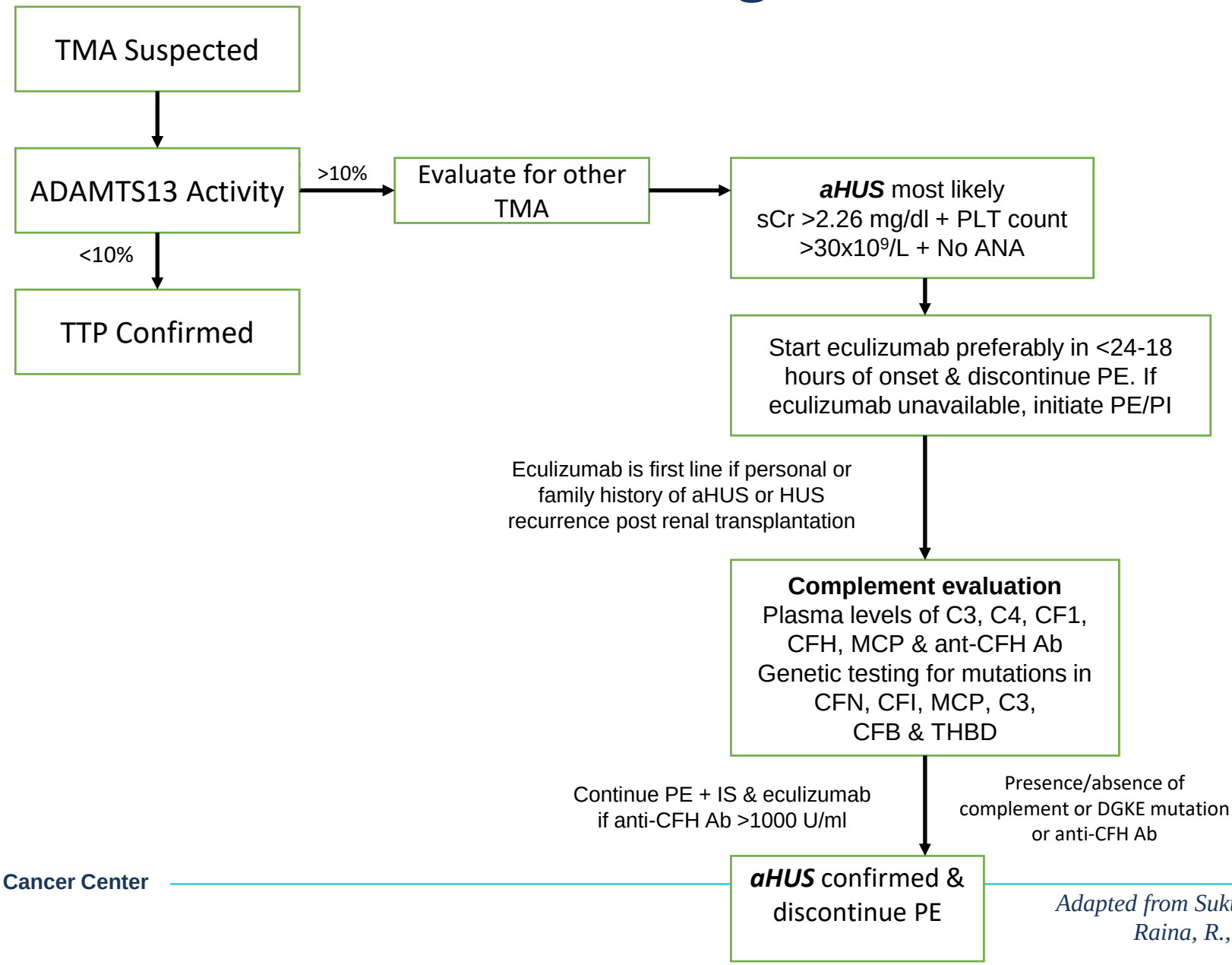


aHUS: Pathophysiology



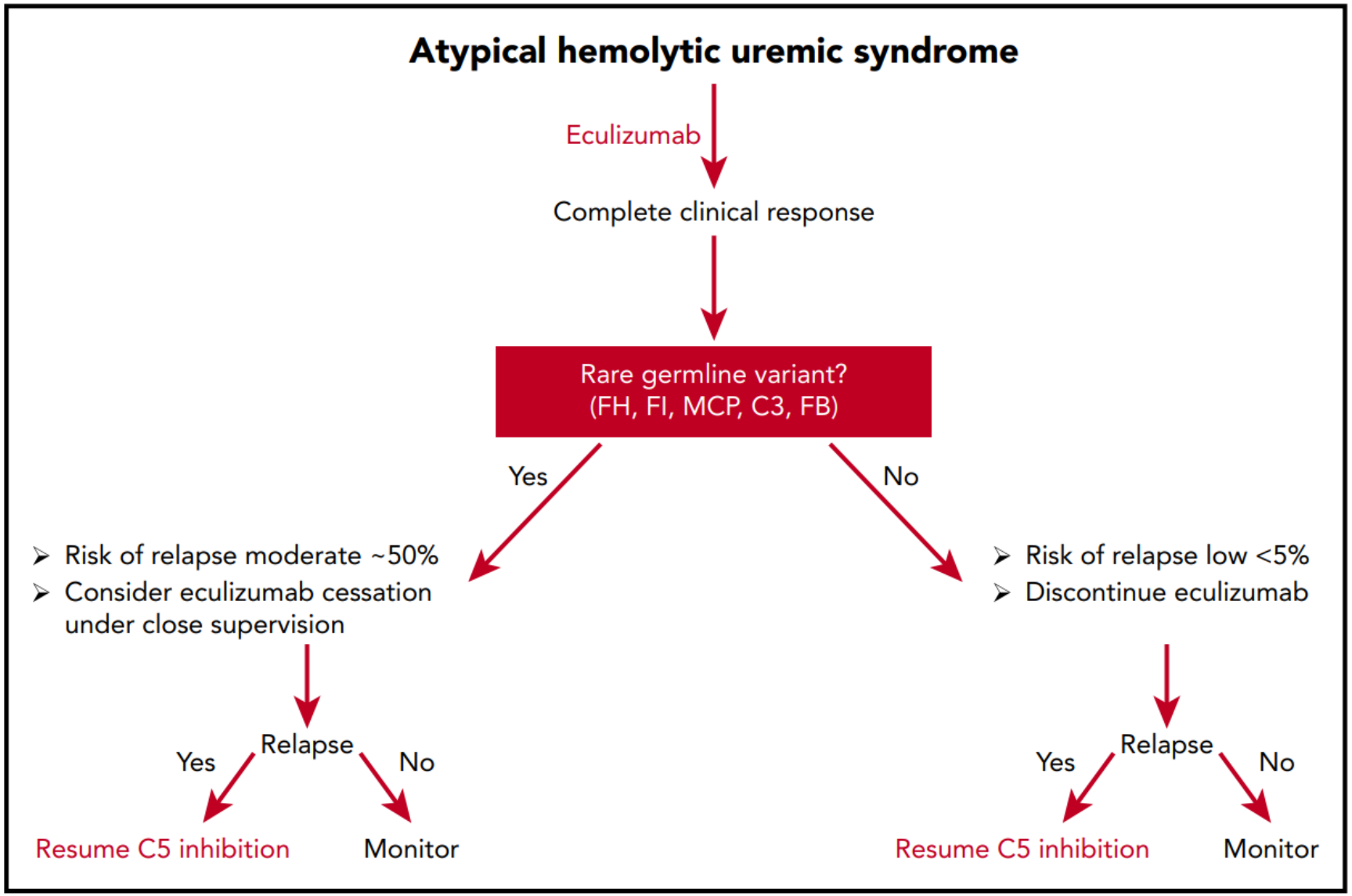
Ther Apher Dial, Volume: 23, Issue: 1, Pages: 4-21, 2018

aHUS: Management



Adapted from Sukumar et al. J. Clin. Med. 2021
Raina, R., et al. (2019). Ther Apher Dial

aHUS: Management with eculizumab

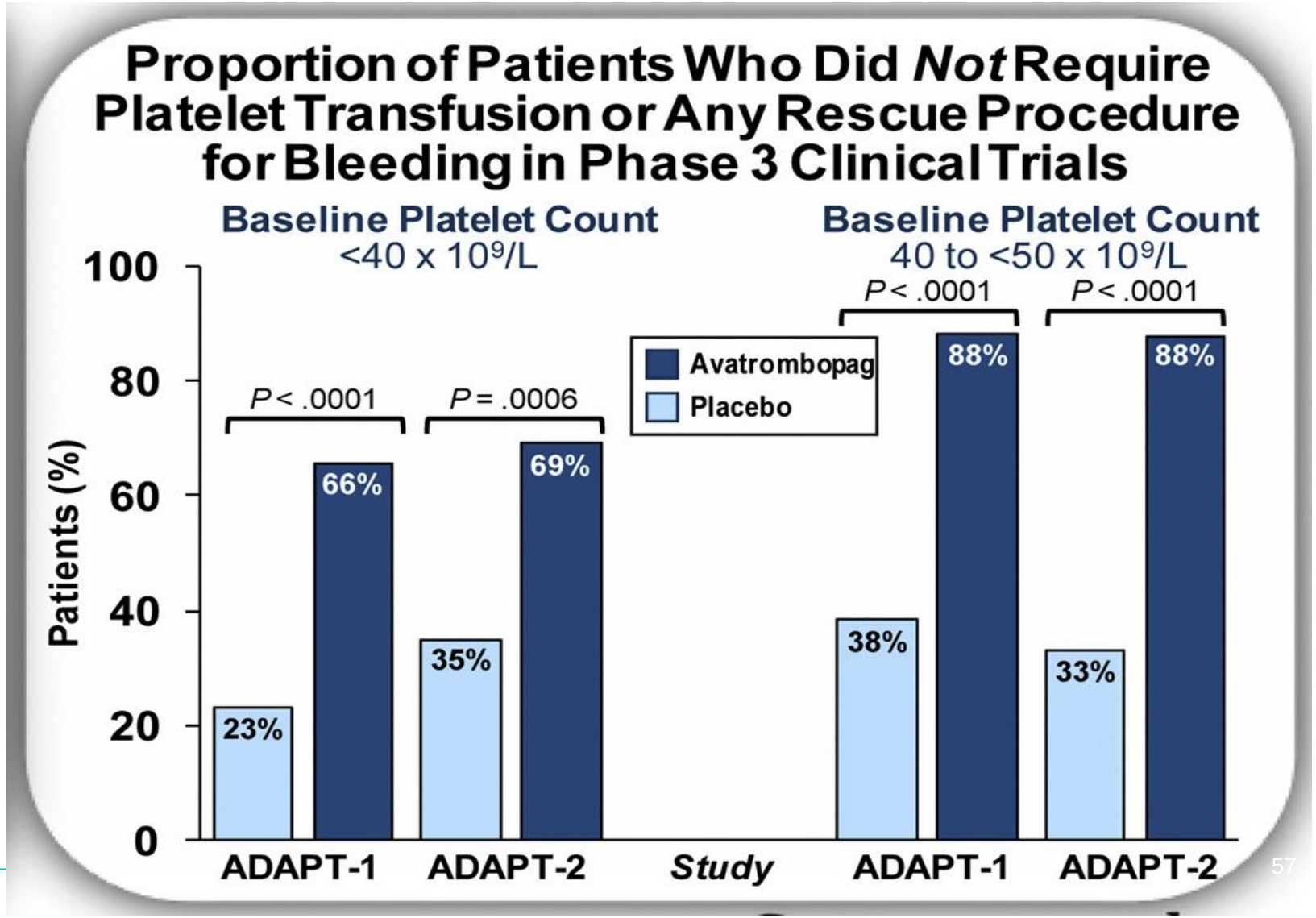


Brodsky, Blood 2021
Fakhouri et al. Blood 2021

Chronic liver disease, Infection, Critical illness, Marrow infiltration

Thrombocytopenia in chronic liver disease

Avatrombopag Before Procedures Reduces Need for Platelet Transfusion in Patients With Chronic Liver Disease and Thrombocytopenia



Terrault et al. Gastroenterology 2018

Platelet transfusion thresholds

Platelet count ($X10^9$/L)	Indication	Quality of evidence	Strength of Recommendation
<150	Accepted definition of thrombocytopenia		
100	Surgery on the brain or the posterior eye (BSH)	Low/None	Not graded
80	Insertion/removal of epidural catheter, Neuraxial Anesthesia (BSH)	Moderate	Low
50	Lumbar puncture, major non neuraxial surgery (AABB)	Very low	Weak
50	Therapeutic enteroscopy, deep abscess drainage, urinary tract interventions (ASGE, SIR)	None	Weak
50	Liver, renal, transbronchial biopsy (BSH)	Low/None	Weak
20	Central line placement (using ultrasound), dialysis access, PICC placement, superficial abscess drainage (AABB, BSH, SIR)	Moderate	Strong
20	Diagnostic enteroscopy (ASGE)	Low/None	Not graded
20	Bronchoscopy with lavage, paracentesis (BTS, SIR)	Low/None	Not graded
20	Unstable, febrile, bleeding patients (AABB)	Moderate	Strong
10	Ppx. for spontaneous bleeding, BM biopsy (AABB)	Moderate	Strong
5	Spontaneous bleeding** (AABB)	High	

Adapted from Nagrebetsky, Brit J Anaesthesia (2019) & Stanworth & Shah, Blood (2022)

Thrombocytopenia in Pregnancy

Thrombocytopenia: Question 3

32 yo female presents **1 week post partum** with fatigue and headaches. BP is elevated at **178/106 HR: 120/min**. O2 sats: 98%.

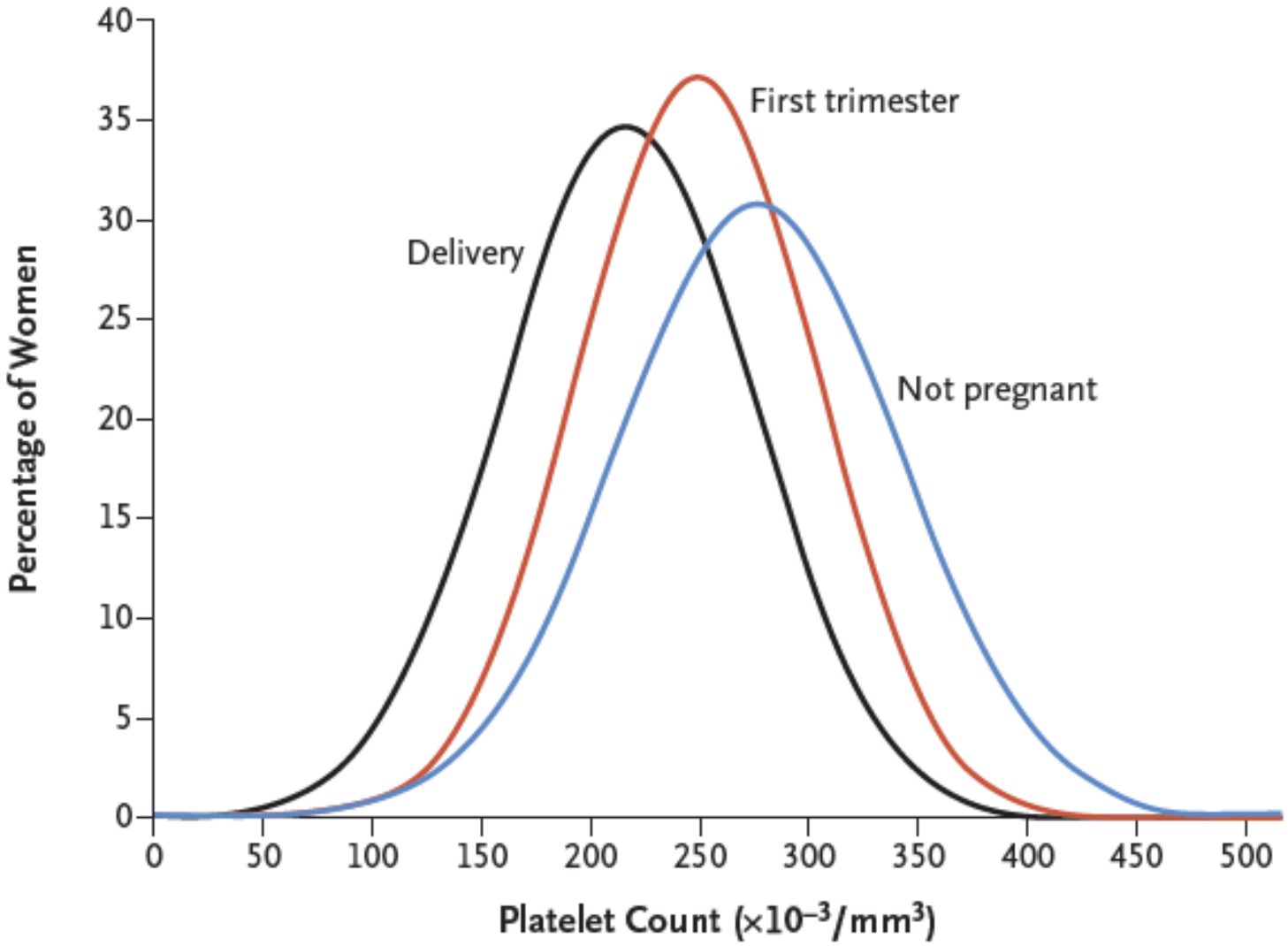
Labs

- WBC: 5500/mm3
- Hb: **11gm/dl→7.5gm/dL; schistocytes +++**
- Platelets: **130 X10^9/L→35 X10^9/L**
- PT/aPTT normal; Fibrinogen: 300mg/dL; AST/ALT: Normal; **LDH: 850U/L**; **Creatinine 0.8mg/dL→4.8mg/dL**

What is the most likely diagnosis?

A. Disseminated Intravascular Coagulation (DIC)
B. Hemolysis, Elevated Liver Enzymes, Low Platelets (HELLP) syndrome
C. Thrombotic Thrombocytopenic Purpura (TTP)
D. Atypical Hemolytic Uremic Syndrome (aHUS)

Thrombocytopenia in pregnancy



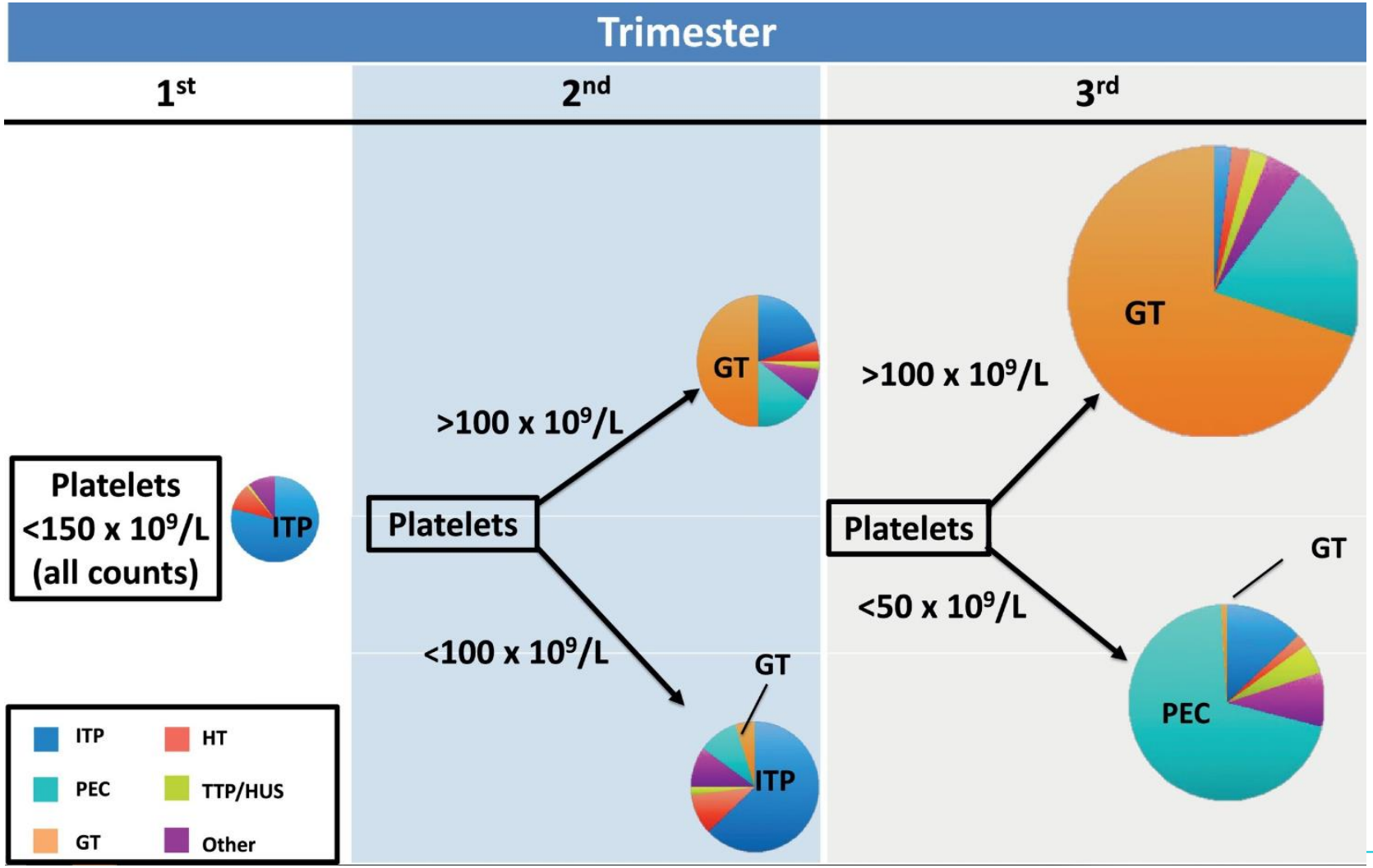
Bussell, Hou and Cines NEJM 2023

Thrombocytopenia in pregnancy

Pregnancy specific	Not related to pregnancy
Gestational thrombocytopenia	ITP
Pre-eclampsia	Hereditary thrombocytopenia
HELLP syndrome	TTP/HUS
Acute fatty liver of pregnancy (AFLP)	Type II VWD
	APLS
	Other: Pseudothrombocytopenia, Infection, DIC, Drugs, PNH, BMF syndromes, leukemia, nutritional deficiencies

Gernsheimer T et al. Blood 2013

Thrombocytopenia in pregnancy



D. B. Cines and L. D. Levine; Blood 2017

Thrombocytopenia in pregnancy

Clinical History & Physical Exam	History of thrombocytopenia Bleeding history Hypertension
Review blood smear	Pseudothrombocytopenia Large platelets, WBC inclusions RBC fragments
Laboratory evaluation	Coagulation testing, vWF Thyroid function LFTs, BMP, LDH, haptoglobin, retics Virus – HIV, HCV, HBV ANA, APL Abs

Gernsheimer T , James A, Stasi R. Blood 2013

“Incidental” (gestational) thrombocytopenia

- Affects up to 10% of “normal” pregnant women
  -No history of prior thrombocytopenia
- **Platelet count > 75 X10^9/L**
- 2^{nd}-3^{rd} trimester
- Pathogenesis--accelerated platelet turnover/hemodilution ?
- May be difficult to distinguish from ITP
- No increased incidence of neonatal thrombocytopenia

Immune thrombocytopenia (ITP) in pregnancy

- Incidence: 1 in 1,000 to 1 in 10,000 pregnancies
- Most common cause of thrombocytopenia in 1st trimester
- Pathogenesis--autoantibodies targeting platelet gp's or T cell dysregulation and direct toxicity
- 31% require intervention
- Incidence of neonatal thrombocytopenia ~20%
  - 4% severe

Gill KK & Kelton JG. Semin Hematol 2000;37:275–289;
Won YW et al. Korean J Intern Med 2005;20:129–134;
Fujimura K et al. Int Hematol 2002;75:426–433

Management of ITP in pregnancy

- Indications for therapy
  - First and second trimesters
    - Symptomatic
    - Platelet count 20–30 $x10^9$/L
    - Procedures
- Monitor more frequently in third trimester
- Therapy based on risk of maternal haemorrhage
  - Therapy of mother does not affect fetal platelet count
- First-line therapy
  - Corticosteroids
  - IVIg
- Combine first-line therapies in refractory patients

Gernsheimer T , James A, Stasi R. Blood 2013 ;121:38-47; Provan D et al. Blood Advances 2019;3: 3780-3817

Management of refractory ITP in pregnancy

Second-line therapies

- IV anti RhD
- Splenectomy
  - Rarely performed, but is best performed in the second trimester
- Azathioprine, Cyclosporine

Not approved (risk to fetus unknown)

- Rituximab
- TPO receptor agonists in the 3rd trimester (??)

Contraindicated

- MMF

Pishko et al. Blood reviews 2021

Delivery considerations

Maternal

Platelets

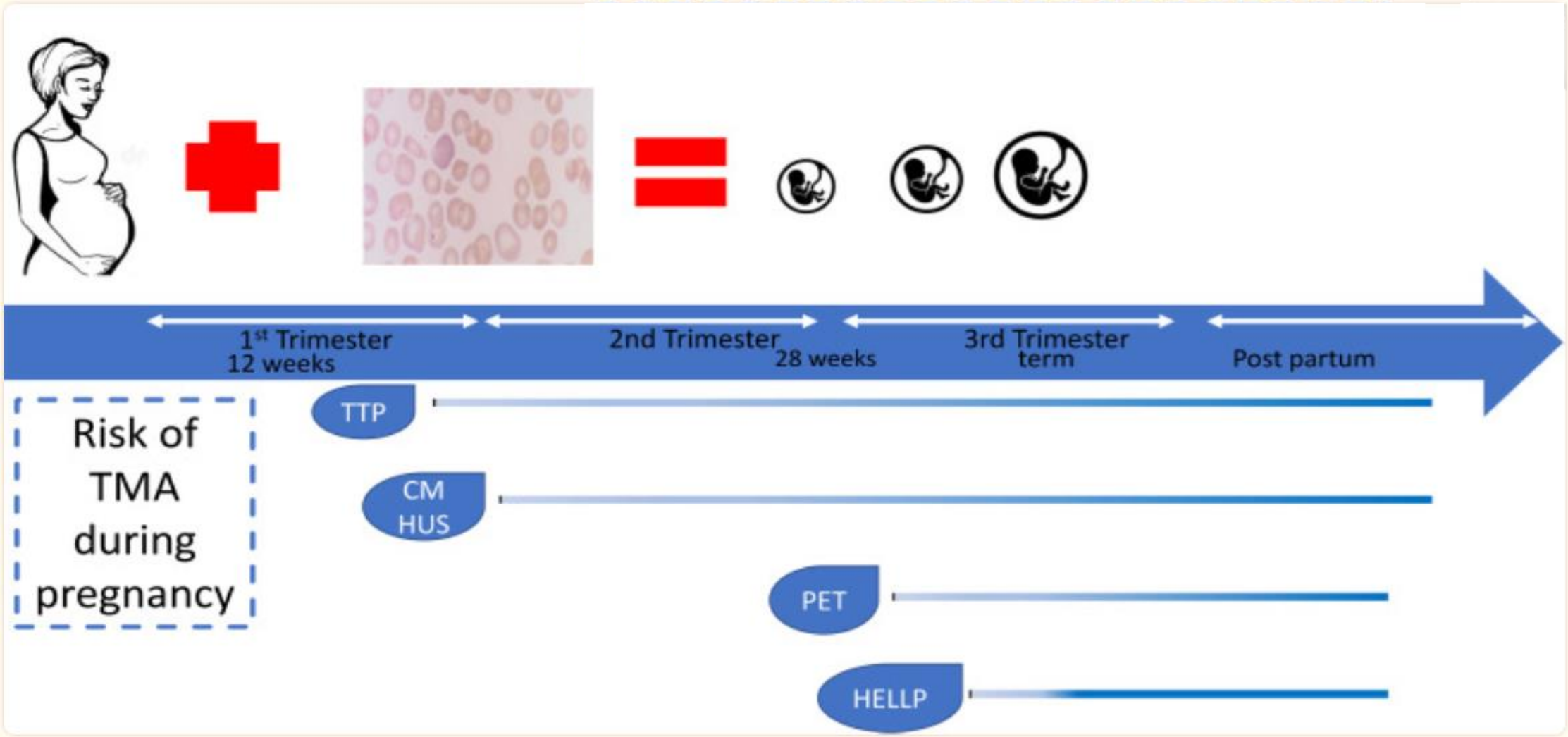
- >20 × 10^9/L for vaginal delivery
- >50 × 10^9/L for cesarean section
- >80 × 10^9/L neuraxial analgesia

Fetal

- 15% of neonates have platelets <150 × 10^9/L
- Most neonatal hemorrhage occurs at 24–48 hrs (0.5% incidence)
- Fetal platelet count measurement not recommended
- Avoid procedures with increased fetal bleeding risk
- May obtain cord blood and post delivery counts

Pishko et al. Blood reviews 2021

TMA: Pre-eclampsia/HELLP/AFLP/TTP/HUS



Scully; Hematology 2021

TMA: Pre-eclampsia/HELLP/AFLP/TTP/HUS

	Preeclampsia/HELLP	TTP	HUS	AFLP
Elevated blood pressure	+++	+	+	++ (50% of cases)
Neurological symptoms	+/++ (headache)	+++ (numbness, weakness, aphasia, mental status)	+	+
Abdominal symptoms	+ (RUQ pain)	++ (unspecific/diffuse)	+	+++ (unspecific/diffuse)
Fever	–	–/+	–/+	–
Easy bruising	–	–/+	–	–
Thrombocytopenia	+/++ (>50 × 10^9/L)	+++ (<20 × 10^9/L)	+ (<100 × 10^9/L)	+
Renal impairment (elevated creatinine; > ~2 mg/dL)	+/++	+/++	+++	++/+++
Hepatic dysfunction and inflammation (AST/ALT)	+	–/+	–/+	+++ (and bilirubin)
Coagulopathy	–/+	–	–	+++
LDH	+	+/+++	+/++	+++
Microangiopathic hemolytic anemia	+	+/+++	+/++	+
Hypoglycemia	–	–	–	+
ADAMTS13 activity	Normal	<10%*	>20%-30%†	>30%

Cines & Levine; Hematology 2017

TMA related to pregnancy

- Pre-eclampsia, HELLP, AFLP
  - Prompt delivery >34 weeks
  - Supportive care
  - Ob/Gyn managed care
  - In patients at high risk for PEC, Aspirin 150 mg versus placebo, with PEC occurring in 1.6% of patients in the aspirin group versus 4.3% in the placebo group (adjusted odds ratio 0.38, p = .004)(ASPIRE trial; NEJM 2017)
  - ATIII concentrates in AFLP, along with RBCs and FFP (?)

Pishko et al. Blood reviews 2021

TMA: TTP/aHUS in pregnancy

- TTP: 1 in 200,000 pregnancies
- Congenital TTP (Upshaw-Schulman syndrome) rare, but up to 1/3 of patients with TTP during pregnancy
- TTP presents first-time during pregnancy in 25–50% of women with congenital TTP, also in 10% of women with acquired TTP

- ADAMTS13 level of <10% diagnostic, genetic testing for congenital TTP
- Unlike HELLP, prompt delivery after diagnosis of TTP not required
- Daily PLEX along with corticosteroids while awaiting diagnostic testing; until platelet count >150 × 10^9/L
- Congenital TTP: scheduled plasma infusions
- Subsequent pregnancies: Prophylactic plasma infusions (Q1-2 weeks) →maintain ADAMTS13 levels >10% as soon as pregnancy confirmed

- aHUS: Eculizumab 900 mg weekly X 4 weeks→1200 mg, then 1200 mg Q2 weeks

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Thrombocytopenia: Question 3

32 yo female presents **1 week post partum** with fatigue and headaches. BP is elevated at **178/106 HR: 120/min**. O2 sats: 98%.

Labs

- WBC: 5500/mm3
- Hb: **11gm/dl→7.5gm/dL; schistocytes +++**
- Platelets: **130 X10^9/L→35 X10^9/L**
- PT/aPTT normal; Fibrinogen: 300mg/dL; AST/ALT: Normal; **LDH: 850U/L**; **Creatinine 0.8mg/dL→4.8mg/dL**

What is the most likely diagnosis?

A. Disseminated Intravascular Coagulation (DIC)

B. Hemolysis, Elevated Liver Enzymes, Low Platelets (HELLP) syndrome

C. Thrombotic Thrombocytopenic Purpura (TTP)

D. Atypical Hemolytic Uremic Syndrome (aHUS)

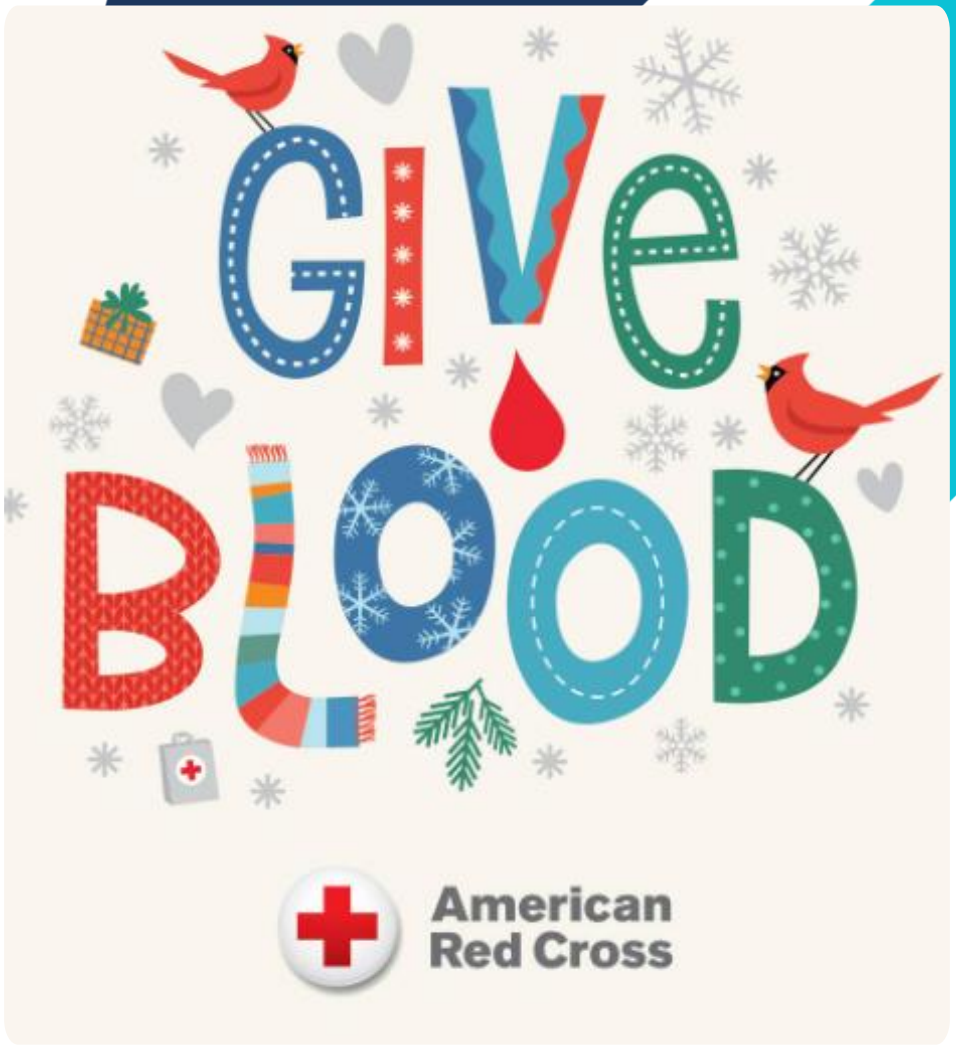
	Preeclampsia/HELLP	TTP	HUS	AFLP
Elevated blood pressure	+++	+	+	++ (50% of cases)
Neurological symptoms	+/++ (headache)	+++ (numbness, weakness, aphasia, mental status)	+	+
Abdominal symptoms	+ (RUQ pain)	++ (unspecific/diffuse)	+	+++ (unspecific/diffuse)
Fever	–	–/+	–/+	–
Easy bruising	–	–/+	–	–
Thrombocytopenia	+/++ (>50 × 10^9/L)	+++ (<20 × 10^9/L)	+ (<100 × 10^9/L)	+
Renal impairment (elevated creatinine; > ~2 mg/dL)	+/++	+/++	+++	++/+++
Hepatic dysfunction and inflammation (AST/ALT)	+	–/+	–/+	+++ (and bilirubin)
Coagulopathy	–/+	–	–	+++
LDH	+	+/+++	+/++	+++
Microangiopathic hemolytic anemia	+	+/+++	+/++	+
Hypoglycemia	–	–	–	+
ADAMTS13 activity	Normal	<10%*	>20%-30%†	>30%

Thrombocytopenia: Summary

Decreased Production	Increased Destruction / Consumption	Combination
Marrow failure	Heparin induced thrombocytopenia; **Vaccine induced thrombotic thrombocytopenia**	**Immune Thrombocytopenia**
Inherited thrombocytopenia	Thrombotic thrombocytopenic purpura/ atypical HUS, DIC	Other autoimmune conditions
Myelodysplasia	**Pre-eclampsia, HELLP syndrome, AFLP**	Infection/sepsis
Marrow infiltration	**Post transfusion purpura**	Liver disease
Irradiation	Neonatal alloimmune thrombocytopenia	**Drugs**
Chemotherapy/drugs	vWD Type IIB	Cyclic thrombocytopenia
Nutritional deficiencies (Vit B12, folate, severe iron deficiency)	Mechanical destruction (valvular dysfunction, cardio-pulmonary bypass, LVADs)	Other ***Pseudothrombocytopenia, gestational/dilutional***
Alcohol	Hypersplenism (sequestration)	***Qualitative platelet disorders***

Fred Hutch Cancer Center

Thank you



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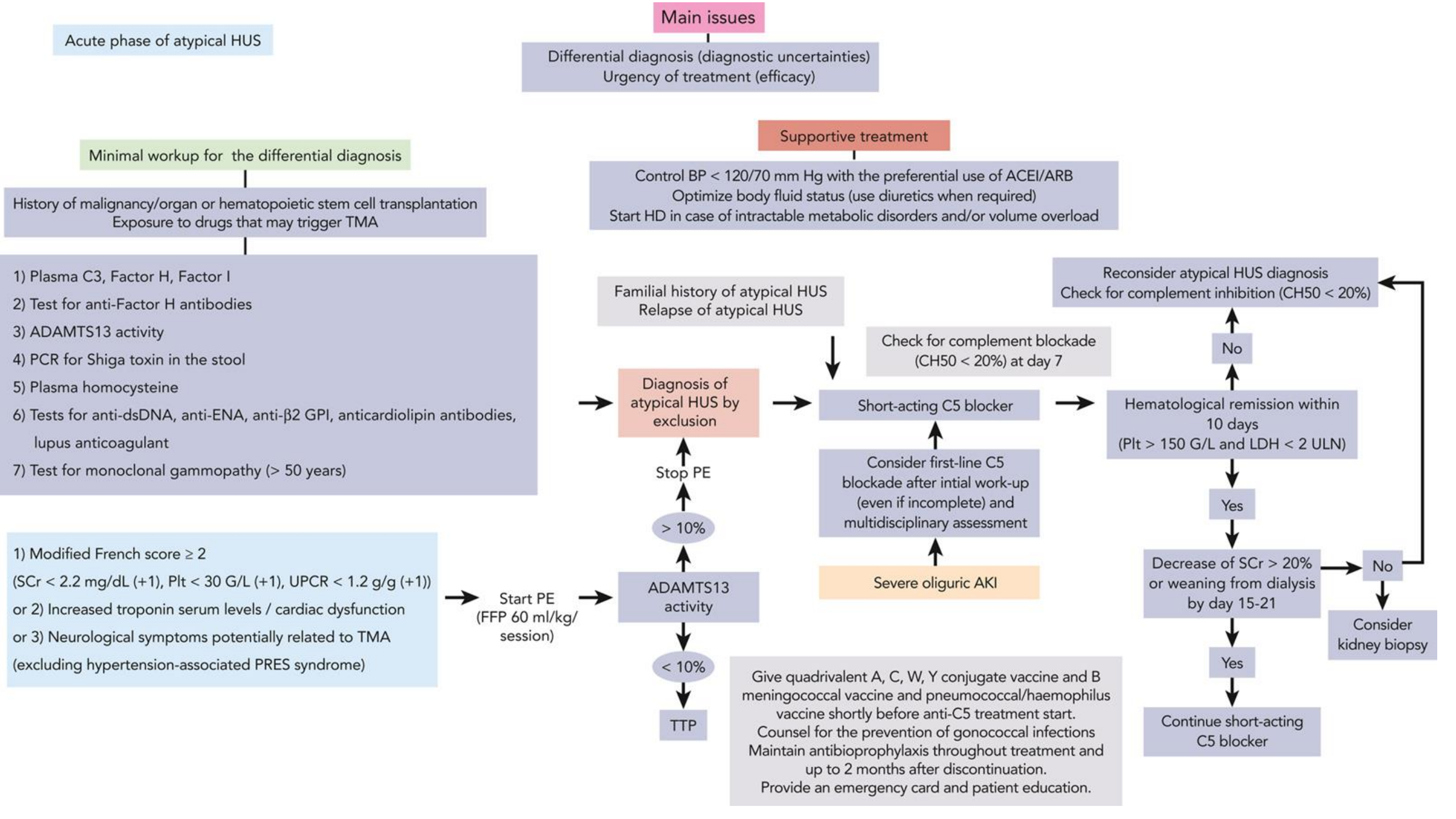
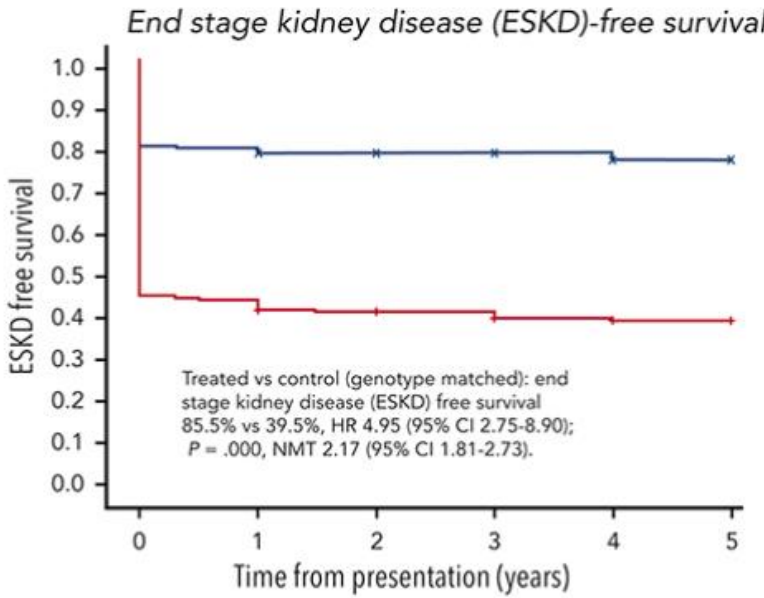

Acute phase of atypical HUS
Main issues
Differential diagnosis (diagnostic uncertainties)
Urgency of treatment (efficacy)
Supportive treatment
Control BP < 120/70 mm Hg with the preferential use of ACEI/ARB
Optimize body fluid status (use diuretics when required)
Start HD in case of intractable metabolic disorders and/or volume overload
Minimal workup for the differential diagnosis
History of malignancy/organ or hematopoietic stem cell transplantation
Exposure to drugs that may trigger TMA
1) Plasma C3, Factor H, Factor I
2) Test for anti-Factor H antibodies
3) ADAMTS13 activity
4) PCR for Shiga toxin in the stool
5) Plasma homocysteine
6) Tests for anti-dsDNA, anti-ENA, anti-β2 GPI, anticardiolipin antibodies, lupus anticoagulant
7) Test for monoclonal gammopathy (> 50 years)
Familial history of atypical HUS
Relapse of atypical HUS
Check for complement blockade (CH50 < 20%) at day 7
Reconsider atypical HUS diagnosis
Check for complement inhibition (CH50 < 20%)
No
Diagnosis of atypical HUS by exclusion
Short-acting C5 blocker
Hematological remission within 10 days
(Plt > 150 G/L and LDH < 2 ULN)
Stop PE
Consider first-line C5 blockade after intial work-up (even if incomplete) and multidisciplinary assessment
Yes
> 10%
Severe oliguric AKI
1) Modified French score ≥ 2
(SCr < 2.2 mg/dL (+1), Plt < 30 G/L (+1), UPCR < 1.2 g/g (+1))
or 2) Increased troponin serum levels / cardiac dysfunction
or 3) Neurological symptoms potentially related to TMA
(excluding hypertension-associated PRES syndrome)
Start PE
(FFP 60 ml/kg/ session)
ADAMTS13 activity
Decrease of SCr > 20% or weaning from dialysis by day 15-21
No
Consider kidney biopsy
< 10%
Yes
TTP
Continue short-acting C5 blocker
Give quadrivalent A, C, W, Y conjugate vaccine and B meningococcal vaccine and pneumococcal/haemophilus vaccine shortly before anti-C5 treatment start.
Counsel for the prevention of gonococcal infections
Maintain antibioprophylaxis throughout treatment and up to 2 months after discontinuation.
Provide an emergency card and patient education.

Atypical Hemolytic Uremic Syndrome (aHUS) in the Era of Terminal Complement Inhibition

UK national center experience of complement mediated atypical hemolytic uremic syndrome (CaHUS). Control n = 279, eculizumab treated n = 243.



Eculizumab non responsiveness: *DGKE*, cobalamin metabolism genes (*MMACHC, MTR*), nephrotic syndrome genes, RNA pathway genes (*EXOSC3, POLR3B, TSEN2*), hypertension genes

Additional findings:

Platelet count
Blood pressure
Age
Outcome predictors
Genotype
Serum creatinine
Time to treatment

Response to eculizumab

Platelet normalisation: 4 days

Majority of renal recovery in 30 days, but ongoing response up to 1 year

Eculizumab complications

x550 fold meningococcal infection despite vaccination and antibiotic prophylaxis

Eculizumab withdrawal

aHUS relapse rate

Pathogenic mutation	1/9.5 person yrs
VUS	1/10.8 person yrs
No rare genetic variant	No relapses

Conclusion: Eculizumab resulted in significantly improved 5-year ESKD-free survival in CaHUS, but response was contingent upon genetic background with *EXOSC3* representing a novel non-complement cause of HUS.

Brocklebank et al. DOI: 10.1182/blood.2022018833

Blood Visual Abstract