



Fred Hutch • Seattle Children's • UW Medicine

Thrombocytopenia: Updated Review

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Discussion of off-label drug use:

Antifibrinolytic agents, anti-RhD, aspirin, azathioprine, cyclophosphamide, cyclosporine, danazol, dapsone, mycophenolate, prostacycline, rituximab, sirolimus, vincristine

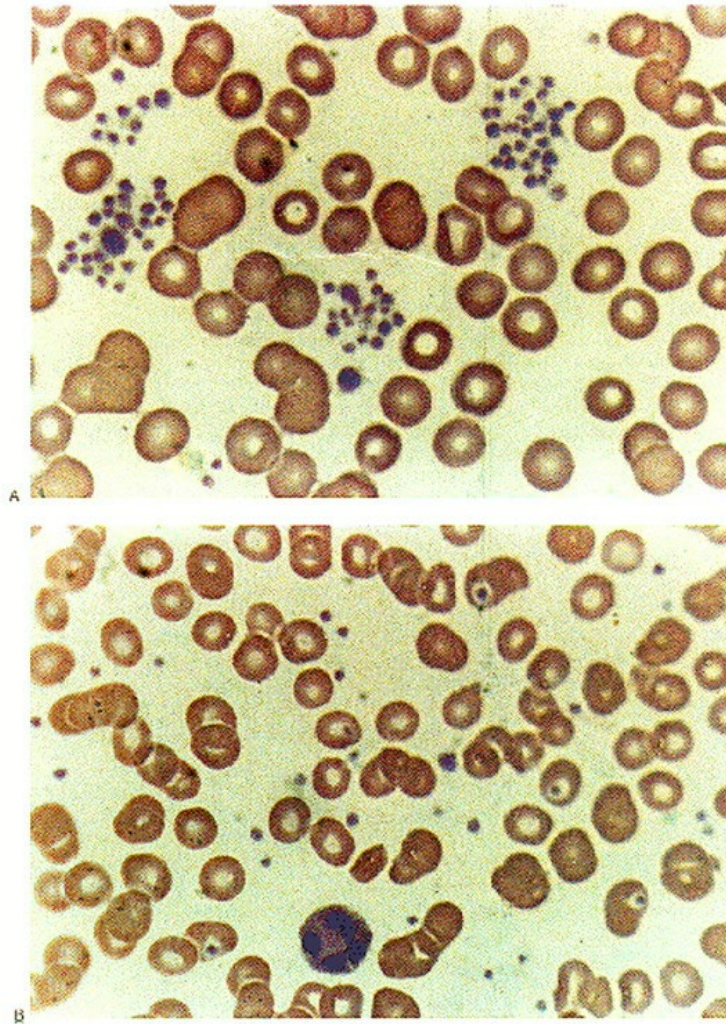
off-label testing:

PF4-ELISA

Approach to thrombocytopenia

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

Pseudo-thrombocytopenia

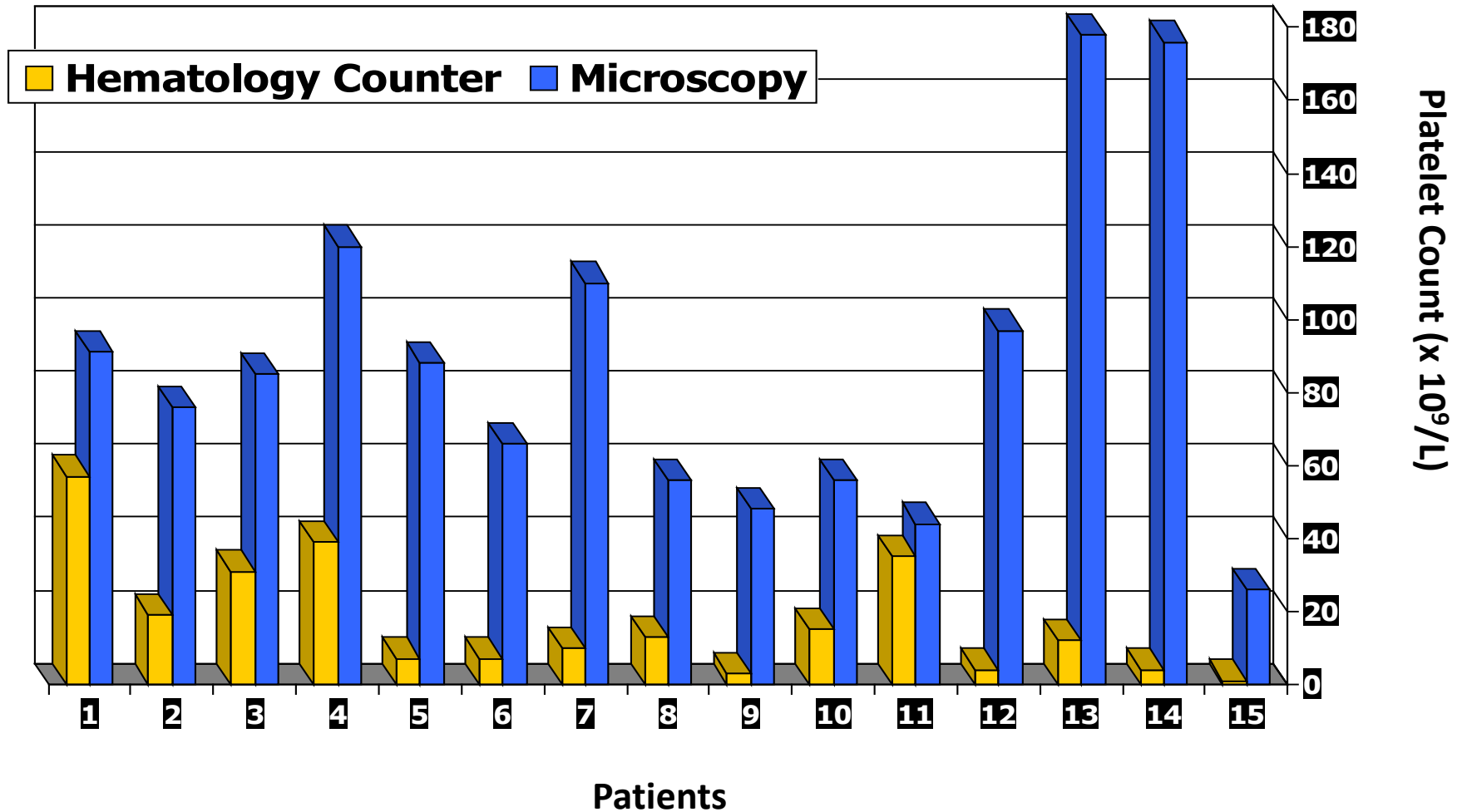


Shalev, O. et. al. N Engl J Med 1993;329:1467



The NEW ENGLAND
JOURNAL of MEDICINE

Platelet count errors in macrothrombocytopenia



Giant platelet on a peripheral blood smear



Mechanisms of thrombocytopenia

- Decreased production
- Increased destruction
- Increased splenic sequestration
- Dilutional

Thrombocytopenia: Production

- Congenital/Hereditary Thrombocytopenias
 - Childhood – severe thrombocytopenic syndromes
 - Adults – milder forms
 - A rare presentation of marrow failure syndromes

Congenital thrombocytopenias

- Microthrombocytopenias
 - Wiskott Aldrich
- Normal platelet size
 - ANDRD26, ETV6
 - Predisposition to MDS and AML (30 X increase)
 - RUNX1
 - MPL
- Macrothrombocytopoenia
 - ACTN-1 related
 - MyH9
 - GP1B
 - GATA1-X-linked

Disorders of production:

MYH9-related platelet disorders

Clinical features	May-Hegglin	Sebastian	Fechner	Epstein
Macrothrombocytopenia	Yes	Yes	Yes	Yes
Leukocyte inclusions	Yes	Yes	Yes	No
Hearing impairment	No	No	Yes	Yes
Cataracts	No	No	Yes	No
Nephritis	No	No	Yes	Yes

Hereditary thrombocytopenia

- Autosomal dominant
 - MYH9 Gene mutations e.g. May Hegglin
 - Tpenia, large platelets, neutrophil inclusions
 - Gray Platelet Syndrome – large, α granules, pmn granules
- Autosomal recessive
 - Congenital amegakaryocytic thrombocytopenia
 - Thrombocytopenia with Absent Radii
 - Bernard Soulier syndrome large plts w/ ↓ GPIb
- Sex-linked recessive
 - Wiskott-Aldrich syndrome –
 - small plts, immunodeficient, eczema

Acquired thrombocytopenia: ↓ Production

Are other Cell Lines Affected?

- Intrinsic marrow abnormalities
- Vitamin deficiencies
- Toxins
- Drugs
- Infection
- Marrow infiltration
- Liver disease

Thrombocytopenia in liver disease

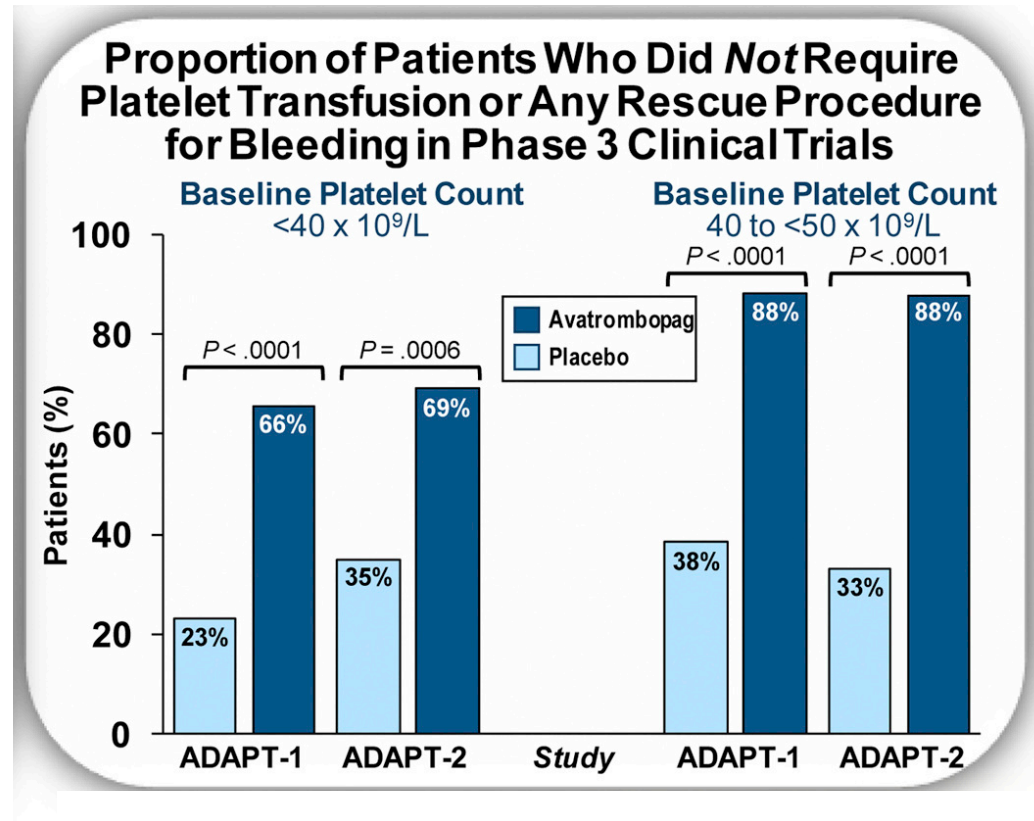
- Multifactorial
 - Splenomegaly
 - Decreased TPO
 - Increased turnover
 - Immune
 - Hepatitis C
 - Autoimmune hepatitis
- Therapy
 - Transfusion
 - Eltrombopag (HCV)
 - Avatrombopag, lusutrombopag for procedures

Increasing platelet production for procedures in cirrhosis

N= placebo 158, Avatrombopag 277

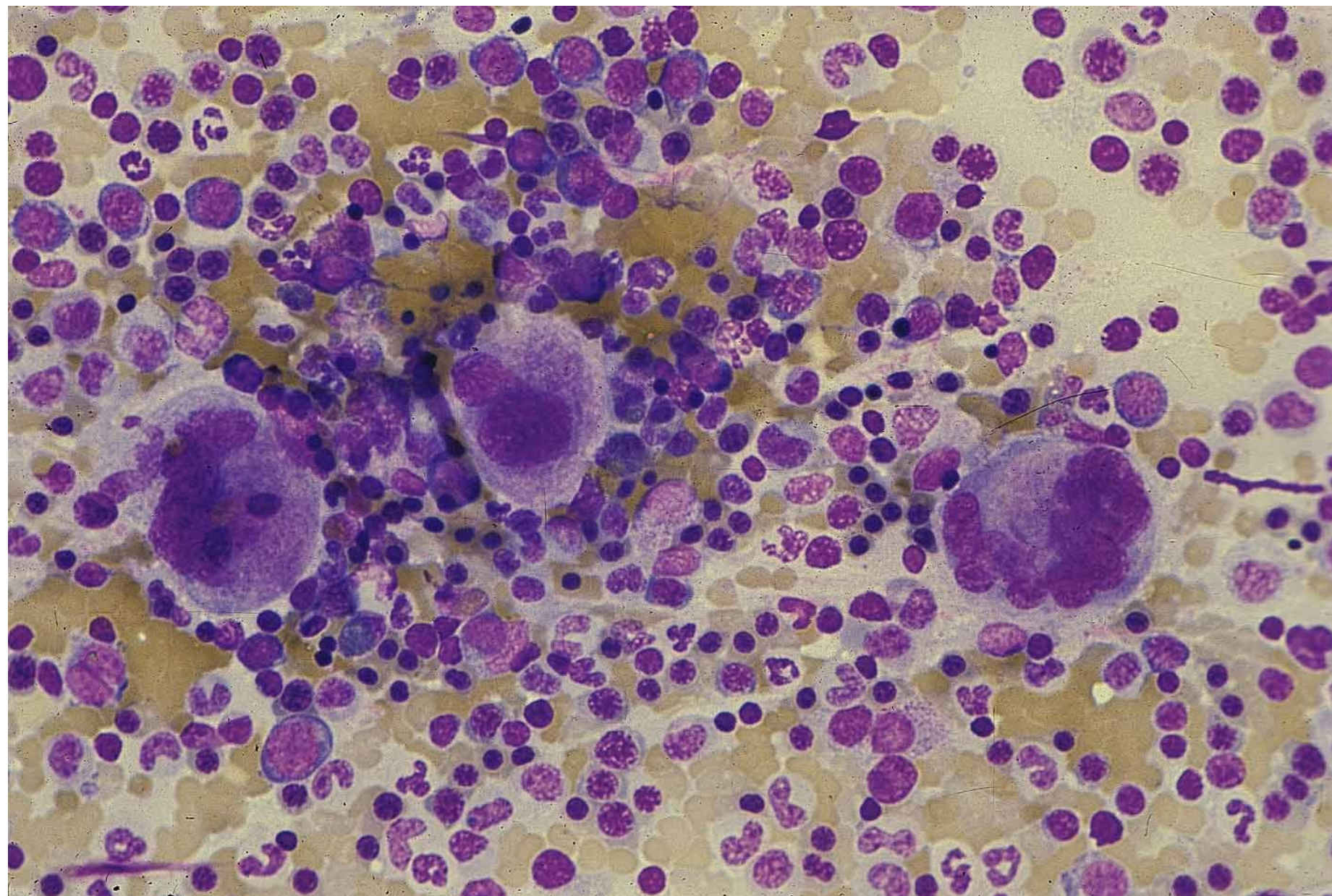
Procedure

Paracentesis
Endoscopy
Colonoscopy
Liver biopsy
Ablation
Chemoembolization
Dental procedures
TIPS
Laparoscopic
Vascular catheterization



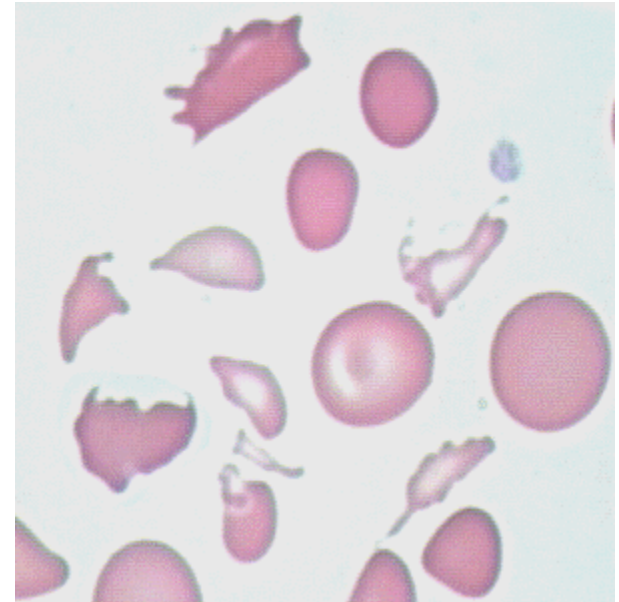
Thrombocytopenia due to increased platelet destruction and consumption

- Platelet lifespan < 10 Days
 - Increased platelet turnover
- Normal or increased megakaryocytes
- Immune or non-immune



Isolated platelet consumption: MAHA

- Disruption of laminar flow
- Vasculitis
- Malignancy
- Malignant hypertension
- Cryoglobulinemia
- Infection
 - Septic emboli, rickettsia
- Thrombotic Thrombocytopenic Purpura & Hemolytic Uremic Syndrome



Is platelet transfusion contraindicated?

Goel et al. Blood. 2015; 125(9):1470-1476

Isolated platelet consumption

- Thrombotic Thrombocytopenic Purpura
 - Adults
 - Classic pentad
 - Rx - plasma exchange
- Secondary TTP
 - Drugs, HIV, pregnancy, malignancy
- Congenital TTP
- Thrombotic microangiopathies with acute kidney injury
 - Complement mediated –C-TMA (HUS)
 - Shigatoxin (Stx HUS) 0157:H7 Ecoli

TTP & atypical HUS

	TTP	C-TMA
Pathophysiology	ADAMTS13 Deficiency	Aberrant activation of alternative C' pathway Factor H gene mutations (25%), others
Clinical	Tpenia/anemia more severe	Renal insufficiency more prominent
Therapy	Plasma Plasma exchange + corticosteroids, rituximab	Chronic C5 inhibition Eculizumab, ravulizumab
High risk disease	Caplacizumab	

Immune platelet destruction

- Auto-Immune
 - Primary – “ITP”
 - Secondary
 - Collagen-Vascular Disease
 - Malignancy
 - Infection
 - HIV
- Drug induced
 - vanc, pcns, quinine
- Allo-immune
 - Post-Transfusion Purpura
 - Neonatal Alloimmune Thrombocytopenia

Recommendations for diagnosis of primary ITP

- Diagnosis principally one of exclusion
- History & PE
- Full blood count, retic & peripheral blood examination
- Helicobacter pylori infection detection by breath test or stool antigen (regional)
- HBV, HIV, HCV
- Quantitative Immunoglobulins
- DAT
- Other testing in selected individuals (ab, imaging)
- Bone marrow in selected individuals only

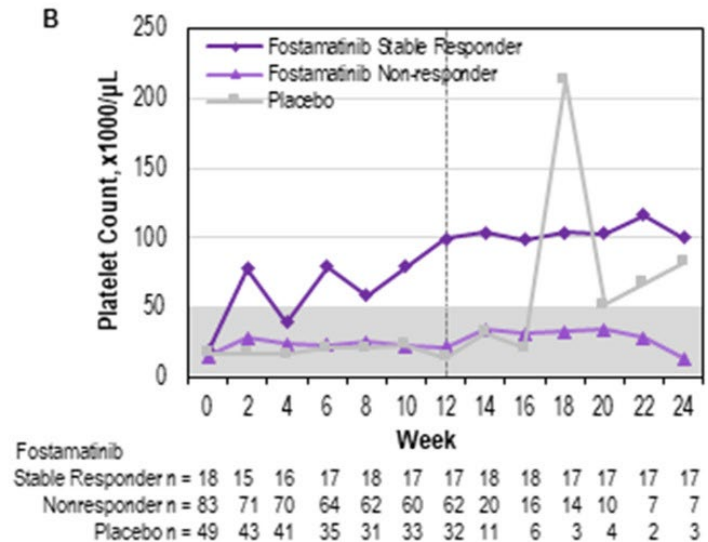
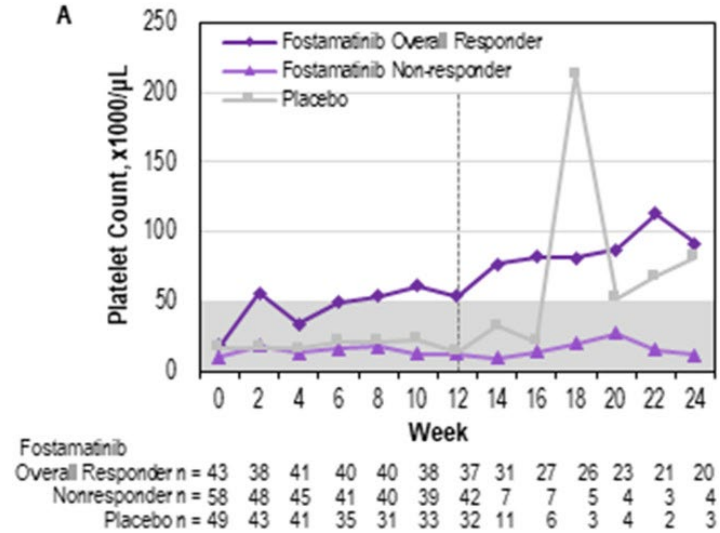
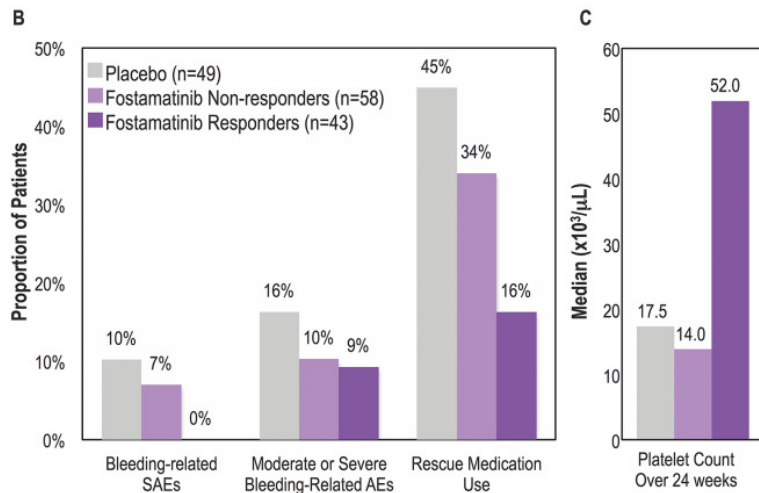
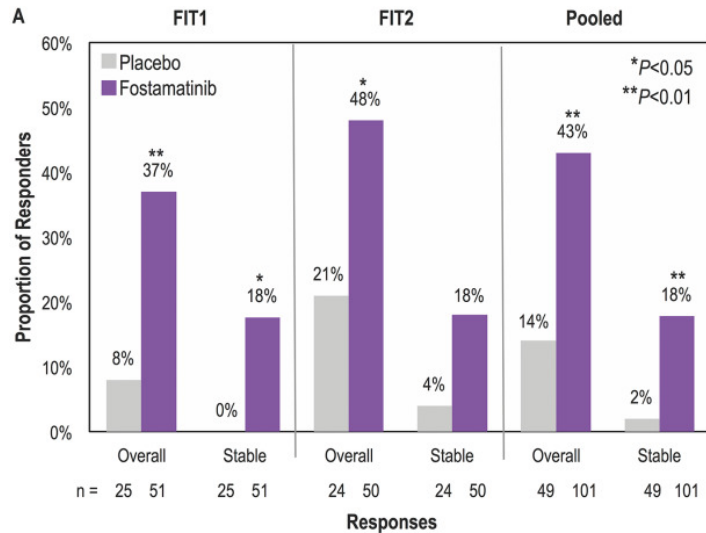
Summary of recommendations for initial treatment of ITP

	ASH 2020 ¹	ICR Recommendations ²
Platelet count threshold for treatment	$\leq 30 \times 10^9/L$	$<20-30 \times 10^9/L$ Individualize to patient & phase
First-line treatment	Corticosteroids (prednisone, methyprednisolone 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

Summary of recommendations for treatment of persistent (>3 months) ITP

Treatment type/parameter	ASH 2020 ¹	ICR Recommendations ²
Platelet count threshold for treatment	$\leq 30 \times 10^9/L$	Treat to maintain platelet count $>20-30 \times 10^9/L$ 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

Syk kinase inhibition: Fostamatinib for refractory persistent/chronic ITP



Treatment of drug induced thrombocytopenia

- Stop offending agent(s)
- Severe: IVIg
- Severe refractory: Plasma exchange
Dialysis
- Severe adjunctive therapy
 - Platelet transfusions
 - Antifibrinolytic agents
- Testing for drug dependent antibody

Clinical diagnosis of HIT

- History of heparin exposure
- Thrombocytopenia during and after heparin exposure (<150,000)
 - Drop in platelet count (>50%) rather than absolute thrombocytopenia
 - Thrombocytopenia recovers after heparin withdrawal
- With or without thrombotic complications
- Unusual presentations
 - Absence of expected increase, skin necrosis, delayed onset

Laboratory tests for HIT

Functional (activation)

- Serotonin release
- ATP release

- Platelet aggregation
- Flow cytometry

- PEA P-selectin Expression Assay

Antigen

- Heparin-PF4 ELISA
- Other IA

Clinical scoring system for HIT pretest probability:

“The 4Ts”

4T's	2 points	1 point	0 point
Thrombocytopenia	Platelet count fall > 50% and platelet nadir $\geq 20^*$	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*.

Alternate thrombotic therapy

Low Molecular Wt Heparin



Anti-platelet agents

Prostacycline, tirofiban,
aspirin

Direct Thrombin Inhibitors

Argatroban

Bivalirudin

DOACs?

Pentasacharides

Fondaparinux

Cardiac surgery with history of HIT

- Delay 3-6 months
- Antibody (ELISA) Neg
- Expose during CPB only
- Use alternate anticoagulation post-op
- Delay not possible:
 - Plasma Exchange
 - IVIg

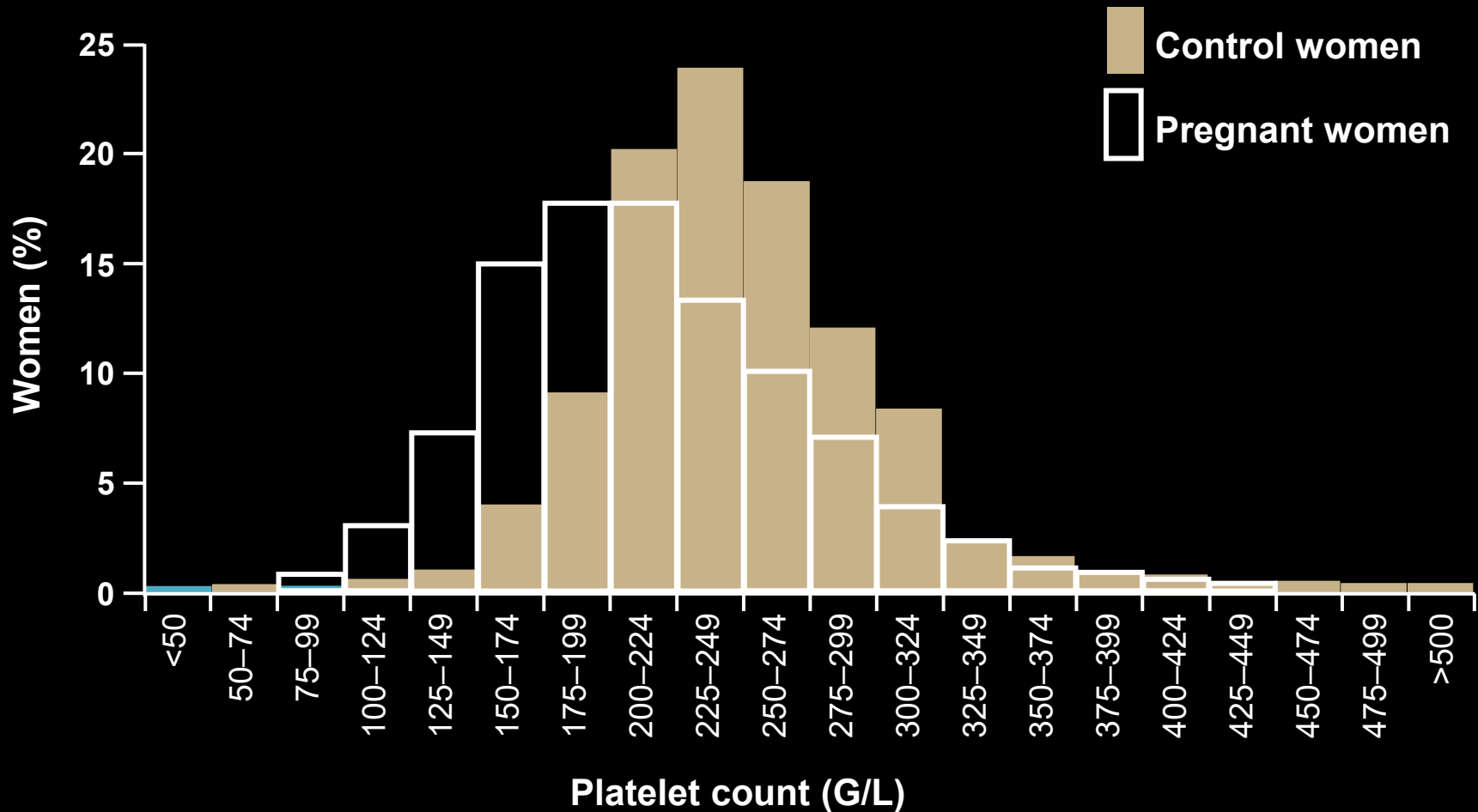
Warfarin in HIT

- Contraindicated until platelet count recovery (or $>100,000$) due to decreased Protein C
- Use with a thrombin inhibitor
 - Associated with progression of DVT to venous limb gangrene
 - Caution if INR >4
- Do not use loading dose

dDX of thrombocytopenia

- Pregnancy – always test in a woman of potential child bearing

Platelet count at term in healthy pregnancy



Pregnancy-associated thrombocytopenia

- Isolated Thrombocytopenia
 - Incidental (Gestational)
 - Immune (ITP)
 - Drug-induced
 - HIT
 - Congenital
 - Type IIb vWD
- Systemic Disorders
 - Preeclampsia
 - HELLP syndrome
 - Acute fatty liver
 - Thrombotic microangiopathies
 - SLE / Antiphospholipid antibodies
 - DIC
 - Viral infection
 - Nutritional deficiencies
 - Hypersplenism
 - Bone marrow dysfunction

Evaluation of thrombocytopenia in pregnancy

Clinical History &
Physical Exam

History of thrombocytopenia
Bleeding history
Hypertension

Review blood smear

Pseudothrombocytopenia
Large platelets
Fragments

Laboratory evaluation

Coagulation testing, vWF
Thyroid testing
LFTs
Virus – HIV, HCV, H Pylori
ANA, Lupus anticoagulant, ACLA

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

Management of ITP in pregnancy

- Indications for therapy
 - First and second trimesters
 - Symptomatic
 - Platelet count $20-30,000 \times 10^9/L$
 - 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

Management of refractory ITP in pregnancy

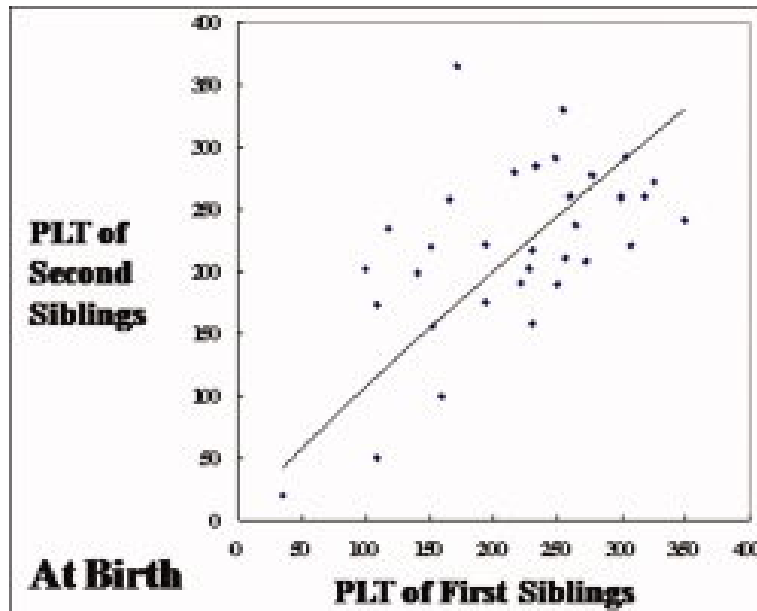
Second-line therapies

- IV anti RhD
- Splenectomy
 - Rarely performed, best performed in the second trimester
- Azathioprine
- Cyclosporine
- HDMP with IVIg or azathioprine if refractory to oral corticosteroids or IVIg

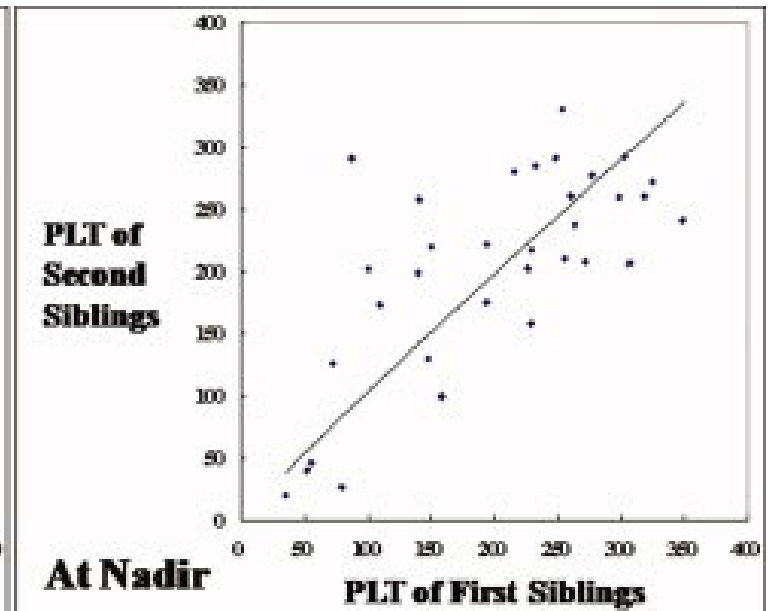
Should not be used

- Other immunosuppressive drugs
- +/- rituximab
- Vinca alkaloids, danazol
- TPO receptor agonists, TPO

Correlation of sibling platelet counts at birth and at nadir



$$P = 0.001$$



$$P < 0.0001$$

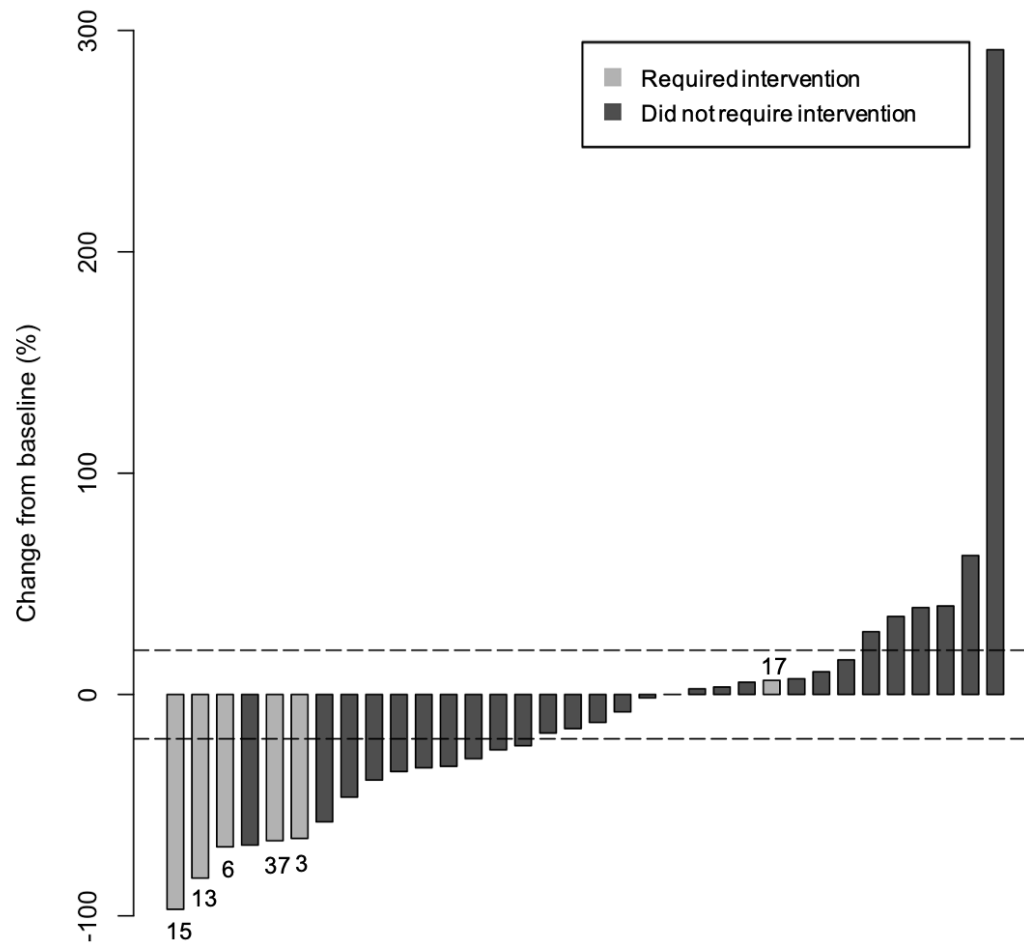
Management of delivery

- Mode of delivery determined by obstetric indications
 - Most neonatal haemorrhage occurs at 24–48 hrs
 - Fetal platelet count measurement not recommended
 - Avoid procedures with increased fetal bleeding risk
- Epidural anaesthesia
 - Risk of spinal hematoma unknown
 - Platelets of 70,000/ μ L
 - Consider other hemostatic parameters and history
 - Usefulness of thromboelastography unclear

COVID-19 and thrombocytopenia

- Infection related
- Vaccine related
 - Acute immune thrombocytopenia
 - Thrombotic thrombocytopenia (VITT)
 - J&J or AstraZeneca
 - IgG PF4 ELISA functional assays +
 - Non-heparin dependent platelet activation
 - Chronic ITP patients

Platelet response in vaccinated ITP patients



Thank you

